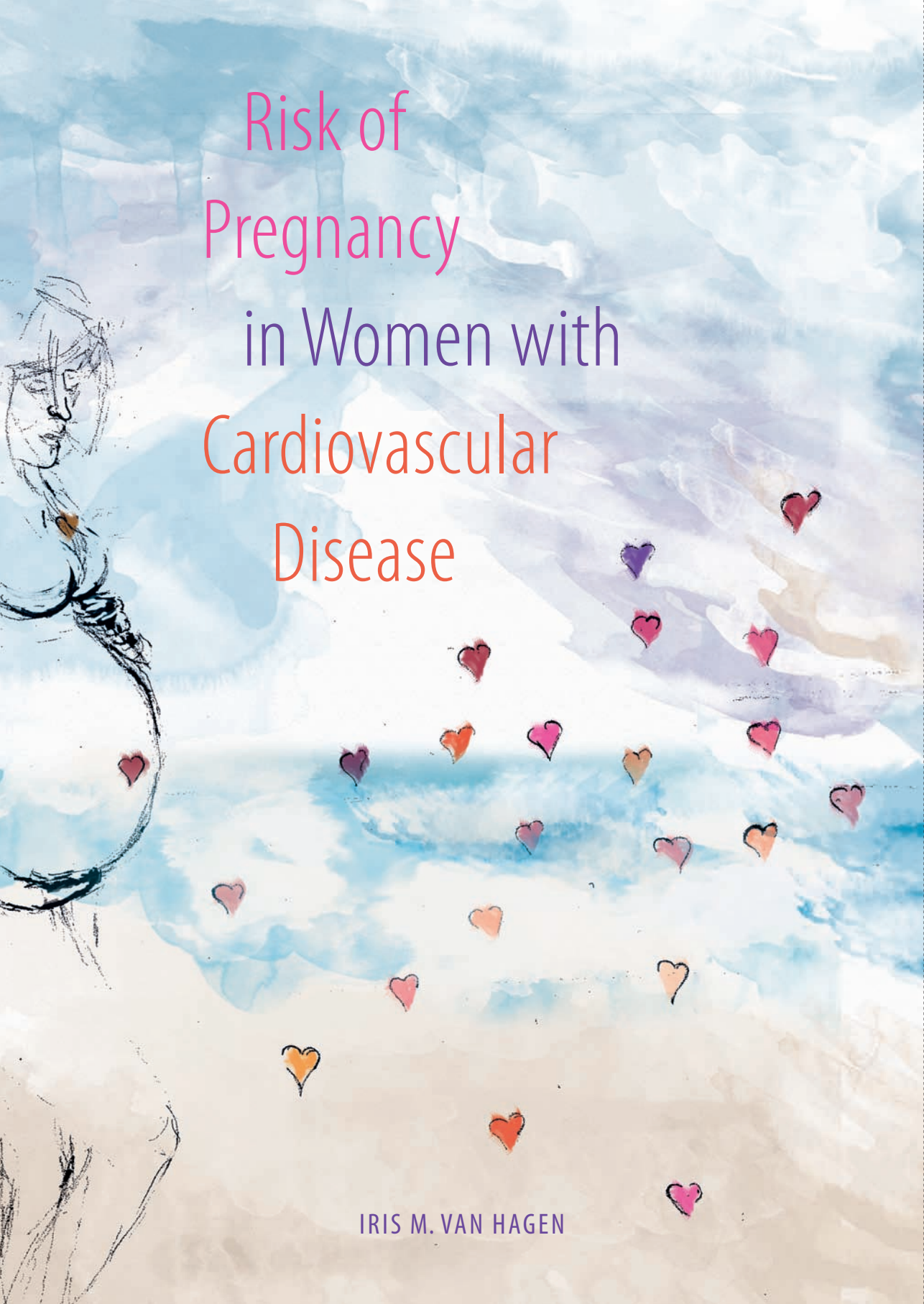
Risk of Pregnancy in Women with Cardiovascular Disease



IRIS M. VAN HAGEN

Risk of Pregnancy in Women with Cardiovascular Disease

Iris Maria van Hagen

Cover design: Inge Kersten
Layout and Printing: Optima Grafische Communicatie *www.ogc.nl*

ISBN 978-94-92683-13-7

Risk of Pregnancy in Women with Cardiovascular Disease

Risico van zwangerschap in vrouwen met een hartafwijking

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 18 april 2017 om 13.30 uur

door

Iris Maria van Hagen
geboren te Eindhoven

Erasmus University Rotterdam

Erasmus

PROMOTIECOMMISSIE

Promotoren:	*Prof. Dr. J.W. Roos-Hesselink*
	Prof. Dr. M.R. Johnson
Overige leden:	*Prof. Dr. E.A. Steegers*
	Prof. Dr. J.J. Takkenberg
	Prof. Dr. J. De Backer

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

CONTENTS

Introduction

Partly based on "van Hagen, Roos-Hesselink. Pregnancy in women with congenital heart disease. *South African Heart Journal*, 2013;10:616-624" and "Care during pregnancy', van Hagen, Roos-Hesselink, book chapter in 'Adult Congenital Heart Disease', 2016.

Thankfully, in the vast majority of pregnancies no severe problems occur. But the woman's body is exposed to major changes throughout pregnancy and subsequently some pregnant women may experience serious events, such as (pre)eclampsia, haemorrhage and even death. The fifth millennium goal from the World Health Organization is to reduce global maternal mortality rates, and as a consequence of improved maternal health care, the number of deaths have declined over the past decades[1]. Remarkably, maternal mortality due to cardiovascular disease showed a paradoxical increase[2,3]. Cardiovascular disease is the leading cause of mortality in pregnant women in countries with an advanced economy. Obstetric complications, such as haemorrhage and sepsis, are the major cause of maternal mortality in Sub-Saharan countries. Apart from these direct obstetric causes, heart disease is the main non-obstetric cause of death also in emerging countries[4].

Haemodynamic physiology of pregnancy

Growing a fetus in the womb requires development and maintenance of a sufficient uteroplacental and fetal circulation. Establishment of this new circulatory system warrants adaptation of the maternal cardiovascular system. Hormonal changes significantly influence circulating volume, vascular resistance and heart rate. Both the heart and the great vessels are subject to structural changes. Pregnancy is a major challenge to the cardiovascular system even in healthy women.

Cardiac output and plasma volume start to raise in the first weeks of gestation, and increase up to 50% above normal values up to the end of the second trimester, together with a 10-20% increase of the heart rate, a 30% increase of stroke volume, and a 30-40% decrease of vascular resistance[5-7]. Left ventricular diastolic dimensions are known to increase approximately 7-12% throughout pregnancy and to return to preconception values 6–12 months after pregnancy in healthy women[8]. Systolic dimensions remain stable, allowing for the increment of stroke volume. Maximum haemodynamic adaptation is generally reached beyond 20 weeks of gestation up to the end of the second trimester[5].

The aortic wall undergoes both functional and structural changes. Aortic dimensions may be influenced by physiological haemodynamic alterations, hormonal changes, but also by hypertensive conditions[9]. In Marfan syndrome, an aortic diameter growth of 3 mm during pregnancy has been described and a decrease after pregnancy was reported, but without full recovery to prepregnancy values[10]. In a post-mortem histology study of pregnant women, loss of medial layer integrity has been shown in the aorta[11]. Hormonal changes are suggested to play a role. Oestrogen and progesterone induce an increase of vascular matrix metalloproteinases (MMPs) and elastin, and a decrease of collagen, resulting in reduced systemic artery stiffness[12,13]. This physiological phenomenon of vascular remodelling is probably key to various pathophysiologic issues during pregnancy[14].

Maternal cardiovascular disease and pregnancy

In patients with heart disease, the capacity of the heart to adapt may be insufficient, leading to cardiac deterioration during pregnancy, and thus a higher risk of complications such as arrhythmias or heart failure. Patients with compromised ventricular function, severe valve disease, pulmonary hypertension or cyanosis are particularly at risk. While pregnancy itself forms a thrombogenic state, pregnancy introduces an additional risk for thrombosis but also for haemorrhage in women with a mechanical valve who require anticoagulation. Also, the risk of aortic dissection and rupture may be elevated during pregnancy due to the vascular wall changes[15,16]. Aortic dissection during pregnancy in healthy pregnant women is rare, but women with aortic disease, such as Marfan syndrome or Loeys Dietz syndrome, clearly are at increased risk. Acute aortic pathology is the most important cause of cardiovascular maternal death in the general pregnant population[2]. Such a devastating event not only involves the life of the mother, but also the life of the fetus is at risk[17]. In women with cardiac disease, there is a higher chance of miscarriage, preterm birth, low birth weight and fetal congenital (heart) disease. Treatment strategy should therefore always be determined by a multidisciplinary team, including at least an obstetrician, a cardiologist and an anaesthetist, with careful consideration of both lives.

Guidelines and need for evidence

Recommendations on the management of pregnancy in women with heart disease have been published in 2003 and first guidelines were published in 2011 by the European Society of Cardiology (ESC)[18,19]. While great efforts have been made to provide evidence based statements, the majority of recommendations were based on level of evidence class C: expert opinion. With an increasing number of women with heart disease getting pregnant it is important to provide solid evidence to support future guidelines. Clearly there are large gaps in knowledge and evidence from randomized-controlled trials is lacking and difficult to obtain.

What we do know is that preconception counselling is of utmost importance and a class I recommendation for all women with known heart disease. In each individual woman, risk stratification may help to determine further approach of counselling and management before, during and after pregnancy. Several risk models have been proposed. The CARPREG (CARdiac disease in PREGnancy) risk score, developed by dr. Siu and his team in Toronto, Canada, was the first tool developed in 2001 for women with cardiac disease in general, based on retrospective data and validated in a prospective cohort[20,21]. The cohort consisted mainly of women with congenital heart disease; few had valvular or other type of heart disease. Four predictors could be identified. These included -a prior cardiac event, -diminished functional class (New York Heart Association class >2) or cyanosis, -left heart obstruction and -left ventricular ejection fraction below 30%. In the presence of 0, 1 or more than 1 predictor the maternal cardiac event rate was 5%, 27% and 75%, respectively. In 2006, the modified

WHO (World Health Organization) risk stratification model was proposed, based on expert opinion (**Table 1**)[22,23]. It included cardiac diagnosis, New York Heart Association class and ventricular function. The ESC guidelines for pregnancy and cardiac disease adopted this risk tool. But prospective data to validate this tool was missing. The ZAHARA (Zwangerschap bij Aangeboren HARtAfwijking) risk score has been developed in 2010 in a large retrospective cohort of women with congenital heart disease in the Netherlands[24]. The group of researchers, led by dr. Pieper, found 3 new predictors: cardiac medication, atrioventricular valve regurgitation, and mechanical valve prosthesis. In women with congenital heart disease, the modified WHO classification seems to be the best tool to predict maternal outcome[25,26].

Table 1 WHO classification.

	Risk	Diagnosis
mWHO I	No to mild increased risk in morbidity compared to normal population	Repaired simple lesion ASD or VSD PDA PAPVR Mild valvular disease Uncomplicated PDA
mWHO II	Small increased risk of maternal mortality and moderate increased risk in morbidity	Unrepaired uncomplicated ASD or VSD Repaired tetralogy of Fallot
mWHO II-III		Mild systemic ventricular dysfunction Repaired coarctation Native or tissue valve disease Marfan (<40 mm) BAV (<45 mm)
mWHO III	Significantly increased risk of maternal mortality and severe morbidity	Mechanical valve Systemic right ventricle Fontan circulation Unrepaired cyanotic heart disease Other complex congenital heart disease Marfan (40-45 mm) BAV (45-50 mm)

Table 1 WHO classification. *(continued)*

	Risk	Diagnosis
mWHO IV	Extremely high risk of maternal mortality or severe morbidity	Pulmonary arterial hypertension
		Severe systemic ventricular dysfunction
		Severe mitral stenosis
		Severe symptomatic aortic stenosis
		Marfan (>45 mm)
		BAV (>50 mm)
		Native severe coarctation

ASD = atrial septal defect; BAV = bicuspid aortic valve; mWHO = modified WHO classification; PAPVR = partial anomalous pulmonary venous return, PDA = persistent ductus arteriosus, VSD = ventricular septal defect
Adapted from: Care during pregnancy. van Hagen, Roos-Hesselink, book chapter in 'Adult Congenital Heart Disease' 2016

Large prospective cohorts in women with any type of cardiac disease are required to support guidelines recommendations.

Gaps in current knowledge

There is a specific need for data on high risk pregnancies and pregnancies in less prevalent conditions: numbers of women included in studies are generally low, which may hamper drawing firm conclusions. Conditions such as pulmonary hypertension and severe left sided obstructive lesions are a reason to avoid pregnancy. But whether a mildly elevated right ventricular systolic pressure or moderate stenotic lesions are associated with much better outcome allowing for a positive advice regarding pregnancy is unknown. And what about women with an artificial heart valve? Young women requiring valve replacement and their treating cardiologist face a difficult dilemma: a mechanical valve lasts hopefully a lifetime, but warrants adequate anticoagulation for the same timespan; and a bioprosthesis, without the need for anticoagulation, requires reoperation after approximately 15 years. Pregnancy may further complicate the decision, as data about adequate and safe anticoagulation is currently lacking, while the effect of pregnancy on bioprosthetic valve function also awaits elucidation. Evidence in order to answer such questions should come from large prospective studies.

The majority of current evidence comes from Western countries, while in emerging countries a different distribution of cardiac morbidity is present with valvular heart disease being much more common in young adults than congenital heart disease[27]. Therefore, future guidelines will benefit from improved knowledge about the outcome of pregnancy in women with heart disease from more remote areas. While randomized controlled trials provide the strongest level of evidence, ethically it is hard to perform such studies during pregnancy. This is why real world observational data are required.

An evolving and potentially high risk group are women with Turner syndrome contemplating pregnancy. Turner syndrome is caused by a partial or total monosomy of the X-chromosome and it is characterised by subfertility in some women and even infertility in others[28]. In the past decades In Vitro Fertilization and oocyte donation have soared, and are now widely used, also in women with Turner Syndrome. But pregnancy in these women may put them at risk of serious events: Turner syndrome is associated with aortic pathology. An increasing number of reports became available showing an alarming relation between Turner syndrome and aortic dissection during pregnancy[29,30]. How many women contemplate pregnancy, and whether some are restrained by their own concerns for cardiovascular complications is unknown. Important questions, such as whether prophylactic aortic surgery puts these women at low(er) risk of aortic complications remain unanswered.

Registry Of Pregnancy And Cardiac disease (ROPAC)

The worldwide prospective ROPAC was initiated in 2007 by a joint effort of the European Society of Cardiology working group on 'valvular heart disease' and working group on 'congenital heart disease'. Principal investigators Professor Roger Hall from the United Kingdom and Professor Jolien Roos-Hesselink from the Netherlands aimed to prospectively observe a large number of women with structural heart disease during pregnancy. ROPAC forms the basis of this thesis. Participating doctors could enter their (anonymous) cases in an online database. Cardiac diagnoses include congenital disorders, valvular heart disease, cardiomyopathy, ischemic heart disease, aortic disease or pulmonary hypertension[31]. By collecting data from all over the world, ROPAC provides a solid basis for risk stratification and future recommendations on specific patient groups. As for all registries, ROPAC has some limitations that need to be appreciated while interpreting the results: women were included only when visiting a participating centre, which means that a selection bias is probably introduced: those who decided not to visit a doctor and do not have any pregnancy complication may be underrepresented in our cohort. Also, participating centres are likely to represent a clinic involving a cardiologist or obstetrician with an interest in the field of pregnancy and heart disease. This may also explain the underrepresentation of emerging countries, where acquisition of specialised clinics is presumably hard to achieve.

The registry is ongoing, but interim analyses were performed in 2011, including 1321 pregnancies in women with cardiovascular disease. The results were published by the principal investigators, dr. Titia Ruys (who wrote a thesis on the first ROPAC results) and participating investigators. Maternal mortality occurred in 1% of pregnancies of women with cardiac disease. Heart failure appears to occur in about 13% of women, mainly by the end of the second trimester, and in the first week after delivery[32]. Another important finding is the fact that caesarean section was not superior to vaginal delivery in most women, while fetal adverse events were more common after caesarean section[33]. Fetal outcome is also influenced by maternal cardiac medication: beta-blockers in particular, are associated

with a significant lower birth weight[34]. In 2014, 2966 pregnancies from 99 hospitals in 39 countries were included and form the basis of several chapters in this thesis. The ongoing collaboration with centers from all over the world, will enable to shed a light on many other maternal and fetal topics.

Aims

The overall aim of this thesis is to provide real world registry data on pregnancy outcome in women with cardiac disease to support the current guidelines, and to create awareness of maternal and fetal pregnancy risks in specific patient groups. To reach these goals, this thesis will focus on the following subjects:

- risk stratification both for maternal as well as for fetal outcome
- incidence and impact of common complications such as arrhythmias
- investigate the outcome of high risk conditions, such as mechanical heart valves
- investigate the impact of socioeconomic factors
- investigate the pregnancy wish in women with Turner Syndrome

REFERENCES

1. UN. The Millennium Development Goals report 2015. New York, 2015.
2. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
3. Tanaka H, Katsuragi S, Osato K, et al. The increase in the rate of maternal deaths related to cardiovascular disease in Japan from 1991-1992 to 2010-2012. *J Cardiol* 2016.
4. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; **367**(9516): 1066-74.
5. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
6. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; **68**(6): 540-3.
7. Cornette J, Ruys TP, Rossi A, et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. *Int J Cardiol* 2012.
8. Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. *Curr Opin Obstet Gynecol* 2012; **24**(6): 413-21.
9. Easterling TR, Benedetti TJ, Schmucker BC, Carlson K, Millard SP. Maternal hemodynamics and aortic diameter in normal and hypertensive pregnancies. *Obstet Gynecol* 1991; **78**(6): 1073-7.
10. Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012; **60**(3): 224-9.
11. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83**(4): 336-41.
12. Natoli AK, Medley TL, Ahimastos AA, et al. Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloproteinase expression. *Hypertension* 2005; **46**(5): 1129-34.
13. Dang Y, Li W, Tran V, Khalil RA. EMMPRIN-mediated induction of uterine and vascular matrix metalloproteinases during pregnancy and in response to estrogen and progesterone. *Biochem Pharmacol* 2013; **86**(6): 734-47.
14. Nolte JE, Rutherford RB, Nawaz S, Rosenberger A, Speers WC, Krupski WC. Arterial dissections associated with pregnancy. *J Vasc Surg* 1995; **21**(3): 515-20.
15. Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the Risk of Aortic Dissection or Rupture: A Cohort-Crossover Analysis. *Circulation* 2016; **134**(7): 527-33.
16. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. *Eur J Obstet Gynecol Reprod Biol* 2010; **149**(1): 120-1.
17. la Chapelle CF, Schutte JM, Schuitemaker NW, Steegers EA, van Roosmalen J, Dutch Maternal Mortality C. Maternal mortality attributable to vascular dissection and rupture in the Netherlands: a nationwide confidential enquiry. *BJOG* 2012; **119**(1): 86-93.
18. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of C. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24**(8): 761-81.
19. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.

20. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
21. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
22. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
23. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart* 2006; **92**(10): 1520-5.
24. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.
25. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014; **100**(17): 1373-81.
26. Lu CW, Shih JC, Chen SY, et al. Comparison of 3 Risk Estimation Methods for Predicting Cardiac Outcomes in Pregnant Women With Congenital Heart Disease. *Circ J* 2015; **79**(7): 1609-17.
27. Sliwa K, Libhaber E, Elliott C, et al. Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. *Heart* 2014; **100**(24): 1967-74.
28. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351**(12): 1227-38.
29. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab* 2011; **96**(2): E260-7.
30. Hagman A, Loft A, Wennerholm UB, et al. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod* 2013; **28**(6): 1598-609.
31. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
32. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.
33. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, et al. Is a planned caesarean section in women with cardiac disease beneficial? *Heart* 2015; **101**(7): 530-6.
34. Ruys TP, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. *Int J Cardiol* 2014; **177**(1): 124-8.

PART I

Risk prediction and complications

CHAPTER 1

Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology

Iris M. van Hagen
Eric Boersma
Mark R. Johnson
Sara A. Thorne
William A. Parsonage
Pilar Escribano Subías
Agata Lesniak-Sobelga
Olga Irtyuga
Khaled A. Sorour
Nasser Taha
Aldo P. Maggioni
Roger Hall
Jolien W. Roos-Hesselink on behalf of the ROPAC investigators and EORP team.

Eur J Heart Fail. 2016 May;18(5):523-33.

ABSTRACT

Aims To validate the modified World Health Organization (mWHO) risk classification in advanced and emerging countries, and to identify additional risk factors for cardiac events during pregnancy.

Methods and Results The ongoing prospective worldwide Registry Of Pregnancy And Cardiac disease (ROPAC) included 2742 pregnant women (mean age 29.2 (±5.5) years) with established cardiac disease: 1827 from advanced countries and 915 from emerging countries. In patients from advanced countries, congenital heart disease was the most prevalent diagnosis (70%) while in emerging countries valvular heart disease was more common (55%). A cardiac event occurred in 566 patients (20.6%) during pregnancy: 234 (12.8%) in advanced countries and 332 (36.3%) in emerging countries. The mWHO-classification had a moderate performance to discriminate between women with and without cardiac events (c-statistic 0.711 and 95%CI 0.686-0.735). However, its performance in advanced countries (0.726) was better than in emerging countries (0.633). The best performance was found in patients with acquired heart disease from developed countries (0.712). Pre-pregnancy signs of heart failure and, in advanced countries, atrial fibrillation and no prior cardiac intervention added prognostic value to the mWHO-classification, with a c-statistic of 0.751 (95%CI 0.715-0.786) in advanced countries and of 0.724 (95%CI 0.691-0.758) in emerging countries.

Conclusion The mWHO risk classification is a useful tool for predicting cardiac events during pregnancy in women with established cardiac disease in advanced countries, but seems less effective in emerging countries. Data on pre-pregnancy cardiac condition including signs of heart failure and atrial fibrillation, may help to improve preconception counselling in advanced and emerging countries.

INTRODUCTION

Cardiovascular disease is the most prevalent cause of maternal mortality[1-3]. As awareness of this fact has increased over recent decades, guidelines on the management of women with cardiac disease have been composed and updated[4,5]. These state that preconception counselling is essential and should be based on the past history, underlying condition and an assessment of the current physical state. The aim is to provide an estimation of individual risk, allowing a patient to make an informed choice about whether or not to embark on pregnancy.

Morbidity and mortality risks in pregnancy for both mother and offspring depend on the underlying type and severity of cardiac disease[6,7]. Further, there may be differences in outcome between centres from advanced and emerging countries. There is likely to be geographic variation in both the epidemiology of maternal cardiac disease and access to health care.

Several risk stratification models have been published: the CARPREG-risk score was derived in 2001 from a large single country cohort[8,9]; the ZAHARA-risk score, which was derived from women with congenital heart disease[10]; and the modified WHO(mWHO) classification, which is based mainly on expert consensus[11]. A recent comparison of these models in a cohort of patients with congenital heart disease showed that the mWHO-classification was optimal in predicting adverse outcome in this patient group[12], although the accuracy of the model could still be improved.

The primary aim of the current study was to validate the mWHO-classification to predict an adverse outcome in a large global patient cohort of women with both congenital and acquired structural cardiac disease including patients from both advanced and emerging countries. Secondly, we evaluated the predictive value of additional clinical features in order to develop a modified risk model with improved discriminative power.

METHODS

The Registry Of Pregnancy And Cardiac disease (ROPAC) was established to prospectively study a large number of pregnant women with structural cardiac disease. The ROPAC is an ongoing worldwide Registry. An extensive description of the data collection has been published previously[6]. The first patients were included in January 2008 and for this study we included the data of patients with a term date up to October 2013, and follow-up up to April 2014. Informed consent was obtained from patients when required by the local independent review board. For this analysis only patients with known cardiac disease were included, while patients in whom cardiac disease had been diagnosed during pregnancy were excluded.

Data

The patient characteristics collected at baseline (before pregnancy) included age, ECG rhythm, diagnosis, risk factors for cardiovascular disease (smoking, diabetes, hypertension), previous interventions, medication, parity, obstetric history and if available echocardiographic parameters. Follow-up was available for all patients up to one week after delivery. The originating countries were divided into advanced and emerging economies according to the International Monetary Fund (IMF) classification of economies[13] (*online supplemental Table)*.

Every patient was stratified according to the mWHO-classification, as stated in the latest guidelines[5,11] by two authors (IH;JRH). Modified WHO-class I implicates no increased risk of events during pregnancy, compared to the general pregnant population. The mWHO-class II has a small increased risk, class II-III a moderate increased risk, and class III has a 'significantly' increased risk. Class IV bears an unacceptable high risk of complications and consensus suggests that pregnancy should be avoided.

Endpoints

The composite primary endpoint was any cardiac event (defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason, or a cardiac intervention) during pregnancy and up to one week following. Previous analysis of this registry has shown that the most common cardiac events were heart failure and arrhythmia[6] and hence subanalysis was performed separately for these endpoints. Heart failure was defined according to ACC/AHA guidelines[14,15], as a clinical syndrome that is characterised by specific symptoms (dyspnea and fatigue) and signs (of fluid retention, such as oedema, rales) on the physical examination as judged by the treating cardiologist. The heart failure episode was only registered when signs or symptoms of HF were present which required new treatment, change of treatment or hospital admission.

Patient characteristics and events were reported by the individual sites and did not undergo centralised adjudication. However, all events were predefined in the CRF.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and differences were assessed with Student's t-test. Median and quartiles are provided when data were not normally distributed. Categorical variables are presented as percentages and differences were assessed using Chi-square tests.

First the mWHO-classification was validated for prediction of cardiac events in the total cohort. Further analyses were performed for advanced and emerging countries separately. Subgroup analysis was performed for congenital heart disease (CHD) and patients with acquired heart disease. All analyses were performed per pregnancy; in other words, a

pregnancy was defined as eventful when at least one cardiac event occurred. Possible new predictors were identified by performing univariable logistic regression analyses. Baseline variables that are integral part of the mWHO-classification (e.g. mechanical valve prosthesis, NYHA-classification and cyanotic heart disease) were excluded from univariable analysis. All variables with a p-value<0.20 were entered into multivariable logistic regression analysis. Variables that were still significantly (p<0.05) associated with outcome in the multivariable analysis using backward selection, were entered in a new model together with the mWHO-classification. Results of regression analyses are reported as an odds ratio (OR), 95%confidence interval, and p-value.

The predicted and observed probabilities were plotted in a calibration plot and Hosmer-Lemeshow Goodness-of-fit tests were checked. A receiver operating characteristic (ROC) curve and c-statistic was computed. Internal validation was done using 1000 bootstrap samples and reporting the potential optimism of the c-statistic. A c-statistic of 0.5-0.7 represents low discriminative power; a c-statistic of 0.7-0.9 represents moderate discriminative power; a c-statistic of >0.9 represents a high discriminative power[16,17]. A risk chart was produced showing the risk of an event (in tertiles) in our cohort within the different mWHO-classes and in the presence or absence of significant independent predictors.

Multiple imputation was used to handle missing data within the following baseline variables: age, body mass index, parity, singleton or multiple pregnancy, atrial fibrillation, signs of heart failure, hypertension, diabetes mellitus, smoking and prior cardiac intervention. Data were missing in no more than 5% of pregnancies, except for smoking (14% missing). It was assumed to be plausible that all these variables were missing at random. We generated 20 imputed data sets. Estimates were pooled and 95%confidence intervals were generated after calculating the standard error following Rubin's method[18,19].

Statistical tests were considered significant if a p-value was less than 0.05 (two-sided). All analyses, except for bootstrapping, were performed with SPSS version 21.0 (IBM Corp., Armonk, NY). Bootstrapping was performed in R version 2.3.0.

RESULTS

The ROPAC included 2966 pregnant women with cardiac disease from 99 centres (84% tertiary centres) in 39 countries, of whom 2742 had a diagnosis known before conception. The other 224 pregnancies were excluded because cardiac disease was discovered only during pregnancy. Cardiac diagnoses were: congenital heart disease (58.2%), valvular heart disease (31.4%), cardiomyopathy (5.9%), ischemic heart disease (0.6%), aortopathy (3.7%) and pulmonary hypertension (0.3%). Baseline characteristics and distribution of characteristics among the mWHO-classes are presented in **Table 1**.

Table 1 Baseline characteristics

	Overall	mWHO-I	mWHO-II	mWHO-II/III	mWHO-III	mWHO-IV	p-value mWHO classes
	n=2742	n=547	n=504	n=849	n=470	n=372	
Age-years(SD)	29.2(±5.5)	29.3(±5.5)	29.0(±5.3)	29.7(±5.7)	29.0(±5.3)	28.8(±5.8)	0.037
BMI-kg/m²(SD)	25.3(±4.8)	24.5(±4.5)	24.5(±4.6)	25.3(±4.8)	25.8(±4.4)	25.8(±5.3)	0.51
Nulliparous	45.4%	49.5	54.0	44.3	40.2	36.8	<0.001
Singleton pregnancy	97.9%	98.3	98.5	97.4	98.1	97.0	0.49
Atrial fibrillation	2.4%	0.6	0.4	1.7	4.7	6.6	<0.001
Hypertension	6.0%	3.6	2.6	9.6	5.8	5.8	<0.001
Diabetes mellitus	1.4%	1.1	1.4	1.7	1.3	1.4	0.93
Signs of heart failure	9.3%	3.5	3.6	6.7	10.7	30.1	<0.001
Current smoking	4.1%	6.0	3.9	4.5	2.6	2.6	0.07
Prior cardiac intervention	56.5%	68.0	59.2	47.8	73.8	33.7	<0.001
Emerging country	33.4%	23.9	18.1	27.7	48.1	62.4	<0.001
Cardiac diagnosis							<0.001
Congenital heart disease	58.2%	77.3	99.4	45.2	39.6	27.7	
Valvular heart disease	31.4%	22.7	0.6	35.1	49.8	54.6	
Cardiomyopathy	5.9%	0	0	10.6	7.0	10.2	
Ischemic heart disease	0.6%	0	0	1.4	0.9	0.3	
Aortic disease	3.5%	0	0	7.7	2.8	5.1	
Pulmonary hypertension	0.3%	0	0	0	0	2.2	
NYHA class							<0.001
I	74.6%	86.7	82.0	78.0	72.3	41.8	
II	22.7%	13.3	18.0	21.8	27.7	38.3	
III	2.5%	0	0	0	0	18.6	
IV	0.2%	0	0	0	0	1.4	

BMI=Body Mass Index; mWHO=modified WHO classification

Cardiac events

A cardiac event occurred in 566 (20.6%) pregnancies: 9.9% of patients in mWHO-I; 7.7% of patients in mWHO-II; 17.7% of patients in mWHO-II/III; 28.9% of patients in mWHO-III and 50.3% of patients in mWHO-IV. Maternal mortality up to 1 week postpartum occurred in 11 (0.4%) of pregnancies. **Figure 1** presents the frequency and type of events per mWHO-class and **Figure 2** presents the percentage of events within centres from emerging and advanced countries. The overall risk of a cardiac event in pregnancy was higher in all mWHO-classes in centres from emerging compared to advanced countries. **Figure 3** shows the risk of events per mWHO class in congenital and acquired heart disease in emerging and advanced countries.

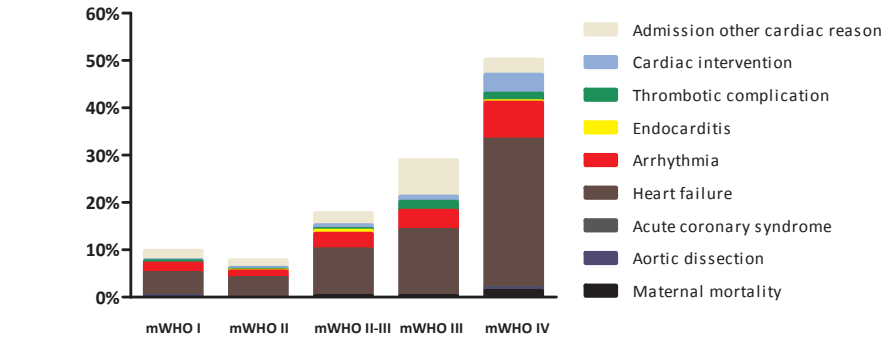


Figure 1 Type of observed cardiac events per modified World Health Organization (mWHO) class.

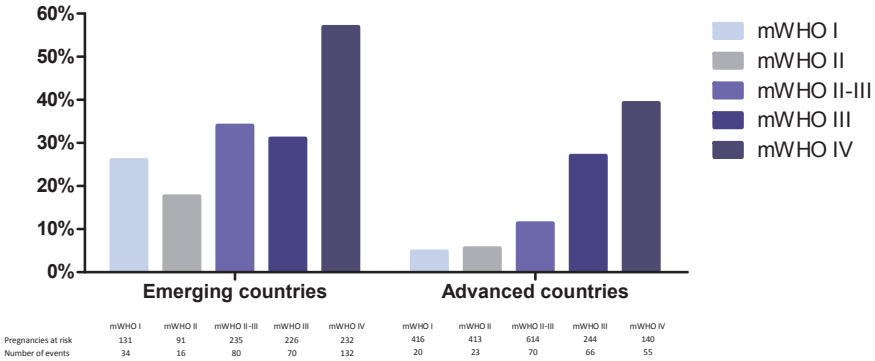


Figure 2 Observed cardiac events in emerging and advanced countries.
mWHO, modified World Health Organization; classes are indicated by Roman numerals.

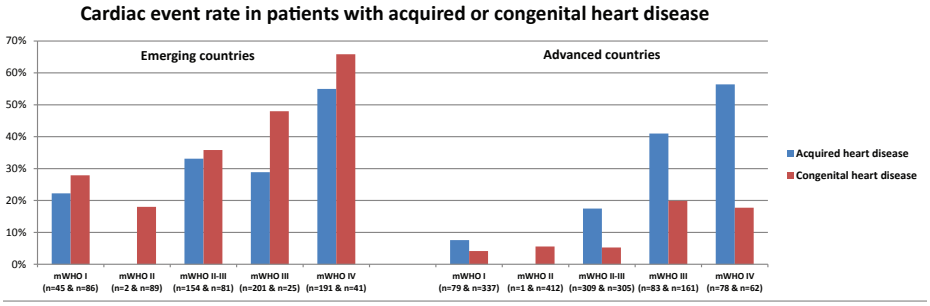


Figure 3 Cardiac event rate in patients with acquired or congenital heart disease.
mWHO, modifiedWorld Health Organization; classes are indicated by Roman numerals.

Validation of mWHO-classification

The c-statistic of the mWHO-classification was 0.711 (95%CI:0.686-0.735) for the entire cohort and the ROC curve is presented in **Figure 4**. The c-statistic was 0.726 (95%CI:0.690-0.762) for centres from advanced countries and 0.633 (95%CI:0.595-0.671) for those from emerging countries.

In patients with CHD, the c-statistic of the mWHO classification to predict cardiac events was 0.659 (95%CI:0.598-0.720) for centres from advanced countries and 0.645 (95%CI:0.577-0.712) for centres from emerging countries. In patients with acquired heart disease, the c-statistic was 0.712 (95%CI:0.661-0.763) for centres from advanced countries and 0.619 (95%CI:0.572-0.666) for centres from emerging countries.

No differences were found in the accuracy of the mWHO classification between left and right sided lesions. The accuracy of the mWHO classification predicting those patients with more than one cardiac event was similar to the accuracy of predicting any event.

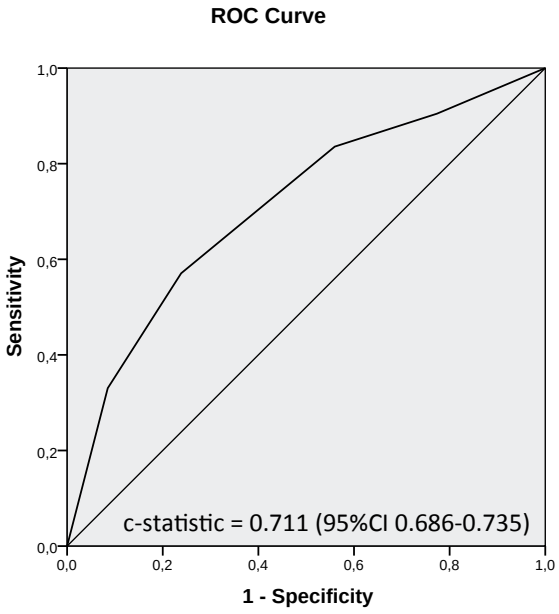


Figure 4 Receiver operating characteristic (ROC) curve of modified World Health Organization (mWHO) classification.
CI, confidence interval.

Additional predictive variables

The associations between baseline characteristics and cardiac events are demonstrated in Table 2. The final combinations of predictors are shown for centres from advanced and emerging countries separately. In both advanced and emerging countries, "signs of heart failure before pregnancy" was predictive, independently from the mWHO-classification. In advanced countries, "atrial fibrillation before pregnancy" and "no prior cardiac intervention" were additionally found to be predictive of cardiac events during pregnancy. The probability of events in the absence or presence of the additional risk factors is depicted in Figure 5.

The additional predictive variables were combined in a model for emerging and advanced countries. The calibration plot and ROC curves for both models are presented in Figure 6. The c-statistic for the model was 0.751 (95%CI:0.715-0.786) for advanced countries and 0.724 (95%CI:0.691-0.758) for emerging countries and both were similar in the unimputed dataset. Bootstrapping revealed an optimism in de c-statistic of 0.01 in advanced countries and an optimism in the c-statistic of 0.02 in emerging countries.

Table 2 Predictors of cardiac events during pregnancy

		Advanced countries (n=1827)			Emerging countries (n=915)		
Univariable analysis		OR	95%CI	p-value	OR	95%CI	p-value
Age		1.02	1.00-1.05	0.09*	0.99	0.97-1.02	0.55
BMI		1.02	0.96-1.08	0.57	1.00	0.96-1.04	0.90
Nulliparous		0.90	0.69-1.19	0.46	0.99	0.74-1.32	0.95
Singleton		1.22	0.47-3.19	0.69	0.82	0.33-2.02	0.66
Atrial fibrillation		11.3	4.32-29.4	<0.001*	1.75	0.97-3.15	0.06*
Hypertension		1.42	0.85-2.38	0.17*	1.53	0.86-2.75	0.15*
Diabetes mellitus		1.33	0.45-3.91	0.61	0.98	0.33-2.94	0.97
Signs of heart failure		7.09	3.83-13.1	<0.001*	5.15	3.70-7.17	<0.001*
Current smoking		0.72	0.34-1.52	0.39	1.23	0.49-3.09	0.66
Prior cardiac intervention		0.66	0.50-0.87	0.003*	0.61	0.46-0.80	<0.001*
Multivariable analysis							
mWHO	II**	1.09	0.59-2.03	0.78	0.56	0.28-1.12	0.10
	II-III	2.21	1.31-3.73	0.003	1.25	0.76-2.05	0.38
	III	6.79	3.95-11.7	<0.001	1.25	0.75-2.06	0.39
	IV	10.1	5.64-18.0	<0.001	2.48	1.50-4.11	<0.001
Age		1.02	0.99-1.05	0.22			
Atrial fibrillation		4.89	1.40-17.0	0.014	1.44	0.76-2.74	0.26
Hypertension		1.08	0.62-1.88	0.80	1.28	0.66-2.48	0.46
Signs of heart failure		3.34	1.68-6.66	0.001	4.22	2.99-5.94	<0.001
Prior cardiac intervention		0.67	0.49-0.90	0.009	0.75	0.55-1.03	0.08

Table 2 Predictors of cardiac events during pregnancy (continued)

		Advanced countries (n=1827)			Emerging countries (n=915)		
New model of mWHO and significant additional predictors							
mWHO	II**	1.08	0.58-2.02	0.80	0.57	0.29-1.14	0.11
	II-III	2.24	1.33-3.77	0.002	1.34	0.82-2.20	0.24
	III	6.77	3.95-11.6	<0.001	1.19	0.72-1.96	0.49
	IV	10.2	5.68-18.1	<0.001	2.77	1.70-4.53	<0.001
Atrial fibrillation		5.07	1.44-17.8	0.012			
Signs of heart failure		3.33	1.68-6.62	0.001	4.22	3.00-5.93	<0.001
Prior cardiac intervention		0.66	0.48-0.89	0.007			

BMI=body mass index;mWHO=modified WHO classification.
*Variables with p<0.20 were entered in multivariable analysis.
**mWHO I is the reference category.

Risk chart

A risk chart was produced based on the probabilities of events in the different mWHO-classes and in the presence or absence of signs of heart failure and/or atrial fibrillation before pregnancy. The chart is shown in **Table 3** for both advanced and emerging countries. "No prior cardiac intervention" was not included, because of the limited additional value as shown in Figure 5.

Table 3 Risk chart for a cardiac event

	Emerging countries				Advanced countries			
Pre-pregnancy:	No	AF	HF	HF+AF	No	AF	HF	HF+AF
mWHO-IV	43	51	76	82	35	73	65	90
mWHO-III	24	31	58	66	25	62	53	84
mWHO-II/III	27	34	61	69	11	37	29	67
mWHO-II	14	18	40	48	5	22	16	49
mWHO-I	22	28	54	62	5	20	15	46

<35%
35-65%
>65%

AF = atrial fibrillation; HF = signs of heart failure; mWHO = modified World Health Organization classification

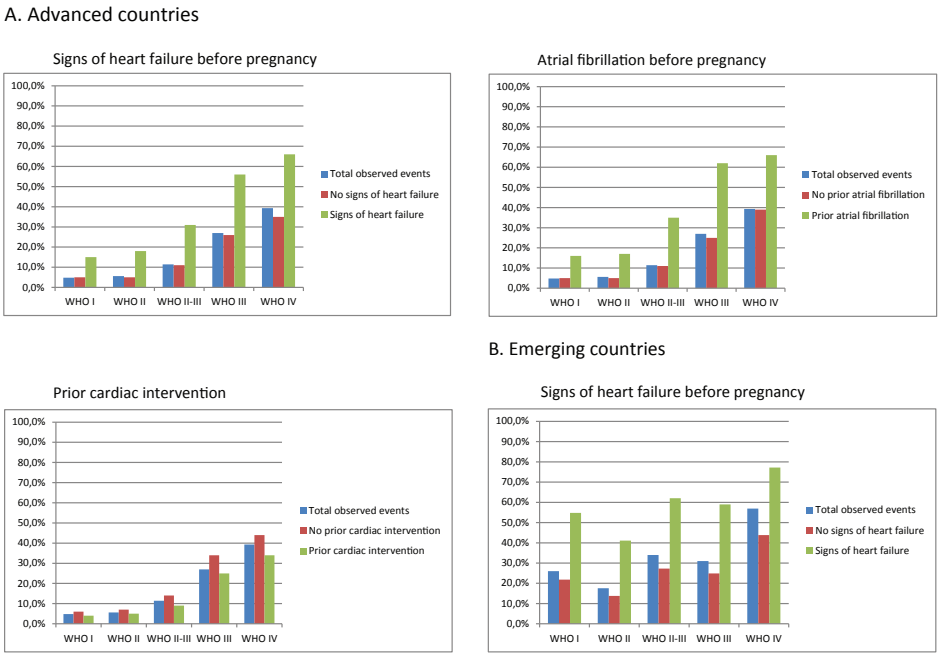


Figure 5 Risks within modified World Health Organization (mWHO) classes (Roman numerals), in the presence and absence of additional risk factors.

Sub analysis of arrhythmic and heart failure events

Arrhythmic events occurred in 94 (3.4%) pregnancies. Regression analysis is presented in *Supplemental Table 1 and 2*. An independent predictor of a new arrhythmic event during pregnancy was "atrial fibrillation before pregnancy" in centres from both advanced and emerging countries. In emerging countries, also "nulliparity" and "signs of heart failure before pregnancy" were predictive of an arrhythmic event. The c-statistic of the mWHO-classification for an arrhythmic event was 0.652 in centres from advanced countries and 0.688 in those from emerging countries. These c-statistics improved by adding the independent predictors (*Supplemental Table 3*).

Heart failure complicated pregnancy in 313 women (11.4%). Regression analysis is shown in the *Supplemental tables*. Independent predictors were "signs of heart failure before pregnancy" and "no prior cardiac intervention", for centres from both advanced and emerging countries. The c-statistic of the mWHO-classification for prediction of heart failure was 0.758 for advanced countries, and 0.627 for emerging countries and could be improved by adding "signs of heart failure before pregnancy" to the model (*Supplemental Table 3*).

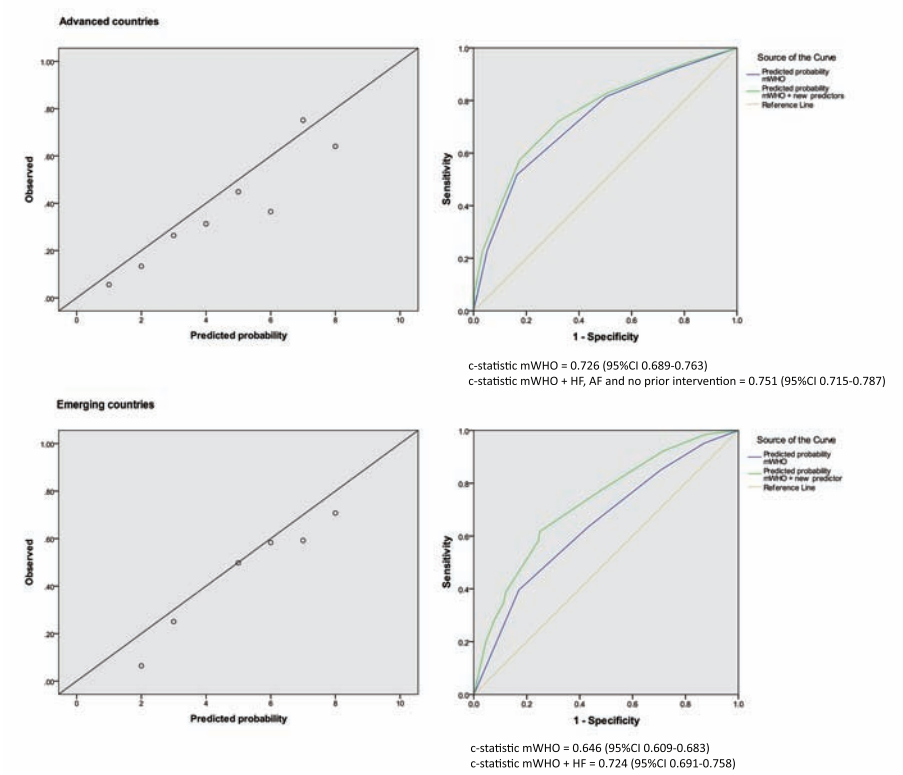


Figure 6 Calibration plots and receiver operating characteristic (ROC) curves of modified World Health Organization (mWHO) classification and enhanced model.
AF, atrial fibrillation; CI, confidence interval; HF, signs of heart failure.

DISCUSSION

This prospective study validates the modified WHO risk classification in a large cohort of women with different types of structural cardiac disease from centres all over the world. The mWHO-classification appeared to perform reasonably well, but better in centres from advanced countries than those from emerging countries. By adding "atrial fibrillation before pregnancy" and "signs of heart failure before pregnancy" to this risk model, estimation of risk improves. This is attributable mainly to the strong association of atrial fibrillation at baseline with the occurrence of an arrhythmic event, and of signs of heart failure at baseline and the occurrence of a heart failure event. Although the mWHO proves to be a useful tool, the risk prediction in women with heart disease can be further improved by using our risk chart, a simple tool for clinicians (see Table 1).

Cardiac events

The cardiac event rate was relatively high compared to the event rate in other studies[9,10,12,20-25], which is not surprising as ROPAC included more high-risk patients, reflecting the high risk caseload of participating centres. At baseline, there were more patients with NYHA class greater than 1, mWHO-class greater than 1 and the percentage of patients with any type of medication preconception is higher in our study population than in other studies[6,9,10,12,20-25]. The most prevalent events were heart failure and arrhythmic events, while mortality occurred in only 0.4%, even though 372 patients were in mWHO-class IV.

Modified WHO-classification

The mWHO-classification was proposed in the latest guidelines[5], and stratifies patients based on their underlying diagnosis together with few echocardiographic and clinical parameters and is based on expert opinion[11]. It is striking that in our study, in centres from advanced and emerging countries the rate of cardiac events in mWHO-class I was as high as 5 and 22% respectively, in the absence of heart failure or atrial fibrillation before pregnancy. The guidelines state that there is no increased risk of complications in this group compared to the general pregnant population. In literature this percentage is 0 to 2.5%[12,24,26]. However, previous studies included less than 100 pregnancies in this mWHO-class, while in our study 547 pregnancies were included. We included patients from emerging countries, while up until now most studies were performed in advanced countries. Although the risk in mWHO-I is limited, women in this group should not be told that the risks are negligible. The percentage of complications in this group indicates that some women in mWHO-class I, in particular in emerging countries, need more careful and frequent follow-up during pregnancy and should be followed and delivered in specialised centres as is advised for women who are assigned to mWHO-class II or higher. This holds for both women with congenital as well as acquired heart disease. Further research is warranted to better subdivide women in mWHO-class I. Remarkably, we did not observe a higher risk in mWHO-class II compared to class I, so probably it is difficult to establish a clear cut off between these two "low risk" categories.

Two other risk stratifications have been proposed in the literature: the CARPREG-risk score, which was conducted in a retrospective study cohort of women with cardiac disease from Canada[8]; and the ZAHARA-risk score, which was developed in a retrospective Dutch study of pregnant women with congenital heart disease[10], both validated in two prospective studies from the same groups[9,12].

Overestimation of risks was found in the validation of both CARPREG and ZAHARA in the intermediate and high-risk groups, due to a relatively low number of patients within these groups[9,10]. In our study, there were 842 (30.7%) patients in mWHO-class III and IV combined. The mWHO-classification with additional predictors shows a relatively good agreement between predicted probability and observed events also for patients with a higher mWHO-class, although overestimation of risks is still present.

We did not compare the mWHO-classification with the CARPREG-risk score, since we do not have information about the patients history of having had a stroke for instance. A recent single centre study validating the CARPREG, ZAHARA and mWHO-risk scores in 179 women with cardiac disease showed that the mWHO-classification was most accurate in predicting cardiac events[26]. Two other studies showed that the mWHO-classification performs better than the other risk scores in patients with congenital heart disease[12,24]. The discriminative accuracy of the mWHO-classification appeared to be better in the congenital heart disease population, compared to our study. This may be related to the fact that our cohort is more heterogenous regarding the underlying cardiac diagnosis. Secondly, our study has a multicenter and multicountry design, providing the first global estimation of accuracy of the mWHO-classification. Indeed, the separate analysis of data from centres in advanced and emerging countries did reveal a distinct difference in accuracy of the mWHO-classification, with the mWHO-classification performing better in advanced countries. This demonstrates the need for additional risk predictors, enabling a more accurate estimation of risks especially in emerging countries.

Advanced and emerging countries

The difference between centres from advanced and emerging countries in accuracy of the mWHO-classification for prediction of cardiac events is remarkable. The low discriminative power found in emerging countries is attributable to the varying frequency of events per mWHO class, whereas the event rate in advanced countries shows the expected gradual increase of events per mWHO class. The discriminative power was similar in CHD patients from advanced and emerging countries, but appeared to be better in patients with acquired heart disease from advanced countries. The event rate is low in CHD patients from advanced countries, in particular in the lower mWHO classes, which may have led to a less distinct difference in event rate between the mWHO classes. This might contribute to a lower discriminative power of the mWHO classification in this patient group. The majority of patients from advanced countries have congenital heart disease[6,25], which is a reflection both of good survival rates of congenital heart disease patients and of the lead taken by congenital heart disease cardiologists in establishing heart disease in pregnancy services.

Acquired heart disease is underrepresented in some mWHO classes, with a subsequent different event rate than expected, which probably influenced the discriminative power. The majority of these patients have valvular disease. However, the mWHO classification is based on Western specialists experience and thus may underestimate the risks in women with rheumatic valvular heart disease.

Indeed, a previous South African study of pregnant women with cardiac disease suggested that these women had a different disease pattern than those in the developed world[7]. They experienced a higher maternal mortality rate, probably attributable to differences in the underlying diagnosis and late presentation or referral to a medical facility.

The number of women in mWHO-class IV is remarkably high in centres from advanced countries (n=140) but even higher in those from emerging countries (n=232). Expert consensus recommends that pregnancy should be avoided in these patients. Given the fact that the mWHO-classification has been in use for several years now, it is possible that patients included in mWHO-class IV in our registry (after clinical implementation of the guidelines), are women with less severe disease than in earlier years. In addition, in some parts of the world, giving birth improves a woman's status and hence a patient might decide to accept a high risk and to even avoid seeing a doctor prior to pregnancy.

Arrhythmic and heart failure events

Heart failure during pregnancy occurs far more often in emerging countries[6]. Not surprisingly, "signs of heart failure before pregnancy" was strongly predictive of heart failure during pregnancy. The accuracy of prediction of events was improved by adding this factor to the mWHO-classification, which holds particularly for emerging countries and for the separate heart failure endpoint. In a large cohort of African heart failure patients, it appeared that patients were often young women with valvular heart disease[27]. Early detection of cardiovascular disease was emphasized, and our study stresses the importance of recognition of signs of heart failure well before conception to minimize the risk of severe deterioration during pregnancy.

For prediction of arrhythmic events we show a fairly high accuracy in emerging countries of the mWHO-classification in combination with the presence of paroxysmal atrial fibrillation prior to pregnancy. It has been shown previously that recurrence of arrhythmias was often seen during pregnancy and, more importantly, that it is associated with an increased risk of adverse fetal events[28].

Introduction in clinical setting

This study implies that adding signs of heart failure and atrial fibrillation before pregnancy to the established mWHO-classification, may be of potential benefit for better risk estimation especially in emerging countries. Our risk chart is a simple tool for clinicians, which is of use after the mWHO-classification has been applied (see Table 1). It may be useful for clinicians during counselling of women with cardiac disease contemplating pregnancy.

Limitations

Our conclusions are mainly applicable to women with heart disease under the care of a heart disease in pregnancy clinic, and extrapolation to those cared for in other settings should be done cautiously. Although our registry included patients prospectively, it only includes those patients seeking medical counselling or support. This does introduce potential inclusion bias. For example patients with mild cardiac defects may be underreported.

The diagnosis of heart failure was reported by the individual centres. Mild peripheral oedema and dyspnoea are frequently encountered during normal pregnancy without actual heart failure. Thus an overestimation of events may be present. However, an event of heart failure was only registered when it required new treatment, change of treatment or hospital admission.

Finally, although this study is the largest cohort to date, the maternal mortality rate did not allow for regression analysis. It would be interesting to have maternal mortality as sole endpoint as this would potentially provide additional evidence for contraindications to pregnancy.

Conclusion

The mWHO-classification is a moderately accurate tool for the prediction of cardiac events during pregnancy, in centres from advanced countries but suboptimal in centres from emerging countries. Signs of heart failure and atrial fibrillation before pregnancy are additional independent risk factors, improving the accuracy of the mWHO-classification. This has clear implications for preconception counselling of women with cardiac disease, especially of those with signs of heart failure or atrial fibrillation, who are at substantially higher risk regardless of their mWHO-risk class. A further modification of the mWHO criteria, based on our findings, merits further independent validation.

Online Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Advanced and emerging countries in ROPAC.
Table S2. Predictors of separate endpoints.
Table S3. Independent predictors of separate endpoints.
Table S4. C-statistics for separate endpoints.
Text S1. ROPAC investigators

Funding

The ROPAC is a registry within the EURObservational Research Programme (EORP) of the European Society of Cardiology. At the time of the Registry, the following companies were supporting the EORP: Abbott Vascular Int., Amgen, Bayer Pharma AG, Boehringer Ingelheim, Boston Scientific, The Bristol Myers Squibb and Pfizer alliance, The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company, Menarini Int.Op., Merck&Co.Int., Novartis Pharma, ResMed, Sanofi, SERVIER. The companies that support EORP were not involved in any part of the study or this report.

Acknowledgements

We would like to thank Daan Nieboer of the department of Public Health, Erasmus MC, Rotterdam, the Netherlands, for his support in the statistical analysis. We would like to thank all ROPAC investigators listed in the Supplementary material online. Our gratitude goes to the EORP team for their contribution, in particular: Elin Folkesson-Lefrancq, Viviane Missiamenou, Gérard Gracia and Myriam Lafay. To join the Registry: http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx.

REFERENCES

1. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
2. Burcin Kavak S, Celik Kavak E, Demirel I, et al. Evaluation of maternal mortality cases in the province of Elazig, Turkey, 2007-2013: a retrospective study. *Glob J Health Sci* 2015; **7**(1): 188-93.
3. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006-2010. *Obstet Gynecol* 2015; **125**(1): 5-12.
4. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of C. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24**(8): 761-81.
5. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
6. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
7. Sliwa K, Libhaber E, Elliott C, et al. Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. *Heart* 2014; **100**(24): 1967-74.
8. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
9. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
10. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.
11. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
12. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014; **100**(17): 1373-81.
13. Fund IM. World Economic Outlook - Recovery Strengthens, Remains Uneven. Washington; April 2014.
14. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; **112**(12): e154-235.
15. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119**(14): 1977-2016.
16. Lusted LB. Decision-making studies in patient management. *N Engl J Med* 1971; **284**(8): 416-24.
17. Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988; **240**(4857): 1285-93.
18. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
19. Schafer JL. Analysis of incomplete multivariate data. London: Chapman & Hall; 1997.

20. Tanous D, Siu SC, Mason J, et al. B-type natriuretic peptide in pregnant women with heart disease. *J Am Coll Cardiol* 2010; **56**(15): 1247-53.
21. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation* 2006; **113**(4): 517-24.
22. Song YB, Park SW, Kim JH, et al. Outcomes of pregnancy in women with congenital heart disease: a single center experience in Korea. *J Korean Med Sci* 2008; **23**(5): 808-13.
23. Jastrow N, Meyer P, Khairy P, et al. Prediction of complications in pregnant women with cardiac diseases referred to a tertiary center. *Int J Cardiol* 2011; **151**(2): 209-13.
24. Lu CW, Shih JC, Chen SY, et al. Comparison of 3 Risk Estimation Methods for Predicting Cardiac Outcomes in Pregnant Women With Congenital Heart Disease. *Circ J* 2015; **79**(7): 1609-17.
25. Avila WS, Rossi EG, Ramires JA, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. *Clin Cardiol* 2003; **26**(3): 135-42.
26. Pijuan-Domenech A, Galian L, Goya M, et al. Cardiac complications during pregnancy are better predicted with the modified WHO risk score. *Int J Cardiol* 2015; **195**: 149-54.
27. Stewart S, Wilkinson D, Hansen C, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008; **118**(23): 2360-7.
28. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006; **97**(8): 1206-12.

CHAPTER 2

Incidence and predictors of obstetric and fetal complications in women with structural heart disease: data from the Registry Of Pregnancy And Cardiac disease (ROPAC) of the European Society of Cardiology.

Iris M. van Hagen
Jolien W. Roos-Hesselink
Valentina Donvito
Csilla Liptai
Marielle Morissens
Daniel J. Murphy
Laura Galian-Gay
Nooshin M. Bazargani
Jérôme Cornette
Roger Hall
Mark R. Johnson.

Submitted

ABSTRACT

Objective Women with cardiac disease becoming pregnant have an increased risk of obstetric and fetal events. The aim of this study was to study the incidence of events, to validate the modified World Health Organization (mWHO) risk classification and to search for event-specific predictors.

Methods The Registry Of Pregnancy And Cardiac disease (ROPAC) is a worldwide ongoing prospective registry that has enrolled 2742 pregnancies in women with known cardiac disease (mainly congenital and valvular disease) before pregnancy, from January 2008 up to April 2014.

Results Mean age was 28.2±5.5 years, 45% were nulliparous and 33.3% came from emerging countries. Obstetric events occurred in 231 pregnancies (8.4%). Fetal events occurred in 651 pregnancies (23.7%). The mWHO-classification performed poorly in predicting obstetric (c-statistic=0.601) and fetal events (c-statistic=0.561). In multivariable analysis, aortic valve disease was associated with pre-eclampsia (OR=2.6, 95%CI=1.3-5.5). Congenital heart disease (CHD) was associated with spontaneous preterm birth (OR=1.8, 95%CI=1.2-2.7). Complex CHD was associated with small-for-gestational-age neonates (OR=2.3, 95%CI=1.5-3.5). Multiple gestation was the strongest predictor of fetal events: fetal/neonatal death (OR=6.4, 95%CI=2.5-16), spontaneous preterm birth (OR=5.3, 95%CI=2.5-11) and small-for-gestational age (OR=5.0, 95%CI=2.5-9.8).

Conclusion The modified WHO classification is not suitable for prediction of obstetric and fetal events in women with cardiac disease. Maternal complex CHD was independently associated with fetal growth restriction and aortic valve disease with pre-eclampsia, potentially offering an insight into the pathophysiology of these pregnancy complications. The increased rates of adverse obstetric and fetal outcomes in women with pre-existing heart disease should be highlighted during counseling.

INTRODUCTION

The physiological changes that occur to ensure adequate blood perfusion of the uteroplacental circulation during pregnancy require significant cardiovascular adaptations. A normal heart has the reserve to adjust to these requirements, but the capacity of an already functionally compromised cardiovascular system is uncertain. Indeed, several studies have highlighted the risk of deterioration in cardiac function in pregnant women with heart disease and documented an increased risk of obstetric and fetal events.[1] Cardiac events have been studied in depth and can be partly predicted by the modified World Health Organization (mWHO) risk classification.[2,3] The mWHO stratifies patients mainly according to their cardiac diagnosis and on some clinical parameters such as ventricular function and New York Heart Association (NYHA) class. The expected risk of an adverse event is low compared to the normal population in mWHO-class I, but the risk rises progressively with each class and women in mWHO IV are at extremely high risk and should avoid pregnancy.

In women with congenital heart disease, increased adverse neonatal events have been reported, including preterm birth and low birth weight in particular.[4,5] Genetic and epigenetic causes have been hypothesized to play a role in the pathophysiologic mechanism of preterm birth[6] and myocardial dysfunction and cyanosis were predictors of overall adverse neonatal outcome in women with congenital heart disease.[4] Interestingly, previous studies found an association between cardiac function and abnormal uteroplacental blood flow, suggesting that pre-existing heart disease may cause abnormal placental development or perfusion.[7] These data suggest that the mWHO-classification may be able to predict obstetric and fetal risk in women with pre-existing heart disease. The aim of our study was to report the incidence of obstetric and fetal events in patients with cardiac disease, and to evaluate the discriminative power of the mWHO-classification in predicting adverse obstetric or fetal outcome. In addition we will search for event-specific predictors.

METHODS

The Registry Of Pregnancy And Cardiac disease (ROPAC) is a large, prospective and global registry. A detailed report of study design has been published previously.[3,8] Patients in this interim analysis were included from January-2008 to April-2014. Patients in whom cardiac disease had been diagnosed during pregnancy were excluded. Patient informed consent was obtained when required by the local independent review board.

Data collection

Patient characteristics collected before pregnancy included age, diagnosis, electrocardiogram rhythm, risk factors (smoking, diabetes, hypertension), previous interventions, medi-

cation, parity, obstetric history and if available echocardiographic parameters. Follow-up was available for all patients up to one week after delivery. The originating countries were divided into developed and emerging countries according to the International Monetary Fund (IMF).[9] Country of residence was included as an independent variable in further analysis (defined as 'living in an emerging country').

Every patient was stratified according to the mWHO-classification, as stated in the latest guidelines by two authors(IH;JRH).[10] Modified WHO-class I implies no increased risk of events during pregnancy, compared to the general pregnant population; class II has a small increased risk; class II-III a moderate increased risk; class III a significantly increased risk; class IV bears an unacceptable high risk of complications and consensus suggests that pregnancy should be avoided.

Endpoints

Obstetric events were defined as maternal non-cardiac death up to one week postpartum, pregnancy induced hypertension (new-onset >140/90mmHg at two occasions), pre-eclampsia (including pre-eclampsia, eclampsia or HELLP syndrome), and haemorrhagic complication, which could be either postpartum haemorrhage (defined as increased blood loss, >500mL after vaginal delivery or >1000mL after Caesarean delivery, up until 24 hours postpartum) or other major haemorrhage (defined as a bleeding resulting in at least 1g/dL decrease in hemoglobin, the need for blood transfusion or end-organ damage such as haemorrhagic cerebrovascular accident or retinal bleeding). A **fetal event** was either premature birth <37weeks, small-for-gestational-age(<10th percentile), poor Apgar score(<7 at 1 minute), fetal death ≥14weeks of gestation, or neonatal death up to one week after delivery. Induced and spontaneous preterm birth were also analysed separately.

A cardiac event was defined as a combined endpoint, including: cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason, or a cardiac intervention. Cardiac event rates are published elsewhere.[3]

Analysis

Categorical variables are presented as frequencies and percentages and differences between groups were assessed using chi-square tests. Continuous variables are presented as mean and standard deviation, or as median and first and third quartiles as appropriate, and differences were assessed using Student's t-test or Mann-Whitney U tests depending on the data distribution.

The mWHO-classification was assessed for its ability to predict obstetric and fetal events in the total cohort, and also in patients with congenital and valvular heart disease separately. The discriminative power of the mWHO-classification was checked by receiver operating characteristic (ROC) curves and c-statistics. A c-statistic of 0.5-0.7 represents low

discriminative power; 0.7-0.9 represents moderate discriminative power; >0.9 represents a high discriminative power.[11]

In the total cohort, and in congenital heart disease and valvular heart disease separately, predictors of separate endpoints were searched for by univariable logistic regression analysis. Variables with a p-value<0.10 were entered into multivariable logistic regression analysis, provided that there was no collinearity between independent variables. One independent variable could be entered per 10 events. Results are presented as odds ratio (OR), 95% confidence interval (95%CI) and p-value. Multiple imputation was used to handle missing data within the following baseline variables: age, systemic ventricular dysfunction (ejection fraction<40%), hypoxia (<90%), parity, singleton or multiple pregnancy, atrial fibrillation, hypertension, diabetes mellitus, signs of heart failure, smoking, and NYHA class. It was assumed to be plausible that all these variables were missing at random. The Bonferroni method was used to correct for multiple hypothesis testing in the multivariable analysis of the separate endpoints (corrected α=0.05/n, with n=number of hypotheses/endpoints tested). All analyses were performed with SPSS version 21.0(IBM Corp., Armonk, NY).

RESULTS

This registry included 2966 pregnancies in women with structural cardiac disease from 99 centres in 39 countries, between January 2008 and April 2014. The cardiac diagnosis was known before conception in 2742 pregnancies, and these pregnancies were included in this analysis. Baseline characteristics are shown in **Table 1**. Congenital heart disease was

Table 1 Baseline characteristics

	Overall	CHD	VHD
N	**2742**	1599	862
Age, years (SD)	29.2 (±5.5)	28.9 (±5.3)	29.5 (±5.9)
BMI, kg/m2 (SD)	25.3 (±4.8)	24.3 (±4.5)	26.2 (±4.7)
Nulliparous	45.4%	52.8%	31.8%
Singleton pregnancy	97.9%	98.5%	96.8%
Systemic ventricle dysfunction	6.5%	5.5%	2.7%
Hypoxia	4.0%	6.5%	1.4%
Atrial Fibrillation	2.4%	0.4%	6.5%
Hypertension	6.0%	5.9%	4.1%
Diabetes Mellitus	1.4%	1.4%	1.4%
Signs of heart failure before pregnancy	9.3%	5.6%	15.7%
NYHA III or IV	2.7%	1.3%	4.6%
Current smoking	4.1%	4.6%	2.4%

Table 1 Baseline characteristics (continued)

	Overall	CHD	VHD
Prior cardiac intervention	56.5%	69.4%	43.9%
Anticoagulants in therapeutic dosage	12.4%	4.8%	28.1%
Emerging country	33.4%	20.1%	58.2%

SD = Standard Deviation; BMI = Body Mass Index.

present in 1599 (58.3%, **Table 2**) women; valvular heart disease in 862 (31.4%, **Table 2**); a cardiomyopathy in 161 (5.9%); ischemic heart disease in 17 (0.6%); aortopathy in 95 (3.5%); and idiopathic pulmonary arterial hypertension in 8 (0.3%) women.

Table 2 Specific congenital and valvular heart diseases

	Number of patients
Complex congenital heart disease:	
Eisenmenger	8
Univentricular heart	5
Tricuspid atresia	11
Pulmonary atresia	16
Double outlet right ventricle	19
Double outlet left ventricle	7
Transposition of the great arteries	100
Congenitally corrected transposition of the great arteries	24
Congenital heart disease of mild/moderate complexity:	
Tetralogy of Fallot	241
Aortic coarctation	156
Atrioventricular septal defect	80
Atrial septal defect	214
Ventricular septal defect	220
Morbus Ebstein	47
Aortic valve abnormality	126
Pulmonary valve abnormality	135
Mitral valve abnormality	48
Pulmonary vein abnormality	18
Patent ductus arteriosus	50
Other congenital heart disease	74
Valvular heart disease:	
Aortic valve disease	189

Table 2 Specific congenital and valvular heart diseases (continued)

	Number of patients
Mitral valve disease	537
Pulmonary valve disease	52
Tricuspid valve disease	15
Other valvular heart disease	69
Ischemic heart disease	17
Cardiomyopathy	161
Aortic disease	95
Pulmonary hypertension	8
Total	2742

Obstetric and fetal complications

Of the 2742 pregnancies, 231 (8.4%) pregnancies were complicated by one or more obstetric events, and one or more fetal events occurred in 651 (23.7%) pregnancies. **Table 3** shows obstetric and fetal events in women with and without a cardiac event during pregnancy.

Table 3 obstetric and fetal events in women with and without a cardiac event

	Women without a cardiac event (n=2176)	Women with a cardiac event* (n=566)	p-value
Preeclamptic toxaemia	1.7%	4.4%	<0.001
Pregnancy induced hypertension	1.9%	3.4%	0.037
Postpartum hemorrhage	3.1%	4.1%	0.24
Other major hemorrhage	0.8%	3.4%	<0.001
Spontaneous preterm birth	4.7%	5.2%	0.60
Induced preterm birth	5.1%	14.8%	<0.001
Fetal/neonatal death	1.7%	3.4%	0.010
Small for gestational age	8.6%	15.8%	<0.001
Poor Apgar (<7)	5.9%	10.4%	<0.001
Median birth weight, gr (Q1-Q3)	3070 (2762-3420)	2900 (2486-3198)	<0.001

*Defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason, or a cardiac intervention

Q1-Q3 = first to third quartile

Maternal non-cardiac mortality

Non-cardiac maternal mortality occurred in two patients (0.07%). One patient with rheumatic aortic and mitral valve disease and elevated pulmonary arterial pressures was delivered by Caesarean section at 35+3 weeks because of fetal distress. The neonate died shortly after delivery. Frank pus was found in the uterus, and the mother died of septic shock two days later. The second patient had idiopathic pulmonary arterial hypertension. She was treated with heparin in the first trimester and with warfarin during the second and third trimester before she was switched back to unfractionated heparin before term. An elective Caesarean section was performed at 38+0 weeks. During delivery, she developed shock due to an acute pulmonary embolism and the patient died shortly after delivery. The neonate survived and was healthy.

Modified WHO classification

Figure 1 shows the adverse obstetric and fetal events that occurred in each mWHO-class. The c-statistic for the mWHO-classification was 0.601 (95%CI=0.563-0.639) for obstetric events and 0.561 (95%CI=0.536-0.586) for fetal events, which means a low discriminative power. The ROC curves are presented in **Figure 2**. The ROC curves of the mWHO-classification for

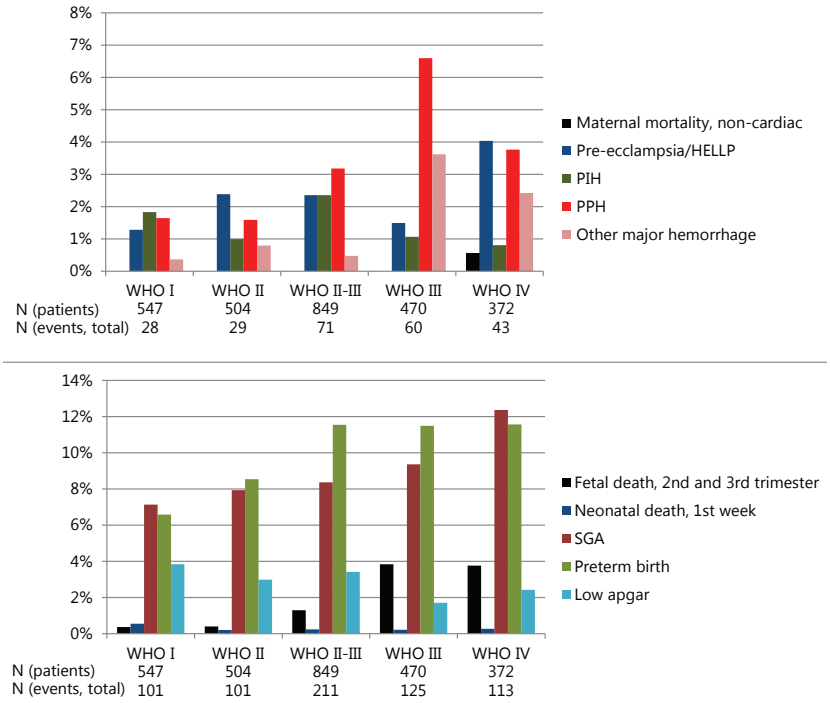


Figure 1 Obstetric and fetal events per mWHO-class

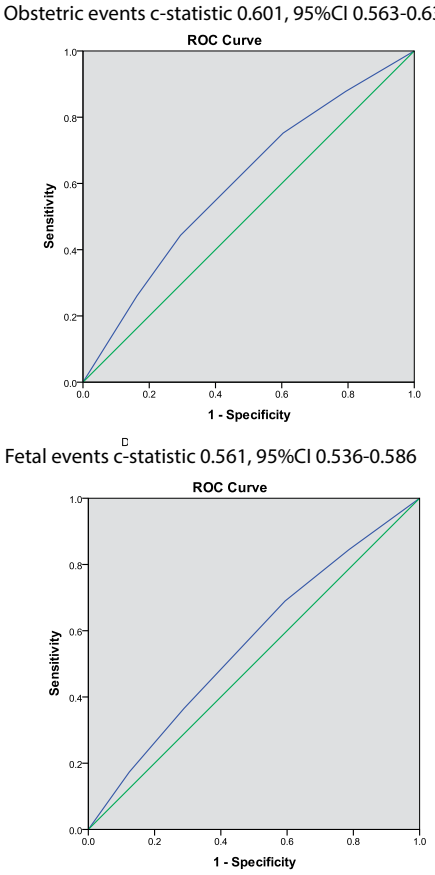


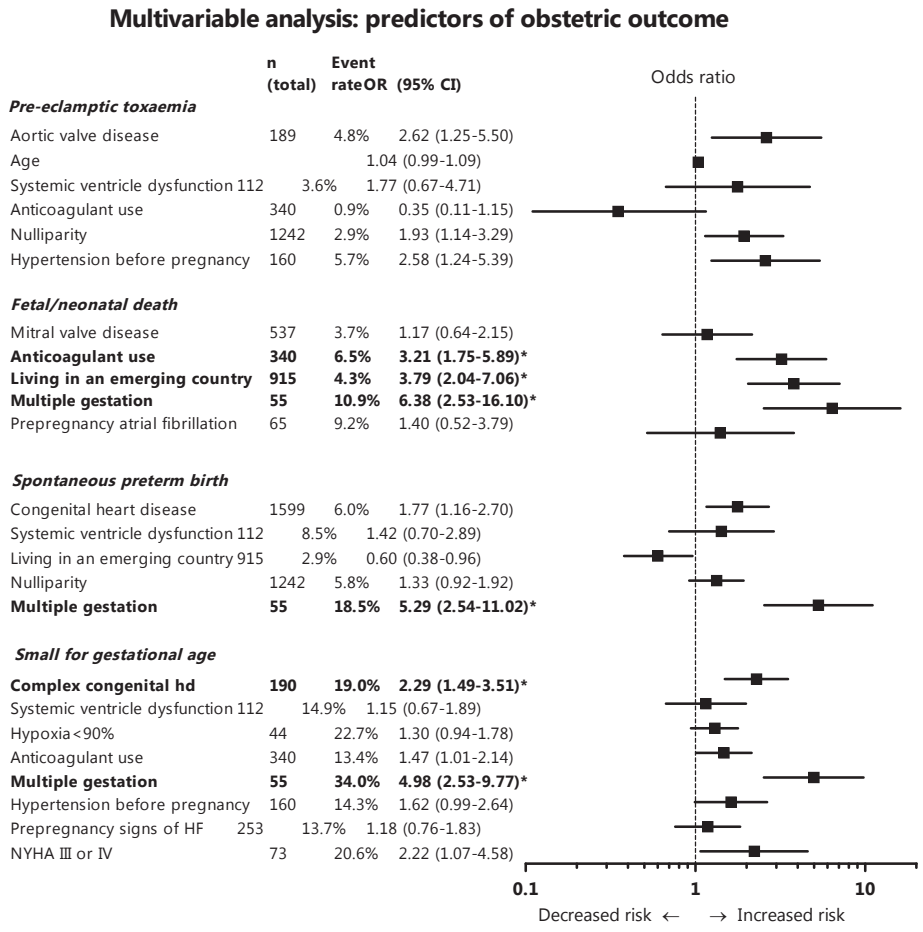
Figure 2 ROCs mWHO-classification

prediction of obstetric and fetal events in patients with congenital heart disease and valvular heart disease separately all show a poor discriminative power (*Figure S1, online supplement*). The mWHO classification did not perform better in emerging or advanced countries.

Predictors of separate events

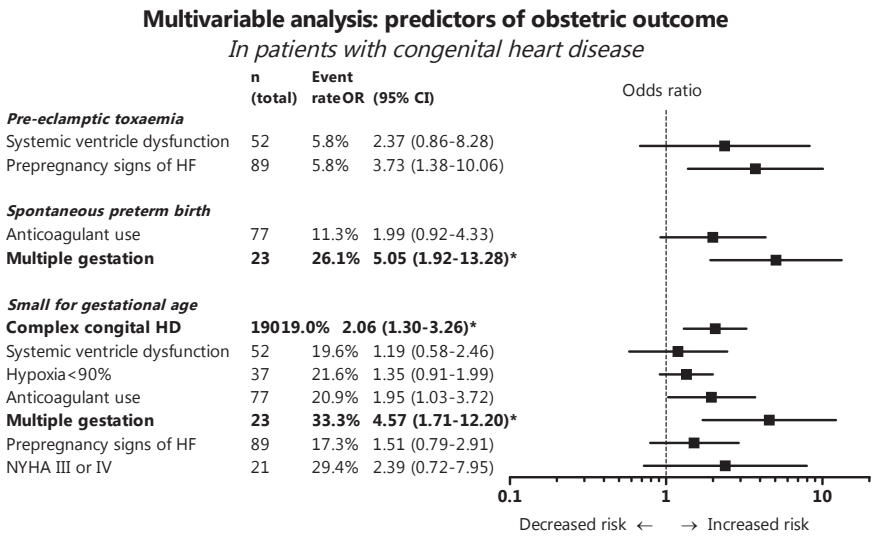
The frequency of separate events within each diagnostic group and in relation to baseline characteristics are shown in *Table S1 (online supplement)*. The results of the univariable and multivariable analyses are shown in *Table S2 and S3 (online supplement),* for all patients in this cohort, and for patients with congenital heart disease and valvular heart disease separately. C-statistics for the new models are shown in Table S3. Indeed, part of the models showed a better discriminative power for predicting the separate endpoints, than the mWHO-classification predicted combined endpoints.

The results for pre-eclampsia, fetal/neonatal death, spontaneous preterm birth and small-for-gestational-age are depicted in Figure 3. The main findings of the multivariable analysis in patients with congenital heart disease and valvular heart disease are presented in Figure 4 and Figure 5.



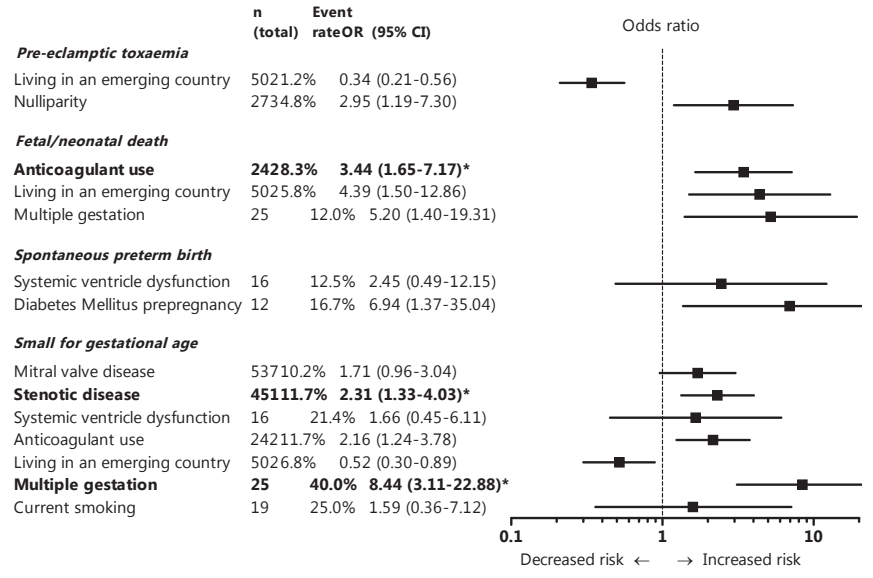
**Variables remained significantly associated with the endpoint after Bonferonni correction (p<0.0055)*

Figure 3 Predictors of obstetric and fetal events



Variables remained significantly associated with the endpoint after Bonferonni correction (p<0.0055)

Figure 4 Predictors of obstetric events in patients with congenital heart disease



Variables remained significantly associated with the endpoint after Bonferonni correction (p<0.0055)

Figure 5 Predictors of obstetric events in patients with valvular heart disease

DISCUSSION

This is the largest prospective cohort of pregnant women with known structural heart disease to date, reporting an obstetric event rate of 8.4% and fetal event rate of 23.7%. The mWHO-classification failed to accurately predict these events, although a gradual increase of events can be observed throughout the mWHO-classes. As in the general population, twin pregnancy and pre-gestational diabetes are important predictors of adverse fetal outcome. Pre-eclampsia is more often seen in women with aortic valve disease, while spontaneous preterm birth is more common in patients with congenital heart disease and small-for-gestational-age neonates in particular in complex congenital heart disease. Women who suffer from a cardiac event during pregnancy are at increased risk of most obstetric and fetal complications. These findings may help to accurately inform women about the risks of obstetric and fetal problems when they contemplate pregnancy.

MODIFIED WHO RISK CLASSIFICATION

The obstetric and fetal event rates are in line with findings of a previous prospective study in patients with any type of cardiac disease.[12] Based on the gradual increase of event rate in each mWHO-class, there seemed to be a relationship between the mWHO-classification and fetal and obstetric outcome, as was also shown in a previous publication.[8] The high incidence of obstetric events in mWHO-class III is mainly due to hemorrhagic complications in women with a mechanical valve who are treated with anticoagulants.[13] Unfortunately, overall, the mWHO-classification failed to show a sufficient discriminative power. This agrees with the results of a previous validation study in congenital heart disease patients.[14] Several explanations may explain the poor predictive power of the mWHO-classification. First, it seems that a cardiac diagnosis as a risk factor is subordinate to the well-established risk factors for obstetric and fetal events in the general population, such as maternal age, multiple pregnancy and nulliparity. The majority of the obstetric and fetal events are associated with these known risk factors, which may have a bigger impact in women with heart disease. This is supported by the high rate of events present in mWHO-class I women. Secondly, the combined endpoint may be too inclusive and unsuitable for designing an accurate prediction tool. For instance, haemorrhage will usually have a different aetiology than pre-eclampsia. In addition, fetal complications can be either the result of primary maternal, fetal or both maternal and fetal deteriorating conditions. Combining events may obscure the actual link between heart disease and specific pregnancy related events.

Obstetric complications

Pre-eclampsia was more common in women with aortic valve disease and, as expected, in nulliparous women and those with pre-existing hypertension. Also, ventricular dysfunction was a significant predictor of pre-eclampsia in the univariable analysis, but none of these predictors were significant (after correction for multiple hypotheses testing) in the multivariable analysis. Subclinical ventricular dysfunction is often seen in patients with aortic valve disease, typically in stenotic lesions.[15] However, pre-eclampsia, in particular early pre-eclampsia, is known to be associated with subclinical cardiac dysfunction, although the cardiac dysfunction is probably secondary to pre-eclampsia.[16] Previous studies have reported poor placental function in association with subclinical ventricular dysfunction.[7] Thus, the link between aortic valve disease and pre-eclampsia warrants further investigation, as the association may provide a valuable insight into the aetiology of pre-eclampsia and these women may benefit from prophylactic medication such as aspirin.[17]

Haemorrhage occurred more often in women with a mechanical valve[13] and is mainly associated with anticoagulation. Another independent predictor of specifically postpartum haemorrhage in the sub analysis of patients with congenital heart disease, was complex disease, which has been described earlier[5]. Anaemia, independent of antepartum haemorrhage, is a known predictor of postpartum haemorrhage[18] and is also often encountered outside pregnancy in patients with complex congenital heart disease,[19] offering another explanation for the predisposition to postpartum haemorrhage. It is unknown whether uterine atony, strongly associated with postpartum haemorrhage, is more prevalent in patients with complex congenital heart disease, still the more prudent use of oxytocin in the third stage and a low threshold to assisted deliveries in this group may contribute to the risk.[20]

Fetal/neonatal complications

The strongest predictor of fetal and neonatal complications in our cohort was multiple pregnancy, being an important predictor of not only fetal demise, but also of preterm birth and small-for-gestational-age. In the general population, fetal/perinatal death is reported in about 0.8-1.2% and increases in twin pregnancies about 4-5 times.[21] In ROPAC fetal/neonatal death occurred in 0.8% of singletons and 10.9% of twins, which is an increase of 13.6. Preterm birth occurs in almost half of the twin pregnancies in the general population, which is at least 7 times more often than reported in singleton pregnancies.[21] In the current series, preterm delivery occurred in 37% of ROPAC twin and 12% of singleton pregnancies. So preterm birth is not more common in twins, in contrast to singletons. But more importantly, it seems that cardiac disease further increased the risk of fetal demise. This may be related to the higher incidence of small-for-gestational-age babies in ROPAC twins: 34% had a birth weight beneath the 10th percentile, compared to 10% of singleton pregnancies. As an illustration, in the general population this rate only increases from about 10-11% to 15%.[22,23]

An obstetric complication occurred in more than 58% of multiple pregnancies (all twin), which is not surprising based on the evidence,[12,24] but it raises the question how to deal with twin pregnancy in women with a severe form of heart disease. Women should certainly be counseled about the risks. Twins should be avoided by performing single embryo transfer in case of in vitro fertilization, and by carefully monitoring ovulation induction. However, it is not possible to prevent the spontaneous conception of twins. To our opinion, reduction or termination of pregnancy should be reserved for strict maternal reasons or social indications. We do not know whether the rate of pregnancy complications is much higher in multiple pregnancies in women with heart disease compared to multiple pregnancies in the general population, and future research is needed to study this.

Premature deliveries are either spontaneous or iatrogenic. Symptomatic women (NYHA class III-IV), and women taking oral anticoagulants, were more likely to have an induced preterm delivery, which is consistent with recommendations made by the guidelines.[10] Interestingly, women with congenital heart disease tended to go into spontaneous preterm labour. Both inflammatory processes, and uteroplacental ischemia can initiate preterm labour.[25,26] The (subclinical) failure of the heart to fully adapt to pregnancy in congenital heart disease may promote inflammation and in more severe cases lead to uteroplacental hypoperfusion and ischemia. Certainly, maternal hypoxia increases cytokines and oxygen free radicals, which may cause abnormal placentation.[27] Indeed, uteroplacental flow has been shown to be abnormal in women with congenital heart disease.[28]

Small-for-gestational-age babies were mainly seen in women with complex congenital heart disease and in symptomatic patients (NYHA class III-IV). Maternal hypoxia was only found to be a predictor in univariable analysis, but its effect may have been influenced by the co-existence of complex congenital heart disease. Women with congenital heart disease and those with ventricular dysfunction should be very closely monitored with regard to fetal growth; preventative treatment like aspirin may need further investigation in this patient group.[29] It is expected to be of less benefit if these women indeed rather suffer from low cardiac output as a cause of growth restriction, instead of insufficient deep placentation due to ischemia.

Intrauterine death is associated with oral anticoagulant use as has been reported in a previous ROPAC study, describing pregnancy in women with a mechanical valve.[13] Oral anticoagulant use in the first trimester predisposed women to an increased risk of fetal death in both the second and third trimester. Miscarriages in the first trimester were excluded from this analysis, but have been reported in several groups of heart disease to be up to 40% in women with a Fontan circulation.[5] Certainly, this excessive rate should be mentioned to women with complex disease.

Emerging countries

In this cohort, 33% of women came from a country with an emerging economy. In these women, fetal loss was more common, which is in line with previous studies of global pregnancy outcome and is partly explained by the limited access to obstetric and neonatal care, increased rates of prolonged pregnancies and infectious disease.[30]

In emerging countries, both induced and spontaneous preterm birth were less common than in developed countries. This is interesting as generally, spontaneous preterm birth is thought to be more common in low-income countries.[31] Specialists in developed countries may be more likely to induce preterm birth as soon as the maternal condition deteriorates and women from these countries may have better and quicker access to obstetric care facilities. Also, a higher prevalence of spontaneous preterm birth was related to advanced age in a large global cohort,[32] which may be the result of uterine dysfunction.[33] However, in our study, age was not related to spontaneous preterm birth. Differences between emerging and developed countries in maternal and fetal outcome in women with cardiac disease are intriguing and deserve attention in future research.

Limitations

Data were missing in no more than 5% of pregnancies, except for smoking(14% missing), systemic ventricular function(37.4% missing) and hypoxia(59.7% missing). These questions were added in the adjusted online case report form in 2012, and data are therefore missing at random. In previous studies, systemic ventricular function and hypoxia were suggested as potential important predictors[4] and therefore we decided to include this predictor in the analysis. Missing variables were handled using multiple imputation, which is considered a reliable tool in such situations where large amounts of data are missing. However, firm conclusions cannot be drawn.

Miscarriage before 14 weeks was excluded from the analysis. The incidence of miscarriage widely ranges in literature concerning the overall healthy population. It is strongly influenced by inclusion bias and therefore hard to interpret. That is why, in line with previous literature, we chose not to include miscarriage in the first trimester as an endpoint.

Being aware of its inferiority, we analysed Apgar score at 1 minute rather than at 5 minutes, because the first value was complete in almost all cases, while Apgar at 5 minutes was missing in more than half.

Conclusion

Women with cardiac disease are at high risk of adverse obstetric and fetal events. The modified WHO classification, conducted for women with structural heart disease is a good predictor for maternal outcome, but does not perform as well for obstetric and fetal events. The majority of events are associated with more general predictors such as twin pregnancy. Other associations were complex congenital heart disease leading to small-for-gestational-

age babies, aortic valve disease predisposing to pre-eclampsia, and the use of anticoagulants leading to fetal demise. Whether factors like twin pregnancy lead to a greater obstetric and fetal risk in women with heart disease than their healthy peers needs to be determined and may influence the counseling of these patients.

Online Supplementary Information

Figure S1 ROC curves mWHO classification
A. Patients with congenital heart disease
B. Patients with valvular heart disease

Table S1 Frequency of events per diagnosis or baseline characteristic

Table S2 Univariable analysis
A. All patients
B. Patients with congenital heart disease
C. Patients with valvular heart disease

Table S3 Multivariable analysis
A. All patients
B. Patients with congenital heart disease
C. Patients with valvular heart disease

Funding

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011-2014), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2017), Bayer (2009-2018), Boehringer Ingelheim (2009-2016), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2016), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2011-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2017), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2017), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2010-2018). The companies that support EORP were not involved in any part of the study or this report.

Acknowledgements

We would like to thank all ROPAC investigators, who are listed in the online supplement. Our gratitude goes to the EORP team for their contribution, in particular: Elin Folkesson Lefrancq (project officer) and Viviane Missiamenou (data manager). To join the Registry: http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx.

REFERENCES

1. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
2. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
3. van Hagen IM, Boersma E, Johnson MR, et al. Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology. *European Journal of Heart Failure* 2016; **18**(5): 523-33.
4. Gelson E, Curry R, Gatzoulis MA, et al. Effect of maternal heart disease on fetal growth. *Obstet Gynecol* 2011; **117**(4): 886-91.
5. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007; **49**(24): 2303-11.
6. de Laat MW, Pieper PG, Oudijk MA, et al. The clinical and molecular relations between idiopathic preterm labor and maternal congenital heart defects. *Reprod Sci* 2013; **20**(2): 190-201.
7. Kampman MA, Bilardo CM, Mulder BJ, et al. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol* 2015; **46**(1): 21-8.
8. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
9. Fund IM. World Economic Outlook - Recovery Strengthens, Remains Uneven. Washington; April 2014.
10. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
11. Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988; **240**(4857): 1285-93.
12. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
13. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015; **132**(2): 132-42.
14. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014; **100**(17): 1373-81.
15. Ng AC, Delgado V, Bertini M, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. *Eur Heart J* 2011; **32**(12): 1542-50.
16. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension* 2011; **57**(1): 85-93.
17. Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJ, Hofmeyr GJ. Pre-eclampsia. *Lancet* 2016; **387**(10022): 999-1011.
18. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev* 2014; (2): CD003249.
19. Collins N, Piran S, Harrison J, Azevedo E, Oechslin E, Silversides CK. Prevalence and determinants of anemia in adults with complex congenital heart disease and ventricular dysfunction (subaortic right ventricle and single ventricle physiology). *Am J Cardiol* 2008; **102**(5): 625-8.

20. Cauldwell M, Von Klemperer K, Uebing A, et al. Why is post-partum haemorrhage more common in women with congenital heart disease? *Int J Cardiol* 2016; **218**: 285-90.
21. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ* 2004; **328**(7434): 261.
22. Martin LJ, Sjors G, Reichman B, et al. Country-Specific vs. Common Birthweight-for-Gestational Age References to Identify Small for Gestational Age Infants Born at 24-28 weeks: An International Study. *Paediatr Perinat Epidemiol* 2016; **30**(5): 450-61.
23. Odibo AO, Cahill AG, Goetzinger KR, Harper LM, Tuuli MG, Macones GA. Customized growth charts for twin gestations to optimize identification of small-for-gestational age fetuses at risk of intrauterine fetal death. *Ultrasound Obstet Gynecol* 2013; **41**(6): 637-42.
24. Herruzo AJ, Martinez L, Biel E, Robles R, Rosales MA, Miranda JA. Perinatal morbidity and mortality in twin pregnancies. *Int J Gynaecol Obstet* 1991; **36**(1): 17-22.
25. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; **371**(9606): 75-84.
26. Adams Waldorf KM, Singh N, Mohan AR, et al. Uterine overdistention induces preterm labor mediated by inflammation: observations in pregnant women and nonhuman primates. *Am J Obstet Gynecol* 2015; **213**(6): 830 e1- e19.
27. Matheson H, Veerbeek JH, Charnock-Jones DS, Burton GJ, Yung HW. Morphological and molecular changes in the murine placenta exposed to normobaric hypoxia throughout pregnancy. *J Physiol* 2016; **594**(5): 1371-88.
28. Pieper PG, Balci A, Aarnoudse JG, et al. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. *Circulation* 2013; **128**(23): 2478-87.
29. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**(5): 491-9.
30. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; **387**(10018): 587-603.
31. Organization WH. Preterm Birth - Fact Sheet No 363. Updated November 2015.
32. Fall CH, Sachdev HS, Osmond C, et al. Association between maternal age at childbirth and child and adult outcomes in the offspring: a prospective study in five low-income and middle-income countries (COHORTS collaboration). *Lancet Glob Health* 2015; **3**(7): e366-77.
33. Main DM, Main EK, Moore DH, 2nd. The relationship between maternal age and uterine dysfunction: a continuous effect throughout reproductive life. *Am J Obstet Gynecol* 2000; **182**(6): 1312-20.

CHAPTER 3

Ventricular tachyarrhythmia during pregnancy in women with heart disease: data from the ROPAC, a registry from the European Society of Cardiology.

Ebru Ertekin
Iris M. Van Hagen
Amar M. Salam
Titia P.E. Ruys
Mark R. Johnson
Jana Popelova
William A. Parsonage
Zeinab Ashour
Avraham Shotan
José M. Oliver
Gruschen R. Veldtman
Roger Hall
Jolien W. Roos-Hesselink

Int J Cardiol. 2016 Oct 1;220:131-6

ABSTRACT

Objectives To describe the incidence, onset, predictors and outcome of ventricular tachyarrhythmia (VTA) in pregnant women with heart disease.

Background VTA during pregnancy will cause maternal morbidity and even mortality and will have impact on fetal outcome. Insufficient data exist on the incidence and outcome of VTA in pregnancy.

Methods and Results From January 2007 up to October 2013, 99 hospitals in 39 countries enrolled 2966 pregnancies in women with structural heart disease. Forty-two women (1.4%) developed clinically relevant VTA during pregnancy, which occurred mainly in the third trimester (48%). NYHA class >1 before pregnancy was an independent predictor for VTA. Heart failure during pregnancy was more common in women with VTA than in women without VTA (24% vs. 12%, p=0.03) and maternal mortality was respectively 2.4% and 0.3% (p=0.15). More women with VTA delivered by Caesarean section than women without VTA (68% vs. 47%, p=0.01). Neonatal death, preterm birth (<37 weeks), low birthweight (<2500 gram) and Apgar score <7 occurred more often in women with VTA (4.8% vs. 0.3%, p=0.01; 36% vs. 16%, p=0.001; 33% vs. 15%, p=0.001 and 25% vs. 7.3%, p=0.001, respectively).

Conclusions VTA occurred in 1.4% of pregnant women with cardiovascular disease, mainly in the third trimester, and was associated with heart failure during pregnancy. NYHA class before pregnancy was predictive. VTA during pregnancy had clear impact on fetal outcome.

INTRODUCTION

Heart disease is an important cause of maternal death and, surprisingly, rates are increasing[1,2]. Interim analysis of the Registry Of Pregnancy and Cardiac disease (ROPAC) reported a 100 times higher maternal mortality rate in women with heart disease compared to the general pregnant population[3]. This raises serious safety concerns for women with structural heart disease and makes it imperative to identify those at greatest risk of complications during pregnancy.

Potentially life-threatening ventricular tachyarrhythmia (VTA) is rare during normal pregnancy (2 per 100,000 pregnancies)[4,5], but may be associated with maternal hemodynamic compromise causing adverse consequences for both mother and fetus[6]. This data, particularly in women with structural heart disease, however is scarce and is generally poorly reported in the literature. The incidence of VTA in pregnant women with heart disease has been documented ranging from 1.0% to 1.4%[1,7]. In patients with congenital heart disease, VTA occurs in up to 1.6%[1,8], whereas there are hardly any reports on the incidence of VTA in pregnant women with valvular heart disease, ischemic heart disease or cardiomyopathy. Also, insufficient data exist on the outcome of VTA during pregnancy. Previous studies mostly report on arrhythmias in general, but it is of major importance to distinguish potentially life-threatening VTA from the mostly benign supraventricular tachycardia. This study describes the incidence, onset, predictors and outcome of VTA during pregnancy in women with structural heart disease.

METHODS

Study design

The Registry Of Pregnancy And Cardiac disease (ROPAC) is part of the EURObservational Research Programme (EORP of the European Society of Cardiology) and was initiated in 2007. From January 2008 pregnant women with heart disease were included prospectively. Patients from 2007 were included retrospectively, assuming that the complete data were available and reliable. All patients included up to October 2013 were included in the current interim analysis. In this period, 99 hospitals in 39 countries contributed to the registry and a total of 2966 pregnant women with congenital heart disease (CHD), valvular heart disease (VHD), cardiomyopathy (CMP), ischemic heart disease (IHD), aortic pathology (AOP) or pulmonary hypertension were enrolled. Non-structural heart disease, for example arrhythmia occurring in the context of a structurally normal heart, was excluded. The study protocol and first results of this registry were published in 2013[3]. Informed consent was obtained from the patients and the study protocol conforms to the ethical guidelines of the 1975

Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Data

VTA has been defined as three or more consecutive ventricular beats with a mean rate of more than 100 beats per minute; however, only clinically relevant VTA (when the patient had physical complaints, needed treatment for VTA or when the patient had more than 100 consecutive beats) was included. Onset of VTA, given in weeks of gestation, was calculated using the expected date of delivery. Data up to one week after delivery was available for all patients. Baseline characteristics before pregnancy were analyzed, including cardiac diagnosis, maternal age, parity, clinical signs of heart failure, hypertension, smoking status, medication use and New York Heart Association (NYHA) functional class. The following cardiac diagnoses were included: CHD, VHD, IHD, CMP, AOP and pulmonary hypertension. The type of cardiac lesions were divided into three categories for the univariable logistic regression analysis: right sided lesions (e.g. Ebstein anomaly, tetralogy of Fallot, pulmonary stenosis), left sided lesions (e.g. aortic valve disease, mitral valve disease and most cardiomyopathies) and shunt lesions (e.g. atrial septal defects and ventricular septal defects). Participating countries were classified as developed or developing according to the International Monetary Fund classification[9].

Statistical methods

Categorical data are presented as frequencies (numbers) and percentages. Normality of continuous data was checked by one-sample Kolmogorov-Smirnov tests and histograms. Continuous data are presented as mean values +/- one standard deviation (SD) when normally distributed. The chi-squared test was used to compare differences in categorical data between independent patient groups. Fisher's exact tests were applied if any expected cell count was less than 5. The Student's t-test was used to compare differences in continuous data between independent patient groups. Mean birthweight was corrected for gestational age, fetal sex, maternal age and diabetes, using linear regression. The birthweight was not normally distributed; therefore both the median birthweight and the corrected mean birthweight are shown in this article. Baseline patient characteristics associated with VTA were identified with univariable logistic regression analysis. Available echocardiographic data (moderate or severely impaired systemic ventricular function) were also analyzed in the univariable logistic regression analysis. The multivariable analysis consists of variables that were associated with an increased incidence of the studied endpoint ($P<0.15$). For each 10 cases/patients, one of the most significant univariable predictors was included in the multivariable analysis. A p-value <0.05 (2-sided test) was considered statistically significant. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago).

RESULTS

Baseline characteristics

Of the 2966 patients included in the registry, 42 (1.4%) patients developed clinically relevant VTA during pregnancy. One patient had ventricular fibrillation (VF), the other patients had ventricular tachycardia. Baseline characteristics of pregnant patients with and without VTA are shown in **Table 1**. The incidence of VTA was 1.2% in CHD patients, 0.6% in VHD patients, 5.9% in CMP patients, 2.1% in IHD patients and 3.0% in AOP patients. VTA was not observed in patients with pulmonary hypertension. The diagnoses per cardiac disease category are shown in **Figure 1**. Before pregnancy, three patients had pacemaker-dependent rhythm. All others were in sinus rhythm.

Table 1 Baseline characteristics of cardiac patients with and without ventricular tachyarrhythmia.

	Total group	Patients with VTA*	Patients without VTA	
	(n=2966)	(n=42)	(n=2924)	p-value
Mean age in years (SD†)	29.3 (5.6)	28.9 (5.7)	29.3 (5.6)	0.78
Nulliparity (%)	45	55	45	0.21
Clinical signs of heart failure (%)	10	21	10	0.02
Hypertension (%)	6.5	4.9	6.5	1.00
Current smoker (%)	4.3	5.1	4.3	0.68
Developing countries (%)	35	45	35	0.17
NYHA class‡				0.002
NYHA class 1 (%)	73	50	73	
NYHA class 2 (%)	22	38	22	
NYHA class 3 (%)	2.9	11.9	2.8	
NYHA class 4 (%)	0.3	0	0.3	
Type of heart disease				
Congenital heart disease (%)	56	48	56	0.28
Valvular heart disease (%)	32	14	32	0.01
Ischemic heart disease (%)	1.6	2.4	1.6	0.68
Cardiomyopathy (%)	7	29	7	<0.001
Aortic pathology (%)	3.4	7.1	3.4	0.18
Pulmonary arterial hypertension(%)	0.4	0	0.4	1.00
Medication use before pregnancy				
Beta-blocker (%)	12	17	12	0.39
Other anti-arrhythmic drugs (%)	3.1	0	3.1	0.64
Diuretics (%)	5.8	9.5	5.7	0.30
ACE inhibitors§ (%)	3.9	4.8	3.9	0.68
Calcium antagonists (%)	0.2	0	0.2	0.34

* VTA = ventricular tachyarrhythmia, † SD = Standard deviation, ‡ NYHA = New York Heart Association, § ACE = Angiotensin Receptor Enzyme

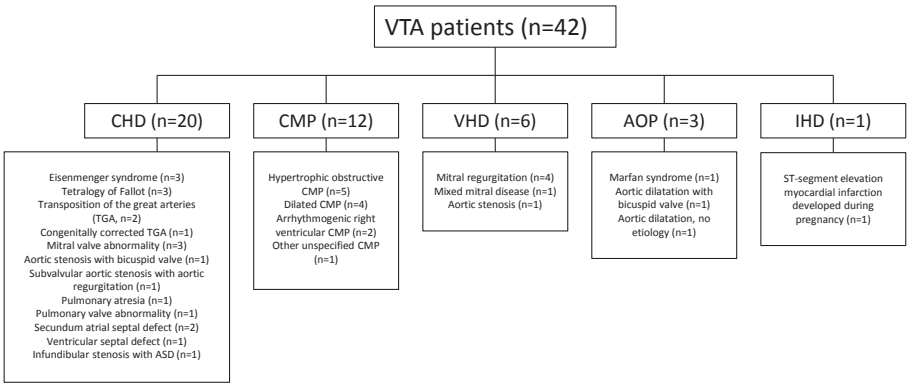


Figure 1 Diagnoses per cardiac disease category.
CHD=congenital heart disease, VHD=valvular heart disease, CMP=cardiomyopathy, AOP=aortic pathology

Onset of VTA

Figure 2 shows that VTA mainly occurred in the third trimester (48%). Figure 3 shows the onset of VTA per cardiac disease category.

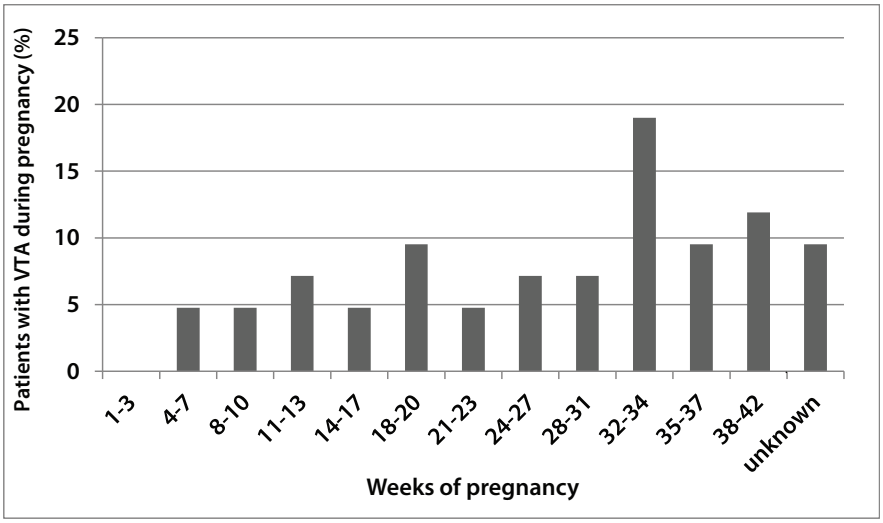


Figure 2 The occurrence (onset) of VTA during pregnancy in women with heart disease.
VTA=ventricular tachyarrhythmia

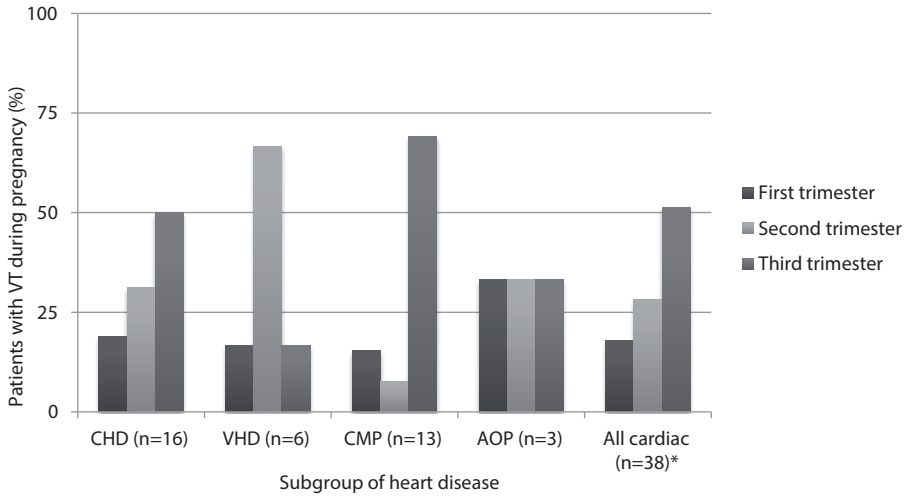


Figure 3 The occurrence of VTA during pregnancy per cardiac disease category.
The number of patients per category is shown between brackets.
CHD=congenital heart disease, VHD=valvular heart disease, CMP=cardiomyopathy, AOP=aortic pathology, All cardiac=CHD+VHD+CMP+AOP.
** The time of onset of VTA was missing in four CHD patients.*

Predictors

The results of the univariable and multivariable logistic regression are shown in **Table 2**.

Table 2 Pre-pregnancy predictors for VTA

Univariable	Odds ratio	95% CI	p-value
Congenital heart disease	0.72	(0.39-1.32)	0.28
Valvular heart disease	0.35	(0.15-0.84)	0.02
Cardiomyopathy	5.76	(2.90-11.4)	<0.001
Right sided lesion	0.72	(0.32-1.62)	0.43
Left sided lesion	1.71	(0.91-3.20)	0.09
Shunt lesion	0.61	(0.26-1.46)	0.27
NYHA class>1	2.98	(1.62-5.49)	<0.001
Nulliparity	1.48	(0.80-2.72)	0.21
Hypertension	0.74	(0.18-3.08)	0.68
Clinical signs of pre-pregnancy heart failure	2.59	(1.23-5.47)	0.01
Developing countries	1.53	(0.83-2.82)	0.17
Any medication use before pregnancy	1.16	(0.60-2.24)	0.66
Beta-blocker use before pregnancy	1.43	(0.63-3.24)	0.39

Table 2 Pre-pregnancy predictors for VTA (continued)

Univariable	Odds ratio	95% CI	p-value
Echo prior to pregnancy			
Systemic ventricular dysfunction moderate/severely impaired	4.59	(1.92-10.96)	0.001
Multivariable			
Cardiomyopathy	2.70	(0.95-7.69)	0.06
NYHA class>1	2.64	(1.12-6.20)	0.03
Clinical signs of pre-pregnancy heart failure	0.88	(0.29-2.64)	0.82
Systemic ventricular dysfunction	2.25	(0.78-6.48)	0.13

Medication before and during pregnancy

Of the 42 patients with VTA, 31% used cardiac medication before pregnancy. The medication used before pregnancy is shown in **Table 1**. During pregnancy, 74% of the VTA patients used medication: 57% used beta-blockers, 12% used other anti-arrhythmic drugs and 12% used diuretics. Amiodarone was used in 3 of the 42 patients with VTA.

Maternal outcome

Pregnancy outcome until one week after delivery is presented in **Table 3**. Heart failure was diagnosed in 10 VTA patients (24%), occurring after VTA in three patients, before in three and at the same time in one and in the remaining three patients the temporal relationship was unclear. Maternal death occurred in one patient (2.4%). This was a 36-year-old woman with pulmonary atresia, who had a bioprosthetic pulmonary valve replacement before pregnancy. She was taking beta-blockers because of aortic dilatation and used LMWH throughout pregnancy. At 17 weeks of pregnancy, she had an out of hospital cardiac arrest due to VF. She survived resuscitation, but was left in a persistent vegetative state. She was ventilated until delivery at 32 weeks and died one week postpartum.

Table 3 Pregnancy outcome in cardiac patients with and without VTA. Outcome until one week after pregnancy.

	Total group (n=2966)	Patients with VTA (n=42)	Patients without VTA (n=2924)	p-value
Maternal mortality (%)	0.4	2.4	0.3	0.15
Cardiac				
Heart failure (%)	13	24	12	0.03
Thromboembolic events (%)	0.8	0	0.8	1.00
Endocarditis (%)	0.2	0	0.2	1.00
Bleeding during pregnancy (%)	6.2	4.8	6.2	1.00
Obstetric				
Intra-uterine growth retardation (%)	4.6	4.8	4.6	0.72
Pregnancy induced hypertension (%)	2.3	0	2.4	0.63
(Pre)eclampsia (%)	2.4	0	2.5	0.63
Caesarean section (%)	48	68	47	0.01
Fetal outcome				
Miscarriage (<24 weeks; %)	2.7	0	2.7	0.26
Late fetal death (≥24 weeks; %)	0.7	0	0.7	1.00
Neonatal death (%)	0.3	4.8	0.3	0.01
Median pregnancy duration (weeks)	38.2	37.4	39.0	<0.001
Apgar score <7 (%)	7.6	25	7.3	0.001
Preterm birth (<37 weeks; %)	16	36	16	0.001
Low birthweight (<2500 g; %)	15	33	15	0.001
Median birthweight (g)	-	2730	3020	0.006
Corrected mean birthweight (g)*	-	3283	3289	0.94

Birthweight corrected for: gestational age, fetal sex, maternal age, and diabetes.

Delivery and fetal outcome

Fetal outcome is shown in **Table 3**. Mode of delivery in patients with VTA was by emergency Caesarean section in 20%, elective Caesarean section in 48% and vaginally in 32%. No fetal death occurred in VTA patients **(Table 3),** but there were two neonatal deaths. A 28-year-old patient with non-obstructive CMP developed VTA in week 6 of pregnancy. She underwent Caesarean section at 29 weeks for cardiac reasons, followed by an unexplained neonatal death. The second neonatal death was due to acute respiratory distress syndrome (ARDS) one week postpartum. The mother of this child had subaortic stenosis and a history of heart failure before pregnancy.

DISCUSSION

This is the first detailed study of pregnancy outcome after VTA in patients with cardiovascular disease. In this large prospective international registry of 2966 pregnancies with heart disease, the incidence of VTA during pregnancy was 1.4% and occurred mainly in the third trimester. NYHA class >1 before pregnancy was an independent predictor of VTA. VTA was associated with a marked increase in the neonatal death rate, preterm birth rate, low birthweight rate and poor Apgar score.

Incidence of VTA

Existing data on the incidence of VTA during pregnancy in patients with heart disease is scarce. Siu et al. studied pregnancy outcome in two cohorts of women with heart disease. VTA occurred in 4 cases in the cohort of 276 pregnancies and in 6 patients in the cohort of 599 pregnancies[1,7]. The incidence of VTA in our study (1.4%) was comparable to the incidence of Siu et al.'s retrospective (1.4%) and prospective (1.0%) studies.

Congenital heart disease – VTA during pregnancy in women with CHD is rare. We observed VTA in 1.2% of CHD patients, in keeping with the reported incidence range from 0.4 to 1.6%[1,8]. Patients with repaired CHD in the study of Niwa et al.[10] had a significantly higher incidence of VTA than healthy pregnant women. In their study, the prevalence of non-sustained VTA was 14% with the highest incidence in patients with previous surgical correction of Tetralogy of Fallot (TOF) [8,10,11]. In our study, VTA occurred in 2.5% of TOF patients (3 out of 119 patients), however, we only included patients with symptomatic VTA.

Cardiomyopathy – VTA occurred remarkably often in patients with CMP (7.4%) in our study. In the study of Grewal et al.[12], VTA occurred in 3% of dilated CMP patients. In patients with hypertrophic CMP, the incidence of arrhythmias (including VTA) was not increased during pregnancy[13]. However, in hypertrophic CMP patients with an Implantable Cardioverter Defibrillator (ICD), VTA is a common complication with an observed incidence of 22% during pregnancy[14]. Some case reports of VTA in patients with peripartum cardiomyopathy (PPCM) have been published previously[15-17]. In our study VTA did not occur in the 33 PPCM patients.

Valvular heart disease – We found that 0.7% of the patients with VHD developed VTA during pregnancy and the majority had mitral valve disease. In the literature, ventricular arrhythmia, not further defined, has been described in 1.5% of pregnant women with VHD[18] and occurred in 1.2% in Siu et al.'s prospective study.

Ischemic heart disease – Although seldom encountered during pregnancy, IHD is a major and increasing cause of maternal death[19]. In the existing literature, cases of VF, but not ventricular tachycardia, have been reported during pregnancy in patients with a myocardial infarction [20,21]. In our registry, VTA occurred in only one patient with IHD (2.1%).

Predictors for VTA

Women with a limited exercise tolerance are at higher risk of developing complications during pregnancy[4], and consequently, we were not surprised to find that NYHA class>1 before pregnancy is an independent predictor of VTA. Any disease process that affects the ventricular myocardium causing hypertrophy, infiltration or scarring may disrupt the electrical integrity of the myocardium and induce VTA[11]. CMP in general is known to be associated with ventricular arrhythmias as it is often associated with diminished ventricular function[22]. In accordance with this, we found that a diagnosis of CMP showed a borderline significance (0.06) in the multivariable analysis.

Onset during pregnancy

Nakagawa et al.[23] studied 11 pregnant women who experienced a new onset of ventricular tachycardia during pregnancy. In their study, the onset of ventricular tachycardia was distributed equally over the three trimesters and did not occur in the postpartum period. Overall, VTA occurred throughout pregnancy but more in the third trimester in our study, with CHD patients experiencing VTA more in the second and third trimester, while CMP patients typically present with VTA at the end of pregnancy (≥32 weeks), perhaps reflecting a different threshold for VTA. These findings raise a number of hypotheses regarding the mechanism of VTA during pregnancy. Cardiac output, induced by a decline in systemic vascular resistance, rises rapidly through the first and second trimesters reaching a peak at around 26 weeks and remaining at this level until the end of pregnancy[24]. The increase in cardiac output is due to an increase in heart rate and stroke volume. The greater filling, resulting in an increase in cardiac end diastolic volumes, will result in myocardial stretch which has been shown to induce VTA[25]. In addition to these physiological changes during normal pregnancy, women with structural heart disease have limited ability to adjust to the hemodynamic requirement of pregnancy, and this may become manifest as systolic and diastolic cardiac dysfunction during pregnancy[24], which again may increase the risk of VTA. Finally, the increased sympathetic activity observed during pregnancy has also been suggested to be responsible for the increased incidence of arrhythmias and it is well known that high plasma catecholamine concentrations and adrenergic receptor sensitivity may trigger VTA[26]. In all patients, the hemodynamic overload may well have contributed to the development of VTA, while the increased sympathetic activity may be more important in specific groups such as cardiomyopathy patients, which may be more susceptible.

Maternal outcome

VTA, outside of pregnancy, is associated with sudden cardiac death, especially in the presence of cardiomyopathy[22,27]. Previous publications on VTA during pregnancy were either case reports or studies which have only reported on its incidence. Therefore, it is not well known whether VTA during pregnancy carries an extra high risk for mortality. We did not

detect a significant increase in maternal mortality, but it must be noted that, although our series is by far the largest, our mortality numbers are still small and we have analyzed outcome only until one week after pregnancy. The timing of heart failure and VTA seemed to be associated in our study. However, a clear cut pattern was not found as some patients developed heart failure shortly after VTA, while others developed heart failure prior to VTA.

Delivery and fetal outcome

Women with VTA during pregnancy had higher rates of neonatal death, preterm birth and poor Apgar score. Certainly, low birthweight was more common in patients with VTA than in patients without VTA and the median birthweight was significantly lower in VTA patients. However, the corrected mean birthweight did not significantly differ between the two groups, suggesting that the difference in birthweight is primarily due to the higher preterm birth rate. Physicians often opt for preterm delivery in women with VTA, partly to shorten the period of hemodynamic compromise and also to be able to institute a more aggressive therapy for VTA, which might have an adverse effect on the fetus. Equally, the decision for early delivery may have a negative impact on neonatal development[28].

Management of VTA during pregnancy

In general, the management of VTA in pregnancy is similar to that outside of pregnancy. For VTA with hemodynamic compromise, immediate cardioversion, which is reported to be safe in all phases of pregnancy, is recommended[4]. When the patient is not hemodynamically compromised, medication should be considered. The concerns with anti-arrhythmic drug use during pregnancy relate to their effects on fetal growth and development. Beta-blockers are the drug of choice for hemodynamically well-tolerated VTA. The use of beta-blockers during pregnancy is generally well tolerated by both mother and fetus, even though it has been associated with a decrease in fetal heart rate, low blood glucose and reduced birthweight[22,29]. In our study, most patients with VTA (57%) were treated with a beta-blocker, other antiarrhythmic drugs were prescribed in 12% of the patients. Amiodarone was used in 3 of the 42 patients with VTA in our study and may have had a deleterious effect on one fetus, perhaps causing growth retardation requiring earlier delivery[22]. A multidisciplinary approach with close monitoring of mother and baby with timely intervention for both is required to optimize maternal and fetal outcomes.

Implications on clinical practice

The significance of VTA during pregnancy in women with heart disease lies in the fact that it carries a higher preterm birth rate and, consequently, lower birthweight and poor Apgar score. Cardiac patients in NYHA class>1 and patients with CMP are at particular risk and should be counselled about the risks before pregnancy and followed closely during pregnancy.

Study Limitations

This dataset, like in other registry collected datapoints, was limited by the availability of information on the past history. In our registry missing data concerning the current pregnancy ranged from 0% to 4% for all parameters except two: smoking (14%) and left ventricular dysfunction (36%). Although VTA is an important complication especially in women with underlying heart disease, its incidence is low, reflected in the number of cases. This makes it difficult to draw any firm conclusions. The severity of the VTAs was not reported in detail.

REFERENCES

1. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
2. Jastrow N, Meyer P, Khairy P, et al. Prediction of complications in pregnant women with cardiac diseases referred to a tertiary center. *Int J Cardiol* 2011; **151**(2): 209-13.
3. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
4. European Society of G, Association for European Paediatric C, German Society for Gender M, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**(24): 3147-97.
5. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol* 2008; **31**(11): 538-41.
6. Tan HL, Lie KI. Treatment of tachyarrhythmias during pregnancy and lactation. *Eur Heart J* 2001; **22**(6): 458-64.
7. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
8. Tateno S, Niwa K, Nakazawa M, et al. Arrhythmia and conduction disturbances in patients with congenital heart disease during pregnancy: multicenter study. *Circ J* 2003; **67**(12): 992-7.
9. (WEO) WEO. *Growth Resuming, Dangers Remain*. 2012. http://www.imf.org/external/pubs/ft/weo/2012/01/index.htm.
10. Niwa K, Tateno S, Akagi T, et al. Arrhythmia and reduced heart rate variability during pregnancy in women with congenital heart disease and previous reparative surgery. *Int J Cardiol* 2007; **122**(2): 143-8.
11. Adamson DL, Nelson-Piercy C. Managing palpitations and arrhythmias during pregnancy. *Heart* 2007; **93**(12): 1630-6.
12. Grewal J, Siu SC, Ross HJ, et al. Pregnancy outcomes in women with dilated cardiomyopathy. *J Am Coll Cardiol* 2009; **55**(1): 45-52.
13. Thaman R, Varnava A, Hamid MS, et al. Pregnancy related complications in women with hypertrophic cardiomyopathy. *Heart* 2003; **89**(7): 752-6.
14. Schuler PK, Herrey A, Wade A, et al. Pregnancy outcome and management of women with an implantable cardioverter defibrillator: a single centre experience. *Europace* 2012; **14**(12): 1740-5.
15. Yahagi N, Kumon K, Nakatani T, et al. Peripartum cardiomyopathy and tachycardia followed by multiple organ failure. *Anesth Analg* 1994; **79**(3): 581-2.
16. Gemici G, Tezcan H, Fak AS, Oktay A. Peripartum cardiomyopathy presenting with repetitive monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol* 2004; **27**(4): 557-8.
17. Puri A, Sethi R, Singh B, et al. Peripartum cardiomyopathy presenting with ventricular tachycardia: a rare presentation. *Indian Pacing Electrophysiol J* 2009; **9**(3): 186-9.
18. Lesniak-Sobelga A, Tracz W, KostKiewicz M, Podolec P, Pasowicz M. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases--maternal and fetal outcome. *Int J Cardiol* 2004; **94**(1): 15-23.

19. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
20. Curry JJ, Quintana FJ. Myocardial infarction with ventricular fibrillation during pregnancy treated by direct current defibrillation with fetal survival. *Chest* 1970; **58**(1): 82-4.
21. O'Donnell M, Meecham J, Tosson SR, Ward S. Ventricular fibrillation and reinfarction in pregnancy. *Postgrad Med J* 1987; **63**(746): 1095-6.
22. European Heart Rhythm A, Heart Rhythm S, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006; **48**(5): e247-346.
23. Nakagawa M, Katou S, Ichinose M, et al. Characteristics of new-onset ventricular arrhythmias in pregnancy. *J Electrocardiol* 2004; **37**(1): 47-53.
24. Cornette J, Ruys TP, Rossi A, et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. *Int J Cardiol* 2012.
25. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; **68**(6): 540-3.
26. Trappe HJ, Tchirikov M. [Cardiac arrhythmias in the pregnant woman and the fetus] Herzrhythmusstorungen bei der Schwangeren und beim Fetus. *Internist (Berl)* 2008; **49**(7): 788-98.
27. Hohnloser SH, Klingenheben T, Bloomfield D, Dabbous O, Cohen RJ. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. *J Am Coll Cardiol* 2003; **41**(12): 2220-4.
28. Gibson AT, Carney S, Cavazzoni E, Wales JK. Neonatal and post-natal growth. *Horm Res* 2000; **53 Suppl 1**: 42-9.
29. Meidahl Petersen K, Jimenez-Solem E, Andersen JT, et al. beta-Blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study. *BMJ Open* 2012; **2**(4).

CHAPTER 4

Atrial Fibrillation or Flutter during Pregnancy in Patients with Structural Heart Disease: data from the ROPAC

Amar M. Salam
Ebru Ertekin
Iris M. van Hagen
Jassim Al Suwaidi
Titia P.E. Ruys
Mark R. Johnson
Lina Gumbiene
Alexandra A. Frogoudaki
Khaled A. Sorour
Laurence Iserin
Magalie Ladouceur
A. Carla C. van Oppen
Roger Hall
Jolien W. Roos-Hesselink.

JACC Clin Electrophys. 2015 Aug; 1 (4): 284-92

ABSTRACT

Background The incidence, timing and consequences of atrial fibrillation or flutter (AF/Afl) during pregnancy in patients with heart disease are not well known.

Objectives AF/Afl during pregnancy in these women is associated with adverse outcome of pregnancy.

Methods Between 2007 and 2011, 60 hospitals in 28 countries prospectively enrolled 1321 pregnant women with congenital heart disease, valvular heart disease, ischemic heart disease or cardiomyopathy in the Registry Of Pregnancy And Cardiac disease (ROPAC). We studied the incidence, onset and predictors of AF/Afl during pregnancy and assessed the pregnancy outcome. An overview of the existing literature is provided.

Results Seventeen women (1.3%) developed AF/Afl during pregnancy, mainly in the second trimester (61.5%). Univariable analysis identified the following pre-pregnancy risk factors for AF/Afl in pregnancy; AF/Afl before pregnancy (OR 7.1, 95% CI 1.5-32.8), mitral valvular heart disease (OR 6.9, 95% CI 2.6-18.3), beta-blocker use (OR 3.3, 95% CI 1.2-9.0), and left sided lesions (OR 2.9, 95% CI 1.0-8.3). Maternal mortality was higher in women with than in women without AF/Afl (11.8% vs. 0.9%, p=0.01), although heart failure was not seen more often. Low birth weight (<2500 gram) occurred more often in women with than in women without AF/Afl (35% vs. 14%, p=0.02).

Conclusions AF/Afl occurs in 1.3% of pregnant patients with structural heart disease with a peak at the end of the second trimester. AF/Afl during pregnancy in cardiac patients is associated with unfavorable maternal outcome and also has impact on fetal birth weight.

INTRODUCTION

Major cardiovascular adaptations occur in women during pregnancy[1]. Cardiac output increases 30-50% above baseline during normal pregnancy. In early pregnancy, increased cardiac output is primarily related to the rise in stroke volume. In late pregnancy, heart rate is the major factor[2]. Pregnancy is also a hypercoagulable state[3]. These physiological alterations have more impact in patients with pre-existing heart disease[4,5].

Arrhythmia, especially supraventricular tachycardia (SVT), is a known complication during pregnancy in patients with heart disease[6 7]. The incidence of SVT seems to increase during pregnancy due to hemodynamic and maybe also hormonal changes, but evidence is scarce[8]. Atrial fibrillation is the most common clinically significant cardiac arrhythmia in the general population. Even though atrial fibrillation or atrial flutter (AF/Afl) is rarely directly life-threatening, it increases the risk of thrombo-embolism and may worsen cardiac function[9-11]. Starting medical treatment for AF/Afl presents a difficult choice in practice, since most anti-arrhythmic drugs can be regarded as potential harmful to the fetus[6,9].

Current literature on the occurrence of arrhythmia during pregnancy and its effect in women with cardiac disease is limited. Therefore, we studied the incidence, onset and predictors of AF/Afl in pregnant patients with heart disease, and report on the maternal and fetal outcome. In addition, we present an overview of the current literature.

METHODS

Study design

The European Registry on Pregnancy and Cardiac disease (ROPAC) was established in 2008 by the European Society of Cardiology (ESC). Pregnant patients from 2007 were included retrospectively, assuming that the complete data of these patients were available and reliable. From January 2008 up to June 2011 patients were included prospectively with follow-up of six months. In this period, 60 hospitals in 28 countries have contributed to the registry and 1321 pregnant patients with structural heart disease were enrolled. Non-structural heart diseases, for example arrhythmias occurring in the context of a normal heart, were excluded.

Data

The study protocol and first results of this registry were published in 2013[7].

Onset of AF/Afl was displayed as weeks of gestational age. Baseline characteristics before pregnancy were analyzed, including cardiac diagnosis, maternal age, nulliparity, clinical signs of heart failure, atrial fibrillation before pregnancy, hypertension, smoking status, beta-blocker use before pregnancy and New York Heart Association (NYHA) functional class.

Recorded cardiac diagnoses were congenital heart disease (CHD), valvular heart disease (VHD), cardiomyopathy (CMP) and ischemic heart disease (IHD). Countries were divided into developed or developing nations according to the International Monetary Fund Classification.

The type of cardiac lesion was classified in three categories for the univariable logistic regression analysis: right sided lesions (e.g. Ebstein anomaly, tetralogy of Fallot, pulmonary stenosis), left sided lesions (e.g. aortic valve disease, mitral valve disease and cardiomyopathies) and shunt lesions (e.g. atrial septal defects and ventricular septal defects). Fractional shortening <30 on echocardiography was also analyzed with the univariable logistic regression analysis.

Statistical methods

Categorical data are presented as frequencies and percentages. Continuous data are presented as mean values +/- one standard deviation (SD) when considered normally distributed as was checked using Kolmogorov-Smirnov tests. The chi-squared test or Fisher's exact tests were used to compare differences in categorical data between independent patient groups, whereas student's t-test was used to compare differences in continuous data between independent patient groups. It was the intention to adjust birth weight by a linear regression for multiple factors. However due to the small number of cases in the AF/AFl group, adjustment was only applied for gestational age. Baseline patient characteristics associated with AF/Afl were identified with univariable logistic regression analysis. Multivariable analysis was not done because of the small number of cases. A p-value <0.05 (2-sided test) was considered statistically significant. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago).

RESULTS

Baseline characteristics

Of the 1321 patients included in the registry, 17 (1.3%) developed AF/Afl during pregnancy. Two of these 17 had one episode of AF before pregnancy, and experienced a new event during pregnancy, while 5 others had pre-existing paroxysmal AF/Afl. Baseline characteristics of patients with and without AF/Afl are shown in **Table 1.** Differences were found in underlying diagnoses. VHD was the most common underlying problem in patients with AF/Afl. No patients with ischemic heart disease developed AF/Afl. The incidence of AF/Afl within each cardiac diagnosis category is depicted in **Figure 1**.

Detailed information on the patients with AF/Afl is provided in **Table 2**.

Table 1 Baseline characteristics of patients with and without AF or AFl

	Total group	Patients with AF/Afl	Patients without AF/Afl	p value
	(n=1321)	(n=17)	(n =1304)	
Mean age in years	30 ± 5.6	32 ± 5.0	30 ± 5.6	0.09
Nulliparity	50	41	50	0.47
Clinical signs of heart failure	11	18	10	0.41
Episode of AF at baseline	2.0	11.8	1.8	0.04
Hypertension	6.7	0	6.7	0.62
Smoking	3.3	0	3.3	1.00
Beta-blocker before pregnancy	14	35	14	0.026
NYHA functional class				
I	70	59	70	0.30
II	25	29	25	0.58
III	3	12	3	0.10
IV	0.3	0	0.3	1.00
Type of heart disease				
Congenital heart disease	66	35	66	0.01
Valvular heart disease	25	59	25	0.003
Cardiomyopathy	6.7	5.9	6.7	1.00
Ischemic heart disease	1.9	0	1.9	1.00

Values are mean ± SD or %

AF = atrial fibrillation; Afl = Atrial flutter; NYHA = New York Heart Association

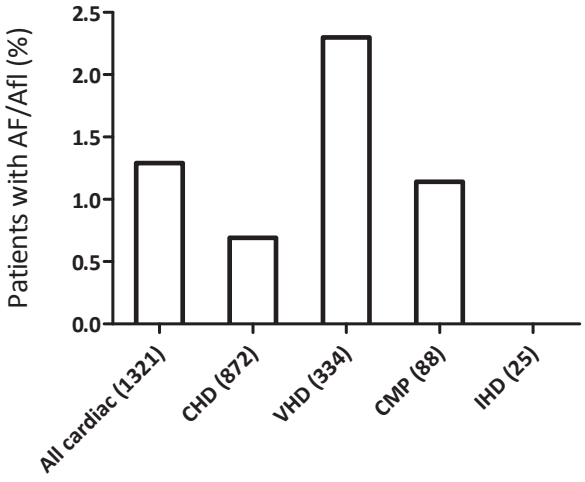


Figure 1 Percentage of patients with AF/Afl within each diagnosis category

The number of patients per group is shown between brackets.

AF/Afl=atrial fibrillation or flutter, All cardiac=CHD+VHD+CMP+IHD, CHD=congenital heart disease, VHD=valvular heart disease, CMP=cardiomyopathy, IHD=ischemic heart disease

Table 2 Characteristics of patients (n=17) with AF/AFl

Patient	Age	Gravida	Status of originating country	Cardiac diagnosis	Medication before pregnancy	History of AF/Afl	Prepregnancy rhythm	Timing echo	Atrial dimensions	Ventricular function	Timing event	Antiarrhythmic medication	Anticoagulation regime during pregnancy	Pregnancy complications	Maternal mortality	Fetal mortality	Pregnancy duration	Mode of delivery	Birth weight
1	37	1	Developed	Hypertrophic obstructive CMP	Metoprolol Furosemid	No	SR	1st trimester	RA dilated, LA severely dilated	Moderate LV dysfunction	23	Atenolol Amiodaron	LMWH	-	-	-	37	CS*	2730
2	31	3	Developed	Unrepaired VSD, severe PS	-	No	SR	2nd trimester	RA normal LA unknown	Normal	32	(Amiodaron because of VT)	LMWH	Ventricular tachycardia	-	-	34	CS^	1865
3	35	5	Emerging	Severe MR, rheumatic	-	Yes	AF	3rd trimester	RA normal LA unknown	Normal	-	Sotalol Digoxin	UH	Heart failure	-	-	39	vaginal	2950
4	40	8	Emerging	Severe MR	-	No	SR	3rd trimester	RA normal, LA severely dilated	Normal LV (RV unknown)	25	Sotalol	OAC; UH during delivery	Heart failure, haemorrhage	-	-	40	vaginal	3000
5	29	4	Emerging	Moderate MS + moderate MR, rheumatic	Digoxin	No	SR	3rd trimester	RA normal, LA severely dilated	Normal	26	Sotalol	OAC; LMWH during delivery	-	1 wk after delivery	-	39	CS^	2700
6	25	1	Emerging	Severe MS + moderate MR, rheumatic	-	-	-	After delivery	RA dilated, LA dilated	Normal	6 weeks postpartum	-	No	early/spontaneous abortion	6 wk after delivery	yes	12	vaginal	-
7	26	1	Emerging	MS, mitral mechanical valve	-	No	SR	2nd trimester	RA unknown, LA severely dilated	Normal LV (RV unknown)	22	-	OAC; UH during delivery	-	-	-	38	vaginal	2700
8	31	10	Developed	DORV, surgically closed VSD (moderate AS)	Atenolol	No	SR	Pre-pregnancy	RA dilated, LA unknown	Normal	24	(Continuation of atenolol)	LMWH	-	-	-	38	CS†	2458
9	38	1	Developed	Severe MR	Betablocker aspirin	No	SR	2nd trimester	RA normal, LA severely dilated	Normal	26	Atenolol	LMWH	IUGR	-	-	35	CS^	2400

Patient	Age	Gravida	Status of originating country	Cardiac diagnosis	Medication before pregnancy	History of AF/Afl	Prepregnancy rhythm	Timing echo	Atrial dimensions	Ventricular function	Timing event	Antiarrhythmic medication	Anticoagulation regime during pregnancy	Pregnancy complications	Maternal mortality	Fetal mortality	Pregnancy duration	Mode of delivery	Birth weight
10	27	2	Developed	MS (severity unknown; undefined previous mitral intervention), rheumatic	Furosemid Atenolol	Yes	AF	1st trimester	RA dilated, LA severely dilated	Unknown	12	(Continuation of atenolol)	LMWH	IUGR	-	-	32	CS^	1230
11	28	1	Developed	moderate MS (undefined previous mitral intervention), rheumatic	Digoxin	No	SR	2nd trimester	Unknown	Unknown	26	-	UH	-	-	-	37	CS^	2800
12	33	1	Developed	surgical correction complete AVSD	-	No	SR	No	-	-	30	Sotalol	LMWH	-	-	-	36	vaginal	2740
13	30	2	Developed	Pulmonary vein abnormality	Metoprolol	Yes	SR	2nd trimester	RA normal, LA mildly dilated	Normal	-	(Continuation of metoprolol)	No	Ventricular arrhythmia	-	-	41	vaginal	3150
14	29	1	Developed	Tricuspid atresia (Fontan procedure)	Warfarin	Yes	SR	2nd trimester	Unknown	Normal Systemic Ventricle	7	Sotalol	Aspirin LMWH	IUGR, vaginal bleeding, threatened miscarriage	-	-	37	CS^	2100
15	42	4	Developed	Moderate MS, (undefined previous mitral intervention), rheumatic	Atenolol	Yes	SR	3rd trimester	RA unknown, LA moderately dilated	Normal	-	(Continuation of atenolol)	LMWH	gestational diabetes	-	-	36	vaginal	1709
16	32	1	Developed	MR (severity undefined)	-	Yes	SR	1st trimester	RA normal, LA mildly dilated	Normal	-	-	No	-	-	-	40	vaginal	3710
17	30	2	Developed	Coarctatio Aortae	-	Yes	SR	2nd trimester	RA unknown, LA severely dilated	Normal LV (RV unknown)	29	-	No	-	-	-	40	vaginal	unknown

CMP = Cardiomyopathy; VSD = Ventricle septal defect; PS = Pulmonary valve stenosis; MR = Mitral valve regurgitation; MS = Mitral valve stenosis; DORV = Double outlet right ventricle; AS = Aortic valve stenosis; AVSD = Atrioventricular septal defect; SR = Sinus rhythm; AF = Atrial fibrillation; RA = Right atrium; LA = Left atrium; LV = Left ventricle; RV= Right ventricle; VT = Ventricular tachycardia; LMWH = Low molecular weight heparin; UH = Unfractionated heparin; OAC = Oral anticoagulation; IUGR = Intrauterine growth retardation; CS = Cesarean section; * Emergency CS for cardiac reason; ^ Planned CS for cardiac reason; † Planned CS for obstetric reason

Predictors and onset of AF/Afl

The results of the univariable logistic regression are shown in **Table 3**. It appeared that patients enrolled in centers with at least one AF/Afl event had different characteristics than the remaining patients. Unfortunately, due to the low number of endpoint events, it was not possible to correct for the differences between the centers. Table 1 of the online supplement shows the differences between centers with AF/Afl events and centers without AF/Afl events. Of the univariable predictors, only pre-pregnancy atrial fibrillation and beta-blocker use were not different in the centers with or without AF/Afl.

In all patients, AF/Afl occurred during pregnancy and once after delivery **(Figure 2)**. Onset of AF/Afl was mainly at the end of the second trimester.

Table 3 Univariable predictors for AF/AFl

	Odds ratio	95% CI	p value
Congenital heart disease	0.3	(0.1-0.8)	0.01
Mitral valve disease	6.9	(2.6-18.3)	<0.001
Cardiomyopathy	0.9	(0.1-6.7)	0.90
Right sided lesion	0.2	(0.03-1.5)	0.12
Left sided lesion	2.9	(1.0-8.3)	0.046
Shunt lesion	0.9	(0.3-2.9)	0.89
NYHA class > II	3.9	(0.9-17.6)	0.08
Nulliparity	0.7	(0.3-1.9)	0.48
Developing countries	2.6	(0.9-7.5)	0.08
Clinical signs of heart failure	1.8	(0.5-6.5)	0.34
Rhythm: Atrial fibrillation before pregnancy	7.1	(1.5-32.8)	0.01
Mechanical valve	1.5	(0.2-11.8)	0.68
Beta-blocker before pregnancy	3.3	(1.2-9.0)	0.02
Echo prior to pregnancy: Fractional Shortening < 30%	2.2	(0.2-24.6)	0.53

CI = Confidence interval, other abbreviations as in Table 1

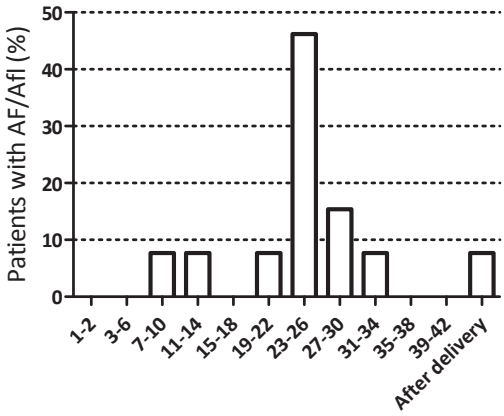


Figure 2 Onset of AF/Afl during pregnancy in patients with heart disease
Exact timing of onset is missing in 4 patients.
AF/Afl=atrial fibrillation or flutter

Medication before and during pregnancy

During pregnancy 14 patients (82%) used medication. Details concerning antiarrhythmic medication and anticoagulants are listed in Table 2.

Delivery

Mode of delivery in patients with AF/Afl was vaginally in 9 (53%), by elective Cesarean section (CS) in 7 (41%) and by emergency CS in one patient, because of cardiac reasons. Elective CS was for cardiac reasons in 7 patients and for obstetric reasons in one.

Maternal and fetal outcome

Maternal mortality occurred in 2 of the 17 patients (12%). The first patient was 29 years old and had moderate mitral stenosis and mitral regurgitation before pregnancy. After delivery anticoagulation was stopped because of severe bleeding. She suddenly died 1 week after delivery and was highly suspected based on clinical judgement of a thromboembolic complication. The second patient was 25 years old and also had a combination of severe mitral stenosis and mitral regurgitation. Early spontaneous abortion occurred in this patient and she died 6 weeks after the expulsion of the pregnancy due to sepsis, which was followed by the event of atrial fibrillation. Both patients did not suffer from heart failure prior to their demise.

There were no significant differences in cardiac and obstetric complications during pregnancy in the patients with versus without AF/Afl (Table 4). Hospitalization during pregnancy was needed for 12 patients (71%). All hospital admissions were for cardiac reasons.

Fetal outcome is summarized in Table 4.

Table 4 Pregnancy outcome in patients with and without AF/AFl

	Total group	Patients with AF/Afl	Patients without AF/Afl	p value
	(n =1321)	(n=17)	(n=1304)	
Maternal mortality	1.0	11.8	0.9	0.01
Cardiac				
Heart failure	13	12	13	1.00
Thrombo-embolic events	0.5	0	0.5	1.00
Endocarditis	0.2	0	0.2	1.00
Bleeding complications during pregnancy	1.6	5.9	1.5	0.34
Bleeding complications postpartum	4.9	5.9	4.9	0.58
Obstetric				
Intra-uterine growth retardation	5.8	17.6	5.6	0.07
Pregnancy induced hypertension	2.4	0	2.5	1.00
(Pre-)eclampsia	3.3	0	3.3	1.00
Caesarean section	41	47	41	0.58
Fetal outcome				
Mean pregnancy duration (weeks)	38.0	37.5	38.0	0.25
Fetal death	1.7	0	1.7	1.00
Neonatal death	0.6	0	0.6	1.00
Apgar score < 7	10	6	10	1.00
Premature birth < 37 weeks	15	29	15	0.16
Birth weight < 2500 gram	14	35	14	0.02
Adjusted mean birth weight (grams)	-	3026	3358	<0.001

Values are %. Abbreviations as in Table 1

DISCUSSION

This is the first study to examine in detail the incidence, predictors and outcome of AF/Afl in pregnant patients with heart disease. In this large prospective international registry of 1321 patients with heart disease, 1.3% experienced documented AF/Afl, which occurred most frequently at the end of the second trimester. Pre-pregnancy predictors of AF/Afl were AF before pregnancy, mitral valve disease, beta-blocker use, and left sided lesions. AF/Afl was associated with higher rates of maternal mortality and lower fetal birth weight.

Literature and Incidence of AF/Afl

Existing data on the incidence of AF/Afl, during pregnancy in patients with heart disease is limited and based on small case series and individual case reports *(online supplement Table 1)*[12-22]. Silversides et al did report on the recurrence rate of SVT during pregnancy in patients with a history of SVT[17]. Li et al[18] reported the prevalence of cardiac arrhythmia

among 136,422 pregnant females hospitalized in a single center. Out of 226 patients who had an arrhythmia, 3 had AF and all these patients had structural heart disease. Two out of the three patients had a previous episode of AF and none of the patients died. Huisman et al[23] assessed the incidence and risk factors for severe maternal morbidity and cardiovascular mortality during pregnancy, delivery and puerperium in the general Dutch population between 2004 and 2006. Out of 2552 cases of severe maternal morbidity, 84 (3.3%) involved the cardiovascular system among which two cases had AF, neither of whom died.

Congenital heart disease – We observed AF/Afl in 0.7% of CHD patients. There was one previous report[12] that assessed the progress and outcome of 482 pregnancies in 232 patients with CHD. Afl occurred in that study in 2 patients (0.4%).
Cardiomyopathy – We report on one patient with CMP who developed AF in the second trimester. The patient delivered in the third trimester by Cesarean section without fetal or maternal complications. There are no prior data in the literature on pregnancy in CMP developing AF/Afl.
Valvular heart disease – AF/Afl occurred in 10 patients with mitral VHD (3%) in our study[7], 4 of them had valve surgery in the past. Available literature on AF/Afl in VHD and pregnancy is in the form of case series reports and incidence varies from 2 to 17.5%[13,14,16].

We also collected the literature regarding AF/Afl in pregnancy in women without structural cardiac disease. This is summarized in *online supplement Table 2*, which is available in the supplementary material. In summary, these studies are mainly case reports of women experiencing AF during the third trimester, with good outcome of both mother and fetus.

Predictors for AF/Afl

It was not surprising to find that AF before pregnancy was an independent predictor of AF/Afl during pregnancy. Silversides et al[17] found a recurrence rate of arrhythmia during pregnancy of 50% in patients with SVT in general and 52% in patients with AF. Adverse fetal events occurred in 35% of patients with paroxysmal AF/Afl and 50% with permanent AF.

Other pre-pregnancy predictors of AF/Afl were mitral valve disease, and left sided lesions, although these associations might be explained by the fact that the centers reporting AF/Afl in these patients were a predilection site for these underlying diagnoses. The physiological changes that occur during pregnancy producing a state of high volume, high output and low cardiovascular resistance are likely responsible mechanisms. These changes may amplify wall stress, which, combined with the prior cardiac abnormalities, causes electrophysiological imbalance and lowers the threshold for onset of arrhythmias. To our surprise, we found no correlation with heart failure.

Patients in our study who had been prescribed medication before pregnancy, in particular beta-blockers, probably had more severe cardiac disease, accounting for the increased

risk of developing AF/Afl in this group. This might be related to the fact that some of the patients were administered beta-blockers before pregnancy because of prior arrhythmias.

Onset during pregnancy

Most of AF/Afl was found in the second trimester in our study, with a peak of occurrence between week 23 and 26. In contrast, previously reported cases of AF in pregnancy were commonly observed in the third trimester. Most comparable is the cohort of Silversides et al and our results do agree with theirs.

Maternal and fetal outcome

We report an increase in maternal deaths in cardiac patients with AF/Afl during or shortly after pregnancy (11.8%). This is probably attributable partly to the severity of the underlying cardiac condition and in addition the thrombo-embolic risk might play a role. As we report on two mortality cases only, a definitive conclusion on causative mechanisms cannot be drawn. Only one previous report[13] has described mortality in a patient due to heart failure.

We did not find any increase in fetal loss in women with AF/Afl. A low birth weight was more common in the offspring of patients with than without AF/Afl. Adjusted for pregnancy duration, the absolute birth weight remained to be remarkably lower in patients suffering AF/Afl during pregnancy. However, it was not appropriate to statistically correct for factors like the use of beta-blockers during pregnancy and type of underlying cardiac disease, which might influence the birth weight as well.

Management of AF/Afl during pregnancy

In the management of patients with AF/Afl in pregnancy several issues should be taken into consideration. First, the teratogenic potential of anti-arrhythmic drugs limits the use of these agents during pregnancy. From many of these drugs, information on safety in pregnancy is lacking and most pharmaceutical companies advice not taking these drugs during pregnancy. Secondly, the hemodynamic alteration during pregnancy can alter the pharmacokinetics of the anti-arrhythmic drugs. For instance, for digoxin the dose needed for adequate serum levels during pregnancy is higher than outside pregnancy. In addition, anticoagulation needs consideration because pregnancy is a thrombogenic state [6]. However, bleeding complications are also more often encountered, in particular during delivery. Anticoagulants and beta-blockers constitute the medications of first choice in the management of patients with AF/Afl in pregnancy and both were used in two thirds of our patients. No increase in bleeding complication rates was observed in our patients on anticoagulants. Finally, electrical cardioversion is reported to be safe during pregnancy, but anesthetic management needs careful consideration in the pregnant woman. In our study this was not reported.

To achieve a more definite management of the arrhythmia in case of poor tolerance and drug resistance, radiofrequency (RF) catheter ablation might be considered. RF ablation for AF/Afl during pregnancy has not been reported to date. There is limited evidence from case reports and series[24,25] on RF ablation being safe in pregnant women suffering from atrial or atrioventricular re-entry tachycardia provided that an electroanatomical mapping system is used instead of fluoroscopy.

Implications for clinical practice and research

Although rare in pregnancy, the management of AF/Afl in women with heart disease poses a unique challenge to physicians. A multidisciplinary approach with close monitoring of mother and baby, and timely therapy is required to optimize maternal and fetal outcomes. Despite our data, experience with the management of such arrhythmias remains limited and further studies in larger numbers of patients are still awaited. In addition, there is recent evidence that non-pregnant patients at risk for AF may have asymptomatic AF which exposes them to the risk of ischemic stroke and other thromboembolic events[26,27]. The observation that most of our patients developed the arrhythmia in the second trimester alerts us to the period of highest risk.

Limitations

As with all registries there was some missing information, which comprised 4% in our registry. Some of the previously identified predictors (e.g. hypothyroidism and stress) were neither confirmed nor contradicted in this study, because these data were not collected. Although AF/Afl is an important complication especially in women with underlying heart disease, its incidence during pregnancy is low. It is difficult to draw firm conclusions for the different cardiac diseases as the numbers of patients with AF/Afl per cardiac disease category were small. Also, the hierarchical structure (60 hospitals within 28 countries), should ideally be accounted for in the analysis. However, unfortunately, due to the low number of AF/Afl events, adequate estimates of hierarchical model parameters could not be obtained. Hence, we were not able to adjust for differences in clinical characteristics between patient populations. Interpretation of our data should be done against this background. Our findings should be seen as first results needing confirmation in larger populations.

Conclusions

In this large prospective international registry of women with heart disease, the incidence of AF/Afl during pregnancy was 1.3% and occurred mainly at the end of the second trimester. AF/Afl before pregnancy, mitral valve disease, beta-blocker use, and left sided lesions were predictors of AF/Afl. Our data suggest an increase in maternal mortality and low birth weight in patients with AF/Afl during pregnancy.

Online Supplementary Information

Table 1 Differences between patients enrolled in centers with and without AF/Afl events

Table 2 Atrial fibrillation in pregnant women with structural heart disease as reported in the medical literature

Table 3 Atrial fibrillation in pregnant women without structural heart disease as reported in the medical literature

REFERENCES

1. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; **68**(6): 540-3.
2. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
3. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. *N Engl J Med* 1996; **335**(2): 108-14.
4. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
5. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
6. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
7. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
8. Tan HL, Lie KI. Treatment of tachyarrhythmias during pregnancy and lactation. *Eur Heart J* 2001; **22**(6): 458-64.
9. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31**(19): 2369-429.
10. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009; **373**(9658): 155-66.
11. Packer DL, Bardy GH, Worley SJ, et al. Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. *Am J Cardiol* 1986; **57**(8): 563-70.
12. Whittemore R, Hobbins JC, Engle MA. Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. *Am J Cardiol* 1982; **50**(3): 641-51.
13. Ayhan A, Yapar EG, Yuce K, Kisnisci HA, Nazli N, Ozmen F. Pregnancy and its complications after cardiac valve replacement. *Int J Gynaecol Obstet* 1991; **35**(2): 117-22.
14. Suri V, Sawhney H, Vasishta K, Renuka T, Grover A. Pregnancy following cardiac valve replacement surgery. *Int J Gynaecol Obstet* 1999; **64**(3): 239-46.
15. Autore C, Conte MR, Piccininno M, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **40**(10): 1864-9.
16. Lesniak-Sobelga A, Tracz W, KostKiewicz M, Podolec P, Pasowicz M. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases--maternal and fetal outcome. *Int J Cardiol* 2004; **94**(1): 15-23.
17. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006; **97**(8): 1206-12.
18. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol* 2008; **31**(11): 538-41.
19. Lin CH, Lee CN. Atrial fibrillation with rapid ventricular response in pregnancy. *Taiwan J Obstet Gynecol* 2008; **47**(3): 327-9.
20. Risius T, Mortensen K, Meinertz T, Willems S. Cluster of multiple atrial tachycardias limited to pregnancy after radiofrequency ablation following senning operation. *Int J Cardiol* 2008; **123**(3): e48-50.

21. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007; **18**(5): 545-7.
22. Walker MG, Colman J, Silversides CK, Gandhi S, Kingdom J. Maternal atrial arrhythmia detected by uterine artery Doppler. *J Obstet Gynaecol Can* 2011; **33**(8): 851-3.
23. Huisman CM, Zwart JJ, Roos-Hesselink JW, Duvekot JJ, van Roosmalen J. Incidence and predictors of maternal cardiovascular mortality and severe morbidity in The Netherlands: a prospective cohort study. *PLoS One* 2013; **8**(2): e56494.
24. Ferguson JD, Helms A, Mangrum JM, DiMarco JP. Ablation of incessant left atrial tachycardia without fluoroscopy in a pregnant woman. *J Cardiovasc Electrophysiol* 2011; **22**(3): 346-9.
25. Szumowski L, Szufladowicz E, Orczykowski M, et al. Ablation of severe drug-resistant tachyarrhythmia during pregnancy. *J Cardiovasc Electrophysiol* 2010; **21**(8): 877-82.
26. Charitos EI, Stierle U, Ziegler PD, et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012; **126**(7): 806-14.
27. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; **366**(2): 120-9.

CHAPTER 5

Managing Cardiac Emergencies in Pregnancy

Iris M. van Hagen
Jérôme Cornette
Mark R. Johnson
Jolien W. Roos-Hesselink

Heart. 2017 Jan 15;103(2):159-173.

INTRODUCTION

Reducing maternal mortality was a major component of the fifth millennium development goal. A drop of 47%, was achieved mainly through reductions in sepsis and haemorrhage.[1] Maternal mortality related to cardiovascular causes did not decrease and, in developed countries, may even have increased.[2,3] Most of these women are not known to have an underlying cardiovascular problem, and the majority die from acute events including aortic dissection, acute coronary syndrome or an arrhythmia. Others have an underlying, pre-existing heart condition, which deteriorates with the increased demands of pregnancy, most commonly resulting in heart failure.[4]

In the group of women with a known cardiac condition, a preconception assessment by an experienced team of specialists is essential in order to minimize the risk of complications during pregnancy. The aim of this assessment is to identify those who may benefit from an operative intervention, to optimize medical treatment, to identify potential complications and to put in place plans to deal with these eventualities. It involves a combination of history, physical examination, VO2 max exercise testing, echocardiography and in some cases cardiac CT or MR. In addition, the thorough evaluation informs pre-conception counseling, which should occur at the same time and which should consider the potential impact of the cardiac condition on pregnancy outcome and, conversely, the potential impact of the pregnancy on the cardiac condition.

The evaluation of maternal risks can be based on several risk tools.[5-7] Of these, the modified World Health Organization (WHO) risk stratification model seems to be the best predictor of overall risk. Women in modified WHO class IV (a severely dilated aorta, pulmonary hypertension, severe systemic ventricular dysfunction, symptomatic left heart obstruction) are at such high risk of complications that they should be advised not to conceive.

In women who present in pregnancy with a major cardiac event, early diagnosis and prompt treatment is essential. Immediate referral to a specialised center is strongly advised. The balance between the maternal condition and fetal maturity will determine whether a conservative or invasive approach is adopted. However, in life-threatening circumstances the health of the mother is always the primary concern. This strategy is usually in the best interest of the fetus.

In this review, the most common acute cardiac complications during pregnancy are discussed. The incidence, diagnosis and management are outlined. A summary flow chart for practical use is provided for each complication.

HEART FAILURE

Incidence and timing

In two large prospective cohorts of pregnant women with cardiac disease, heart failure was the most common cardiac complication [4,6] and in the largest study it was the most important cause of cardiac death. [8] The incidence varies depending on the underlying cardiac condition, ranging, in a review of series and case reports, from 4.8% in women with congenital heart disease in general, to more than 21.1% in patients with Eisenmenger syndrome.[9] In prospective studies of patients with any cardiac disease, the overall incidence was up to 13.1%,[4] but was highest women with shunt lesions, diminished cardiac function and pulmonary hypertension (41%). Other patients at particular risk are those with a left heart obstruction.[10-13] In patients with congenital heart disease with a baffle or conduit *in situ*, prosthesis related problems should be ruled out.

Heart failure typically occurs at the end of the second trimester or immediately postpartum. At the end of the second trimester, the cardiovascular adaptation to pregnancy, with increase in cardiac output and plasma volume, reaches its maximum [14], while immediately post partum, uterine contraction is associated with an auto-transfusion of between 500-1000ml of blood results into the maternal circulation. These events may explain the timing of heart failure during pregnancy and are summarised in **Figure 1.**[8,14,15] The timing of heart failure varies with the underlying cardiac diagnosis: shunt lesions (atrial and ventricular septal defects) show a peak incidence of heart failure at the end of the second trimester, cardiomyopathies and stenotic lesions at the end of pregnancy and postpartum.[8]

NT-proBNP levels predict cardiovascular events during pregnancy, but are also elevated in pre-eclamptic women without any cardiac abnormality, which is probably attributable to the pressure overload and associated cardiac dysfunction.[16-18] Therefore, while a low NT-proBNP does have a strong negative predictive value, a high value does not have a strong positive predictive value. There is a remarkable association between pre-eclampsia and heart failure. A study assessing cardiac function by echo in patients with either preterm or term pre-eclampsia and compared with normotensive controls showed signs of diastolic and systolic ventricular dysfunction mainly in women with preterm pre-eclampsia which is the more severe form.[19] Interestingly, 30% of cardiac patients with pre-eclampsia, also developed heart failure during pregnancy.[8] Whether the (subclinical) cardiac dysfunction is the cause or result in this situation is uncertain, however, the pathogenesis of peripartum cardiomyopathy has been related to endothelial dysfunction which also occurs in pre-eclampsia mediated through VEGF and TGFβ antagonism; this possibility needs further investigation.[20,21]

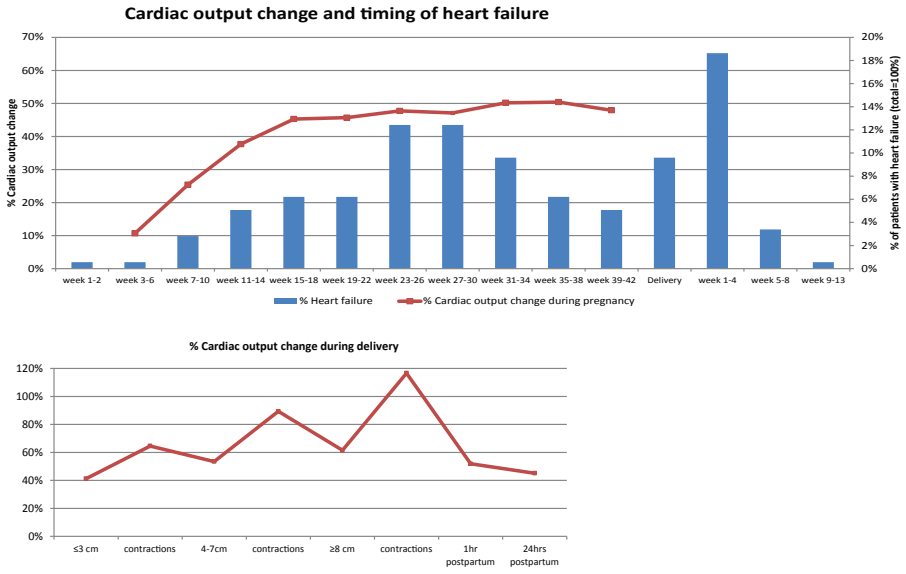


Figure 1 Cardiac output change and timing of heart failure during pregnancy, delivery and postpartum. *Data extracted from Robson et al[14, 15] and Ruys et al.[31]*

Management (Figure 2)

An experienced center from Germany published their management algorithm for use in pregnant patients with acute heart failure.[22] A multidisciplinary team decides on the management plan based on the maternal and fetal condition: if the fetus is viable, the choice is between immediate delivery or continuing the pregnancy with heart failure therapy. If the heart failure is severe and the fetus is showing signs of distress, then the advice will be to deliver. If, on the other hand, the heart failure is mild and the fetal assessment reassuring, then the advice will be to continue. As gestation advances, the threshold for delivery will reduce. The final decision is determined by the parents.[5] If the fetus is not viable, then maximum heart failure therapy is administered directly.

In case of acute heart failure, bedrest is advised and with few exceptions, the pharmacological management of acute heart failure during pregnancy follows the guidelines for non-pregnant patients.[23,24] Management should always be determined in cooperation with an obstetrician. Diuretics can be given and are considered safe during pregnancy,[25] but the dosage should be increased with caution, to avoid intravascular volume depletion. ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy due to their fetotoxic effects[26] and can only be used in exceptional circumstances as stated by the U.S. Food and Drug Administration (FDA category D). The FDA classification is commonly used in the setting of pregnancy, but decisions in the emergency situation should always be

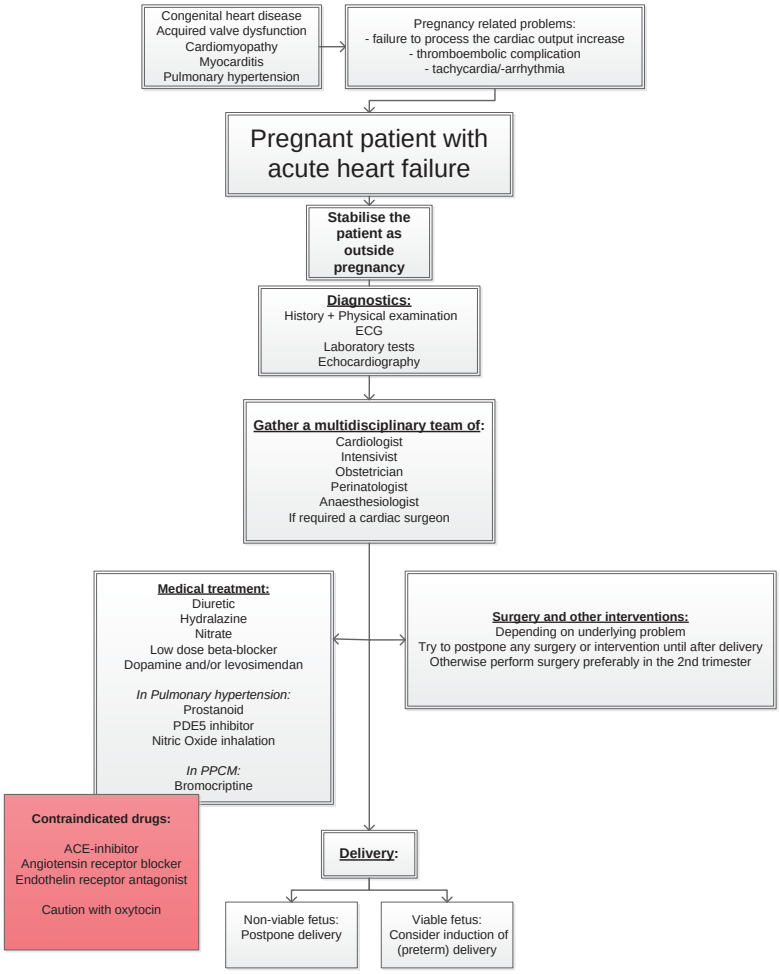


Figure 2 Management of pregnant patients with acute heart failure

individualised. An acute pharmacological intervention can be justified while long-term use of the same medication is contraindicated. Hydralazine and nitrates can be used for after-load reduction [27] and low dose beta-blockers can be considered to control sinus tachycardia and maintain sinus rhythm or for the treatment of hypertension. Inotropic therapy may be used in those who are haemodynamically unstable: dopamine and levosimendan are then first choice agents, although their use in pregnant women Is controversial as evidence of efficacy and safety is limited.[5,28,29] In patients with ventricular dysfunction, due to the risk of a cardiac thrombus and systemic embolisation, therapeutic anticoagulation is recommended with either low molecular weight heparin or unfractionated heparin with strict monitoring of coagulation. Sinus rhythm should be aimed for in all patients with heart failure. Extensive

information about cardiac medication is available in the ESC guidelines on the management of cardiovascular disease during pregnancy.[5]

If the pharmacological treatment achieves stabilization of the maternal condition, a vaginal delivery is preferred as close as possible to term. A Caesarean section (CS) confers no benefit in most women with cardiac disease and increases the risk of infection, thrombosis and haemorrhage.[30,31] However, in individual cases, a CS might be considered, especially in those women with further deterioration in cardiac function, in whom heart function is so precarious that it might not cope with the strain of substantial fluctuations in cardiac output accompanying contractions during delivery.[5] Because of the large volume shifts shortly after delivery, women with a history of heart failure should still be monitored intensively for at least 48 hours.

Heart failure in patients with pulmonary hypertension

In patients with heart failure due to pulmonary arterial hypertension, treatment with pulmonary vasodilators should be considered to lower the pulmonary pressure. Some of these agents have teratogenic effects, in particular endothelin receptor antagonists, and are contraindicated. Experience with the use of other advanced pulmonary arterial hypertension therapies, such as prostaglandin therapy and PDE5 inhibitors during pregnancy is limited, but seem to be safe and their use associated with improved maternal survival.[32] Nitric oxide (NO) inhalation is considered as a last resort; but it may acutely reduce pulmonary vascular resistance and its use has been associated with a maternal survival in the region of 68%.[33-35] The decision regarding the mode of delivery should be made on an individual basis. During delivery, vaginal or a Caesarean section, every effort should be made to prevent major haemodynamic changes. The two key points are the delivery of the placenta, which is associated with the return of 500-1000mls of blood into the maternal circulation, and the immediate post-partum period, when inadequate use of uterotonics may result in an increased risk of post-partum haemorrhage. The presence of an experienced team, including a cardiac anaesthetist is essential.

Heart failure in patients with peripartum cardiomyopathy

Women with no cardiac history, who present in the last month of pregnancy or first months after delivery with symptoms and signs of heart failure and who are found to have diminished left ventricular function should be considered to have peripartum cardiomyopathy. It is the diagnosis of exclusion and is probably related to dilated cardiomyopathy. Prolactin has been suggested to play an important role in the pathophysiology.[36,37] Heart failure management is the same as in other pregnant patients, but in addition, bromocriptine, a dopamine-2D agonist that inhibits prolactin secretion, has shown to improve left ventricular function in small studies, [38,39] and is currently being investigated in a randomised controlled trial.[38]

ARRHYTHMIAS

Supraventricular tachycardia (Figure 3)

Palpitations, dizziness and (near)syncopal events, occur commonly during normal pregnancy and are mostly benign: only 10% of symptomatic episodes are actually caused by an arrhythmia.[40] In women with an arrhythmic event before pregnancy, the recurrence rate of supraventricular arrhythmia during pregnancy is approximately 50%.[41] The occurrence of new onset symptomatic supraventricular tachycardia during pregnancy is rare. An incidence of 1.3% has been reported in women with cardiac disease. In pregnant women without cardiac history the incidence of supraventricular arrhythmia is presumably much lower and mainly described in case reports, often in the third trimester.[42] The workup in new onset atrial fibrillation is the same as outside pregnancy and includes a careful history and physical examination, an ECG, serum electrolytes and thyroid function and an echocardiography to identify any underlying abnormality.

Antiarrhythmic agents should be considered to be potentially fetotoxic.[5] Also, the haemodynamic changes during pregnancy influence drug pharmacokinetics, meaning that dose adjustments may be necessary in pregnant women. Similar to the situation outside pregnancy, treatment decisions depend on the maternal condition, the duration of the arrhythmia and hemodynamic status. Most therapeutic approaches are based on observational data, these have been reviewed extensively by Tan and Lie in 2001.[43] Current treatment recommendations are summarised in **Figure 3**.

In the case of an atrioventricular (nodal) re-entrant tachycardia, vagal manoeuvres are the first line followed by adenosine. Both are reported to be safe in pregnancy.[44,45] Atrial tachycardia, including intra-atrial re-entry tachycardia, may also be treated with adenosine and if unsuccessful, a beta-blocker or digoxin can be started as rate control. Most beta-blockers are FDA category C, except for atenolol, which is considered FDA category D, and should be avoided.

For atrial fibrillation, sotalol can be used for rhythm control and is considered FDA class B. Alternatives include intravenous ibutilide[46] or flecainide (FDA class C). In haemodynamic unstable patients or if pharmacological cardioversion failed, immediate direct current cardioversion should be performed, which is considered safe during pregnancy. Cardioversion should be performed under strict fetal and maternal monitoring and with an obstetric team and facilities available for immediate emergency Caesarean section if necessary.[47] Agents that are not first choice treatment but can be considered because of their effectiveness outside pregnancy are: amiodarone (only for short-term use, FDA D),[48] procainamide (FDA C, limited experience), propafenon (FDA C, limited experience), and verapamil (FDA C, risk of maternal hypotension and subsequent placental hypoperfusion).

The indications for anticoagulant therapy are the same during pregnancy,[49] but since pregnancy and the puerperium are thrombogenic states a lower threshold for treatment

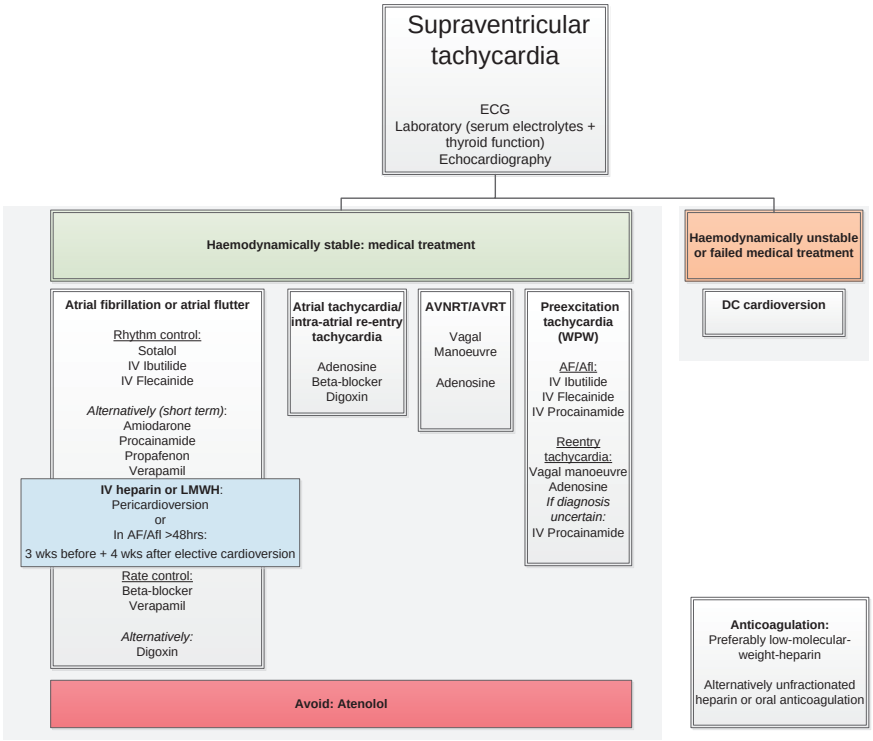


Figure 3 Management of supraventricular tachycardia during pregnancy
LMWH, low-molecular-weight heparin.

should be used. Vitamin K antagonists (VKA, FDA category D) have severe teratogenic effects and changing to heparin, usually lower molecular weight (LMWH, FDA category B), should be considered as soon as pregnancy is confirmed, particularly when high doses are needed.[50,51] There are minimal data for new oral anticoagulation (NOAC) therapy during pregnancy. In rats, most NOACs have been shown to cross the placenta, consequently NOACs should not be used, although short-term use of rivaroxaban in the first trimester did not reveal severe problems.[52]

Ventricular tachycardia

Although the incidence of ventricular arrhythmia is less than supraventricular tachycardia, they are associated with worse outcome. Overall, the incidence of ventricular tachycardia in women with cardiac disease is approximately 1.0-1.4%.[6,53] Hormonal changes are suggested to play a role in the pathophysiological mechanism.[54,55] A ventricular arrhythmia in the third trimester or postpartum period in previously healthy woman, may also be the first presentation of peripartum cardiomyopathy.[56,57] A remarkable reduced risk of events in long

QT syndrome has been observed during the course of pregnancy, whilst the postpartum period seems to be associated with an increased risk.[58]

In all patients, the aim is to achieve and maintain haemodynamic stability, for the benefit of the mother and fetus. In a haemodynamically unstable patient with any type of ventricular tachycardia, immediate defibrillation is indicated.[59] If a patient is stable, chemical cardioversion can be considered. First choice drugs in a monomorphic ventricular tachycardia, without signs of long-QT syndrome, is IV sotalol (FDA B) or procainamide (FDA C).[60] In the case of sustained refractory or recurrent ventricular tachyarrhythmias, not directly responding to defibrillation, IV amiodarone is an alternative. In patients with idiopathic right ventricular outflow tract tachycardia, which is probably the most common ventricular arrhythmia in an otherwise healthy pregnant woman, verapamil or beta-blockers are usually

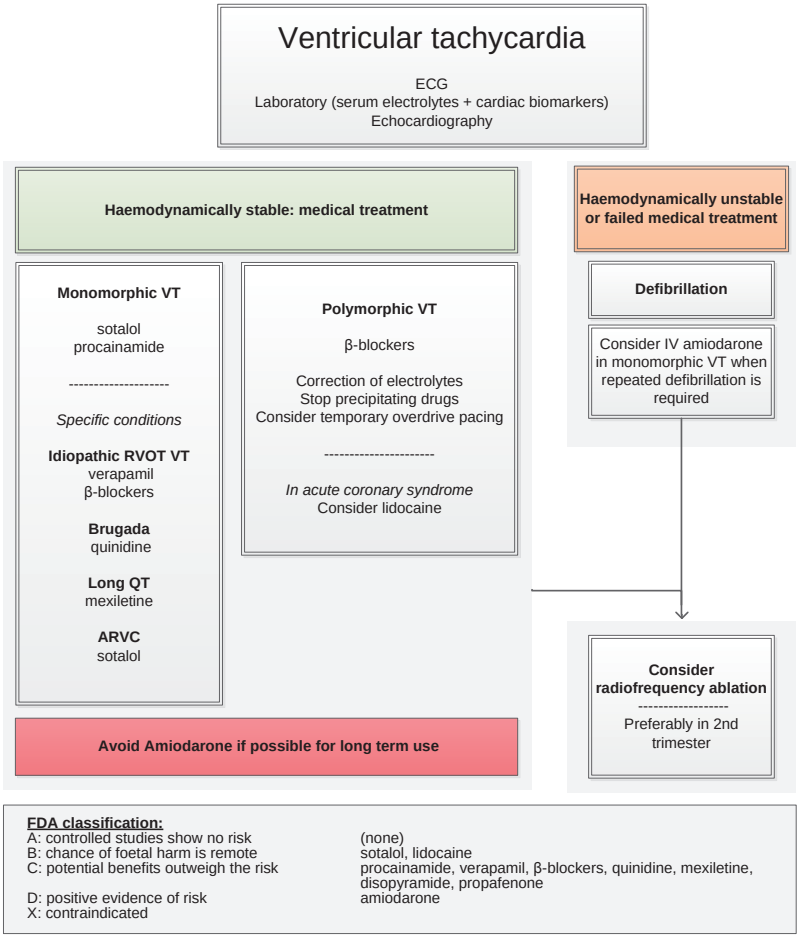


Figure 4 Management of ventricular tachycardia during pregnancy
FDA, US Food and Drug Administration.

effective for the prevention of recurrence. [43] The management of ventricular arrhythmias is summarised in **Figure 4.**[61,62]

In patients with a poorly tolerated and drug resistant tachyarrhythmia, radio frequency ablation can be considered. Evidence of safety during pregnancy is lacking and limited to case reports. The general advice is to perform the ablation in the second trimester if possible under ultrasound guidance, to minimise the potential influence of radiation on the fetus.[59,63] Limited experience with an implantable cardioverter-defibrillator (ICD) during pregnancy has revealed no major problems.[64-66] Reports of experience with ICD implantation during pregnancy are lacking, but a subcutaneous ICD is a promising technique as fluoroscopy is not required.[59]

Resuscitation

Several guidelines provide practical advices concerning the treatment of maternal cardiac arrest, which are summarised in **Table 1**. [67,68] Immediate basic life support and, when available, advanced life support should be initiated as outside pregnancy. After, 20 weeks, aortocaval compression should be avoided by left lateral manual displacement of the gravid uterus or by putting a wedge under her right side. If resuscitation is not successful by 4 minutes, emergency perimortem Caesarean section should be performed immediately with the aim of improving the chance of successful resuscitation by relieving aortocaval compression and creating a sudden autotransfusion of blood from the uteroplacental circulation. As an additional benefit it increases fetal survival as the uteroplacental perfusion is poor during arrest and chest compressions.[69,70]

The hand position for chest compressions has been studied recently. Previously, it was suggested that the hands should be placed in a higher sternal position during pregnancy

Table 1 Resuscitation of pregnant women

BLS and position	Supine position
	Chest compressions as usual
	Left uterine displacement to relieve aortocaval compression (in obvious gravid uterus)
	Remove fetal monitors
ACLS	As usual
	Provide intravenous therapy above diaphragm level
	Experienced provider for advanced airway placement is preferred
	If patient received IV/IO magnesium prearrest, stop magnesium and give IV/IO calcium chloride 10mL in 10% solution, or calcium gluconate 30mL in 10% solution

Table 1 Resuscitation of pregnant women (continued)

		Bleeding/DIC
		Embolism: coronary, pulmonary, amniotic
		Anesthetic complications
		Uterine atony
Possible contributing factors	BEAU-CHOPS	**C**ardiac disease (MI/ischemia/aortic dissection/cardiomyopathy)
		Hypertension/preeclampsia/eclampsia
		Other: differential diagnosis of standard ACLS guidelines
		Placenta abruptio/previa
		Sepsis
Obstetric intervention	If no ROSC by 4 minutes, consider performing immediate CS	
	Aim for delivery within 5 minutes of onset	
Post resuscitation		
Temperature management	Depends on individual	
	If used, than follow the guidelines in non-pregnant women and monitoring of fetus should take place	
Fetal considerations		
Post resuscitation continuous fetal monitoring	In case of maternal shock, the uterus/fetus is considered a non-vital organ: consider to perform emergency delivery	

Partly adapted and modified from AHA algorithm cardiac arrest in pregnancy basic and advanced life support 2015

on the basis that the maternal heart is displaced superiorly in the third trimester.[71] However, an MRI in 34 pregnant females, showed no significant displacement of the heart, suggesting that there is no need to adjust the hand position.

The outcome of cardiopulmonary resuscitation during pregnancy has been described by a population-based cohort study from Canada. The authors reported a survival of 36.9%, which was better than the survival in matched non-pregnant women.[72]

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction (AMI) occurs 3 to 4 times more often during pregnancy.[73] In population-based studies, the incidence ranges from 1:35,700 [74] to a more recent estimation of 1:17,000 [73] with a maternal mortality rate of 5-7%. Older pregnant women, in particular those >40 years, women with a history of pre-eclampsia and women with cardiovascular

risk factors, such as smoking and diabetes, are at highest risk of AMI.[73,74] Patients with known ischemic heart disease have a 10% risk of a cardiac event (cardiac arrest, heart failure, acute coronary syndrome, or ventricular arrhythmia) in a subsequent pregnancy.[75]

Diagnostic tests

The first presentation of an acute myocardial infarction may be cardiogenic shock (38%) or with a ventricular arrhythmia (12%).[76] The initial assessment in suspected acute coronary syndrome (ACS) should be the same as in non-pregnant patients as the time to intervention is as critical in an ST-elevation myocardial infarction (STEMI) as in non-pregnant patients. The key is to maintain a high index of suspicion of ACS and so to perform an ECG promptly. Subsequently, cardiac markers may support the diagnosis, as may wall motion abnormalities on echocardiography. Pregnancy does not influence Troponin I and an elevated level is indicative of an AMI.[77-79] Urgent imaging of the underlying coronary anatomy by coronary angiography is key to the further management of a STEMI; however, iatrogenic dissection has been reported. The most common diagnosis is an acute coronary dissection.[80] In a review of literature between 2006 and 2011, the angiogram showed: coronary dissection in 43% (mainly postpartum); atherosclerosis in 27%; coronary thrombus in 17% (both mainly in second or third trimester); normal in 9%; vasospasm in 2%; Tako tsubo in 2% (postpartum) of AMI.[76] The risk of iatrogenic dissection has lead some to advise a non-invasive approach in stable, low-risk women with a non-ST-elevation myocardial infarction.

Treatment of myocardial infarction

Treatment of pregnant women with an AMI depends on the aetiology and is further delineated in **Figure 5**. In case of a coronary dissection, thrombolysis should be avoided because of the increased risk of local bleeding, which might exacerbate the situation.[76] Percutaneous coronary intervention (PCI) is the first choice intervention. Although PCI does expose the fetus to radiation, the potential benefits outweigh the risks.[81] Most experience exists with bare-metal stents because knowledge on (prolonged) antiplatelet therapy such as clopidogrel in pregnancy is limited (FDA class B). The use of low dose aspirin is safe. Glycoprotein IIb/IIIa should be avoided as there is a lack of experience with its use during pregnancy. Nitrates are widely used in pregnant women for tocolysis and have proven to be safe.[82] Nifedipine is the calcium antagonist that has been used most frequently during pregnancy for hypertension and tocolysis[83] and is the drug of choice in women with vasospasm-associated complaints. Statins are currently contraindicated during pregnancy (FDA class X).

Coronary artery bypass grafting (CABG) is associated with high fetal loss, and should be performed after delivery if the fetus is viable. Cardiac surgery during pregnancy has mainly been reported in valvular or aortic disease while CABG experience consists of case reports

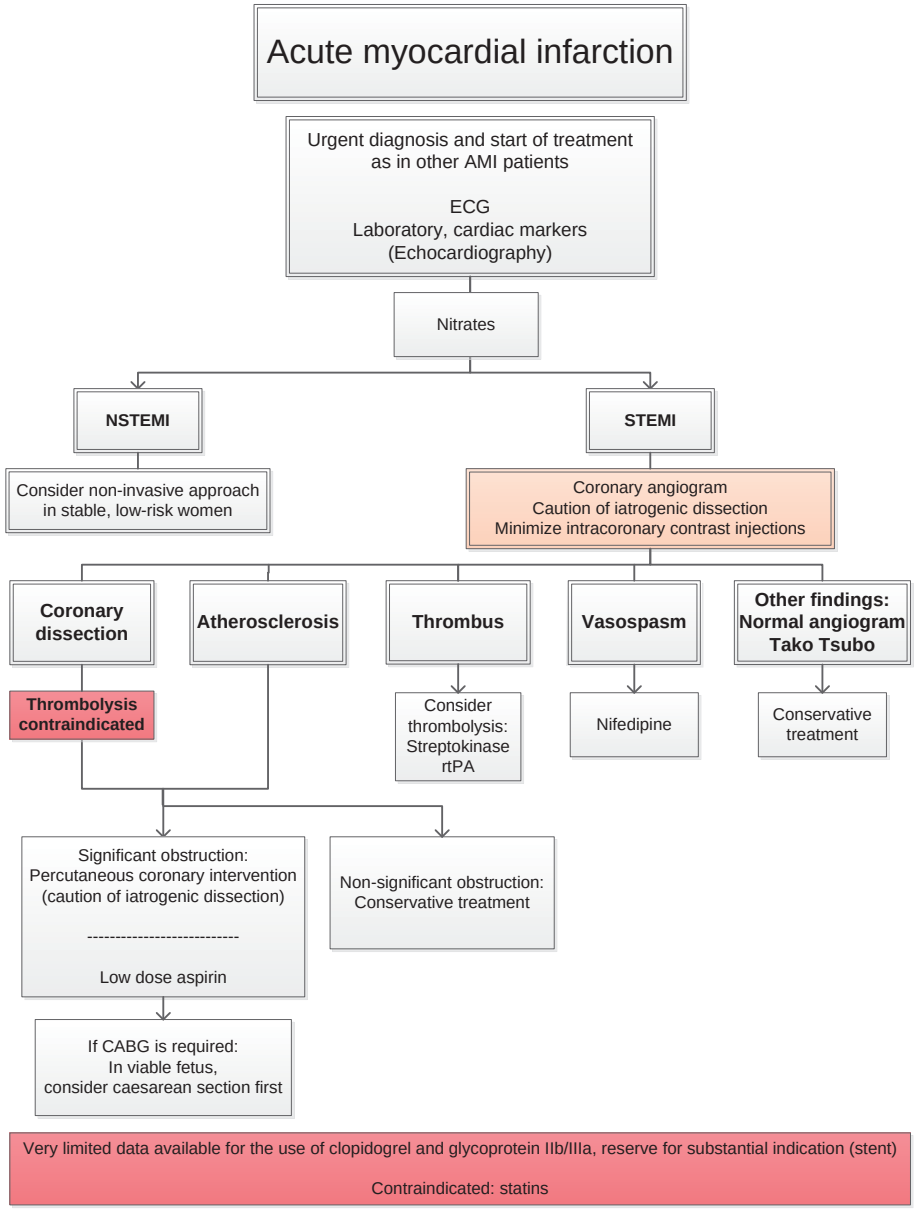


Figure 5 Management of acute myocardial infarction during pregnancy

CABG, coronary artery bypass grafting; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

only.[84] When unavoidable, the second trimester is probably the safest period and surgery is best performed in the left lateral position in normothermic condition with high pump flow.

In patients with a coronary thrombus, thrombolysis may be considered. The available evidence of thrombolysis during pregnancy for myocardial infarction is limited,[85] and is mainly based on the use of recombinant tissue plasminogen activator. Most experience during pregnancy for other reasons than AMI, involved the use of streptokinase.[86]

After the course of a successfully treated ischemic event during pregnancy, the preferred mode of delivery is vaginal, with Caesarean section reserved for obstetric indications.[87,88]

AORTIC DISSECTION

Incidence

Pregnancy induces not only induces marked haemodynamic changes, but it can also influence the integrity of the vessel wall. A morphological study showed marked fragmentation of reticular fibres in the tunica media of the aorta in pregnant women without aortic disease.[89] Also, smooth muscle cells in the aortic media were subject to both hypertrophy and hyperplasia, compared to non-pregnant women. These adaptations are usually well tolerated by healthy women: the incidence of aortic dissection in women of reproductive age is low (0.4 per 100,000 person years).[90] But women with aortic disease are at increased risk . It was the most important cause of cardiac maternal death in the UK 2006-8.[2] Women with Marfan syndrome, an autosomal dominant connective tissue disease, are at high risk with a reported rate of pregnancy-related aortic dissection of up to 4.5% in prospective studies [91-93] and up to 6.4% in retrospective studies.[94-98] Women with Loeys-Dietz,[99] vascular type Ehlers Danlos,[100] *SMAD3* mutation or Aneurysm Osteoarthritis Syndrome,[101,102] *ACTA2* mutation,[103] *TGFB3* mutation,[104] unspecified familial thoracic aortic aneurysm and dissection syndrome, Turner syndrome[105,106] and bicuspid aortic valve need careful preconception assessment and follow-up during pregnancy.[107] Studies reporting vascular complications during pregnancy in these women are scarce and small; the largest studies included mainly women with Marfan syndrome. Important and independent risk factors are initial aortic size and rate of diameter change during pregnancy.[98 5]

Management of type A aortic dissection (Figure 6)

As mortality due to aortic dissection remains high,[108] each symptomatic pregnant patient with known aortic disease or with signs or symptoms of aortic dissection should be immediately evaluated. Echocardiography should be done promptly, followed by computed tomography if necessary. Although MRI avoids fetal radiation exposure, CT can be performed much faster in the acute situation. The management of aortic dissection is the same as outside pregnancy and has been recently described in detail.[109] Recommendations

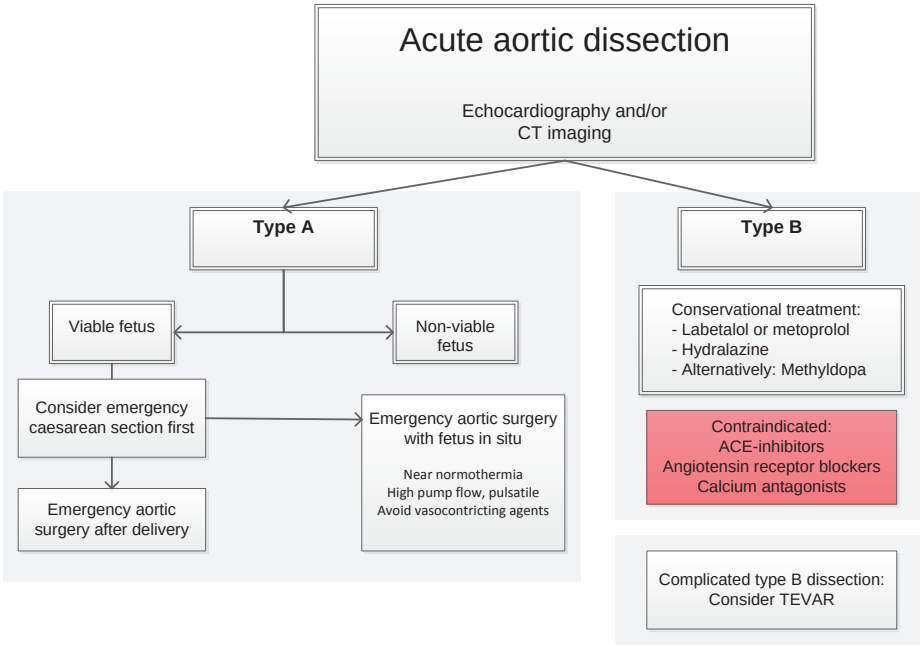


Figure 6 Management of acute aortic dissection during pregnancy

for the management of aortic dissection during pregnancy are limited, probably due to lack of evidence. Type A aortic dissection warrants emergency aortic surgery. Whether this should be performed before, together with or after delivery depends on the viability of the fetus and the local situation (**Figure 6**).[110] A high intraoperative fetal mortality rate has been reported in many case reports and series, suggesting that delivery before surgery in case of a viable fetus is preferable.[5]

Management of type B aortic dissection (Figure 6)

The guidelines recommend conservative management in type B aortic dissections. Strict blood pressure regulation is warranted, with bedrest until delivery. Fetal demise is as high as 35%, probably due to compromised uteroplacental perfusion.[111,112] Frequent monitoring of the aortic status by MRI should be done during follow-up. An alternative approach in complicated dissections of the descending aorta is an endovascular procedure (TEVAR). A few studies have reported favourable outcomes, some in acute type B aortic dissection.[113] Recently, a successful result with an endograft during pregnancy as a bridging step to an open repair was presented.[114] More studies are warranted to determine further the safety and efficacy of this approach is pregnant women.

Although the role of beta-blockers in prevention of aortic dissection is equivocal, the benefit of use in patients with aortic dissection is clearer. In the IRAD study, beta-blockers were associated with better survival mainly after type A aortic dissection.[115] During pregnancy, first choice beta-blockers are labetalol or metoprolol. Labetalol combines alpha and beta blocking properties, also reducing vascular resistance. During pregnancy, beta-blockers can be administered safely, with close monitoring of fetal growth.[116] Calcium channel blockers also reduced mortality but ACE inhibitors had no effect. Interestingly, calcium channel blockers exacerbated aneurysm growth in a mouse model outside pregnancy,[117] and should be used with caution. Hydralazine is an alternative, but again used with caution as it can induce marked hypotension and compromise uteroplacental perfusion.[118] Methyldopa, is another alternative, but there is little or no evidence on its use with aortic dissection.

MECHANICAL VALVE THROMBOSIS

Incidence

Pregnancy is a hypercoagulable state, with decreased levels of anticoagulant proteins such as protein S and increased levels of clotting factors and fibrinogen.[119,120] The risk of mechanical valve thrombosis is increased and can lead to a catastrophic outcome of both mother and child. The reported incidence of valve thrombosis varies from 3.7% to 9.4%.[121-127] Women with a mechanical valve in mitral or tricuspid position or with low flow due to ventricular dysfunction are at higher risk.[128] Meticulous attention to anticoagulation is essential, particularly when switching anticoagulant agents in the first trimester and peripartum period.[129]

Diagnostics and Management (Figure 7)

Valve thrombosis should be suspected in a pregnant patient with a mechanical valve prosthesis who presents with dyspnea, fatigue, palpitations, signs of heart failure, soft or absent prosthetic valve sounds or a systemic emboli. [129,130] Transthoracic echocardiography should be performed initially, if the diagnosis cannot be confirmed, and/or the patient is haemodynamically stable, a transoesophageal echocardiography (TOE) provides higher resolution images, better views of the atrial edge and a more accurate assessment of thrombus size, which predicts embolic risk.[131] If the diagnosis is still not clear, fluoroscopy might provide more insight with little radiation exposure to the fetus.[81,129]

In a haemodynamically unstable patient, with an obstructive thrombosis, emergency surgery is indicated, preceded by Caesarean section if the fetus is viable.[132] In a haemodynamically stable woman, different strategies are available, broadly in line with the approach of non-pregnant patients. Oral anticoagulant therapy or heparin may be continued and optimised in patients with a recent sub therapeutic INR, APTT or anti-Xa level, and non-obstructive left sided valve thrombosis.[5,133] In other patients, thrombolysis or surgery should

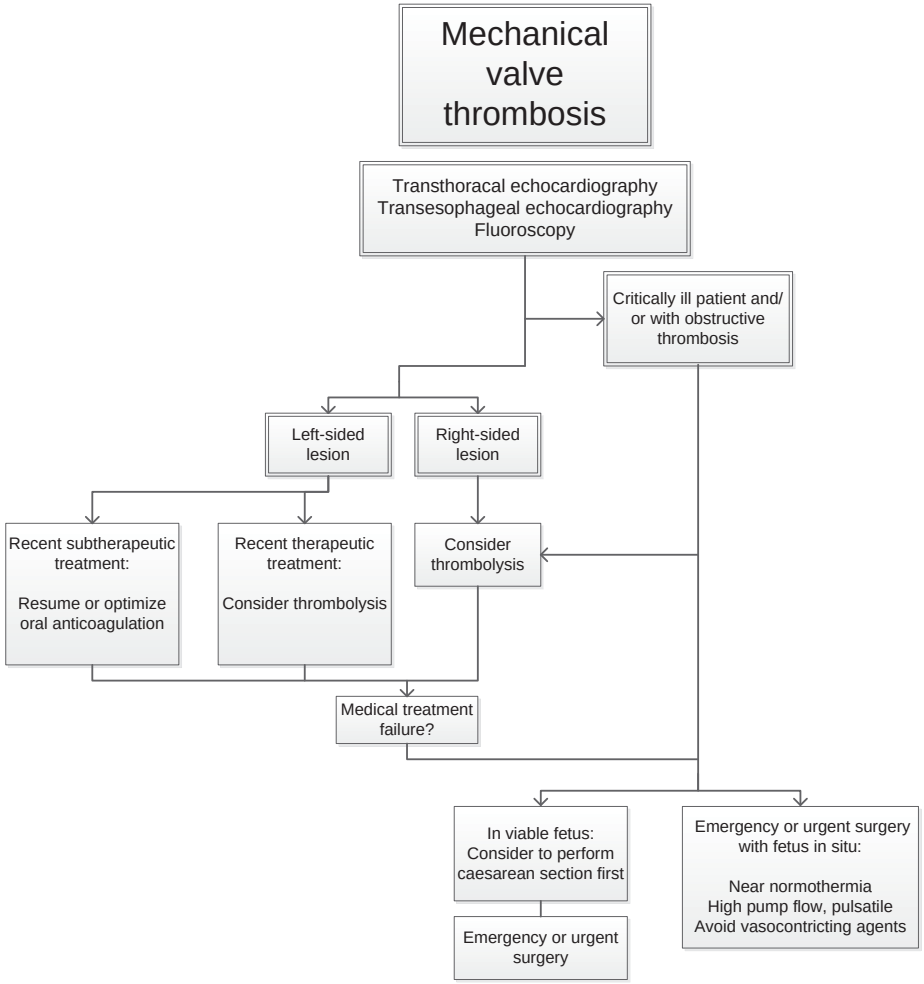


Figure 7 Management of mechanical valve thrombosis during pregnancy

be considered. Outside pregnancy, the advantages of thrombolysis make it the first choice, [134,135] however, randomised controlled trials are not yet available,[133] and the estimated sample size for a definitive studies will be hard to achieve.[134]

Fibrinolytic therapy either does not cross the placenta or does so to a limited extent, but experience is insufficient during human pregnancy, in particular in women with a mechanical valve. However, the main concern is that fibrinolysis may release systemic emboli, consequently, it should be avoided in patients with large, mobile thrombi, a left atrial thrombus as determined by TOE [130,136] or with evidence of a recent systemic embolus. Outside pregnancy, thrombolysis has shown to be an effective therapy, with high success rate in selected patients.[137] In patients with a right-sided valve thrombosis or when surgery

is contra-indicated in a severely ill patient, it is the first choice therapy.[132] One study of 24 consecutive women (2004-2012) with valve thrombosis during pregnancy, treated with a specific thrombolysis protocol had reassuring results.[130] Patients were treated with slow infusion of low dose tissue plasminogen activator (t-PA, 25 mg) over 6 hours, which was repeated up to 6 times, to a maximum dose of 150mg. The need for repeated treatment was determined by serial TOE, which is also current practice outside pregnancy.[136,138,139] Complete thrombolysis was achieved in all case with no maternal mortality, however five early pregnancies miscarried between 1 and 5 weeks after thrombolytic therapy. The results of this study are encouraging, but the authors also emphasise that these treatment options are complementary: high-risk patients or those with a contraindication to or failure of thrombolysis, should still be considered for surgical therapy. In addition, delivery of a woman with recent thrombolysis would be a very unattractive option.

Surgical valve replacement or thrombectomy is preferred in patients with obstructive thrombosis and those who are critically ill.[132] Also, immediate surgery may be considered for large and mobile thrombi. [140] However, surgery is associated with a high rate of fetal mortality (20-30%) and considerable morbidity,[141] although outcomes seem to have improved over time, [142-144] which is why a viable fetus should be delivered prior to surgery. Uteroplacental hypoperfusion is the reason for the high rate of fetal demise.[145] Normothermic surgery may have lower risks for the fetus than hypothermia.[146] Surgery should be performed in left lateral position and a higher pump flow is desired to maintain placental perfusion.

SUMMARY

A multidisciplinary, high-risk team should evaluate all pregnant women presenting with an acute cardiac event. Such events are potentially devastating if not recognised early and treated by experienced specialists. Management decisions are determined by the severity the maternal condition and fetal viability. The management of most cardiac complications is similar in pregnant and non-pregnant women. There are no large studies investigating the management of cardiac emergencies in pregnant women, hence, therapeutic strategies are mainly based on expert opinion and small observational studies. Risks and benefits for both mother and child need to be balanced, with the over-riding aim to achieve and maintain maternal haemodynamic stability.

KEY POINTS

- Treating pregnant women for a cardiac event means that there are two lives to save. Generally, the same therapeutic approach should be used in pregnant and non-

pregnant patients. If the fetus is viable, urgent delivery should be performed, if safe for the mother, as this will broaden the therapeutic options for the mother and reduce the cardiac burden.

- Heart failure is the most common cardiac complication during pregnancy. Preconception, cardiomyopathy and a WHO class of 3 or 4 are strong predictors of the occurrence of heart failure during pregnancy. The treatment of cardiac failure should be optimised before conception. ACE inhibitors and angiotensin receptor blockers are contraindicated, but otherwise, heart failure treatment is similar in pregnant and nonpregnant women.
- The main aim of treating arrhythmias is to achieve or maintain haemodynamic stability. Immediate defibrillation is therefore indicated in any haemodynamically unstable patient. Safety data for antiarrhythmic agents are scarse, but a life threatening maternal event justifies their use in the acute setting.
- In the case of a maternal cardiac arrest, if resuscitation is unsuccessful after 4 minutes, a perimortem emergency Caesarean section should be performed.
- Acute myocardial infarction is a potential catastrophic event and, in the case of a STEMI, the underlying coronary anatomy should be imaged urgently, as this has therapeutic implications. A coronary dissection is the most common cause, which is a contraindication for thrombolysis.
- An acute aortic dissection should be managed in the same way as in a non-pregnant patient. In Type A dissection, fetal viability determines whether delivery should be performed before aortic surgery.
- For a mechanical valve thrombosis, thrombolysis should be considered using the same criteria as used outside of pregnancy, namely: patients with a right-sided prosthesis, with recent subtherapeutic anticoagulation and non-critically ill patients. Emergency surgical replacement, performed directly after Caesarean section, is reserved for left-sided lesions and haemodynamically unstable patients.

REFERENCES

1. UN. The Millennium Development Goals report 2015. New York, 2015.
2. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
3. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006-2010. *Obstet Gynecol* 2015; **125**(1): 5-12.
4. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
5. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
6. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
7. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.
8. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.
9. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007; **49**(24): 2303-11.
10. Hameed A, Karaalp IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001; **37**(3): 893-9.
11. Lesniak-Sobelga A, Tracz W, KostKiewicz M, Podolec P, Pasowicz M. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases--maternal and fetal outcome. *Int J Cardiol* 2004; **94**(1): 15-23.
12. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol* 2003; **91**(11): 1382-5.
13. Yap SC, Drenthen W, Pieper PG, et al. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol* 2008; **126**(2): 240-6.
14. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
15. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. *Br Med J (Clin Res Ed)* 1987; **295**(6607): 1169-72.
16. Bakacak M, Serin S, Ercan O, Kostu B, Bakacak Z, Kiran H. Association of serum N-terminal pro-brain natriuretic peptide levels with the severity of preeclampsia. *Journal of Maternal-Fetal & Neonatal Medicine* 2015: 1-5.
17. Giannubilo SR, Cecchi S, Tidu E, Ciavattini A. Maternal NT-proBNP in chronic hypertensive pregnancies and superimposed preeclampsia. *Int J Cardiol* 2014; **176**(3): 1227-9.
18. Kampman MA, Balci A, van Veldhuisen DJ, et al. N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. *Eur Heart J* 2014; **35**(11): 708-15.
19. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011; **58**(4): 709-15.

20. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010; **376**(9741): 631-44.
21. Verlohren S, Melchiorre K, Khalil A, Thilaganathan B. Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. *Ultrasound Obstet Gynecol* 2014; **44**(3): 293-8.
22. Hilfiker-Kleiner D, Westhoff-Bleck M, Gunter HH, et al. A management algorithm for acute heart failure in pregnancy. The Hannover experience. *Eur Heart J* 2015; **36**(13): 769-70.
23. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**(14): 1787-847.
24. Writing Committee M, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**(16): e240-327.
25. Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. *Br Med J (Clin Res Ed)* 1985; **290**(6461): 17-23.
26. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; **354**(23): 2443-51.
27. Murali S, Baldisseri MR. Peripartum cardiomyopathy. *Crit Care Med* 2005; **33**(10 Suppl): S340-6.
28. Biteker M, Duran NE, Kaya H, et al. Effect of levosimendan and predictors of recovery in patients with peripartum cardiomyopathy, a randomized clinical trial. *Clin Res Cardiol* 2011; **100**(7): 571-7.
29. Benezet-Mazuecos J, de la Hera J. Peripartum cardiomyopathy: a new successful setting for levosimendan. *Int J Cardiol* 2008; **123**(3): 346-7.
30. Asfour V, Murphy MO, Attia R. Is vaginal delivery or caesarean section the safer mode of delivery in patients with adult congenital heart disease? *Interact Cardiovasc Thorac Surg* 2013; **17**(1): 144-50.
31. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, et al. Is a planned caesarean section in women with cardiac disease beneficial? *Heart* 2015; **101**(7): 530-6.
32. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. *J Am Coll Cardiol* 2015; **65**(18): 1976-97.
33. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009; **30**(3): 256-65.
34. Budts W, Van Pelt N, Gillyns H, Gewillig M, Van De Werf F, Janssens S. Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome. *Heart* 2001; **86**(5): 553-8.
35. Leuchte HH, Schwaiblmair M, Baumgartner RA, Neurohr CF, Kolbe T, Behr J. Hemodynamic response to sildenafil, nitric oxide, and iloprost in primary pulmonary hypertension. *Chest* 2004; **125**(2): 580-6.
36. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *European Journal of Heart Failure* 2010; **12**(8): 767-78.
37. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, et al. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. *Circulation* 2010; **121**(20): 2169-75.
38. Sliwa K, Blauwet L, Tibazarwa K, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation* 2010; **121**(13): 1465-73.
39. Haghikia A, Podewski E, Libhaber E, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. *Basic Res Cardiol* 2013; **108**(4): 366.

40. Shotan A, Ostrzega E, Mehra A, Johnson JV, Elkayam U. Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. *Am J Cardiol* 1997; **79**(8): 1061-4.
41. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006; **97**(8): 1206-12.
42. Salam AM, Ertekin E, van Hagen IM, et al. Atrial Fibrillation or Flutter During Pregnancy in Patients With Structural Heart DiseaseData From the ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC: Clinical Electrophysiology* 2015; **1**(4): 284-92.
43. Tan HL, Lie KI. Treatment of tachyarrhythmias during pregnancy and lactation. *Eur Heart J* 2001; **22**(6): 458-64.
44. Elkayam U, Goodwin TM. Adenosine therapy for supraventricular tachycardia during pregnancy. *Am J Cardiol* 1995; **75**(7): 521-3.
45. Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. *Drug Saf* 1999; **20**(1): 85-94.
46. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007; **18**(5): 545-7.
47. Barnes EJ, Eben F, Patterson D. Direct current cardioversion during pregnancy should be performed with facilities available for fetal monitoring and emergency caesarean section. *BJOG* 2002; **109**(12): 1406-7.
48. Widerhorn J, Bhandari AK, Bughi S, Rahimtoola SH, Elkayam U. Fetal and neonatal adverse effects profile of amiodarone treatment during pregnancy. *Am Heart J* 1991; **122**(4 Pt 1): 1162-6.
49. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**(21): 2719-47.
50. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999; **33**(6): 1637-41.
51. Pauli RM. Mechanism of bone and cartilage maldevelopment in the warfarin embryopathy. *Pathol Immunopathol Res* 1988; **7**(1-2): 107-12.
52. Hoeltzenbein M, Beck E, Meixner K, Schaefer C, Kreutz R. Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre. *Clin Res Cardiol* 2015.
53. Siu SC, Sermer M, Harrison DA, et al. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997; **96**(9): 2789-94.
54. Brodsky M, Doria R, Allen B, Sato D, Thomas G, Sada M. New-onset ventricular tachycardia during pregnancy. *Am Heart J* 1992; **123**(4 Pt 1): 933-41.
55. Sharif-Kazemi MB, Emkanjoo Z, Tavoosi A, et al. Electrical storm in Brugada syndrome during pregnancy. *Pacing Clin Electrophysiol* 2011; **34**(2): e18-21.
56. Nishimoto O, Matsuda M, Nakamoto K, et al. Peripartum cardiomyopathy presenting with syncope due to Torsades de pointes: a case of long QT syndrome with a novel KCNH2 mutation. *Intern Med* 2012; **51**(5): 461-4.
57. Gemici G, Tezcan H, Fak AS, Oktay A. Peripartum cardiomyopathy presenting with repetitive monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol* 2004; **27**(4): 557-8.
58. Seth R, Moss AJ, McNitt S, et al. Long QT syndrome and pregnancy. *J Am Coll Cardiol* 2007; **49**(10): 1092-8.

59. Authors/Task Force M, Priori SG, Blomstrom-Lundqvist C, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015.
60. Allen NM, Page RL. Procainamide administration during pregnancy. *Clin Pharm* 1993; **12**(1): 58-60.
61. Adamson DL, Nelson-Piercy C. Managing palpitations and arrhythmias during pregnancy. *Heart* 2007; **93**(12): 1630-6.
62. van den Bosch AE, Ruys TP, Roos-Hesselink JW. Use and impact of cardiac medication during pregnancy. *Future Cardiol* 2015; **11**(1): 89-100.
63. Damilakis J, Theocharopoulos N, Perisinakis K, et al. Conceptus radiation dose and risk from cardiac catheter ablation procedures. *Circulation* 2001; **104**(8): 893-7.
64. Natale A, Davidson T, Geiger MJ, Newby K. Implantable cardioverter-defibrillators and pregnancy: a safe combination? *Circulation* 1997; **96**(9): 2808-12.
65. Boule S, Ovart L, Marquie C, et al. Pregnancy in women with an implantable cardioverter-defibrillator: is it safe? *Europace* 2014; **16**(11): 1587-94.
66. Schuler PK, Herrey A, Wade A, et al. Pregnancy outcome and management of women with an implantable cardioverter defibrillator: a single centre experience. *Europace* 2012; **14**(12): 1740-5.
67. Lipman S, Cohen S, Einav S, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the management of cardiac arrest in pregnancy. *Anesth Analg* 2014; **118**(5): 1003-16.
68. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac Arrest in Pregnancy: A Scientific Statement From the American Heart Association. *Circulation* 2015; **132**(18): 1747-73.
69. Katz V, Balderston K, DeFreest M. Perimortem cesarean delivery: were our assumptions correct? *Am J Obstet Gynecol* 2005; **192**(6): 1916-20; discussion 20-1.
70. Dijkman A, Huisman CM, Smit M, et al. Cardiac arrest in pregnancy: increasing use of perimortem caesarean section due to emergency skills training? *BJOG* 2010; **117**(3): 282-7.
71. Holmes S, Kirkpatrick ID, Zelop CM, Jassal DS. MRI evaluation of maternal cardiac displacement in pregnancy: implications for cardiopulmonary resuscitation. *Am J Obstet Gynecol* 2015; **213**(3): 401 e1-5.
72. Lavecchia M, Abenhaim HA. Cardiopulmonary resuscitation of pregnant women in the emergency department. *Resuscitation* 2015; **91**: 104-7.
73. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation* 2006; **113**(12): 1564-71.
74. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. *Obstet Gynecol* 2005; **105**(3): 480-4.
75. Burchill LJ, Lameijer H, Roos-Hesselink JW, et al. Pregnancy risks in women with pre-existing coronary artery disease, or following acute coronary syndrome. *Heart* 2015; **101**(7): 525-9.
76. Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. *Circulation* 2014; **129**(16): 1695-702.
77. Shivvers SA, Wians FH, Jr., Keffer JH, Ramin SM. Maternal cardiac troponin I levels during normal labor and delivery. *Am J Obstet Gynecol* 1999; **180**(1 Pt 1): 122.
78. Joyal D, Leya F, Koh M, et al. Troponin I levels in patients with preeclampsia. *Am J Med* 2007; **120**(9): 819 e13-4.
79. Aydin C, Baloglu A, Cetinkaya B, Yavuzcan A. Cardiac troponin levels in pregnant women with severe pre-eclampsia. *J Obstet Gynaecol* 2009; **29**(7): 621-3.

80. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996; **125**(9): 751-62.
81. Colletti PM, Lee KH, Elkayam U. Cardiovascular imaging of the pregnant patient. *AJR Am J Roentgenol* 2013; **200**(3): 515-21.
82. Schleussner E, Moller A, Gross W, et al. Maternal and fetal side effects of tocolysis using transdermal nitroglycerin or intravenous fenoterol combined with magnesium sulfate. *Eur J Obstet Gynecol Reprod Biol* 2003; **106**(1): 14-9.
83. Magee LA, Schick B, Donnenfeld AE, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. *Am J Obstet Gynecol* 1996; **174**(3): 823-8.
84. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *J Am Coll Cardiol* 2008; **52**(3): 171-80.
85. Leonhardt G, Gaul C, Nietsch HH, Buerke M, Schleussner E. Thrombolytic therapy in pregnancy. *J Thromb Thrombolysis* 2006; **21**(3): 271-6.
86. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**(2 Suppl): e691S-736S.
87. Cohen WR, Steinman T, Patsner B, Snyder D, Satwicz P, Monroy P. Acute myocardial infarction in a pregnant woman at term. *JAMA* 1983; **250**(16): 2179-81.
88. Ray P, Murphy GJ, Shutt LE. Recognition and management of maternal cardiac disease in pregnancy. *Br J Anaesth* 2004; **93**(3): 428-39.
89. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83**(4): 336-41.
90. Thalmann M, Sodeck GH, Domanovits H, et al. Acute type A aortic dissection and pregnancy: a population-based study. *Eur J Cardiothorac Surg* 2011; **39**(6): e159-63.
91. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995; **173**(5): 1599-606.
92. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005; **26**(9): 914-20.
93. Omnes S, Jondeau G, Detaint D, et al. Pregnancy outcomes among women with Marfan syndrome. *Int J Gynecol Obstet* 2013; **122**(3): 219-23.
94. Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981; **71**(5): 784-90.
95. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997; **104**(2): 201-6.
96. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. *Eur J Obstet Gynecol Reprod Biol* 2001; **98**(1): 28-35.
97. Pacini L, Digne F, Boumendil A, et al. Maternal complication of pregnancy in Marfan syndrome. *Int J Cardiol* 2009; **136**(2): 156-61.
98. Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012; **60**(3): 224-9.
99. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006; **355**(8): 788-98.
100. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**(10): 673-80.

101. van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat Genet* 2011; **43**(2): 121-6.
102. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol* 2012; **60**(5): 397-403.
103. Regalado ES, Guo DC, Estrera AL, Buja LM, Milewicz DM. Acute aortic dissections with pregnancy in women with ACTA2 mutations. *American Journal of Medical Genetics Part A* 2014; **164A**(1): 106-12.
104. Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF-beta ligand, TGFB3, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol* 2015; **65**(13): 1324-36.
105. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab* 2011; **96**(2): E260-7.
106. Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. *J Med Genet* 2007; **44**(12): 745-9.
107. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. *JAMA* 2008; **300**(11): 1317-25.
108. Pape LA, Awais M, Woznicki EM, et al. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol* 2015; **66**(4): 350-8.
109. Goldfinger JZ, Halperin JL, Marin ML, Stewart AS, Eagle KA, Fuster V. Thoracic aortic aneurysm and dissection. *J Am Coll Cardiol* 2014; **64**(16): 1725-39.
110. Immer FF, Bansi AG, Immer-Bansi AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003; **76**(1): 309-14.
111. Rajagopalan S, Nwazota N, Chandrasekhar S. Outcomes in pregnant women with acute aortic dissections: a review of the literature from 2003 to 2013. *Int J Obstet Anesth* 2014; **23**(4): 348-56.
112. Zeebregts CJ, Schepens MA, Hameeteman TM, Morshuis WJ, de la Riviere AB. Acute aortic dissection complicating pregnancy. *Ann Thorac Surg* 1997; **64**(5): 1345-8.
113. Waterman AL, Feezor RJ, Lee WA, et al. Endovascular treatment of acute and chronic aortic pathology in patients with Marfan syndrome. *J Vasc Surg* 2012; **55**(5): 1234-40; disucssion 40-1.
114. De Martino RR, Johnstone J, Baldwin EA, Brost BC, Connolly HM, Pochettino A. Endograft as Bridge to Open Repair for Ruptured Thoracic Aneurysm in a Pregnant Marfan Patient. *Ann Thorac Surg* 2015; **100**(1): 304-7.
115. Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2012; **109**(1): 122-7.
116. Ruys TP, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. *Int J Cardiol* 2014; **177**(1): 124-8.
117. Doyle JJ, Doyle AJ, Wilson NK, et al. A deleterious gene-by-environment interaction imposed by calcium channel blockers in Marfan syndrome. *Elife* 2015; **4**.
118. Blumenfeld JD, Laragh JH. Management of hypertensive crises: the scientific basis for treatment decisions. *Am J Hypertens* 2001; **14**(11 Pt 1): 1154-67.
119. Cerneca F, Ricci G, Simeone R, Malisano M, Alberico S, Guaschino S. Coagulation and fibrinolysis changes in normal pregnancy. Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis. *Eur J Obstet Gynecol Reprod Biol* 1997; **73**(1): 31-6.

120. de Boer K, ten Cate JW, Sturk A, Borm JJ, Treffers PE. Enhanced thrombin generation in normal and hypertensive pregnancy. *Am J Obstet Gynecol* 1989; **160**(1): 95-100.
121. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; **160**(2): 191-6.
122. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000; **107**(2): 245-53.
123. Ashour ZA, Shawky HA, Hassan Hussein M. Outcome of pregnancy in women with mechanical valves. *Tex Heart Inst J* 2000; **27**(3): 240-5.
124. Nassar AH, Hobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM. Pregnancy outcome in women with prosthetic heart valves. *Am J Obstet Gynecol* 2004; **191**(3): 1009-13.
125. Mazibuko B, Ramnarain H, Moodley J. An audit of pregnant women with prosthetic heart valves at a tertiary hospital in South Africa: a five-year experience. *Cardiovasc J Afr* 2012; **23**(4): 216-21.
126. Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anti-coagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. *BJOG* 2012; **119**(8): 1008-13; discussion 12-3.
127. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015; **132**(2): 132-42.
128. Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. *Heart* 2007; **93**(1): 137-42.
129. Deviri E, Sareli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. *J Am Coll Cardiol* 1991; **17**(3): 646-50.
130. Ozkan M, Cakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation* 2013; **128**(5): 532-40.
131. Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *J Am Coll Cardiol* 2004; **43**(1): 77-84.
132. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**(19): 2451-96.
133. Gunduz S, Yesin M, Gursoy MO, Kalcik M, Ozkan M. Management of Patients With Prosthetic Valve Thrombosis After Failed Thrombolytic Therapy. *J Am Coll Cardiol* 2015; **66**(7): 875-6.
134. Caceres-Loriga FM, de Sousa MR, de Castilho FM. The Dilemma of Management of Prosthetic Valve Thrombosis: Thrombolysis or Surgery. *J Card Surg* 2015.
135. Keuleers S, Herijgers P, Herregods MC, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. *Am J Cardiol* 2011; **107**(2): 275-9.
136. Ozkan M, Gunduz S, Biteker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *JACC Cardiovasc Imaging* 2013; **6**(2): 206-16.
137. Ozkan M, Gunduz S, Gursoy OM, et al. Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcomE: The Ultra-slow PROMETEE trial. *Am Heart J* 2015; **170**(2): 409-18.
138. Dogan V, Basaran O, Altun I, Biteker M. Transesophageal echocardiography guidance is essential in the management of prosthetic valve thrombosis. *Int J Cardiol* 2014; **177**(3): 1103-4.

139. Biteker M, Duran NE, Gunduz S, et al. Thrombolysis of an acute prosthetic mitral valve thrombosis presented with cardiogenic shock under the guidance of continuous transoesophageal monitoring. *Eur J Echocardiogr* 2009; **10**(3): 468-70.
140. Roudaut R, Lafitte S, Roudaut MF, et al. Management of prosthetic heart valve obstruction: fibrinolysis versus surgery. Early results and long-term follow-up in a single-centre study of 263 cases. *Arch Cardiovasc Dis* 2009; **102**(4): 269-77.
141. Weiss BM, von Segesser LK, Alon E, Seifert B, Turina MI. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984-1996. *Am J Obstet Gynecol* 1998; **179**(6 Pt 1): 1643-53.
142. John AS, Gurley F, Schaff HV, et al. Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg* 2011; **91**(4): 1191-6.
143. Elassy SM, Elmidany AA, Elbawab HY. Urgent cardiac surgery during pregnancy: a continuous challenge. *Ann Thorac Surg* 2014; **97**(5): 1624-9.
144. Patel A, Asopa S, Tang AT, Ohri SK. Cardiac surgery during pregnancy. *Tex Heart Inst J* 2008; **35**(3): 307-12.
145. Goldstein I, Jakobi P, Gutterman E, Milo S. Umbilical artery flow velocity during maternal cardiopulmonary bypass. *Ann Thorac Surg* 1995; **60**(4): 1116-8.
146. Pomini F, Mercogliano D, Cavalletti C, Caruso A, Pomini P. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg* 1996; **61**(1): 259-68.

CHAPTER 6

Influence of socioeconomic factors on pregnancy outcome in women with structural heart disease: data from ROPAC, an ESC registry

Iris M. van Hagen
Sara Baart
Rebekka Fong Soe Khioe
Karen Sliwa
Nasser Taha
Malgorzata Lelonek
Luigi Tavazzi
Aldo Maggioni
Mark R. Johnson
Nikos Maniadakis
Richard Fordham
Roger Hall
Jolien W. Roos-Hesselink

Submitted

ABSTRACT

Aims Cardiac disease is the leading cause of indirect maternal mortality. The aim of this study was to analyse to what extent socioeconomic factors at a country level, such as income inequality (Gini coefficient), health expenditure, and birth rate, influence the outcome of pregnancy in women with heart disease.

Methods and results The Registry Of Pregnancy And Cardiac disease (ROPAC) is a global prospective registry. For this analysis, countries that enrolled at least 10 patients were included. A total of 30 countries enrolled 2924 patients from 89 centres. Countries were grouped into human development index (HDI) categories, with 74% of the women living in countries with a very high HDI. A combined cardiac endpoint included maternal cardiac death, arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason or a cardiac intervention; which occurred in 645 women (22.1%). Age, New York Heart Association, and modified World Health Organization risk classification, were associated with the combined endpoint and explained 37% of variance in outcome in a three-level model (patient-centre-country). Gini coefficient and country-specific birth rate explained an additional 4%. There were large differences between the individual countries, but the need for multilevel modelling to account for these differences disappeared after adjustment for patient characteristics, Gini and country specific birth rate.

Conclusion While there are definite interregional differences in pregnancy outcome in women with cardiac disease, these differences seem to be mainly driven by individual patient characteristics. Adjustment for country characteristics refined the results to a limited extent, but maternal condition seems to be the main determinant of outcome.

INTRODUCTION

Cardiac disease is an important cause of maternal mortality and morbidity. An increasing amount of research on this topic has been published in the past decades, mainly from advanced but also from emerging countries. From pregnancy research in the general population it is known that outcome does depend on demography [1,2]. The Registry Of Pregnancy And Cardiac disease (ROPAC) is a global cohort including pregnant patients from both advanced and emerging countries. Several analyses from ROPAC data have been published with marked differences between advanced and emerging countries[3-5]. These differences could be partly explained by variations in underlying cardiac condition, with acquired valvular disease being more prevalent in emerging countries[6] and congenital heart disease in advanced countries. In addition, the demographic differences may also influence outcome. For instance, in some cultures women gain status by having (many) children and thus they may be reluctant to take a doctor's advice to avoid pregnancy. Also, there is widespread difference in the availability of health care and access to female contraception. Although tertiary care is provided in the urban areas, many women in less developed countries are from rural areas and, consequently, might present with pregnancy complaints much later than their peers from rural areas in countries with more advanced economies[7].

Interpretation of ROPAC results needs to be done with caution in the light of these differences. Insights in country level socioeconomic data and the associated pregnancy outcomes will help interpreting existing and future analyses. Such an analysis could define the influence of socioeconomic background on pregnancy outcome exerted by the countries of residence, the alternative approach, of an in depth analysis of individual socioeconomic data, is not possible.

The aim of this study was to elucidate the interregional differences in the countries contributing to ROPAC, by analysing to what extent socioeconomic factors on country level, such as GDP, income distribution (Gini-coefficient), HDI, health expenditure, birth rate, number of hospital beds and schooling, influence the outcome of pregnancy in women with heart disease. We hypothesized that country level socioeconomic indices do influence pregnancy outcome and that cardiac status (such as severity of disease and NYHA) affects the outcome of mother and baby to a greater extent.

METHODS

The Registry Of Pregnancy And Cardiac disease (ROPAC) is an ongoing prospective worldwide registry that includes all consecutive pregnant women with structural heart disease. Study design and methods have been described in detail previously[3]. Patient enrollment

started from January 2008 and for this interim analysis we included patients with a term date up to October 2013, and 6 months follow-up in April 2014.

Data

The patient characteristics collected at baseline (before pregnancy) included age, ECG rhythm, New York Heart Association (NYHA) functional classification, diagnosis, risk factors for cardiovascular disease (smoking, diabetes, hypertension), previous interventions, medication, parity, obstetric history and if available echocardiographic parameters. Every patient was stratified according to the modified World Health Organization (WHO) classification, as stated in the latest guidelines[8,9] by two authors (IH;JRH). Modified WHO-class I implies no increased risk of events during pregnancy, compared to the general pregnant population. Modified WHO-class II has a small increased risk, class II-III a moderate increased risk, and class III has a 'significantly' increased risk. Class IV bears an unacceptable high risk of complications and consensus suggests that pregnancy should be avoided.

For the current study, pre-pregnancy patient characteristics that were included in statistical modelling were age, nulliparity, modified WHO class, NYHA class and signs of heart failure.

Socioeconomic data on patient level were not available. As a result, pre-defined socioeconomic factors were assigned to represent country characteristics, and included: human development index (HDI), Gini-coefficient, health expenditure, schooling, gross domestic product per capita based on purchasing power parity (GDP), birth rate per 1,000, and hospital beds per 1,000. Definitions and sources of these characteristics are listed in **Supplementary Material Appendix 1**. HDI is a combination of three factors; life expectancy from birth, mean years of schooling and the country standard of living. As these factors correlate with the other predefined country characteristics, the HDI was not included in further modelling. The HDI categories (low, medium, high, very high) were only used to categorize and understand the frequency of events within the different categories.

Endpoints

The following endpoints that occurred up to one week after delivery were studied: combined cardiac endpoint (including maternal cardiac death, arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason, or a cardiac intervention), heart failure, fetal or neonatal mortality (excluding miscarriage in the first trimester), and small-for-gestational-age (SGA, birth weight $<10^{th}$ percentile). All-cause mortality data was also collected, but not used for statistical modelling due to low numbers. Heart failure was defined according to ACC/AHA guidelines[10], as a clinical syndrome that is characterised by specific symptoms (dyspnea and fatigue) and signs (of fluid retention, such as oedema, rales) on the physical examination as judged by the treating cardiologist. The heart failure episode was only registered when

signs or symptoms of HF were present which required new treatment, change of treatment or hospital admission.

Statistical analysis

Categorical variable differences were tested using chi-square tests and are presented as percentages. Continuous variables are presented as mean and standard deviation (SD), or as median and first and third quartile (Q1-Q3), as appropriate. Differences were tested using Student's t-tests.

Generalized linear mixed models (GLMM) were used as a result of the multilevel structure in the data. The ROPAC database consists of three levels: patients (level 1) were nested in centres (level 2), and centres were nested in countries (level 3). To account for differences in outcome between countries and between centres, random effects for country and centre were added to the model. Patient and country characteristics were entered as fixed effects and those with a significant trend ($p<0.10$) in univariable analysis were assessed in multivariable analysis. Countries that included less than 10 patients were excluded from this study.

To determine the influence of fixed and random effects in our cohort, we further analysed the model for the combined cardiac endpoint. A conditional R^2 (for GLMM) was derived from the model before and after including the fixed effects (patient characteristics, followed by country characteristics) [11]. This is an estimate of the percentage explained variance by the complete model (fixed and random effects). The random effect estimates of the individual countries for the combined cardiac endpoint were plotted with 95% confidence intervals (caterpillar plot), unadjusted and adjusted for the fixed effects.

The rate of missing patient and country characteristics was relatively low, and therefore a complete case analysis approach was taken (96%). All analyses, except for multilevel modelling, were performed in SPSS version 21.0 (IBM Corp., Armonk, NY). Multilevel modelling was performed in R version 3.1, package lme4 [12].

RESULTS

From January 2008 until April 2014, 2966 patients were included, from 99 centres in 39 countries. Nine countries enrolled less than 10 patients, and were excluded. The remaining 30 countries enrolled 2924 patients from 89 centres. An overview of the countries is presented and arranged according to the HDI categories in **Table 1**. Socioeconomic indexes, including HDI, Gini coefficient, health expenditure, schooling, GDP, birth rate per 1,000 and hospital beds per 1,000 are presented for all countries in *Supplemental material Table S1*.

Baseline characteristics are presented for patients per HDI category (**Table 2**). Maternal age at conception was higher in women from countries with a very high HDI, while these women were also more often nulliparous. Fewer women from countries with a medium or

Table 1 Human development index categories

	Low	Medium	High	Very high
Human development index*	<0.555	0.555-0.699	0.700-0.799	≥0.800
		(n=634)	(n=118)	(n=2130)
Countries in ROPAC		Egypt	Azerbaijan	Argentina
		South-Africa	Russian Federation	Australia
				Austria
				Belgium
				Canada
				Czech Republic
				France
				Greece
				Germany
				Hungary
				Italy
				Japan
				Lithuania
				Israel
				Malta
				Netherlands
				Norway
				Poland
				Portugal
				Slovenia
				Spain
				Sweden
				Switzerland
				United Arab Emirates
				United Kingdom
				United States
		<10 patients per country	*<10 patients per country*	*<10 patients per country*
			Brazil	Ireland
			Bulgaria	
			Georgia	
			Macedonia	
			Romania	
			Serbia&Montenegro	
			Turkey	

*Human development index for female according to United Nations Development Report 2013. No value was available for Bosnia&Herzegovina (<10 inclusions)

Table 2 Baseline characteristics

	Total*	Low HDI	Medium HDI	High HDI	Very High HDI	p
N (% of total inclusions)	2966	0	634 21.7%	118 4.0%	2172 74.3%	
Mean age (sd)	29.3 ±5.6		27.7 ±5.9	26.4 ±5.3	29.9 ±5.4	<0.001
Nulliparous	1334 45.2%		160 25.2%	57 48.3%	1099 50.7%	<0.001
Pre-existent hypertension	188 6.5%		26 4.1%	18 16.2%	139 6.5%	<0.001
Current smoker	110 4.3%		11 1.8%	4 3.6%	95 5.3%	0.001
Pre-existent diabetes	46 1.6%		10 1.6%	1 0.8%	34 1.6%	1.000
Prior cardiac intervention	1585 53.6%		223 35.2%	44 37.3%	1304 60.1%	<0.001
NYHA functional class						<0.001
NYHA I	2154 74.1%		399 62.9%	48 42.1%	1686 79.3%	
NYHA II	659 22.7%		191 30.1%	62 54.4%	395 18.6%	
NYHA III	86 3.0%		42 6.6%	4 3.5%	39 1.8%	
NYHA IV	7 0.2%		2 0.3%	0 0.0%	5 0.2%	
Signs of HF before pregnancy	283 9.7%		138 21.8%	66 58.4%	74 3.5%	<0.001
AF before pregnancy	68 2.3%		47 7.4%	1 0.9%	20 0.9%	<0.001
Prior medication	824 27.9%		292 46.1%	17 14.4%	510 23.5%	<0.001
Beta-blocker	365 12.3%		75 11.8%	7 5.9%	280 12.9%	0.073
Anti-arrhythmic	90 3.0%		58 9.1%	3 2.6%	28 1.3%	<0.001
ACE-inhibitor	116 3.9%		38 6.0%	9 7.6%	67 3.1%	0.001
Diuretic	170 5.8%		93 14.7%	7 5.9%	68 3.1%	<0.001
Cardiac diagnosis						<0.001
Congenital heart disease	1654 55.9%		88 13.9%	91 77.1%	1458 67.1%	
Valvular heart disease	942 31.8%		489 77.1%	15 12.7%	424 19.5%	
Ischemic heart disease	47 1.6%		7 1.1%	0 0.0%	40 1.8%	
Cardiomyopathy	201 6.8%		45 7.1%	4 3.4%	151 7.0%	
Aortic pathology	101 3.4%		3 0.5%	6 5.1%	90 4.1%	
Pulmonary hypertension	13 0.4%		2 0.3%	2 1.7%	9 0.4%	
WHO classification						<0.001
WHO class I	583 19.7%		73 11.5%	27 22.9%	474 21.8%	
WHO class II	520 17.6%		18 2.8%	17 14.4%	481 22.1%	
WHO class II-III	932 31.5%		150 23.7%	34 28.8%	735 33.8%	
WHO class III	486 16.4%		187 29.5%	8 6.8%	286 13.2%	
WHO class IV	437 14.8%		206 32.5%	32 27.1%	196 9.0%	

*Percentages are of total valid cases, excluding missing cases.*Total cohort includes countries with less than 10 patients. ACE = Angiotensin Receptor Enzym; AF = Atrial fibrillation; HDI = Human development index; HF = Heart failure; NYHA = New York Heart Association; WHO = World Health Organization.*

high HDI had a prior cardiac intervention and were in NYHA class I, compared to women from countries with a very high HDI. Indeed, signs of heart failure prior to pregnancy were more common; cardiac medication, mainly diuretics, were more commonly used before pregnancy by women from countries with a medium or high HDI compared to those from countries with a very high HDI. Valvular heart disease was much more common in women from countries with a medium HDI, while women from countries with a high or very high HDI more often had congenital heart disease.

Women with modified WHO class III or IV more often came from countries with a medium or high HDI, while women with a lower risk WHO class more often came from countries with a very high HDI.

Frequency of endpoints

Clinical event rates are presented for each HDI group (**Figure 1**) and for all countries separately (**Table 3**). A combined cardiac endpoint occurred in 645 women (22.1%); heart failure in 365 (12.5%); fetal/neonatal loss in 60 (2.1%); small-for-gestational age in 270 (10.6%). Maternal mortality up to one week postpartum occurred in 11 cases (0.9% medium HDI, 0.8% high HDI, and 0.2% very high HDI, p=0.016) and was not included in the univariable or multivariable analysis.

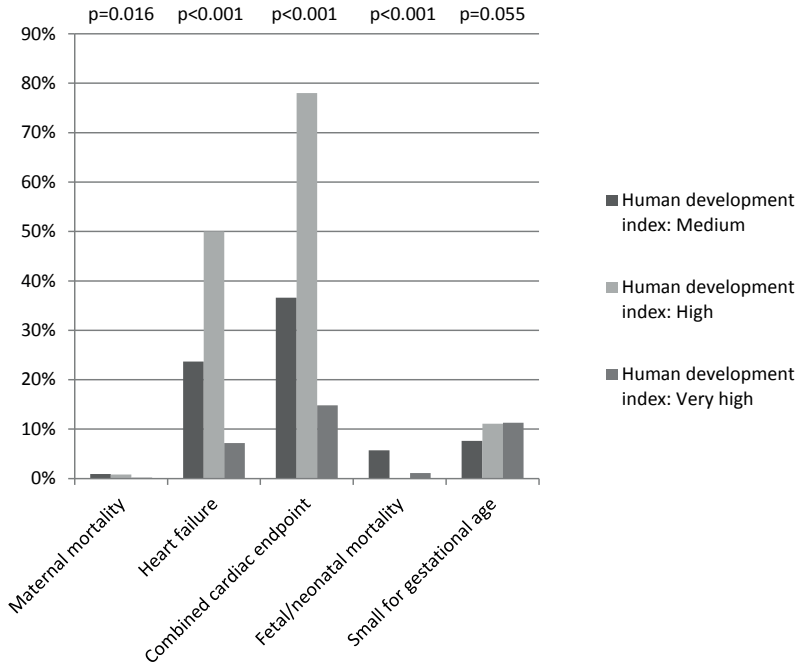


Figure 1 Event rate for HDI categories

Table 3 Events per country

		Maternal mortality (all cause)		Heart failure		Combined cardiac endpoint		Fetal/neonatal mortality (no miscarriage)		Small for gestational age	
	total n	n	%	n	%	n	%	n	%	n	%
ARGENTINA	10	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	10,0%
AUSTRALIA	19	0	0,0%	2	10,5%	4	21,1%	0	0,0%	2	10,5%
AUSTRIA	83	0	0,0%	1	1,2%	4	4,8%	1	1,2%	1	1,2%
AZERBAIJAN	10	0	0,0%	2	20,0%	2	20,0%	0	0,0%	0	0,0%
BELGIUM	125	0	0,0%	2	1,6%	5	4,0%	0	0,0%	3	2,4%
CANADA	57	1	1,8%	3	5,3%	6	10,5%	2	3,5%	2	3,5%
CZECH REPUBLIC	14	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%
EGYPT	573	6	1,0%	120	20,9%	198	34,6%	31	5,4%	30	5,2%
FRANCE	58	0	0,0%	13	22,4%	26	44,8%	0	0,0%	10	17,2%
GERMANY	229	0	0,0%	3	1,3%	10	4,4%	1	0,4%	23	10,0%
GREECE	27	0	0,0%	3	11,1%	11	40,7%	0	0,0%	6	22,2%
HUNGARY	44	0	0,0%	0	0,0%	1	2,3%	1	2,3%	4	9,1%
ISRAEL	61	0	0,0%	19	31,1%	25	41,0%	1	1,6%	7	11,5%
ITALY	238	1	0,4%	12	5,0%	33	13,9%	3	1,3%	28	11,8%
JAPAN	33	0	0,0%	2	6,1%	2	6,1%	0	0,0%	6	18,2%
LITHUANIA	60	0	0,0%	5	8,3%	5	8,3%	1	1,7%	8	13,3%
MALTA	19	0	0,0%	0	0,0%	1	5,3%	0	0,0%	2	10,5%
NETHERLANDS	299	0	0,0%	9	3,0%	38	12,7%	2	0,7%	23	7,7%
NORWAY	28	0	0,0%	4	14,3%	6	21,4%	0	0,0%	1	3,6%
POLAND	113	0	0,0%	11	9,7%	27	23,9%	3	2,7%	13	11,5%
PORTUGAL	13	0	0,0%	0	0,0%	0	0,0%	1	7,7%	0	0,0%
RUSSIAN FEDERATION	108	1	0,9%	57	52,8%	90	83,3%	0	0,0%	13	12,0%
SLOVENIA	128	0	0,0%	2	1,6%	10	7,8%	3	2,3%	12	9,4%
SOUTH AFRICA	61	0	0,0%	30	49,2%	34	55,7%	5	8,2%	8	13,1%
SPAIN	221	1	0,5%	20	9,0%	32	14,5%	3	1,4%	29	13,1%
SWEDEN	33	0	0,0%	5	15,2%	7	21,2%	1	3,0%	6	18,2%
SWITZERLAND	45	0	0,0%	2	4,4%	5	11,1%	0	0,0%	5	11,1%
UNITED ARAB EMIRATES	31	0	0,0%	13	41,9%	16	51,6%	0	0,0%	5	16,1%
UNITED KINGDOM	120	1	0,8%	16	13,3%	31	25,8%	0	0,0%	15	12,5%
UNITED STATES	64	0	0,0%	9	14,1%	16	25,0%	1	1,6%	6	9,4%
TOTAL	2924	11	0,4%	365	12,5%	645	22,1%	60	2,1%	270	9,2%

Associations of patient and country characteristics with clinical endpoints

Univariable analysis of pre-pregnancy patient characteristics for the combined cardiac endpoint is shown in **Table 4**. The only variable that was not significantly associated with the combined cardiac endpoint was nulliparity. Modified WHO II was not significantly different from modified WHO I. Of the country characteristics, Gini coefficient (p=0.017) and birth rate (although p=0.050) were independently associated with the combined cardiac endpoint, in addition to age, NYHA class, modified WHO class and signs of heart failure before pregnancy.

The univariable and multivariable analysis of the remaining endpoints are shown in the *online supplemental data*. The results for heart failure as a separate endpoint were largely comparable to the results of the combined cardiac endpoint (*online supplemental Table S2*). While schooling, GDP, birth rate and number of hospital beds were associated with fetal/neonatal mortality in the univariable analysis, only GDP was independently associated with this endpoint (*online supplemental Table S3*). None of the country characteristics were

Table 4 Univariable and multivariable analysis of patient and country characteristics with the combined cardiac endpoint

	Univariable		Multivariable	
Variable	**Estimate**	**p-value**	**Estimate**	**p-value**
Age	0.026	0.004	0.019	0.047
Nulliparity	-0.046	0.662		
NYHA I	NA	NA	NA	NA
NYHA II	1.006	<0.001	0.665	<0.001
NYHA III	2.217	<0.001	1.119	<0.001
NYHA IV	3.258	0.005	2.009	0.079
WHO I	NA	NA	NA	NA
WHO II	0.085	0.717	-0.003	0.990
WHO II-III	0.816	<0.001	0.689	<0.001
WHO III	1.470	<0.001	1.351	<0.001
WHO IV	2.126	<0.001	1.600	<0.001
Signs of heart failure	1.427	<0.001		
Gini	0.534	<0.001	0.332	0.017
Health expenditure	-0.303	0.204		
Schooling	-0.035	0.924		
GDP	-0.305	0.220		
Birth Rate	1.063	<0.001	0.484	0.050
Hospital beds	-0.345	0.143		

Data are clustered within hospitals within countries. The categorical variable NYHA classification and WHO are tested against the reference category I. WHO II is not significantly different from WHO I. The only variable that is not significant is nulliparity.

GDP = Gross domestic product, NYHA = New York Heart Association, WHO = World Health Organization

associated with SGA, on top of NYHA II and III, and modified WHO class III and IV (*online supplemental Table S4*).

Influence of variability between countries and centres

The total explained variability of the model, the conditional R^2, for the combined cardiac endpoint including patient characteristics only, was 37%. By adding the country characteristics, the R^2 increased by 4% to 41%. Without any of these fixed effects in the model the conditional R^2 including random effects only, was 33%. **Figure 2** depicts the estimated unadjusted and adjusted odds ratios for a combined cardiac endpoint for each country compared to the average odds ratio. Several countries do not include the 0 in their 95% confidence interval in the unadjusted model. But when adjusted for patient and country characteristics, the 95% confidence intervals of almost all countries do include 0. This means that for the vast majority of the countries, the need to account for random effects (patient within centre, within country) disappears when adjusting for patient and country characteristics.

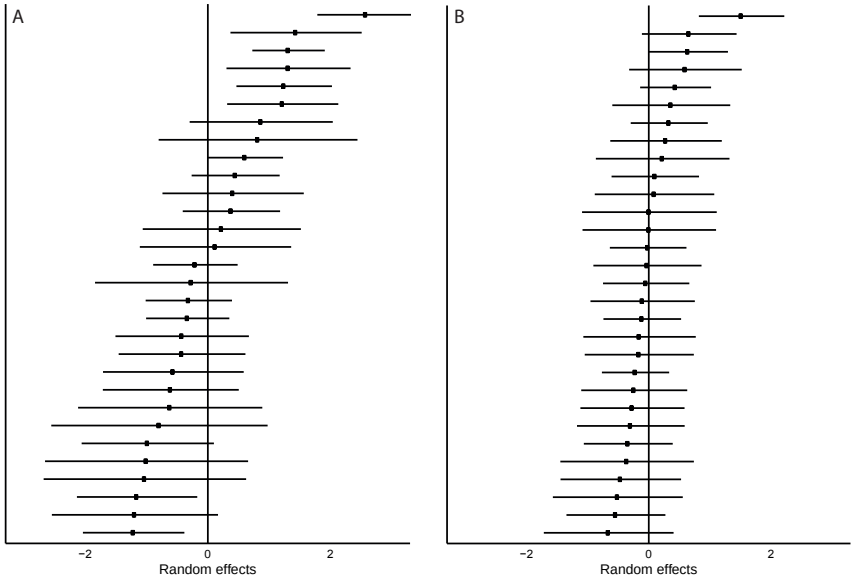


Figure 2 Between country differences in outcome, unadjusted for fixed effects (A) and adjusted for fixed effects (B)

The random effects estimates of the individual countries, plotted with 95% confidence intervals. A country with average proportion of the combined cardiac endpoint has a random effect (log odds) of 0.

DISCUSSION

The ROPAC registry is the largest recorded cohort of pregnant women with cardiac disease. Women from many different countries were included. Results may be influenced by the multicenter and multinational nature of the registry. The current study shows that indeed there are differences in outcome between centres and countries, but these differences are largely explained by differences in individual patient characteristics, such as NYHA classification, prior signs of heart failure and modified WHO classification. Only a few country characteristics had some impact: maternal cardiac event was associated with Gini coefficient and to a lesser extent with birth rate of the patients' residential country. Also fetal outcome, such as small for gestational age was mainly associated with the maternal condition and to a minor extent with country characteristics.

Maternal outcome and socioeconomic influences

Previous studies have shown that human development index is a strong predictor of maternal and fetal mortality rate in the global population[13]. Inequality of socioeconomic determinants within a country further increases the rate of maternal death[14]. A lower educational level and lower HDI have been reported to be associated with maternal adverse outcome[15,16]. Less educated women, for instance, have an increased risk of presenting to an emergency department in a severe condition[15]. This may be related to several issues: women from emerging countries tend to have a later presentation to a medical centre, which is probably associated with limited knowledge and awareness of risks, but also to factors like a less well developed infrastructure, longer travel-time and perhaps less availability of skilled medical staff. To what extent these correlations can be extrapolated to women with pre-existent cardiac disease, and whether they need to be taken into account while analysing multinational registry data, has not been determined until now.

Although the number of maternal deaths was too low to allow for statistical analysis, the risk of a cardiac event (combined endpoint) was indeed associated with income inequality (expressed as the Gini-coefficient) in a country. Also, a higher country birth rate correlated with a higher frequency of heart failure. These socioeconomic parameters need to be considered when interpreting data from registries, however, we feel that the number of factors actually showing a relationship to pregnancy outcome in these high risk patients, is actually relatively small compared to their impact in the general pregnant population. In fact, the most important determinant of pregnancy outcome was the underlying medical condition.

Fetal outcome

With regard to fetal and obstetric outcome, previous reports showed that a higher income inequality (Gini coefficient) and educational level, rather than household income, seem to be associated with intrauterine growth but not with shorter gestational age at delivery[17,18].

The exact underlying mechanism is difficult to determine. A recent large prospective cohort study of pregnant women showed that women from low socioeconomic subgroups have higher placental resistance indices, which may contribute to a higher incidence of pregnancy complications[19].

In our cohort of women with cardiac disease, country characteristics did not significantly influence the SGA rate, while maternal condition expressed as NYHA class and modified WHO classification did influence the frequency of SGA. In women with reduced cardiac function, an abnormal uteroplacental flow is present, which is an important predictor of adverse obstetric and fetal outcome[20] and this may explain the association in this study.

Research and clinical implications

The results imply that interregional differences need to be acknowledged, also in research, but that the maternal condition seems to outweigh the influence of socioeconomic factors on reported cardiac and fetal outcome. A clear association between socioeconomic factors and events was present in univariable analysis, but it largely disappeared after correction for maternal condition. Thus, the higher event rate in emerging compared to advanced countries is mainly based on a worse pre-pregnancy condition of patients. Also, the need for multilevel modelling in this analysis was lost after adding the patient and country characteristics.

Data on cultural background were lacking, but would be very interesting to study. Differences in pregnancy outcome between emerging and advanced countries, may be related to for instance religion. Women may have a strong feeling that their fate is predetermined and therefore less sensible to a doctor's advice. But this hypothesis is rather philosophical and needs further investigation to determine whether this indeed influences pregnancy outcome.

Reducing adverse pregnancy outcome in any region, but in particular in remote areas, is an important goal as formulated by the WHO. While this goal resulted in major declines in maternal death rates globally, this trend has definitely not been observed in maternal death due to cardiac disease[21]. Creating awareness in young women with cardiac disease about the potential high risks of pregnancy should be part of standard care and preferably initiated at a young age. The fifth millennium goal of the World Health Organization is reduction of maternal mortality, by means of increasing the number of women receiving at least 4 antenatal care visits and the number of births attended by skilled staff[22]. An increase in the number of women receiving this level of care and a decline in maternal death rate has been observed in the past 10-15 years, but about 50% of women still do not receive the recommended minimum of four antenatal visits. Also, a well-developed infrastructure for cardiovascular health screening is warranted to ensure early diagnosis and management[23]. Improvements in these medical resources may also reduce the burden of adverse events in pregnant women with cardiac disease.

Other global observational studies, for instance those dealing with factors influencing secondary cardiovascular prevention, did find related socio-economic factors. One study pointed out that the country level socio-economic factors explained two-thirds of the variation in preventive drug use compared to only a third explained by individual factors (such as smoking, gender, education)[24]. Although these results are not in line with our findings, this knowledge needs to be appreciated for our population as well: it does show the between-country differences in (level of) health care availability.

Limitations

While ROPAC provides a unique view on global pregnancy outcome, including women from 39 countries, the current distribution of countries was within a range of medium to very high HDI. However, the range of country specific characteristics was sufficient to illustrate the differences between more developed countries and those with poorer resources. Including patients from countries categorised with a low HDI may strengthen this study, but is hard to achieve with limited availability of organised/specialised medical care in these countries.

In previous studies, ethnicity was shown to influence maternal outcome[25]. In particular, non-Hispanic black women seem to have an increased risk of pregnancy-related mortality[26]. ROPAC did not include demographic socioeconomic data at a patient level, which is why we performed the analysis at a country level. If the socio-economic data (income, education, social status, employment, among others) were available at patient level, it may had been possible to find stronger relationships. Since we performed the statistical analyses at three levels (patient, within centre, within country), we believe that meaningful conclusions can be drawn from our data.

The majority of the participating centres were university or tertiary centres (86%). Unfortunately, only 75% responded to the question whether they were a university, community or private clinic, which is why we did not include this information in the statistical analysis. But it is likely that our data are derived from women cared for in larger centres with a specialised department for pregnancy.

ROPAC included 6 months follow-up postpartum. However, due to large differences in follow-up availability between countries, it was decided not to include these results to this analysis. Follow-up at 1 week was available in all patients. For future research, inclusion of long-term follow-up would be favourable. Finally, the number of pregnancies complicated by fetal and neonatal mortality was relatively low, which hampered statistical modelling and conclusions should be interpreted carefully.

Conclusion

Socioeconomic factors were partly explainable for differences in pregnancy outcome in women with cardiac disease, but the main denominator was the individual's condition. Raising awareness and improving access to medical resources as advocated by the World

Health Organization, will help to improve the outcome for pregnant women, hopefully also for women with heart disease.

Online Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Socioeconomic indices per country
Reference numbers from World Bank/ UNDP / UNESCO / HDI UNDESA

Table S2 Univariable and multivariable analysis of patient and country characteristics with heart failure

Table S3 Univariable and multivariable analysis of patient and country characteristics with fetal/neonatal mortality

Table S4 Univariable and multivariable analysis of patient and country characteristics with small-for-gestational-age

Appendix 1 Definitions

REFERENCES

1. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9947): 980-1004.
2. Collaborators GBDMM. Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**(10053): 1775-812.
3. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
4. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015; **132**(2): 132-42.
5. van Hagen IM, Boersma E, Johnson MR, et al. Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology. *European Journal of Heart Failure* 2016; **18**(5): 523-33.
6. Sliwa K, Libhaber E, Elliott C, et al. Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. *Heart* 2014; **100**(24): 1967-74.
7. Soma-Pillay P, Seabe J, Sliwa K. The importance of cardiovascular pathology contributing to maternal death: Confidential Enquiry into Maternal Deaths in South Africa, 2011-2013. *Cardiovasc J Afr* 2016; **27**(2): 60-5.
8. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
9. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
10. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119**(14): 1977-2016.
11. Nakagawa S, Schielzeth H. A general and simple method for obtaining R^2 from generalized linear mixed-effects models. *Methods in Ecology and Evolution* 2013; **4**: 133-42.
12. https://cran.r-project.org/web/packages/lme4/index.html.
13. Lee KS, Park SC, Khoshnood B, Hsieh HL, Mittendorf R. Human development index as a predictor of infant and maternal mortality rates. *J Pediatr* 1997; **131**(3): 430-3.
14. Ignacio Ruiz J, Nuhu K, Tyler McDaniel J, Propoff F, Izcovich A, Martin Criniti J. Inequality as a Powerful Predictor of Infant and Maternal Mortality around the World. *PLoS One* 2015: 1-11.
15. Tuncalp O, Souza JP, Hindin MJ, et al. Education and severe maternal outcomes in developing countries: a multicountry cross-sectional survey. *BJOG* 2014; **121 Suppl 1**: 57-65.
16. Sheldon WR, Blum J, Vogel JP, et al. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 2014; **121 Suppl 1**: 5-13.
17. Fujiwara T, Ito J, Kawachi I. Income inequality, parental socioeconomic status, and birth outcomes in Japan. *Am J Epidemiol* 2013; **177**(10): 1042-52.
18. Nkansah-Amankra S, Dhawain A, Hussey JR, Luchok KJ. Maternal social support and neighborhood income inequality as predictors of low birth weight and preterm birth outcome disparities: analysis

of South Carolina Pregnancy Risk Assessment and Monitoring System survey, 2000-2003. *Matern Child Health J* 2010; **14**(5): 774-85.

19. Bouthoorn SH, van Lenthe FJ, Gaillard R, et al. Socioeconomic inequalities in placental vascular resistance: a prospective cohort study. *Fertil Steril* 2014; **101**(5): 1367-74.
20. Pieper PG, Balci A, Aarnoudse JG, et al. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. *Circulation* 2013; **128**(23): 2478-87.
21. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
22. UN. The Millennium Development Goals report 2015. New York, 2015.
23. Sliwa K, Acquah L, Gersh BJ, Mocumbi AO. Impact of Socioeconomic Status, Ethnicity, and Urbanization on Risk Factor Profiles of Cardiovascular Disease in Africa. *Circulation* 2016; **133**(12): 1199-208.
24. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011; **378**(9798): 1231-43.
25. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Race, ethnicity, and nativity differentials in pregnancy-related mortality in the United States: 1993-2006. *Obstet Gynecol* 2012; **120**(2 Pt 1): 261-8.
26. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006-2010. *Obstet Gynecol* 2015; **125**(1): 5-12.

PART II

Valvular heart disease

CHAPTER 7

Pregnancy outcome in women with rheumatic mitral valve disease: results from the Registry Of Pregnancy And Cardiac disease (ROPAC) of the European Society of Cardiology

Iris M. van Hagen
Sara A. Thorne
Nasser Taha
Ghada Youssef
Amro Elnagar
Harald Gabriel
Yahia ElRakshy
Bernard Iung
Mark R. Johnson
Roger Hall
Jolien W. Roos-Hesselink on behalf of the ROPAC investigators and EORP team.

Submitted

ABSTRACT

Aims To study pregnancy outcome in women with rheumatic mitral valve disease.

Methods and Results The Registry of Pregnancy and Cardiac Disease is a worldwide prospective registry, and all women with rheumatic mitral valve disease and no pre-pregnancy valve replacement were selected(n=390). The majority came from emerging countries(75%). Mitral stenosis (MS) with or without mitral regurgitation (MR) was present in 273 women; isolated MR in 117. The degree of MS was mild in 20.9%, moderate in 39.2%, severe in 19.8%. Maternal death during pregnancy occurred in 1 patient with severe MS. Hospital admission occurred in 23.1% of the women with MS, and the main reason was heart failure (mild MS 15.8%; moderate 23.4%; severe 48.1%,$p<0.001$). Heart failure occurred in 23.1% of patients with moderate or severe MR. An intervention during pregnancy was performed in 16 patients, 14 had valvular balloon dilatation and 2 had surgical valve replacement (1 for MS; 1 for MR). Independent pre-pregnancy predictors of maternal cardiac events were NYHA class≥II, RVSP>30mmHg, severe MS and older age. Follow-up at 6 months was available for 53% and three more patients died (1 with severe MS; 1 with moderate MS; 1 with moderate to severe MR).

Conclusion Although mortality is low, patients with severe rheumatic MS have a nearly 50% risk of developing heart failure. Also, patients with significant MR have an increased risk of heart failure. Patients with elevated RVSP and higher NYHA are at highest risk. Pre-pregnancy treatment in selected patients is indicated to prevent these complications.

INTRODUCTION

Rheumatic heart disease is a major problem, with up to 1.4 million people dying each year, and is a leading disease in the young, especially in emerging countries. In more developed economies, the diagnosis of rheumatic heart disease is rare and typically found in recent immigrants[1-3]. It poses a particular problem in pregnant women, in whom the diagnosis is often delayed. In emerging countries, rheumatic valve disease is the commonest cardiac disease in pregnant women and the most important cause of maternal death[4-7]. Mitral valve stenosis in particular is a high risk condition[8].

Maternal mortality in general has decreased in the past decade, but over the same period, cardiac maternal death has not declined[9,10]. Large prospective studies in pregnant women with heart disease in general and specifically in women with rheumatic heart disease are lacking. Such studies are needed to provide evidence for guidelines on the management of pregnancy in women with heart disease[11,12] and to counsel women with rheumatic heart disease who are contemplating a pregnancy. Further, contemporary data on the outcome of pregnancy in women with rheumatic mitral valve disease will help to stratify risk, enabling high risk women to be identified and appropriately counselled and managed. The aim of this study is to assess maternal and fetal outcome of pregnancy in women with rheumatic mitral valve disease.

METHODS

The Registry Of Pregnancy And Cardiac disease (ROPAC) is a worldwide prospective and ongoing registry that was established to study a large number of pregnant women with structural heart disease. ROPAC was initiated by the European Society of Cardiology (ESC) working groups on congenital heart disease and valvular heart disease in 2007. Prospective data collection started in January 2008 and for the current study we included data from patients with a term date up to October 2013, and follow-up up to April 2014. Informed consent was obtained from patients if required by the local independent review board. An extensive description of the study protocol and methods has been published previously[4]. For this analysis the outcome of pregnancy for all patients with rheumatic mitral valve disease in ROPAC was analysed. Women with a mechanical or bioprosthetic valve have already been described elsewhere and were excluded from the current study[13].

Data collection

Pre-pregnancy patient characteristics that were collected included age, parity, cardiac diagnosis, previous interventions, medication, smoking, diabetes, hypertension, obstetric history, and if available, echocardiographic parameters. Countries were defined as emerging

or advanced, according to the International Monetary Fund (IMF)[14]. Cardiac, obstetric and fetal outcome data were collected. Heart failure was defined according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[15] as a clinical syndrome that is characterized by specific symptoms (dyspnoea and fatigue) and signs (of fluid retention, such as oedema, rales) on physical examination, as judged by the treating cardiologist. An episode of heart failure was only registered when signs or symptoms of HF were present which required new treatment, change of treatment, or hospital admission.

Maternal cardiac event was defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, endocarditis, hospitalisation for cardiac reason, or a cardiac intervention. *Fetal adverse outcome* was defined as fetal death after 14 weeks, or neonatal death < 1 week, low Apgar score, preterm birth, and small for gestational age.

Follow-up was available up to 1 week after delivery for all patients. Limited follow-up data at 6 months postpartum were available in some patients (53%) and are reported separately.

Definition of valve disease

Mitral valve disease was defined according to the *European Association of Echocardiography* and *American Society of Echocardiography* recommendations for echocardiographic assessment of valve stenosis[16]. The severity of mitral valve stenosis (MS) was defined as follows:

- Mild MS = valve area >1.5 cm^2 or if area not available: mean gradient<6 mmHg
- Moderate MS = valve area 1.0-1.5 cm^2 or if area not available: mean gradient 6-12 mmHg
- Severe MS = valve area <1.0 cm^2 or if area not available: mean gradient >12 mmHg

Mitral valve regurgitation (MR) quantification was based on visual inspection and quantitative measurements and was determined by the treating cardiologist. NYHA classification was used to define whether patients were asymptomatic (NYHA class I) or symptomatic (NYHA class ≥II).

Statistical analysis

Continuous variables are presented as mean and standard deviation, or median and first and third quartiles (Q1-Q3), and differences between groups were assessed using Students t-test or Mann-Whitney test as appropriate. In case of 3 categories (mild, moderate, severe stenosis) one-way ANOVA tests were performed. Categorical variables are presented as frequencies and percentages, and differences were studied using chi-square or Fisher's exact test as appropriate. In case of 3 categories chi square trend tests were performed. We compared pregnancy outcome of women with isolated mild mitral valve regurgitation to those with moderate/severe mitral valve regurgitation. Similarly, we divided women with mitral valve stenosis, (whether or not accompanied by mitral valve regurgitation) into mild, moderate or severe stenosis and compared the outcome of these three groups. Separate analysis was performed for symptomatic and asymptomatic patients. Patients with isolated

moderate/severe mitral valve stenosis were compared with those with moderate/severe mixed mitral valve disease (MS+MR). Univariable and multivariable logistic regression analysis were performed to search for predictors of maternal cardiac events and of adverse fetal outcome. Odds ratios and 95% confidence intervals are provided. Statistical tests were considered significant if a *P*-value was less than 0.05 (two-sided). All analyses were performed with SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Of the 2966 patients included in the ROPAC registry from January 2008 until April 2014, 390 women had rheumatic mitral valve disease. Mean age was 28.9 years (±6.0) and 103 women (26.4%) were primigravida. The majority lived in countries with an emerging economy (75.2%) and were known to have mitral valve disease before pregnancy (75.1%). The type of mitral valve disease is presented in **Table 1**. MS with or without MR was present in 273 women, while 117 had MR only. The degree of stenosis was mild in 57 (20.9%), moderate in 107 (39.2%), severe in 54 (19.8%) and unknown in 55 (20.1%). Baseline characteristics are presented in **Table 2**, stratified for severity of disease. Before pregnancy, a percutaneous or surgical valve repair had been performed in 26.9% of all patients, but in fewer patients with MR and severe MS. Women with MS had signs of heart failure before pregnancy more often than women with only MR (34.1% vs 10.3%, p=0.019), and in particular those with moderate or severe MS. Women with MS also received cardiac medication prior to pregnancy more often than women with MR (38.6% vs 24.8%, p=0.009).

Table 1 Severity of rheumatic mitral valve disease

	No mitral valve regurgitation	Mild mitral valve regurgitation	Moderate mitral valve regurgitation	Severe mitral valve regurgitation	Unknown severity regurgitation	Total
No mitral valve stenosis	0	43	35	30	9	117
Mild mitral valve stenosis	14	20	13	7	3	57
Moderate mitral valve stenosis	37	28	27	13	2	107
Severe mitral valve stenosis	19	19	11	5	0	54
Unknown severity stenosis	27	7	4	2	15	55
Total	97	117	90	57	29	390

Table 2 Baseline characteristics of patients with rheumatic mitral valve disease

	Rheumatic mitral valve disease, all		Mitral Regurgitation (no MS)					Mitral stenosis (± MR)						
			Mild MR		Moderate or severe MR			Mild MS		Moderate MS		Severe MS		
	n=390		n=43		n=65		p-value (MR)	n=57		n=107		n=54		p-value (MS)
Age, years (±SD)	28.9	(±6.0)	29.2	(±6.8)	28.1	(±5.2)	0.32	28.9	(±6.2)	29.8	(±5.8)	27.5	(±6.0)	0.07
Living in an emerging country	75.2%		36	83.7%	58	89.2%	0.40	39	68.4%	77	72.0%	46	85.2%	0.045
Primigravida	26.3%		7	16.3%	13	20.0%	0.63	19	33.3%	26	24.3%	23	42.6%	0.31
Twin pregnancy	4.4%		0	0.0%	4	6.8%	0.14	1	1.9%	5	4.9%	2	4.3%	0.61
Current smoking	1.9%		1	2.3%	0	0.0%	0.40	3	5.6%	1	1.0%	0	0.0%	0.07
Prior diabetes	1.3%		1	2.3%	0	0.0%	0.40	1	1.8%	0	0.0%	0	0.0%	0.51
Prior hypertension	3.6%		2	4.8%	4	6.3%	1.00	3	5.3%	4	3.7%	0	0.0%	0.18
Prior intervention	26.9%		4	9.3%	7	10.8%	1.00	22	38.6%	40	37.4%	7	13.0%	0.004
Signs of heart failure before pregnancy	21.2%		1	2.3%	13	20.0%	0.007	7	12.3%	25	23.6%	18	34.0%	0.007
Atrial fibrillation before pregnancy	7.0%		1	2.3%	2	3.1%	1.00	2	3.5%	8	7.5%	4	7.7%	0.44
Cardiac medication before pregnancy	34.6%		8	18.6%	18	27.7%	0.28	14	24.6%	48	44.9%	16	30.2%	0.50
RVSP>30 mmHg	31.4%		1	2.3%	21	32.8%	<0.001	20	35.7%	43	41.0%	23	42.6%	0.46
Any mitral valve regurgitation	74.9%		43	100%	65	100%	na	43	75.4%	70	65.4%	35	64.8%	0.23

Unknown severity of disease: n=65. RVSP= Right ventricular systolic pressure, SD= standard deviation

Mitral valve stenosis

The outcome of pregnancy is presented in **Table 3**, stratified for mild, moderate and severe stenosis. Maternal death during pregnancy occurred in 1 patient with MS (1.9% of severe MS). This patient died at 35 weeks of pregnancy due to acute heart failure. Two other women died during follow-up (after one week postpartum). One of these two women was a patient with severe MS (5.3% of patients with severe MS available for follow-up), who died two weeks after spontaneous abortion, complicated by sepsis, atrial fibrillation and cardiogenic shock. The other one was a patient with moderate MS (1.7% of patients with moderate MS available for follow-up) who developed atrial fibrillation treated with heparin peripartum, which was discontinued because of hemorrhage of the Caesarean section wound. In the second week postpartum she developed sudden severe abdominal pain and dyspnea and she died after a cardiac arrest. An aortic embolism or acute mesenteric vascular occlusion was suspected, but autopsy was denied.

Of all patients with MS, hospital admission for a cardiac reason was required in 23.1% during pregnancy. The main reason was heart failure, in particular in women with severe MS (49.1%). The risk was also significant in moderate MS: 31.8% developed heart failure (22.0% of previously asymptomatic women with moderate MS and 41.1% of previously symptomatic women with moderate MS, p=0.036). Timing of heart failure in patients with MS was: 71% during pregnancy only; 14% during pregnancy and up to 1 week after delivery; 15% after delivery only. Episodes of heart failure in the presence of mitral stenosis were treated mainly with diuretics (59.5%) and/or beta-blockers (41.2%), and/or ACE-inhibitors (4.7%).

A cardiac intervention was performed during pregnancy in 15 patients with MS (5.9%): 14 patients had valvular balloon dilatation and one patient had a surgical valve replacement. Timing of intervention was during the first trimester in 2 patients, second trimester in 7 patients, and third trimester in 4 patients (and unknown in 2). The course of pregnancy was uneventful after these interventions. Women with mitral stenosis from countries with an advanced economy had an intervention during pregnancy more often than those from countries with an emerging economy (11.4% versus 3.1%, p=0.015), and this difference persisted when assessing women with isolated mitral stenosis only (19.4% versus 4.9%, p=0.036).

Miscarriage or fetal death was reported in 5.1% of all women with MS, versus 3.4% of women with MR (p=0.46). Women with MS gave birth to small-for-gestational-age babies more often compared to women with MR (14.0% vs 3.5%, p=0.009). Women with severe MS delivered earlier (p=0.041) and their babies had a lower birth weight (p=0.007).

The outcome of women with moderate or severe MS in the presence and absence of significant MR is presented in **Table 4**. Women with mixed mitral valve disease were more likely to have pulmonary hypertension before pregnancy than women with isolated MS (48.2% versus 23.6%, p=0.007). A cardiac intervention was performed only in patients with

Table 3 Outcome of pregnancy

	Rheumatic mitral valve disease, all	Mild MR		Moderate or severe MR			Mild MS		Moderate MS		Severe MS		
	n=390	n=43		n=65		p-value (MR)	n=57		n=107		n=54		p-value (MS)
Maternal mortality, up to 1 week postpartum	0.3%	0	0.0%	0	0.0%	na	0	0.0%	0	0.0%	1	1.9%	0.25
Hospital admission for a cardiac reason	20.2%	2	4.7%	13	20.0%	0.024	9	15.8%	25	23.4%	18	33.3%	0.031
Heart failure	26.6%	3	7.0%	15	23.1%	0.029	9	15.8%	34	31.8%	26	48.1%	<0.001
Cardiac intervention performed	4.1%	0	0.0%	0	0.0%	na	0	0.0%	4	3.7%	8	15.1%	0.001
Supraventricular tachycardia	4.3%	0	0.0%	1	1.5%	1.00	1	1.8%	6	5.6%	4	7.4%	0.20
Ventricular tachycardia	0.3%	0	0.0%	0	0.0%	na	0	0.0%	1	0.9%	0	0.0%	1.00
Thrombotic complication	0.3%	0	0.0%	0	0.0%	na	0	0.0%	1*	0.9%	0	0.0%	1.00
Pregnancy induced hypertension	1.8%	2	4.7%	2	3.1%	1.00	1	1.8%	2	1.9%	0	0.0%	0.69
(Pre-) eclampsia or HELLP	1.5%	0	0.0%	1	1.5%	1.00	2	3.5%	0	0.0%	1	1.9%	0.69
Postpartum haemorrhage	2.8%	0	0.0%	1	1.5%	1.00	3	5.3%	4	3.7%	1	1.9%	0.45
Caesarean section	52.2%	15	36.6%	28	45.2%	0.39	28	50.0%	67	63.2%	31	60.8%	0.24
Emergency caesarean section for a cardiac reason	3.1%	1	2.3%	2	3.1%	1.00	0	0.0%	3	2.8%	5	9.4%	0.011
Abortus provocatus:													
Maternal reason	0.5%	0	0.0%	1	1.5%	1.00	0	0.0%	0	0.0%	0	0.0%	na
Fetal reason	0.3%	0	0.0%	0	0.0%	na	0	0.0%	0	0.0%	0	0.0%	na
Miscarriage <24 weeks	3.8%	0	0.0%	3	4.6%	0.27	2	3.5%	4	3.7%	3	5.6%	0.64
Fetal death ≥24 weeks	1.0%	0	0.0%	1	1.5%	1.00	0	0.0%	1	0.9%	1	1.9%	0.37
Low Apgar (<7)	8.1%	4	12.1%	1	2.5%	0.17	3	6.5%	5	5.6%	5	11.9%	0.42
Preterm birth	9.5%	0	0.0%	2	3.6%	0.51	2	3.8%	9	9.3%	10	21.3%	0.005
Birthweight <2500gr	16.4%	5	11.6%	4	6.2%	0.48	4	7.0%	18	16.8%	17	31.5%	0.001
Small for gestational age	11.2%	0	0.0%	3	6.8%	0.26	2	4.3%	10	10.8%	9	19.6%	0.020

Table 3 Outcome of pregnancy (continued)

	Rheumatic mitral valve disease, all	Mild MR		Moderate or severe MR			Mild MS		Moderate MS		Severe MS		
	n=390	n=43		n=65		p-value (MR)	n=57		n=107		n=54		p-value (MS)
Median pregnancy duration, weeks (Q1-Q3)	39.0 (38.0-39.6)	39.0	(38.3-39.9)	39.0	(38.3-39.4)	0.29	39.0	(38.3-39.9)	39.0	(38.0-39.4)	38.7	(37.0-39.3)	0.041
Median birthweight, grams (Q1-Q3)	2900 (2610-3100)	3050	(2750-3300)	2925	(2750-3110)	0.09	2925	(2690-3200)	2900	(2640-3100)	2700	(2400-3000)	0.007
Follow-up after 6 months	52.7%	18	41.9%	26	40.0%	1.00	37	64.9%	58	54.2%	19	35.2%	0.006
Mortality after 1 week, <6 months	1.5%	0	0.0%	1	3.8%	1.00	0	0.0%	1	1.7%	1	5.3%	0.30

Unknown severity of disease: n=65, no maternal mortality occurred in this group

Table 4 Isolated mitral valve stenosis versus mixed mitral valve disease

	Isolated moderate/severe MS		Moderate/severe MS combined with moderate/severe MR		
	n=56		n=56		p-value
Baseline characteristics					
Age (years)	30.0	(±5.8)	28.5	(±6.2)	0.18
Living in an emerging country	39	69.6%	46	82.1%	0.12
Primigravida	17	30.4%	15	26.8%	0.68
Prior intervention	18	32.1%	16	28.6%	0.68
Signs of heart failure before pregnancy	15	26.8%	15	27.8%	0.91
Atrial fibrillation before pregnancy	6	10.7%	5	9.1%	0.78
Cardiac medication before pregnancy	25	44.6%	21	38.2%	0.49
RVSP>30 mmHg	13	23.6%	27	48.2%	0.007
Severe mitral valve stenosis	19	33.9%	16	28.6%	0.54
Pregnancy outcome					
Maternal mortality, up to 1 week postpartum	0	0.0%	0	0.0%	na
Hospital admission for a cardiac reason	16	28.3%	13	23.2%	0.52
Heart failure	24	42.9%	19	33.9%	0.33
Supraventricular tachycardia	6	10.7%	3	5.4%	0.49
Cardiac intervention performed	7	12.5%	0	0.0%	0.013
Caesarean section	30	55.6%	36	65.5%	0.29
Emergency caesarean section for a cardiac reason	3	5.4%	5	8.9%	0.72
Miscarriage <24 weeks	1	1.4%	5	8.9%	0.21
Fetal death ≥24 weeks	1	1.8%	0	0.0%	1.00
Low Apgar (<7)	2	4.1%	5	12.5%	0.24
Preterm birth	10	19.2%	5	10.2%	0.20
Birthweight <2500gr	11	19.6%	14	25.0%	0.50
Small for gestational age	6	11.8%	5	11.1%	0.92
Median pregnancy duration, weeks (Q1-Q3)	38.4	(37.0-39.4)	38.9	(38.0-39.3)	0.43
Median birthweight, grams (Q1-Q3)	2800	(2600-3100)	2775	(2500-3000)	0.44
Follow-up after 6 months	24	42.9%	24	42.9%	1.00
Mortality after 1 week, <6 months	0	0.0%	2	8.3%	0.49

MR= mitral regurgitation; MS= mitral stenosis; na=not applicable; Q1-Q3 = first and third quartile; RVSP= right ventricular systolic pressure

isolated MS (0% versus 12.5%, p=0.013). The outcome of pregnancy was not different in mixed mitral valve disease compared to isolated MS.

Isolated mitral valve regurgitation

One patient with severe mitral regurgitation died (**Table 3**, 3.8% of patients available for follow-up). She was asymptomatic before pregnancy and had a normal left ventricular function. She developed a cardiogenic shock pre-delivery at 39 weeks, with the subsequent perinatal death of her child. Urgent surgical valve repair was planned directly after pregnancy, but she discharged herself against medical advice and she died weeks later due to cardiogenic shock.

Hospital admission for cardiac reason was required in 13.7% of women with MR, mainly because of heart failure, which occurred in 16.2% compared to 31.1% of MS patients (p=0.002). Heart failure in the presence of mitral regurgitation was treated mainly with diuretics (47.4%); some received beta-blockers (15.8%), and/or ACE-inhibitors (5.3%). Surgical valve replacement was performed in one patient (0.9% of MR patients) after 10 weeks of gestation. She received a mechanical valve and was treated with vitamin K throughout pregnancy, with a switch to heparin before vaginal delivery, with good fetal outcome.

Outcome of pregnancy is stratified for emerging and advanced economies in **Table 5**.

Symptomatic patients

Before pregnancy, 168 patients (43.1%) were in NYHA class ≥II as shown in **Table 6**. Compared to asymptomatic patients (n=217), they had signs of heart failure, pulmonary hypertension, took cardiac medication more often and had severe MS more frequently. During pregnancy, hospital admission was required in 33.3% of symptomatic patients, mainly for heart failure, but also for supraventricular arrhythmias. The majority of cardiac interventions were performed in the symptomatic group. A higher incidence of small for gestational age babies was found in symptomatic versus asymptomatic patients (15.1% versus 7.7%, p=0.038).

Predictors of adverse outcome

Results of univariable and multivariable regression analysis are presented in **Table 7**. Pre-pregnancy NYHA class of >I, severe mitral stenosis, elevated RVSP and older age were independent predictors of maternal cardiac events. Severe mitral stenosis was independently associated with adverse fetal outcome.

Table 5 Outcome of pregnancy in emerging and advanced economies

	Mitral stenosis (Isolated or mixed)					Mitral regurgitation (isolated)				
	Emerging		Advanced			Emerging		Advanced		
	n=194		n=79		p-value	n=100		n=17		p-value
Pregnancy outcome										
Maternal mortality, up to 1 week postpartum	1	0.5%	0	0.0%	1.00	0	0.0%	0	0.0%	na
Hospital admission for a cardiac reason	36	18.6%	27	34.2%	0.005	15	15.0%	1	5.9%	0.46
Heart failure	62	32.0%	23	29.1%	0.65	17	17.0%	2	11.8%	0.74
Supraventricular tachycardia	11	5.7%	4	5.1%	1.00	2	2.0%	0	0.0%	1.00
Ventricular tachycardia	1	0.5%	0	0.0%	1.00	0	0.0%	0	0.0%	na
Cardiac intervention performed	6	3.1%	9	11.4%	0.015	1	1.0%	0	0.0%	1.00
Caesarean section	106	55.2%	47	61.8%	0.32	36	62.1%	10	58.8%	0.11
Emergency caesarean section for a cardiac reason	5	2.6%	4	5.1%	0.29	3	3.0%	0	0.0%	1.00
Miscarriage <24 weeks	10	5.2%	1	1.3%	0.19	3	3.0%	0	0.0%	1.00
Fetal death ≥24 weeks	2	1.0%	1	1.3%	1.00	1	1.0%	0	0.0%	1.00
Low Apgar (<7)	11	7.3%	8	10.5%	0.41	4	6.2%	2	11.8%	0.60
Preterm birth	11	6.4%	19	26.0%	<0.001	3	3.5%	0	0.0%	1.00
Birthweight <2500gr	32	16.5%	22	27.8%	0.033	10	0.0%	0	0.0%	0.35
Small for gestational age	16	9.8%	17	23.6%	0.005	2	2.9%	1	5.9%	0.49
Median pregnancy duration, weeks (Q1-Q3)	39.0	(38.0-39.6)	38.1	(36.7-39.0)	<0.001	39.0	(38.3-39.6)	39.0	(38.3-39.6)	0.34
Median birthweight, grams (Q1-Q3)	2980	(2700-3100)	2790	(2400-3000)	0.009	3000	(2725-3175)	3090	(2843-3287)	0.20
Follow-up after 6 months	97	50.0%	56	70.9%	0.002	40	40.0%	12	70.6%	0.019
Mortality after 1 week, <6 months	2	2.1%	0	0.0%	0.53	1	2.5%	0	0.0%	1.00

na= not applicable; Q1-Q3 = first and third quartile; RVSP= right ventricular systolic pressure.

Table 6 Baseline and pregnancy outcome in asymptomatic and symptomatic patients

	Asymptomatic		Symptomatic		
	n=217		n=168		p-value
Baseline characteristics					
Age (years)	29.2	(±6.2)	28.4	(±5.7)	0.17
Living in an emerging country	162	74.7%	130	77.4%	0.54
Primigravida	46	21.2%	55	32.7%	0.011
Prior intervention	61	28.1%	43	25.6%	0.58
Signs of heart failure before pregnancy	3	1.4%	77	46.4%	<0.001
Atrial fibrillation before pregnancy	12	5.6%	13	7.8%	0.37
Cardiac medication before pregnancy	60	27.8%	72	42.9%	0.002
RVSP>30 mmHg	48	22.3%	72	43.6%	<0.001
Severe mitral valve regurgitation*	27	17.2%	28	18.4%	0.18
Severe mitral valve stenosis*	21	11.1%	31	22.0%	0.007
Pregnancy outcome					
Maternal mortality, up to 1 week postpartum	0	0.0%	1	0.6%	0.44
Hospital admission for a cardiac reason	21	9.7%	56	33.3%	<0.001
Heart failure	42	19.4%	60	35.7%	<0.001
Supraventricular tachycardia	4	1.8%	12	7.1%	0.010
Cardiac intervention performed	3	1.4%	13	7.7%	0.002
Caesarean section	102	47.9%	93	57.4%	0.07
Emergency caesarean section for a cardiac reason	3	1.4%	7	4.2%	0.11
Miscarriage <24 weeks	8	3.7%	6	3.6%	0.95
Fetal death ≥24 weeks	2	0.9%	2	1.2%	1.00
Low Apgar (<7)	12	7.5%	11	7.8%	0.91
Preterm birth	19	9.7%	12	8.1%	0.59
Birthweight <2500gr	31	14.3%	31	18.5%	0.27
Small for gestational age	13	7.7%	22	15.1%	0.038
Median pregnancy duration, weeks (Q1-Q3)	39.0	(38.0-39.6)	39.0	(38.0-39.6)	0.21
Median birthweight, grams (Q1-Q3)	2900	(2658-3188)	2900	(2600-3000)	0.10
Follow-up after 6 months	104	47.9%	100	59.5%	0.024
Mortality after 1 week, <6 months	1	1.0%	2	2.0%	0.62

Q1-Q3 = first and third quartile; RVSP= right ventricular systolic pressure. *Percentage of patients with known severity of disease.

Table 7 Predictors of adverse outcome

	Univariable analysis		Multivariable analysis	
	OR	95%CI	OR	95%CI
Adverse cardiac events* (n= 152, 39.0%)				
age	1.03	(1.00-1.07)	**1.05**	**(1.01-1.10)**
Primigravida	1.17	(0.74-1.85)		
Signs of heart failure before pregnancy	3.12	(1.88-5.18)	1.32	(0.66-2.64)
AF before pregnancy	2.74	(1.21-6.22)	1.02	(0.34-3.03)
NYHA>1	3.32	(2.16-5.09)	**2.86**	**(1.62-5.08)**
RVSP>30 mmHg	2.29	(1.47-3.55)	**2.14**	**(1.26-3.64)**
Severe mitral stenosis	2.89	(1.59-5.26)	**2.35**	**(1.20-4.62)**
Severe mitral regurgitation	1.49	(0.84-2.64)		
Adverse fetal outcome^ (n=81, 20.8%)				
Age	1.03	(0.99-1.07)		
Primigravida	1.23	(0.71-2.11)		
Signs of heart failure before pregnancy	0.96	(0.52-1.78)		
AF before pregnancy	2.65	(1.15-6.08)	1.10	(0.29-4.22)
NYHA>1	1.29	(0.78-2.13)		
RVSP>30 mmHg	1.55	(0.93-2.59)		
Severe mitral stenosis	2.62	(1.35-5.07)	**2.39**	**(1.19-4.79)**
Severe mitral regurgitation	1.22	(0.62-2.41)		
Anticoagulation during pregnancy	2.29	(1.18-4.45)	1.09	(0.36-3.31)
Beta-blocker during pregnancy	1.77	(1.03-3.03)	1.32	(0.69-2.53)

95%CI= 95% confidence interval; AF= episode of atrial fibrillation at baseline; NYHA = New York Heart Association functional class; OR= odds ratio; RVSP= right ventricular systolic pressure.

* Defined as cardiac arrest, cardiac death, new episode of arrhythmia requiring treatment, heart failure, thromboembolic event, endocarditis, hospitalisation for cardiac reason, or a cardiac intervention

^ Defined as fetal death after 14 weeks, or neonatal death < 1 week, low apgar score, preterm birth, small for gestational age

DISCUSSION

This global prospective registry included the largest number of women with rheumatic mitral valve disease reported to date. It provides contemporaneous data showing that women with mild and asymptomatic rheumatic mitral valve disease tolerate pregnancy well, but that morbidity and mortality is high especially in women with severe mitral valve stenosis. Heart failure occurred in up to 48% of women with severe mitral stenosis, patients with pre-pregnancy NYHA class II or greater and elevated right ventricular systolic pressure being at particularly high-risk of maternal cardiac events. This is not surprising as pregnancy induces an expansion of the plasma volume, which is poorly tolerated in the presence of severe

left-sided stenosis. The stenotic mitral valve compromises the ability of the heart to increase cardiac output, increasing left atrial and pulmonary pressures and resulting in cardiac failure. In addition, an increase in cardiac output is required to provide sufficient uteroplacental blood flow, when this is compromised fetal growth may be reduced[17].

Mitral valve stenosis

While mild stenosis is usually well tolerated outwith pregnancy, this study revealed that women with mild disease had a significant risk of heart failure of 15.8%, while those with moderate and severe disease had risks of 31.8 and 48.1% respectively. These data are consistent with an earlier, smaller study, which reported pulmonary oedema in mild (24%), moderate (34%) and severe (56%) mitral valve stenosis during pregnancy[18]. The degree of stenosis, together with NYHA class and RVSP in those with mild or moderate stenosis, may help to distinguish between women who are likely to tolerate pregnancy well and those who have an unacceptably high risk of pregnancy complications; we found that severe MS, RVSP greater than 30 mmHg and NYHA class II or higher were independent significant predictors of maternal cardiac events. A previous prospective study reporting on pregnancy outcome in 192 patients with rheumatic heart disease, including 61% with a mitral valve lesion, also found that heart failure (7 vs. 49%) and arrhythmic (2 vs. 21%) events occurred more often in NYHA class III or IV women than in NYHA class I or II women[19].

In women with severe mitral valve stenosis and NYHA class III or IV, an increase of pulmonary capillary wedge pressure immediately postpartum has been described[20]. In our study, 30% of the cases developing heart failure in the presence of MS, occurred in the first week after delivery, whether or not preceded by an episode during pregnancy. Thus, close monitoring of the hemodynamic situation intrapartum and in the first days after delivery is essential, and efforts should be made to limit large fluctuations in pre- and afterload. Heart failure should be treated just as in non-pregnant patients, although ACE-inhibitors and angiotensin receptor blockers should be avoided during all trimesters because of teratogenicity.

It is noteworthy that 75% of women were known to have mitral valve disease before pregnancy. A third of all women with mitral stenosis were symptomatic before pregnancy, and half of the women with severe mitral stenosis went on to need hospital admission for heart failure during their pregnancy, representing significant morbidity and cost. It is possible to speculate that if those with isolated severe mitral stenosis had undergone balloon mitral valvuloplasty pre conception, they would have had a lower risk pregnancy with less chance of morbidity and hospital admission.

We have shown a remarkable difference in birth weight and pregnancy duration between emerging and advanced economies. Our data clearly are a reflection of the iatrogenic influence on pregnancy outcome: physicians from advanced economies are eager to induce labour for the benefit of the mother. However, this approach did not result in a significant

difference in maternal outcome, although this conclusion is partly restricted by low numbers.

Valve intervention during pregnancy

Sixteen women, almost all of them with MS, had an intervention during pregnancy, most commonly (14 of 16 cases) with a percutaneous balloon mitral commisurotomy (PBMV). This is an effective treatment option for selected patients with isolated mitral valve stenosis, with rapid decrease of left atrial pressure and pulmonary artery pressure[2]. PBMV is effective and safe during pregnancy[21] and is preferred to a surgical procedure, as the latter still carries a risk of fetal demise of around 20%[22]. However, patients with severe mitral valve stenosis in the presence of significant mitral valve regurgitation are less suitable for a percutaneous intervention[23]. Treating patients with severe symptomatic mixed disease during pregnancy is complex and evidence-based recommendations on the approach are lacking. Indeed, in our study, two women with mixed disease died in the second week after pregnancy.

Despite the fact that more women from emerging countries had severe stenotic disease, the number of valvular interventions was greater in countries with an advanced economy, probably because of the greater access in these countries[3]. Enhanced flowcharts for the choice of intervention in women with valve disease in different settings have been proposed[24]. Although, ideally, any percutaneous or surgical intervention should be undertaken before conception, the threshold for intervention during pregnancy, particularly for PBMV in isolated severe mitral stenosis, should be low. The best timing for intervention has been suggested to be after the fourth month.[11]

Isolated mitral valve regurgitation

Mild mitral regurgitation is generally classified as a modified World Health Organization (WHO) class I (no detectable increased risk of maternal mortality and no or mild increased risk of morbidity) [11]. The results of this study support this statement, with low maternal and fetal morbidity. Also, moderate to severe MR is often seen as benign, however, in our study it was associated with a surprisingly high rate of heart failure (23%) and should therefore not be underestimated. As commented on earlier, there are marked changes in haemodynamic function during pregnancy[25,26], which may be poorly tolerated in the context of substantial mitral valve regurgitation.

Clinical implications

It might be well that mortality and cardiac deterioration in this cohort could have been reduced by appropriate pre-pregnancy assessment and intervention as suggested by the guidelines[23]. A delay in patients seeking help is often the main contributing factor to maternal cardiovascular death in emerging countries[6]. Hence, adequate counselling of adolescents and young women with rheumatic heart disease about the risks of pregnancy is

of utmost importance to convince them to see a cardiologist first, before getting pregnant. There seems to be a real task here and this societal issue might need political support.

Also, the question remains how to deal with women with asymptomatic moderate MS, who are not yet candidates for valve intervention, but who are contemplating pregnancy. Pregnancy in these women is associated with a significant risk of heart failure. Most of these women seem to have favorable clinical, and probably also anatomical conditions, for balloon commissurotomy. Therefore, the availability of a low-risk intervention is an incentive to consider wide indications of balloon commissurotomy in young women with moderate or severe MS who have a desire for pregnancy, even if they are asymptomatic.

Limitations

Although this is the largest prospective study about pregnancy in women with rheumatic mitral valve disease, it would be desirable to collect data on even more women, specifically including more patients from low income countries. Definition of valve disease varies between the different guidelines and is subject to updating in newer versions of the guidelines. We were restricted to the guidelines used when the majority of the patients were included[16,23]. However, having symptoms of valve disease has direct consequences with regard to intervention in current guidelines[27], which is why we decided to perform a sub-analysis in patients with and without symptoms. This study was conducted from a voluntary registry, and therefore potential reporting bias should be taken into account when interpreting the results. Furthermore, although follow-up until 1 week postpartum was complete in all patients, follow-up until 6 months postpartum was available in only 53% of the patients.

In our cohort, mitral valve area, mean gradient and pressure half time were available in some patients and at very different time points, which hampered statistical analysis to study their potential value as predictors of adverse outcome.

Conclusion

Women with moderate or severe rheumatic mitral stenosis, who were symptomatic or had elevated right ventricular systolic pressures, are at high risk of complications during pregnancy. In particular women with symptomatic or severe mitral stenosis should be advised against pregnancy until valve intervention has taken place. Women with mild stenosis, and those with more than mild mitral regurgitation should be adequately counselled about their significant risk of complications. Close follow-up during pregnancy will allow early recognition of symptoms and timely intervention to avoid an unfavourable maternal or fetal outcome.

REFERENCES

1. Carapetis JR, Beaton A, Cunningham MW, et al. Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers* 2016; **2**: 15084.
2. Remenyi B, ElGuindy A, Smith SC, Jr., Yacoub M, Holmes DR, Jr. Valvular aspects of rheumatic heart disease. *Lancet* 2016; **387**(10025): 1335-46.
3. Zuhlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J* 2015; **36**(18): 1115-22a.
4. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
5. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. *BMC Cardiovasc Disord* 2012; **12**: 23.
6. Soma-Pillay P, Seabe J, Sliwa K. The importance of cardiovascular pathology contributing to maternal death: Confidential Enquiry into Maternal Deaths in South Africa, 2011-2013. *Cardiovasc J Afr* 2016; **27**(2): 60-5.
7. Haththotuwa HR, Attygalle D, Jayatilleka AC, Karunaratna V, Thorne SA. Maternal mortality due to cardiac disease in Sri Lanka. *Int J Gynaecol Obstet* 2009; **104**(3): 194-8.
8. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart* 2007; **93**(5): 552-8.
9. UN. The Millennium Development Goals report 2015. New York, 2015.
10. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
11. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
12. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; **31**(23): 2915-57.
13. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015; **132**(2): 132-42.
14. Fund IM. World Economic Outlook - Recovery Strengthens, Remains Uneven. Washington; April 2014.
15. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119**(14): 1977-2016.
16. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009; **10**(1): 1-25.
17. Kampman MA, Bilardo CM, Mulder BJ, et al. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol* 2015; **46**(1): 21-8.
18. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol* 2003; **91**(11): 1382-5.
19. Rezk M, Gamal A. Maternal and fetal outcome in women with rheumatic heart disease: a 3-year observational study. *Arch Gynecol Obstet* 2016; **294**(2): 273-8.

20. Clark SL, Phelan JP, Greenspoon J, Aldahl D, Horenstein J. Labor and delivery in the presence of mitral stenosis: central hemodynamic observations. *Am J Obstet Gynecol* 1985; **152**(8): 984-8.
21. Joshi HS, Deshmukh JK, Prajapati JS, Sahoo SS, Vyas PM, Patel IV. Study of Effectiveness and Safety of Percutaneous Balloon Mitral Valvulotomy for Treatment of Pregnant Patients with Severe Mitral Stenosis. *J Clin Diagn Res* 2015; **9**(12): OC14-7.
22. Pomini F, Mercogliano D, Cavalletti C, Caruso A, Pomini P. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg* 1996; **61**(1): 259-68.
23. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**(19): 2451-96.
24. Sliwa K, Johnson MR, Zilla P, Roos-Hesselink JW. Management of valvular disease in pregnancy: a global perspective. *Eur Heart J* 2015; **36**(18): 1078-89.
25. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
26. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol* 1994; **170**(3): 849-56.
27. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**(22): 2438-88.

CHAPTER 8

Risk of Pregnancy in Moderate and Severe Aortic Stenosis: Results from a Multinational Registry (ROPAC)

Stefan Orwat
Gerhard-Paul Diller
Iris M. van Hagen
Renate Schmidt
Daniel Tobler
Matthias Greutmann
Regina Jonkaitiene
Amro Elnagar
Mark R. Johnson
Roger Hall
Jolien W. Roos-Hesselink
Helmut Baumgartner, on behalf of the ROPAC investigators.

J Am Coll Cardiol. 2016 Oct 18;68(16):1727-1737.

ABSTRACT

Background Controversial results on maternal risk and fetal outcome have been reported in women with aortic stenosis (AS).

Objectives To investigate maternal and fetal outcome in patients with AS in a large cohort.

Methods The Registry on Pregnancy and Cardiac Disease (ROPAC) is a global, prospective observational registry of women with structural heart disease providing a uniquely large study population. Data of women with moderate (peak gradient 36-63mmHg) and severe AS (peak gradient ≥64mmHg) were analyzed.

Results Out of 2,966 pregnancies in ROPAC, we identified 99 pregnancies in women with AS, who had at least moderate AS (34 severe AS). No deaths were observed during pregnancy and the first week after delivery. However, 20.8% of women required hospitalisation for cardiac reasons during pregnancy. This was significantly more common in severe AS compared to moderate AS (35.3% vs. 12.9%, p=0.02) and reached the highest rate (42.1%) in severe, symptomatic AS. Pregnancy was complicated by heart failure in 6.7% of asymptomatic and 26.3% of symptomatic patients but could be managed medically except for one patient who was symptomatic prior to pregnancy and required balloon valvotomy. Children of patients with severe AS had a significantly higher percentage of low birth weight (35.0% vs. 6.0%; p=0.006).

Conclusion Mortality in pregnant women with AS, including those with severe AS appears to be close to zero in the current era. Symptomatic and severe AS does, however, carry a substantial risk of heart failure and is associated with high rates of hospitalisation for cardiac reasons although heart failure can nearly always be managed medically. The results highlight the importance of appropriate preconceptional patient evaluation and counselling.

INTRODUCTION

Pregnancy carries a very low risk of death in developed countries, but overall cardiac reasons remain the leading cause of maternal mortality[1]. Consistent with this, women with pre-existing heart disease have a 100 times greater mortality than normal[2]. Pregnancy is associated with profound changes in haemodynamic parameters, perhaps explaining why pre-existing heart disease has such an adverse impact on morbidity and mortality in pregnant women[3]. Although there is clear evidence that pregnancy is a high risk endeavour in women with complex heart disease and especially those with severe pulmonary hypertension[4,5], available data are limited in women with less complex heart disease. Obstructive heart lesions will be aggravated by the increase in stroke volume occurring with pregnancy and are therefore of particular concern. Aortic stenosis (AS) is one of these lesions but it is relatively uncommon in women of childbearing age. However, when present, it has been reported to be associated with increased risk of maternal cardiovascular events – including death, obstetric morbidity such as preterm birth, and fetal complications including growth restriction, miscarriage, and stillbirth[6]. The evidence in this setting is nevertheless limited and the results of published reports are conflicting. Unfortunately, prior studies either encompassed all forms of heart disease[7,8] or included mild AS[9]. In addition, some series report on historic patient cohorts[6]. As a consequence the reported maternal mortality rate ranges between 2% and 17.4% and the risk in contemporary cohorts of women presenting with severe AS remains unclear[6,9].

The purpose of this study was therefore to investigate maternal and fetal adverse events in contemporary patients with moderate or severe AS based on a prospective observational study of a large number of pregnancies in patients with AS included in the Registry Of Pregnancy And Cardiac disease (ROPAC).

METHODS

ROPAC is a global, prospective, observational registry of women with heart disease. It was initiated by the European Society of Cardiology (ESC) working groups on congenital heart disease and valvular heart disease and is part of the EURObservational Research Programme of the ESC. The Registry allows for the inclusion of patients with structural or ischaemic heart disease, aortic pathology and pulmonary hypertension. The Registry started in January 2008. Patients who were pregnant in 2007 could also be included retrospectively, from January 2008 patients were included prospectively. The overall mortality in the registry has been reported at 1%. Further details on the Registry and the Institutional Review Board/ethical approval have previously been published[2,10]. The current study is covered by approval under the umbrella of the general ROPAC project.

The present study retrospectively analyzed the outcome and complications in pregnant women with moderate or severe AS included in the Registry up to April 2014. We focused exclusively on women with moderate or severe AS. Patients with additional congenital or acquired heart disease (with the exception of simple corrected pre-tricuspid shunts, aortic coarctation) were not included in the current study. The severity of AS was graded based on available transthoracic echocardiographic data at baseline. Moderate AS was defined as a peak transaortic gradient ≥36 mmHg (corresponding to a peak velocity of ≥3 m/s), while severe AS was defined as a peak aortic gradient ≥64 mmHg (corresponding to a peak velocity of ≥4 m/s) based on the simplified Bernoulli equation[11,12]. This is in agreement with current guidelines and general recommendations for assessing the severity of AS in the presence of normal flow rate[13]. Patients who had undergone aortic valve replacement prior to pregnancy were included if they fulfilled the haemodynamic criteria described above. However, further analyses were also performed and presented separately since prosthetic valve related risks require additional consideration.

Baseline characteristics included maternal age, general cardiovascular risk factors, major non-cardiac disease, cardiac diagnosis, prior interventions, cardiac symptoms, medication and obstetric history. Heart failure prior to pregnancy was defined according to current guidelines clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat)[14]. Maternal mortality was defined as death during pregnancy or up to one week after delivery. Miscarriage was defined as loss of pregnancy up to 24 weeks of gestation or a fetus weighting <500 gramm while fetal mortality was defined as fetal loss beyond 24 weeks of pregnancy. Outcome measures included maternal mortality, maternal hospital admission (all-cause and admission for cardiac reasons), preterm labour (<37 weeks of gestation), neonatal mortality (neonatal death <30 days postpartum), low birth weight (defined as a birth weight <2500 grams according to WHO criteria), small for gestational age neonates (weight below the 10th percentile for gestational age) and the need for Caesarean section.

Statistical analysis

Data are presented as numbers (percentage) for categorical variables or mean±standard deviation [SD] or median (interquartile range [IQR], 25th to 75th percentile) for continuous variables, depending on data distribution. Groups were compared with the use of Chi-square, t-tests or nonparametric Mann-Whitney U tests, respectively. The relation between baseline parameters and outcome was assessed with the use of univariable and multivariable logistic regression analyses and odds ratios (OR) with 95% confidence intervals are provided. Models were built by including significant univariable parameters into a multivariable

analysis. For all analyses, a two-tailed p-value <0.05 was used as the criterion for statistical significance. Analyses were performed with the use of Medcalc statistical software version 14.12.0 (Medcalc Software, Ostend, Belgium).

RESULTS

Baseline characteristics

Based on the ROPAC registry, including 2,966 pregnancies from 99 centres in 40 countries (enrolled between 2008 and 2014), we identified 99 pregnancies in 96 women with at least moderate AS, who had adequate baseline echocardiographic data at a mean(±SD) of 52±347 days before conception. Of these 44% were performed before conception. No significant difference in the mean peak aortic gradient was seen between patients with and without pre-conceptional echocardiographic assessment (59±22mmHg vs. 64±29mmHg, p=0.33). Overall, 22 women had already one child, 17 women two children and 13 had three or more children. Baseline maternal characteristics are presented in **Table 1**. The median age at pregnancy was 30 years. Before pregnancy 62.5% of AS patients were asymptomatic, while 33.3 % were classified as NYHA class II and 4.2% as NYHA class III. Approximately 50% of patients had a previous successful pregnancy. Stratifying patients by the severity of the underlying AS revealed that the 34 women with severe AS were more likely to be symptomatic or to have pre-existing heart failure symptoms (**Table 1**). In the current study, bicuspid aortic valve was the most prevalent aetiology for AS (53.5%). In addition, 18 patients had rheumatic aortic valve disease. None of patients had connective tissue disorders such as Marfan or Ehlers Danlos syndrome. Two patients had aortic dilatation (45 mm and 50 mm aortic diameter). In total 12 patients had repaired aortic coarctation (9 of them with bicuspid aortic valve). The peak aortic gradient was (mean±SD) 62.1±26.3 mmHg, while the mean aortic gradient was found to be 39.1±17.9 mmHg. With the exception of one woman with an ejection fraction of 39%, all patients had a normal left ventricular systolic function.

Overall, 8 patients had a previously implanted bioprosthesis (7 in aortic position, 1 in mitral position). Of these only the patient with the mitral bioprosthesis had severe native AS (peak gradient 71 mmHg, mean gradient 49 mmHg), while the patients with aortic bioprostheses exhibited only moderate AS (peak gradient 47.1±6.5 mmHg, mean gradient 28.1±5.4 mmHg). In addition, 13 patients had a previously implanted mechanical heart valve (4 in mitral position, 10 in aortic position and 1 in both positions). The peak and mean Doppler gradients in those patients with a mechanical aortic valve were 64.4±26.7 and 39.0±20.2 mmHg, respectively. Anticoagulation was performed with oral vitamin K antagonists throughout pregnancy or staged therapy with low molecular heparin during the first trimester followed by vitamin K antagonists in 10 patients. Low molecular weight heparin was used throughout pregnancy in 3 patients. None of the patients developed a

Table 1 Maternal Baseline Characteristics

	All AS Patients	Moderate AS	Severe AS	p-value	Asymptomatic pts.	Symptomatic pts.	p-value
Number of patients	96	62	34		60	36	
Age in years (Median, IQR)	30.3 [26.0 - 32.8]	29.8 [26.3 - 32.9]	30.6 [25.9 - 32.7]	*0.96*	30.5 [26.2 - 33.4]	29.9 [25.8 - 32.8]	*0.67*
Nulliparous (%)	47 (49%)	36 (58.1 %)	11 (32.4 %)	***0.028***	36 (60 %)	11 (30.6 %)	***0.01***
Prior cardiac intervention (%)	48 (50%)	34 (54.8 %)	14 (41,2 %)	*0.11*	30 (50.0 %)	18 (50 %)	*0.83*
NYHA class							
NYHA class I	60 (62.5 %)	45 (72.6 %)	15 (44.1 %)	***0.02***	60 (100 %)	-	-
NYHA class II	32 (33.3 %)	15 (24.2 %)	17 (50.0 %)		-	32 (88.9 %)	
NYHA class III	4 (4.2 %)	2 (3.2 %)	2 (5.9 %)		-	4 (11.1 %)	
NYHA class IV	0 (0 %)	0 (0 %)	0 (0 %)		-	0 (0 %)	
Aortic stenosis location							
Valvular	59 (61.5 %)	45 (72.6 %)	18 (52.9 %)	***0.02***	35 (58.3 %)	24 (66.7 %)	*0.49*
Subvalvular	22 (22.9 %)	11 (17.7 %)	11 (32.4 %)		16 (26.7 %)	6 (16.7 %)	
Supravalvular	0 (0 %)	0 (0 %)	0 (0 %)		0 (0 %)	0 (0 %)	
Not specified	15 (15.6 %)	10 (16.1 %)	5 (14.7 %)		9 (15.0 %)	6 (16.7 %)	
Bicuspid aortic valve	46 (53.5 %)	34 (60.7 %)	12 (40.0 %)	*0.18*	35 (64.8 %)	11 (34.4 %)	***0.02***
Aortic peak gradient (mmHg, mean ± SD)	62.1 ± 26.3	47.5 ± 6.9	88.7 ± 28.0	***<0.0001***	56.8 ± 20.1	71.1 ± 32.7	***0.006***
Aortic mean gradient (mmHg, mean ± SD)	39.1 ± 17.9	27.8 ± 5.3	55.1 ± 17.4	***<0.0001***	35.4 ± 16.0	44.3 ± 19.5	***0.006***
Left ventricular function (ejection fraction %, , mean ± SD)	65.6 ± 8.7	67.4 ± 6.2	62.4 ± 11.5	*0.27*	66.6 ± 7.1	64.0 ± 10.7	*0.60*

Table 1 Maternal Baseline Characteristics (continued)

	All AS Patients	Moderate AS	Severe AS	p-value	Asymptomatic pts.	Symptomatic pts.	p-value
Hypertension (%)	11 (11.5 %)	9 (14.5 %)	2 (5.9 %)	*0.35*	6 (10 %)	5 (13.9 %)	*0.80*
Smoker, current or previous (%)	11 (12.8 %)	8 (14.0 %)	3 (10.3 %)	*0.73*	7 (12.5 %)	4 (13.3 %)	*0.73*
Diabetes (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Pre-existing heart failure symptoms (%)	13 (13.5 %)	3 (4.8 %)	10 (29.4 %)	***0.002***	0 (0 %)	13 (36.1 %)	***<0.0001***
Cardiac medication (%)	14 (35.9 %)	9 (34.6 %)	5 (38.4 %)	*0.91*	8 (33.3 %)	6 (40.0 %)	*0.94*
Beta-blocker (%)	7 (12.5 %)	4 (11.1 %)	3 (15.0 %)	*0.22*	5 (13.9 %)	2 (10.0 %)	*0.56*
ACE-Inhibitors / ARB (%)	3 (5.4 %)	2 (5.6 %)	1 (5.0 %)	*0.60*	1 (2.8 %)	2 (10.0 %)	*0.60*
Anticoagulation (%)	11 (19.6 %)	9 (33.3 %)	2 (10.0 %)	*0.68*	8 (22.2 %)	3 (15.0 %)	*0.53*

Values are n, median (IQR), n (%), or mean ± SD. p Values refer to differences between patients with moderate and severe AS or asymptomatic and symptomatic patients, respectively. P Values in **bold** are statistically significant.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AS = aortic stenosis; IQR = interquartile range; NYHA = New York Heart Association.

valve thrombosis, neither in the entire cohort, nor specifically in those with a mechanical aortic valve.

Maternal cardiac complications

No patient died during pregnancy or within 1 week postpartum. However, cardiovascular events and hospitalisations were common. Overall, 35.8% of patients required at least one hospital admission during pregnancy; 20.8% admission for cardiac reasons (**Table 2**). Women with severe AS were significantly more likely to be admitted during pregnancy (35.3% cardiac admissions) compared to those with only moderate AS (12.9 %, p=0.02). The mean gestational week for the occurrence of heart failure was 27.2±7.5 weeks, for the first hospital admission for cardiac reasons 24.3±9.7 weeks and for hospital admissions for all reasons 26.9±9.5 weeks. The highest rate of hospitalisation for cardiac reasons was seen in symptomatic severe AS patients with a rate of 42.1%. Pregnancy was complicated by heart failure in 6.7% of patients asymptomatic prior to pregnancy but 26.3% of symptomatic patients with severe AS.

The leading cardiac complications were new or worsening heart failure during pregnancy and arrhythmias. In contrast, cerebrovascular complications or pulmonary embolism were not recorded in this cohort and only one patient was reported to have developed endocarditis during pregnancy.

Heart failure could be managed medically in all patients, except for one case requiring aortic valvotomy. This patient with a history of two previous pregnancies was unaware of the severe AS although she had suffered from severe dyspnoea after a previous delivery. She presented with critical AS and heart failure at 20 weeks of gestation and had impaired left ventricular systolic function. Aortic valvuloplasty was performed, resulting in a reduction in both peak and mean gradients from 156 and 71mmHg pre-intervention to 113 and 55mmHg post-intervention, respectively and in moderate aortic regurgitation. The further course of the pregnancy and delivery was uneventful. The patient delivered vaginally at 38 weeks a baby of 3,200 grams. However, one month after delivery, the patient presented again with severe symptoms and underwent aortic valve replacement (AVR).

One patient underwent AVR with a mechanical prosthesis during pregnancy as a consequence of aortic valve endocarditis at 4 months into pregnancy. The further course of the pregnancy was uneventful in this patient with a vaginal delivery at 38 weeks.

Obstetric and fetal outcomes

Median pregnancy duration was 38.6 [IQR 37.2-39.8] weeks, and this was significantly shorter in patients with severe AS (37.9 [IQR 35.2-39.0] vs. 39.0 [IQR 38.0-40.0] weeks, p=0.001, **Table 2**). Women with severe AS also had a significantly higher rate of Caesarean section compared to those with moderate AS (75.0% vs. 48.3%, p=0.008). The main reason for Caesarean section was a cardiac indication, recorded in 65.9% of patients. A low Apgar

Table 2 Maternal and Fetal Outcomes

	All AS Patients	Moderate AS	Severe AS	p-value	Asymptomatic pts.	Symptomatic pts.	p-value
Maternal mortality (%)	0%	-	-	-	-	-	-
Maternal hospital admission (%)	34 (35.8 %)	17 (27.4 %)	17 (51.5 %)	***0.027***	21 (35.0 %)	13 (37.1 %)	*0.42*
Maternal cardiac hospital admission (%)	20 (20.8 %)	8 (12.9 %)	12 (35.3 %)	***0.02***	9 (15.0 %)	11 (30.6 %)	*0.12*
Cardiac complications							
Heart failure	11 (11.5%)	5 (8.1 %)	6 (17.6 %)	*0.29*	5 (8.3 %)	6 (16.7 %)	*0.36*
Arrhythmias (SVT)	1 (1.0 %)	1 (1.6 %)	0 (0 %)	*0.76*	1 (1.7 %)	0 (0 %)	*0.80*
Arrhythmias (VT/VF)	1 (1.0 %)	0 (0 %)	1 (2.9 %)	*0.76*	0 (0 %)	1 (2.8 %)	*0.79*
Endocarditis (%)	1 (1.0 %)	1 (1.6 %)	0 (0 %)	*0.76*	1 (1.7 %)	0 (0 %)	*0.80*
Valve thrombosis (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Cerebrovascular complication (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Pulmonary embolism (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Deep venous thrombosis (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Obstretic complications							
Pregnancy-induced hypertension (%)	3 (3.2 %)	2 (3.2 %)	1 (3.0 %)	*0.57*	2 (3.3 %)	1 (2.9 %)	*0.63*
(pre-)Eclampsia (%)	3 (3.2 %)	3 (4.8 %)	0 (0 %)	*0.50*	3 (5.0 %)	0 (0 %)	*0.46*
Caesarean section (%)	54 (57.4 %)	30 (48.3 %)	24 (75.0 %)	***0.008***	30 (50.0 %)	24 (70.6 %)	***0.029***
Haemorrhagic events (%)	4 (4.2 %)	4 (6.5 %)	0 (0 %)	*0.33*	4 (66.7 %)	0 (0 %)	*0.29*

Table 2 Maternal and Fetal Outcomes (continued)

	All AS Patients	Moderate AS	Severe AS	p-value	Asymptomatic pts.	Symptomatic pts.	p-value
Fetal outcome							
Apgar score <7 (%)	8 (9.0 %)	3 (5.2 %)	5 (16.1 %)	*0.21*	4 (7.0 %)	4 (12.5 %)	*0.37*
Pregnancy duration (weeks)	37.2 ± 5.2	38.0 ± 4.4	35.5 ± 6.4	***0.002***	37.0 ± 6.2	37.5 ± 2.8	*0.08*
Preterm birth < 37 weeks (%)	18 (20.9 %)	8 (16.0 %)	10 (35.7 %)	***0.017***	10 (18.2 %)	8 (25.8 %)	*0.49*
Mean birth weight (g)	3010 ± 691	3198 ± 549	2648 ± 797	***0.003***	3091 ± 642	2878 ± 758	*0.24*
Low birth weight (<2,500 g)	16 (16.2 %)	4 (6.0%)	12 (35.0 %)	***0.006***	6 (10.0 %)	10 (27.8 %)	***0.037***
Small for gestational age	8 (9.3 %)	2 (3.4 %)	6 (21.4 %)	***0.022***	3 (5.5 %)	5 (16.1 %)	*0.21*
Miscarriages (%)	2 (2.1 %)	2 (3.2 %)	0 (0 %)	*0.76*	2 (3.3 %)	0 (0 %)	*0.71*
Fetal death (%)	0 (0 %)	0 (0 %)	0 (0 %)	-	0 (0 %)	0 (0 %)	-
Neonatal death (%)	1 (1.1 %)	0 (0 %)	1 (3.3 %)	*0.05*	0 (0 %)	1 (3.0 %)	*0.38*

Values are n (%) or mean ± SD. p Values refer to differences between patients with moderate and severe AS or asymptomatic and symptomatic patients, respectively. p Values in bold are statistically significant.

AS = aortic stenosis; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

score below 7 was present in 9.0% of neonates (5.2% vs. 16.1% of pts. with moderate and severe AS, respectively; p=0.21). Children of patients with severe AS had a significantly lower birth weight (3200 [IQR 2932-3490] vs. 3000 [IQR 2145-3227]g, p=0.0025).

There were 2 miscarriages (both in moderate AS), no fetal losses between 24 weeks and delivery and 1 neonatal death (in severe AS). The neonatal death occurred after a pregnancy duration of 30 weeks and 2 days. The child that died was delivered by Caesarean section, and was small for gestational duration with a weight of 1000 g; the exact reason for delivery was not documented but the child died due to respiratory distress syndrome. This event occurred in a mother with severe AS, who had a previous unsuccessful pregnancy complicated by heart failure and arrhythmias.

Predictors of maternal or fetal complications

Figure 1-3 present predictors of adverse maternal or fetal outcome. As illustrated in **Figure 1**, the odds ratio of hospitalisation in women with severe AS was 2.77 compared to those with only moderate AS. In addition, peak aortic gradient on transthoracic echocardiography was significantly associated with a higher risk of maternal hospitalisation during pregnancy (OR 1.245/10 mmHg, p=0.024). On multivariable analysis, peak aortic gradient emerged as an independent predictor of maternal outcome. Regarding fetal outcome, again, severity of AS and peak aortic gradient on echocardiography proved to be independent predictors of low birth weight (**Figure 2**) and small for gestational age neonates , respectively (**Figure 3**).

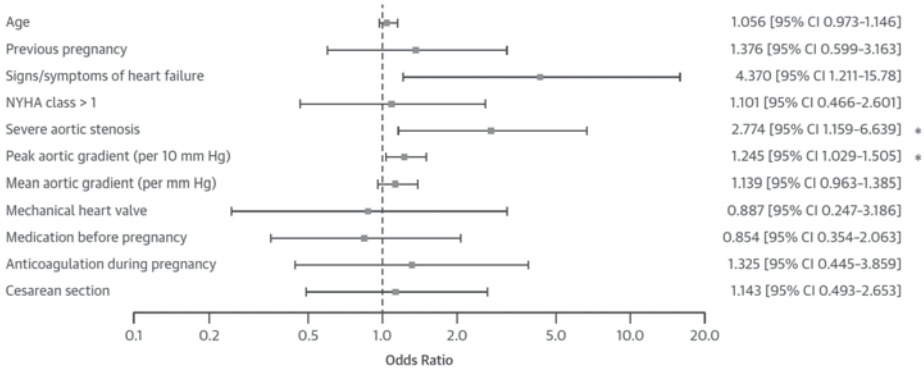


Figure 1 Predictors of adverse maternal outcome

Forrest plots illustrating the results of the univariate logistic regression analysis for adverse maternal outcome, defined as hospital admission during pregnancy. Severe aortic stenosis and the peak aortic gradient were significantly related to worse outcome. An asterisk denotes significant results. CI = confidence interval; NYHA = New York Heart Association.

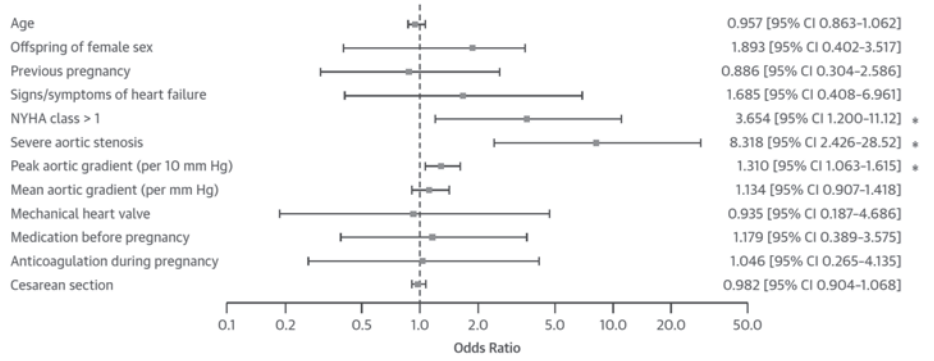


Figure 2 Predictors of low birth weight

Forrest plots illustrating the results of the univariate logistic regression analysis for adverse fetal outcome (low birth weight, defined as birth weight <2,500 g). Severe aortic stenosis, peak aortic gradient, and NYHA class >1 at baseline were predictive of worse fetal outcome. An asterisk denotes significant results. Abbreviations as in Figure 1.

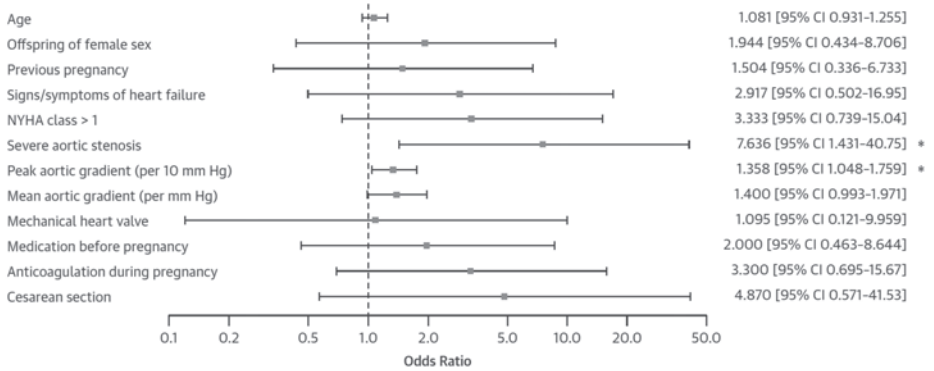


Figure 3 Predictors of small for gestational age infants

Forrest plots illustrating the results of the univariate logistic regression analysis for adverse fetal outcome (small for gestational age). Severeaortic stenosis and peak aortic gradient were predictive of worse fetal outcome. An asterisk denotes significant results. Abbreviations as in Figure 1.

Differences between countries of the European Union (EU)/United States (US) and non EU countries

Seventy-four pregnancies were reported from inside the EU or the US (Group A) and 25 from outside the EU or the US (Group B). Group B included 16 cases from Egypt, 5 from the Russian Federation, 2 from the Arab Emirates and one from each Turkey and Serbia/Montenegro. Comparing the two cohorts revealed no significant differences between the groups regarding the severity of AS (severe AS 28.3% vs. 52.0% in group A and group B countries, p=0.057), the peak aortic gradient (group A: 59.7±25.8 vs. group B: 68.4±25.9 mmHg, p=0.16) or the

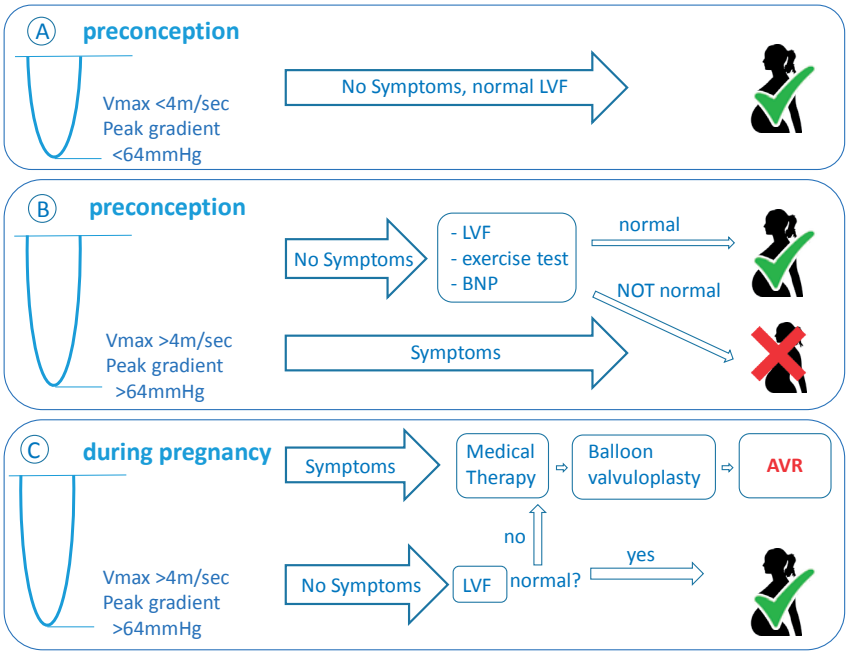
mean aortic gradient (group A: 37.4±18.1 vs group B: 42.9±16.6 mmHg, p=0.11). Women from Group B countries were however more frequently symptomatic at baseline (56.0% vs. 29.7%, p=0.034) and required more hospital admissions during pregnancy (52.0% vs. 30.1%, p=0.049 overall and 48.0% vs. 12.2%, p=0.0005 for cardiac reasons) compared to those from Group A countries. The rate of fetal complications such as small for gestational age (group A: 9.4% vs. group B: 9.1%, p=0.70) and preterm birth (group A: 21.7% vs. group B: 14.3%, p=0.40) was similar between the cohorts.

DISCUSSION

The current registry based study suggests that mortality risk in pregnant women with AS, including those with severe AS, is close to zero. However, pregnancies may be associated with a relatively high burden of morbidity such as hospital admissions for cardiac reasons in up to one third of patients with severe AS. The leading maternal complication during pregnancy was heart failure which occurred primarily in patients with severe AS, already symptomatic prior to pregnancy. In contrast, patients asymptomatic prior to pregnancy – even with haemodynamically severe AS – had a relatively low rate of heart failure occurrence (6.7%). It is alarming, however, that over 50% of patients with severe AS had symptoms and therefore an indication for valve replacement before pregnancy emphasizing the need for improvement in cardiac evaluation and appropriate preconceptional counselling of patients. Fortunately, heart failure could be managed, in all but one women medically. The main predictor of maternal complications besides symptoms of AS prior to pregnancy was the haemodynamic severity of AS. Severe fetal complications were rare but preterm birth and a low birth weight were observed in approximately one third of patients.

It is well recognised that valvular heart disease patients are more likely than other groups of women with structural heart disease to require hospitalisation, suffer from supraventricular arrhythmias, or experience postpartum haemorrhagic complications. A previous report based on the ROPAC registry found aortic valve disease to be present in 23% of pregnant patients with valvular heart disease, with AS being the second most common stenotic valve lesion in this cohort[2]. Current guidelines consider symptomatic severe AS as a high risk condition and recommend to avoid pregnancy[1,4]. In asymptomatic patients a comprehensive preconception assessment, including an exercise test evaluating physical capacity and blood pressure response to exercise is recommended (see **Central Illustration**). This approach is, however, controversial due to absent/limited data regarding the prognostic value of prepregnancy exercise testing in the setting of AS[4].

Even women with AS who remain asymptomatic during pregnancy are subjected to additional hemodynamic stress at the time of delivery and the immediate postpartum period.



Central illustration Evaluation of women with moderate or severe aortic stenosis

Figure Legend: A and B: Preconception counseling. Only patients with severe AS and symptoms or asymptomatic patients with reduced left ventricular function, abnormal exercise test or high brain natriuretic peptide plasma levels should be counseled against pregnancy and AS should be treated.

C: Management of women with severe AS during pregnancy. In case of heart failure symptoms patient are first treated medically (primarily diuretics in addition to restricting physical activities). If medical treatment is insufficient, percutaneous aortic balloon valvuloplasty can be considered to delay surgical valve replacement until the postpartum period. In case of persistent severe heart failure symptoms despite valvuloplasty or when patients are not eligible for valvuloplasty, aortic valve replacement (AVR) should be considered during pregnancy. Asymptomatic patients with normal LVF are followed without treatment. Strenuous physical activities should be avoided.

BNP = brain natriuretic peptide; LVF = left ventricular function; Vmax = peak velocity of blood flow across the valve

Therefore, these women may become symptomatic at the time of delivery and should be managed in a team approach including experienced cardiologists, obstetricians and anesthesiologists. In asymptomatic patients in good clinical condition, with normal cardiac function, spontaneous labour is generally preferred to induced labour[1]. In contrast, there is less consensus on the recommended mode of delivery in symptomatic patients. Generally, vaginal delivery carries a lower risk of complications for mother and fetus. Compared with caesarean section, it normally causes smaller shifts in blood volume, less haemorrhage, the absence of abdominal surgery, decreased thrombogenic risk and fewer infections. Furthermore, the hypertrophied left ventricle in AS may be sensitive to abrupt changes in preload (e.g. from anesthetic agents or haemorrhage). Early epidural analgesia is generally

recommended. Caesarean section should be reserved mainly for obstetric indications or in case of aortic dilatation or overt heart failure[1]. Nevertheless in some centers caesarean section seems to be a preferred mode of delivery in women with AS. This may be explained by various factors related to personal physician and mother's preferences, cultural aspects, local standards and logistical reasons affecting the choice of delivery mode.

While historic series report maternal mortality rates, ranging from 11 to 20%,[6,9,15-17] in more recent series the cardiac event rates were lower with approximately 10% of patients suffering a cardiac event and mortality being rare[15,17,18]. However, some of these studies also included women with mild AS, diluting the clinically interesting group of patients with moderate/severe AS. The current multinational study based on 99 pregnancies between 2007 and 2014 and focusing specifically on moderate or severe AS showed no maternal mortality, thus supporting the notion that maternal morbidity rather than mortality is the main clinical problem in this setting. Previous studies suggest a risk of heart failure during pregnancy of approximately 10%[1,15]. Our data are consistent with this estimate, showing that heart failure occurred in 11.5% of patients with moderate or severe AS. However, in patients with pre-existing symptoms pregnancy was complicated by heart failure in 26.3%. Arrhythmias are also a recognized common complication during pregnancy in this setting, with a reported incidence of 3-25% in previous reports[1]. In the current series arrhythmias were also reported as a complication but with a relatively low rate of around 3%.

Overall, 57% of women included in the current study delivered by Caesarean section. This rate is comparable to a recent AS study[18] but higher than the overall Caesarean section rate of 42% reported in the ROPAC registry[19] and higher in comparison to previous AS studies[17,20]. This difference may be related to the fact that the current study included a larger proportion of patients with severe AS and a considerable number of patients required anticoagulation. While current recommendations support a vaginal delivery with assisted second stage of labour in the majority of patients, Caesarean section continues to be advocated by some physicians in women with severe AS and in those requiring anticoagulation[1]. Furthermore, country specific preferences may account for some of the differences as discussed in detail previously[21].

Severe fetal complications were rare in the current study but preterm birth and low birth weight were observed in one third of patients with severe AS. In addition, newborns of women with severe AS were more likely to have a low Apgar score, to present with low birth weight and to be small for gestational age. The underlying reasons remain speculative but are likely multifactorial. Women with severe AS had a significantly shorter pregnancy duration compared to those with moderate AS (35.5±6.4 vs. 38.0±4.4; p=0.002), potentially related to the higher rate of Caesarean section in this setting. In addition haemodynamic compromise due to AS resulting in a reduced utero-placental blood flow is a plausible alternative explanation for the impaired intrauterine fetal growth seen in this study and this

is supported by the higher prevalence of small for gestational age (accounting for duration of pregnancy) newborns in the severe AS cohort[22].

The most important predictor of, both, maternal and fetal adverse events in the current study was the haemodynamic severity of AS. In fact, patients with severe AS had an approximately 2.8-fold increased risk of maternal complications and a 7.6-fold increased risk of fetal complications compared to women with only moderate AS. Interestingly, the peak aortic gradient before pregnancy - as a continuous variable – emerged as the only independent predictor of complications on multivariable logistic regression analysis. This finding, although conceivable, is novel as previous studies could not confirm a statistical association between baseline severity of AS and outcome in this setting[15,17].

Two women included in this study required aortic valve intervention during pregnancy. Both procedures were successful and the patients continued to have uneventful pregnancies with vaginal deliveries of healthy babies. This illustrates that, in experienced hands, complications can be managed successfully in the current era, however, the risks associated with these procedures (especially the risk of fetal loss) should not be underestimated[23]. Therefore, appropriate preconceptional assessment and counselling are paramount to avoid pregnancy complications and to allow for elective procedures to be performed before pregnancy especially in symptomatic women with severe AS. On the other hand, the low complication rate in asymptomatic patients – even those with haemodynamically severe AS – supports a conservative approach and avoidance of prophylactic surgery in this group considering the dilemma of managing pregnancy in the presence of a prosthetic valve[1].

Limitations

Due to the multinational nature of the registry we included pregnancies in developed and emerging countries. We accept that outcomes may be different in the latter setting. However, the vast majority of patients included (74 %) were from resource rich countries of the EU or from the US. In addition, obstetric outcomes were not statistically different between the EU/US and the remaining countries. Based on the haemodynamic inclusion criteria we also enrolled 13 patients with a mechanical heart valve. It is well appreciated that mechanical heart valves are associated with increased morbidity during pregnancy and worse fetal outcomes[24]. Under haemodynamic aspects, however, we believe that physiological changes during pregnancy should affect prosthetic and native valves similarly. In addition, in this series no prosthetic valve related complication was observed. Furthermore, comparing morbidity between patients with severe AS and those with prosthetic valves revealed higher rates of complications in the former group (17.6% vs. 11.5%, 35.3% vs. 20.8% and 51.5% vs. 35.8% for heart failure and cardiac or all-cause hospitalisation, respectively), supporting the notion that the degree of haemodynamic compromise rather than sequalae related to previous surgery relate to higher rates of complications during pregnancy.

The definition of maternal death employed here differs from the published WHO definition by considering mortality during pregnancy and within 7 days of delivery as opposed to a period of 42 days of termination of pregnancy recommended by the WHO[25]. In contrast to other cardiovascular disorders such as Marfan syndrome, pulmonary hypertension or cardiomyopathy, mortality beyond one week post partum nevertheless related directly to effect of the pregnancy on the disease is, however, unlikely in AS based on avialble literature and our own experience. Thus, a longer observation postpartum should not have significantly altered the results. In addition, the causality between pregnancy and later mortality may be difficult to establish in AS.

The current study did not investigate the problem of ascending aortopathy, which is associated especially with bicuspid aortic valve disease. Nevertheless, we did not observe pregnancy-associated aortic dissection in our cohort. Awareness of this potential complication and appropriate preconception and pregnancy assessment of aortic dimensions should be part of routine care for patients with known bicuspid aortic valve.

Not all of the patients had pre-pregnancy echocardiographic assessment. We are aware that gradients are expected to increase with increasing cardiac output. Therefore, the classification of AS severity before pregnancy may have been different in some patients with borderline measurements and first presentation during advanced pregnancy (i.e. some of the patients classified to have severe AS during pregnancy may have had moderate AS when pre-pregnancy data would have been available).

Conclusions

The current multinational study including 99 pregnancies in women with at least moderate AS managed in the current era, highlights the ongoing challenge of pregnancy in this setting. Although, maternal mortality rate was zero in this cohort, hospitalisations for cardiac reasons were frequent and both preterm birth and low birth weight were observed in one third of patients with severe AS. The fact that heart failure – the most frequent maternal complication – occurred predominantly in patients with severe AS who had at least mild symptoms indicating intervention already before pregnancy, emphasizes the importance of appropriate preconception patient evaluation and counselling.

REFERENCES

1. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
2. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
3. Uebing A, Steer PJ, Yentis SM, Gatzoulis MA. Pregnancy and congenital heart disease. *BMJ* 2006; **332**(7538): 401-6.
4. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; **31**(23): 2915-57.
5. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009; **30**(3): 256-65.
6. Arias F, Pineda J. Aortic stenosis and pregnancy. *J Reprod Med* 1978; **20**(4): 229-32.
7. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
8. Avila WS, Rossi EG, Ramires JA, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. *Clin Cardiol* 2003; **26**(3): 135-42.
9. Hameed A, Karaalp IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001; **37**(3): 893-9.
10. Greutmann M, Silversides CK. The ROPAC registry: a multicentre collaboration on pregnancy outcomes in women with heart disease. *Eur Heart J* 2013; **34**(9): 634-5.
11. Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation* 1985; **71**(6): 1162-9.
12. Hatle L, Angelsen BA, Tromsdal A. Non-invasive assessment of aortic stenosis by Doppler ultrasound. *Br Heart J* 1980; **43**(3): 284-92.
13. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009; **10**(1): 1-25.
14. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**(14): 1787-847.
15. Yap SC, Drenthen W, Pieper PG, et al. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol* 2008; **126**(2): 240-6.
16. Easterling TR, Chadwick HS, Otto CM, Benedetti TJ. Aortic stenosis in pregnancy. *Obstet Gynecol* 1988; **72**(1): 113-8.
17. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol* 2003; **91**(11): 1386-9.
18. Lesniak-Sobelga A, KostKiewicz M. Outcome of pregnancy in patients with bicuspid aortic valve - a study of 89 patients (RCD code: VII-IV-1D. 2o). *Journal of Rare Cardiovascular Disease* 2014; (2): 9-14.
19. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.
20. Tzemos N, Silversides CK, Colman JM, et al. Late cardiac outcomes after pregnancy in women with congenital aortic stenosis. *Am Heart J* 2009; **157**(3): 474-80.

21. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, et al. Is a planned caesarean section in women with cardiac disease beneficial? *Heart* 2015; **101**(7): 530-6.
22. Pieper PG, Balci A, Aarnoudse JG, et al. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. *Circulation* 2013; **128**(23): 2478-87.
23. Kapoor MC. Cardiopulmonary bypass in pregnancy. *Ann Card Anaesth* 2014; **17**(1): 33-9.
24. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation* 2015; **132**(2): 132-42.
25. Organization WH, UNICEF, Bank W, Fund UNP. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNFPA, and The World Bank. *Geneva, Switzerland: The World Health Organization* 2007: 1-48.

CHAPTER 9

Pregnancy in Women with a Mechanical Heart Valve: Data of the European Society of Cardiology Registry Of Pregnancy And Cardiac disease (ROPAC)

Iris M. van Hagen
Jolien W. Roos-Hesselink
Titia P.E. Ruys
Waltraut M. Merz
Sorel Goland
Harald Gabriel
Malgorzata Lelonek
Olga Trojnarska
Wael Abdulrahman Al Mahmeed
Hajnalka Olga Balint
Zeinab Ashour
Helmut Baumgartner
Eric Boersma
Mark R. Johnson
Roger Hall, on behalf of the ROPAC investigators and the EORP team.

Circulation. 2015 Jul 14;132(2):132-42.

ABSTRACT

Background Pregnant women with a mechanical heart valve (MHV) are at a heightened risk of a thrombotic event while their absolute need for adequate anticoagulation puts them at considerable risk of bleeding and, with some anticoagulants, fetotoxicity.

Methods and Results Within the prospective, observational, contemporary, worldwide *Registry Of Pregnancy And Cardiac disease* (ROPAC) we describe the pregnancy outcome of 212 patients with a MHV. We compare them to 134 patients with a tissue heart valve (THV) and 2620 other patients without a prosthetic valve (NoPHV). Maternal mortality occurred in 1.4% of the MHV patients, in 1.5% of THV patients (p=1.000) and in 0.2% of NoPHV patients (p=0.025). Mechanical valve thrombosis complicated pregnancy in 10 (4.7%) MHV patients; in five of them the valve thrombosis occurred in the first trimester, and all five had been switched to some form of heparin. Hemorrhagic events occurred in 23.1% of MHV patients, in 5.1% of THV patients (p<0.001) and in 4.9% of NoPHV patients (p<0.001). Only 58% of the MHV patients had a pregnancy free of serious adverse events, versus 79% of THV patients (p<0.001) and 78% of NoPHV patients (p<0.001). Vitamin K antagonist use in the first trimester compared with heparin was associated with a higher rate of miscarriage (28.6% versus 9.2%, p<0.001) and late fetal death (7.1% versus 0.7%, p=0.016).

Conclusions Women with a MHV have only a 58% chance of experiencing an uncomplicated pregnancy with live birth. The markedly increased mortality and morbidity warrants extensive pre-pregnancy counseling and centralization of care.

INTRODUCTION

The true extent of the adverse impact of structural heart disease on the outcome of pregnancy has become clearer over the last decade[1-3]. The marked hemodynamic changes and the hypercoagulable state in pregnancy increase the risk of complications in patients with cardiovascular disease and fetal development can be compromised by a failure of cardiac function or the need for cardiac medication. This is particularly true of women with a mechanical heart valve prosthesis (MHV), where the hypercoagulable state makes the maintenance of effective anticoagulation challenging[4,5]. More than 200,000 aortic valve replacements are performed each year worldwide[6], let alone replacements of heart valves in other positions. But the exact percentage of women of reproductive age having a mechanical valve is unknown. Indeed, having a MHV has been shown to be a predictor of adverse outcome of pregnancy[2,7], but studies are scarce and numbers are small.

In women at reproductive age with a MHV, the need to maintain adequate anticoagulation to prevent mechanical valve thrombosis (MVT) has to be balanced against the risks of teratogenicity, fetotoxicity and bleeding. Current guidelines recommend Vitamin K Antagonists (VKA) in the first trimester for the highest risk patients, while in the other patients dose adjusted low-molecular-weight-heparin (LMWH), unfractionated heparin (UFH) or VKA can be used[8,9]. Thereafter, a VKA is recommended until 36 weeks, when it should be replaced with (low-molecular-weight) heparin mainly to prevent fetal intracranial hemorrhage during vaginal delivery. These guidelines however, are based on weak scientific evidence (level C) and the optimal anticoagulation regime to use in pregnancy remains very uncertain[2]. We have carried out a prospective observational study of a large number of pregnancies in MHV patients in a broad range of clinical practices from developed and emerging countries. We compared them with women with structural heart disease without a prosthetic valve, and with women with a tissue heart valve (THV), and looked at the use and impact of the different anticoagulation regimes.

METHODS

Study design

The Registry of Pregnancy and Cardiac Disease (ROPAC) began in January 2008 as part of the Euro Heart Survey, which since 2009 is called EURObservational Research Programme (EORP) of the European Society of Cardiology. Details of the study design were previously published[3]. Pregnant women with structural heart or aortic disease were prospectively enrolled. When a center joined the Registry, they were allowed to include patients up to 6 months retrospectively. If required, ethical approval or Institutional Review Board approval was obtained (e.g. The Netherlands, Germany, USA, Canada, and Belgium) and subjects gave

written informed consent. However, in some countries the procedure to obtain ethical approval was waived because of the anonymized and untraceable nature of the data.

The first term of data collection ran until June 2011 and reports were published on these data[3,10]. The current study reports on the outcome and complications of pregnancy in women included in the Registry up to April 1st 2014, who had a MHV compared to the outcome of women with a THV and of women with structural heart disease but no prosthetic heart valve (NoPHV). To put the results in perspective, outcome of the normal pregnant population is also reported based on available literature[3,11].

Clinical data

Baseline characteristics included maternal age, general cardiovascular risk factors, major non-cardiac disease, cardiac diagnosis, prior interventions, cardiac symptoms, medication and obstetric history. The countries of origin were subdivided in emerging and developed countries according to the International Monetary Fund (IMF) classification[12].

Maternal mortality was defined as death during pregnancy and up to one week after delivery. Miscarriage was defined as loss of pregnancy up to 24 weeks and fetal mortality as fetal loss beyond 24 weeks. Thrombotic events include valve thrombosis, pulmonary embolism, deep vein thrombosis or any ischemic cardio- or cerebrovascular event. Major bleeding was defined as a hemorrhage resulting in at least a 1 gm/dl (or 0.62 mmol/l) decrease in hemoglobin, need for blood product transfusion, or end-organ damage such as hemorrhagic cerebrovascular accident or retina bleeding. Postpartum hemorrhage was defined as increased blood loss (more than 500 mL after vaginal delivery or more than 1000 mL after caesarean delivery) directly after delivery and up until 24 hours postpartum. Serious adverse events were maternal mortality, fetal loss, thrombotic events, major hemorrhagic events, supraventricular or ventricular arrhythmia requiring treatment, heart failure, endocarditis, acute coronary syndrome, aortic dissection, pre-eclampsia or HELLP (Hemolysis Elevated Liver enzymes Low Platelets) syndrome. The endpoint live birth was defined as pregnancies resulting in a live neonate.

Further definition of pregnancy outcome is described in the first ROPAC paper[3].

Data Analysis

We focused on the differences of outcome between women with a MHV and women with NoPHV. Secondary, we compared patients with a MHV to patients with a tissue heart valve (THV) and we assessed the differences in pregnancy outcome between emerging and developed countries. The anticoagulant regime used was analyzed for each patient, summarizing the anticoagulants in three clinically relevant intervals:

- the first trimester (up to 14 weeks)
- from 14 weeks until 36 weeks (if full-term; otherwise until the pre-delivery period)

- the pre-delivery period (36 weeks to delivery; or in case of preterm delivery an earlier transition of anticoagulants in view of the approaching labor)

Clearly, there is no second period of anticoagulation for patients with a pregnancy loss or maternal mortality in the first trimester; consequently these cases were excluded from the analysis of anticoagulation regimes.

Categorical data are presented as frequencies and percentages, and chi-square tests or Fisher's exact tests are used, as appropriate, to reveal differences between patients independent subgroups. After evaluation of normality by Kolmogorov-Smirnov tests, continuous data are presented as mean ± one standard deviation (SD), or median with first and third quartiles range (Q1-Q3). Student's t and Mann Whitney tests are used, as appropriate, to study differences between two groups. Univariable logistic regression analyses are used to assess associations between subgroups and outcome, followed by multivariable logistic regression to adjust for potential confounders. We adjusted for baseline characteristics that were significantly different between the subgroups. Results are presented as odds ratios (ORs) with 95% confidence interval. P-values are considered significant if smaller than 0.05 in context of a 2-sided test. The statistical analysis is carried out using IBM SPSS Statistics 21.0 (SPSS Inc., Chicago IL, USA).

RESULTS

Among the 2966 pregnancies enrolled in the Registry there were 212 patients with a MHV, 134 patients with a THV and 2620 patients with NoPHV (**Figure 1** and **Table 1**). MHV patients had mainly acquired valvular heart disease, while in other patients congenital heart disease was most common. MHV patients were more likely to be multiparous, and to have clinical signs of heart failure and atrial fibrillation prior to conception, while NYHA class was similar for MHV and NoPHV patients.

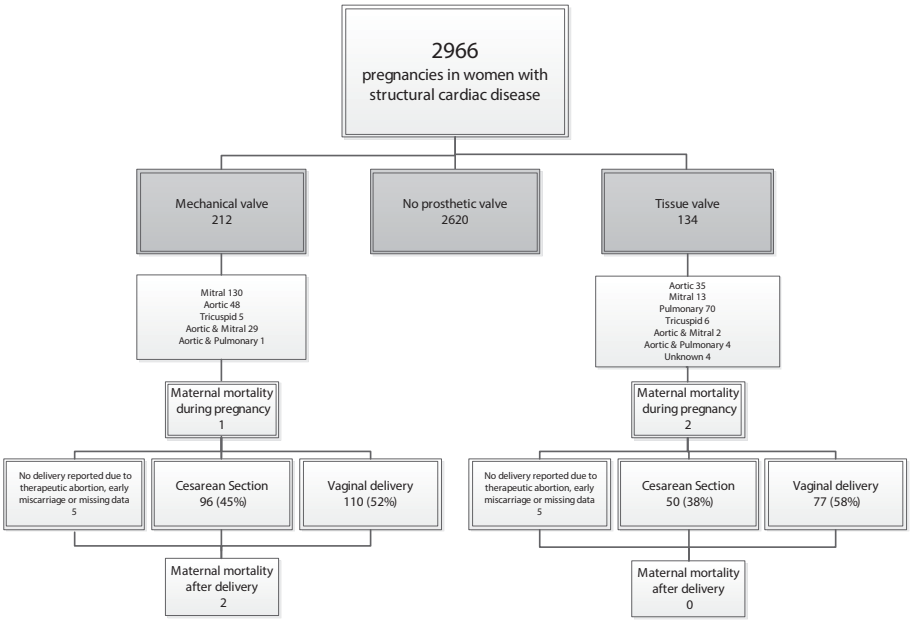


Figure 1 Flowchart of inclusion in the Registry Of Pregnancy And Cardiac disease

Table 1: Baseline characteristics

	Normal maternal population	Mechanical valve	No prosthetic valve	p-value mechanical vs no prosthetic valve
		n = 212	n = 2620	
Mean age (sd)	30	28.4 (±5.3)	29.3 (±5.7)	0.034
Nulliparous (%)	44%	66 (31.1)	1213 (46.4)	<0.001
Pre-existent hypertension (%)	7%	6 (2.8)	176 (6.9)	0.023
Current smoker (%)	10%	4 (2.0)	103 (4.6)	0.087
Pre-existent diabetes (%)	1.8%	3 (1.4)	42 (1.7)	1.00
Prior cardiac intervention (%)	<0.5%	212 (100)	1243 (47.5)	<0.001
NYHA functional class				0.760
NYHA I (%)		156 (73.9)	1899 (73.8)	
NYHA II (%)		50 (23.7)	584 (22.7)	
NYHA III (%)		5 (2.4)	81 (3.1)	
NYHA IV (%)		0 (0)	8 (0.3)	
Clinical signs of HF (%)	0%	32 (15.1)	247 (9.6)	0.010
Left ventricular dysfunction (%)		8 (4.5)	116 (7.2)	0.183
AF before pregnancy (%)		22 (10.4)	46 (1.8)	<0.001

Table 1: Baseline characteristics (continued)

	Normal maternal population	Mechanical valve	No prosthetic valve	p-value mechanical vs no prosthetic valve
		n = 212	n = 2620	
Prior medication				
Beta-blocker (%)	<0.5%	33 (15.6)	311 (11.9)	0.114
Anti-arrhythmic (%)	<0.5%	20 (9.4)	69 (2.6)	<0.001
ACE-inhibitor (%)	<0.5%	7 (3.3)	107 (4.1)	0.576
Diuretic (%)	<0.5%	23 (10.8)	141 (5.4)	0.001

ACE indicates angiotensin-converting enzyme. AF = Atrial fibrillation. HF = Heart failure. NYHA = New York Heart Association.

Pregnancy outcomes

Maternal mortality was higher for MHV (1.4%) than for NoPHV (0.2%, p=0.025), which in itself was much higher than in the non-cardiac pregnant population (**Table 2**). In patients with a MHV, two of the three deaths were directly prosthetic valve related due to MVT (patients 1 and 2 in Table 4) and one to pre-existing poor LV function exacerbated by H1N1 flu at 24 weeks. THV patients are further described below.

Table 2 Outcome of pregnancy until 1 week postpartum

	Normal maternal population	Mechanical valve	No prosthetic valve	p-value mechanical vs. no prosthetic valve
		(n=212), n (%)	(n=2620), n (%)	
Maternal mortality	0.007-0.043%	3 (1.4)	6 (0.2)	0.025
Maternal hospital admission	2%	77 (36.7)	621 (24.5)	<0.001
Maternal hospital admission for cardiac reason		48 (22.6)	328 (12.5)	<0.001
Cardiac				
Heart failure	0%	16 (7.5)	345 (13.2)	0.018
Endocarditis	0.007%	0 (0.0)	6 (0.2)	1.00
Supraventricular arrhythmias	<0.5%	6 (2.8)	47 (1.8)	0.285
Ventricular arrhythmias	<0.5%	1 (0.5)	44 (1.7)	0.254
Thrombotic complication, total		13 (6.1)	10 (0.4)	<0.001
Mechanical valve thrombosis		10 (4.7)		
DVT	0.093%	0 (0.0)	3 (0.1)	1.00
PE	0.037%	0 (0.0)	1 (0.0)	1.00
iCVA	0.0009%	3 (1.4)	2 (0.1)	0.004

Table 2 Outcome of pregnancy until 1 week postpartum (continued)

	Normal maternal population	Mechanical valve	No prosthetic valve	p-value mechanical vs. no prosthetic valve
		(n=212), n (%)	(n=2620), n (%)	
Hemorrhagic complication, total (%)		49 (23.1)	128 (4.9)	<0.001
Major hemorrhagic event		32 (15.1)	81 (3.1)	<0.001
Postpartum hemorrhage	1.2%	22 (10.4)	68 (2.6)	<0.001
Obstetric				
Pregnancy-induced hypertension	2.5%	0 (0.0)	64 (2.5)	0.014
(Pre-)Eclampsia	4%	0 (0.0)	67 (2.6)	0.018
Caesarean Section	23%	96 (46.6)	1212 (48.2)	0.668
Offspring				
Miscarriage <24 weeks	12-15%	33 (15.6)	47 (1.7)	<0.001
Fetal mortality ≥ 24 weeks	0.35%	6 (2.8)	15 (0.6)	0.003
Therapeutic abortion: maternal condition		2 (0.9)	9 (0.3)	0.197
Therapeutic abortion: fetal abnormalities		1 (0.5)	1 (0.0)	0.144
Apgar score < 7	1%	12 (8.0)	171 (7.6)	0.868
Preterm birth < 37 weeks	8%	29 (17.6)	364 (15.6)	0.506
Median pregnancy duration, weeks (Q1-Q3)	40	38.7 (37.3-39.4)	39.0 (37.7-39.9)	0.045
Median birth weight, gr (Q1-Q3)	3190	2900 (2600-3080)	3050 (2700-3400)	<0.001

DVT = Deep Vein Thrombosis. iCVA = Ischemic CerebroVascular Accident. PE = Pulmonary Embolism. Q1-Q3 = quartiles 1 to 3

Miscarriage before and fetal death after 24 weeks were both much higher in MHV than in NoPHV patients (**Table 2**) and the percentage of pregnancies ending with a live mother and child was significantly less with MHV (81.6%) than with NoPHV (97.7%, p<0.001). When all serious adverse events were considered, the chances of an event free pregnancy with a live birth was 58.0% for women with MHV and 78.1% for NoPHV (p<0.001). The assessment of adjusted ORs for the significant different outcomes are presented in **Table 3**.

Table 3 Odds ratios for pregnancy complications in women with a mechanical valve compared to women without a prosthetic valve

	OR	95% CI	adjusted OR*	95% CI
Maternal mortality**	6.3	1.6-25.1		
Hospital admission	1.8	1.3-2.4	1.6	1.2-2.2
Hospital admission for cardiac reason	2.0	1.5-2.9	1.8	1.2-2.6
Heart failure	0.5	0.3-0.9	0.3	0.2-0.6
Thrombotic event**	17	7.4-39		
All hemorrhagic event	5.9	4.1-8.4	5.2	3.5-7.6
Major hemorrhagic event	5.6	3.6-8.6	4.7	2.9-7.4
Postpartum hemorrhage	4.3	2.6-7.2	3.8	2.2-6.4
Miscarriage < 24 weeks	10	6.6-17	8.8	5.4-15
Fetal mortality ≥ 24 weeks**	5.1	1.9-13		

*adjusted for baseline characteristics: maternal age, nulliparity, hypertension prior to pregnancy, signs of heart failure and atrial fibrillation; since there were 35 cases for miscarriage this OR was adjusted for nulliparity, signs of heart failure and atrial fibrillation

**due to limited number of events, no adjusted OR could be determined

Thrombotic and hemorrhagic events

Thrombotic events were significantly more common with MHV than with NoPHV and this difference was due to the occurrence of the very serious complication of MVT in ten patients (4.7%) **(Table 4)**. There was no significant difference in the occurrence of MVT in mitral mechanical valves (4.4%) versus aortic mechanical valves (2.6%, p=1.00). MVT emerged at all stages of pregnancy and on every possible anticoagulation regime. However, 50% of the MVTs occurred in the first trimester and all these five patients had been switched from VKA to heparin in some form. No MVTs in the first trimester occurred in patients taking VKA. This difference was not statistically significant (MVT in 0% of patients on VKA, versus MVT in 3.6% of patients on some form of heparin, p=0.169).

Bleeding complications were also significantly more common in patients with MHV than with NoPHV (p<0.001), and were mainly around the time of delivery. Hemorrhage did not induce other adverse events such as heart failure, maternal mortality or fetal demise.

Anti-Xa measurements in patients receiving LMWH were performed and reported in 57% of patients receiving LMWH. Most women (60%) had a target level of 1.0 to 1.2 U/ml, versus a minority who had a target level of 0.6-1.0 U/ml or 0.8-1.2 U/ml. The number of measurements varied between 3 and 42 times. The percentage of measurements that were within the target range was 73%. Three patients experienced a mechanical valve thrombosis while having respectively three out of five, four out of five and four out of four anti-Xa measurements within the target range.

Table 4 Mechanical Valve Thrombosis

Patient	Region	Age	Diagnosis	Valve position	VKA + dosage	Anti-Xa levels	AC <14 weeks	AC 14-36 weeks	AC pre delivery	AC delivery	Events during pregnancy	Onset MVT	Treatment	Pregnancy duration	Delivery	Fetal mortality	Maternal mortality	Cause of death	6 month follow-up
1	Northern Africa	28	Mitral valve abnormality	Mitral			UFH				CHF, severe bronchopneumonia and MVT	12	no treatment started due to acute cardiogenic shock	12+0		yes, due to maternal hypoxia	yes, at 12 weeks	MVT and severe broncho-pneumonia	
2	Northern Africa	17	Rheumatic MS with mild secondary PAH	Mitral	warfarin 3 mg		*	VKA	UFH	UFH	CVA/TIA in second trimester (INR not reported)	34	streptokinase	34+0	primary CS because of MVT	no	yes, 2 days after delivery	MVT, no availabe emergency surgery	
3	Mediterranean	30	M. Ebstein	Tricuspid	unknown	3/5 within range of 1.0-1.2 peak value	LMWH	VKA	UFH	UFH	MVT and epistaxis not needing transfusion	7	Acetylsalicylacid and diuretics, whereafter decrease of gradient	34+0	assisted VD	no	no		alive
4	Middle East	22	Rheumatic MS	Mitral	warfarin 12 mg	not checked before MVT	LMWH (by family doctor)	VKA	LMWH	LMWH	Hospital admission 5 times. MVT and HF at 8 weeks. Subdural hematoma at 10 weeks.	8	surgical valve replacement at 8 weeks	37+6	VD	no	no		alive
5	Mediterranean	37	Rheumatic MR&MS	Mitral	warfarin 5mg	4/5 within range of 0.8-1.2 peak value	LMWH				CHF and MVT	12	surgical valve replacement at 12 weeks	12+0		yes, during surgery	no		not available
6	Western Europe	32	Tetralogy of Fallot	Aortic	acenocoumarol, dosage unknown	4/4 within range of 0.6-1.0 peak value	LMWH	VKA	LMWH	no	TIA, designated as MVT due to LMWH (no signs of valve thrombosis on TEE)	13	Switch back to VKA	33+0	PROM at 32 weeks, CS for obstetric reason	no	no		alive

Table 4 Mechanical Valve Thrombosis (continued)

Patient	Region	Age	Diagnosis	Valve position	VKA + dosage	Anti-Xa levels	AC <14 weeks	AC 14-36 weeks	AC pre delivery	AC delivery	Events during pregnancy	Onset MVT	Treatment	Pregnancy duration	Delivery	Fetal mortality	Maternal mortality	Cause of death	6 month follow-up
7	Western Europe	31	MR	Mitral	fenprocoumon, dosage unknown		VKA + prophylactic LMWH	VKA+ prophylactic LMWH	VKA	VKA	Family doctor stopped VKA, MVT	15	surgical valve replacement at 15 weeks	26+5	emergency CS for obstetric reason.	no	no		alive
8	Northern Africa	19	Rheumatic MS	Mitral	warfarin 4 mg	Not reported	LMWH	LMWH	LMWH	UFH	MVT	25	surgical valve replacement after IUFD	25+2	induced VD	yes	no		alive
9	Northern Africa	33	Rheumatic MR	Mitral	warfarin 10 mg		VKA	VKA	VKA	UFH	MVT (INR not reported)	27	surgical valve replacement at 28 weeks	28+0	CS	yes, during surgery	no		not available
10	Western Europe	31	Rheumatic MR&MS	Aortic & Mitral	fenprocoumon, variable dosage		LMWH	VKA	LMWH	UFH	Aortic MVT due to sub therapeutic INR	35	Heparin; 3 months after delivery: surgical valve replacement	35+5	urgent primary CS, postpartum transfusion	no	no		2nd month: CHF, 3rd month aortic valve replacement. Alive at 6 months.

AC=anticoagulation. CHF=congestive heart failure. CVA=cerebrovascular accident. IUFD=intrauterin fetal death. MR=mitral regurgitation. MS=mitral stenosis. MVT=mechanical valve thrombosis. PAH=pulmonary arterial hypertension. PROM=premature rupture of membrane. TEE=transesophageal echocardiography. TIA=transient ischemic attack. *Used anticoagulant is missing.

Anticoagulation regimes

The anticoagulants and regimes used are summarized in **Figure 2** and **Figure 3**. Heparin, in some form, was the most commonly used medication in the first trimester. When UFH was used, it was usually given subcutaneously. Most women received VKA from 14-36 weeks and the majority of deliveries were covered with UFH. Only 7 women were on VKA at delivery and 5 of these were delivered by Cesarean Section (CS). Two were delivered vaginally without an adverse event. The main difference between the regimes **(Figure 3)** was that the use of VKA during pregnancy resulted in fewer live births (p=0.026). **Figure 4** depicts the association between anticoagulation in the first trimester and fetal mortality. The use of VKA in the first trimester was associated with a higher rate of miscarriage (28.6% versus 9.2% in women receiving heparin, p<0.001) and late fetal death (7.1% versus 0.7%, p=0.016). Rates of miscarriage or fetal loss in high versus low dosage VKA (≤ 5mg warfarin or ≤2mg acenocoumarol or ≤3mg phenprocoumon) were not significantly different. Complications and their relation to the anticoagulant therapy used, is presented in *Figure S1 in the online supplement*.

Aspirin was used in the second and third trimester in only 13 patients in addition to other anticoagulation regimes. There were no patients administered on aspirin as monotherapy. MVT in the second or third trimester did not occur in the 13 patients (0.0%) on aspirin, while five of the 199 patients (2.5%) without aspirin (p=1.00) developed MVT. Hemorrhagic events occurred in eight patients (61.5%) on aspirin and in 41 patients (20.6%) without aspirin (p=0.002).

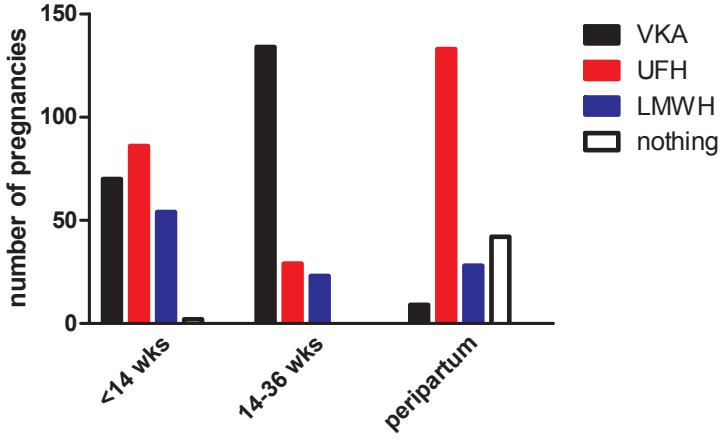


Figure 2 Use of anticoagulants in patients with a mechanical heart valve during pregnancy
LMWH=Low Molecular Weight Heparin. UFH=Unfractionated Heparin. VKA=Vitamin K Antagonist.

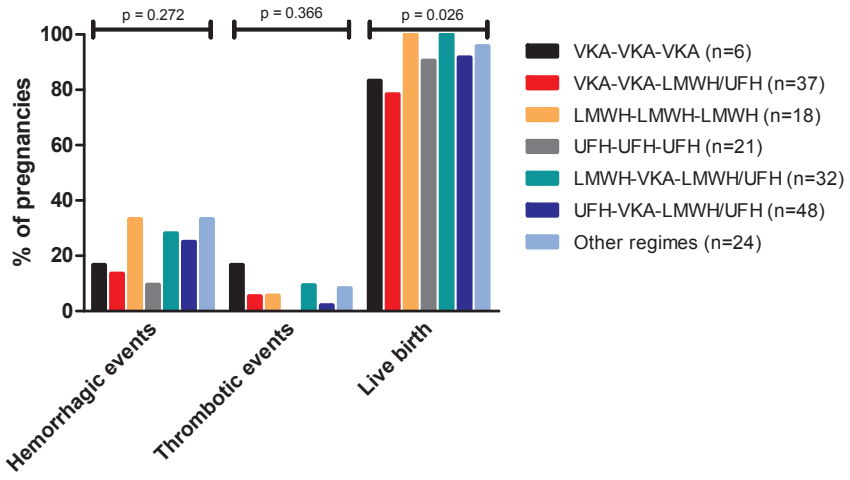


Figure 3 Complications in mechanical heart valve patients on different anticoagulation regimes

The intended anticoagulation regime of 26 patients was unknown due to loss of pregnancy in the first trimester. Four of these patients had a thrombotic or hemorrhagic complication: 1 patient had a severe hemorrhage related to abortion, while receiving UH; 1 patient had a valve thrombosis while receiving UH; 1 patient had a valve thrombosis while receiving LMWH, 1 patient had an ischemic stroke while receiving UH. LMWH=Low Molecular Weight Heparin. UFH=Unfractionated Heparin. VKA=Vitamin K Antagonist.

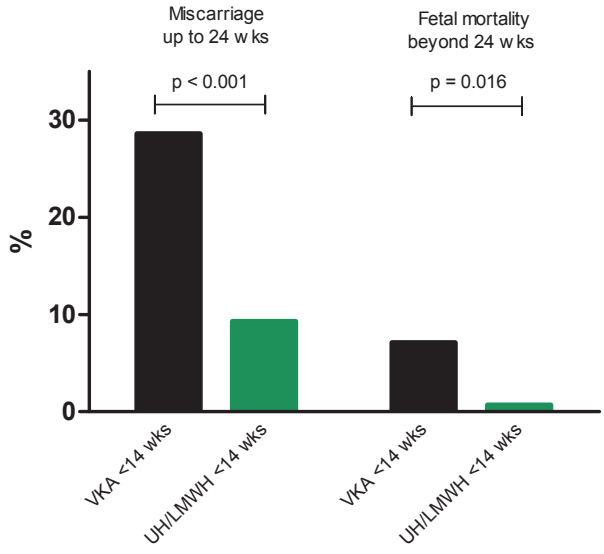


Figure 4 Fetal mortality in relation to anticoagulation in the first trimester

LMWH=Low Molecular Weight Heparin. UFH=Unfractionated Heparin. VKA=Vitamin K Antagonist.

Congenital abnormalities

Two neonates were diagnosed with congenital heart disease. One child of a woman taking VKA in the first trimester had a combination of atrial septal defect, persistent ductus arteriosus and pulmonary stenosis. The heart defect of the other neonate was not specified. Hydrocephalus occurred in two children (both mothers took VKA in the first trimester). One twin of a mother taking VKA in the first trimester had an unspecified congenital disorder. Taken together, congenital abnormalities were present in 6•8% of the live births of mothers receiving VKA in the first trimester versus 0•8% when they were receiving some form of heparin (p=0•055).

Developed versus emerging countries

There was a clear difference between the anticoagulation regimes used in the different parts of the world, with a preference for the use of UFH in any stage of the pregnancy in emerging countries **(Table 5 and 6)**.

Patients with a MHV in developed countries were admitted to the hospital more frequently than patients in emerging countries, also for cardiac reasons. Patients from developed countries had more hemorrhagic complications, with a similar rate of postpartum hemorrhage in developed (11.8%) and emerging countries (10.3%, p=0.214). Patients with a MHV in developed countries were more often delivered by CS, which was often preterm and resulted in a lower birth weight. The rate of emergency CS was not statistically different (14.5% in developed countries and 7.7% in emerging countries, p=0.140).

Table 5 Outcome of pregnancy in women with a mechanical valve in developed and emerging countries

	Developed countries	Emerging countries	p-value
	(n=56, 26%), n (%)	(n=156, 74%), n (%)	
Anticoagulation regimes*			<0.001
VKA-VKA-VKA	2 (4.0)	4 (2.9)	
VKA-VKA-LMWH/UFH	5 (10.0)	32 (23.5)	
LMWH-LMWH-LMWH	14 (28.0)	4 (2.9)	
UFH-UFH-UFH	2 (4.0)	19 (14.0)	
LMWH-VKA-LMWH/UFH	19 (38.0)	13 (9.6)	
UFH-VKA-LMWH/UFH	1 (2.0)	47 (34.6)	
Other	7 (14.0)	17 (12.5)	
Outcome			
Maternal mortality	1 (1.8)	2 (1.3)	1.00
Hospital admission	30 (54.5)	47 (30.3)	0.001
Hospital admission for cardiac reason	18 (32.1)	30 (19.2)	0.048
Heart failure	5 (8.9)	11 (7.1)	0.768
Thrombotic events	6 (10.7)	7 (4.5)	0.110

Table 5 Outcome of pregnancy in women with a mechanical valve in developed and emerging countries (continued)

	Developed countries	Emerging countries	p-value
	(n=56, 26%), n (%)	(n=156, 74%), n (%)	
Valve thrombosis	5 (8.9)	5 (3.2)	0.134
Hemorrhagic events	23 (41.1)	26 (16.7)	<0.001
Cesarean section	33 (64.7)	63 (40.6)	0.003
Miscarriage <24 weeks	6 (10.7)	27 (17.3)	0.243
Fetal mortality ≥ 24 weeks	0 (0.0)	6 (3.8)	0.344
Apgar < 7	7 (16.3)	5 (4.7)	0.039
Preterm birth < 37 weeks	19 (41.3)	10 (8.4)	<0.001
Median birthweight (Q1-Q3)	2690 (2265 - 3035)	2945 (2715 - 3100)	0.001
Median pregnancy duration (Q1-Q3)	37.8 (35.1 - 38.9)	39.0 (38.0 - 39.6)	<0.001

* regimes could only be determined if a patient had a live pregnancy beyond the first trimester (n=50 in developed countries and n=136 in emerging countries)
LMWH = Low molecular Weight Heparin. UFH = Unfractionated Heparin. VKA = Vitamin K Antagonist.

Table 6 Odds ratios for complications in women with a mechanical valve in emerging countries, compared to those in developed countries

	OR	95%CI	adjusted OR*	95%CI
Hospital admission	0.4	(0.2-0.7)	0.4	(0.2-0.8)
Hospital admission for cardiac reason	0.5	(0.3-1.0)	0.5	(0.2-1.0)
Hemorrhagic events	0.3	(0.1-0.6)	0.3	(0.1-0.5)
Caesarean Section	0.4	(0.2-0.7)	0.4	(0.2-0.8)
Preterm birth	0.1	(0.1-0.3)	0.2	(0.1-0.4)
Apgar<7**	0.3	(0.1-0.8)	0.4	(0.1-1.2)

*adjusted for maternal age, parity, signs of heart failure and hypertension
**due to limited number of events, adjusted only for gestational age

Tissue valves

Table 7 and 8 demonstrate the differences between patients with a MHV and patients with a THV. There was no significant difference in maternal mortality. However, the two cases of death in the MHV group were directly prosthesis related, while this was not the case in the THV group: there was one unexplained out of hospital arrest (ventricular fibrillation) and one death during emergency Caesarean section (CS) performed for fetal rather than for cardiac reasons.

Patients with a MHV had significantly fewer pregnancies resulting in a live mother and child than patients with a THV (81.6% versus 97.0%, p<0.001). The chance of a pregnancy free of serious adverse events was 58.0% for MHV, compared to 79.1% for women with a THV (p<0.001). Overall the risk of complications remained higher for MHV patients, after adjustment for baseline characteristics (Table 8).

Table 7 Pregnancy in Women with a Mechanical versus a Tissue Valve

	Mechanical valve	Tissue Valve	p-value mechanical vs tissue valve
Baseline	n = 212	n = 134	
Mean age (sd)	28.4 (±5.3)	29.7 (±4.7)	0.029
Nulliparous (%)	66 (31.1)	60 (44.8)	0.010
Current smoker (%)	4 (2.0)	3 (2.8)	0.698
Clinical signs of HF (%)	32 (15.1)	5 (3.8)	0.001
Left ventricular dysfunction (%)	8 (4.5)	4 (4.1)	1.00
AF before pregnancy (%)	22 (10.4)	0 (0.0)	<0.001
Outcome			
Maternal mortality (%)	3 (1.4)	2 (1.5)	1.00
Maternal hospital admission (%)	77 (36.7)	37 (27.6)	0.082
Maternal hospital admission for cardiac reason (%)	48 (22.6)	11 (8.2)	0.001
Cardiac			
Heart failure (%)	16 (7.5)	11 (8.2)	0.823
Endocarditis (%)	0 (0.0)	1 (0.7)	0.387
Thrombotic complication, total (%)	13 (6.1)	1 (0.7)	0.013
Hemorrhagic complication, total (%)	49 (23.1)	7 (5.1)	<0.001
Obstetric			
(Pre-)Eclampsia (%)	0 (0.0)	4 (3.0)	0.022
Caesarean Section (%)	96 (46.6)	50 (39.4)	0.196
Offspring			
Miscarriage <24 weeks (%)	33 (15.6)	2 (1.5)	<0.001
Fetal mortality ≥ 24 weeks (%)	6 (2.8)	0 (0)	0.086
Apgar score < 7 (%)	12 (8.0)	8 (6.6)	0.664
Preterm birth < 37 weeks (%)	29 (17.6)	24 (19.2)	0.723
Median pregnancy duration, weeks (Q1-Q3)	38.7 (37.3-39.4)	38.3 (37.1-39.7)	0.911
Median birth weight, gr (Q1-Q3)	2900 (2600-3080)	2950 (2520-3250)	0.150

AF = Atrial fibrillation. HF = Heart failure. Q1-Q3 = Quartiles 1 to 3.

Table 8 Odds ratios for pregnancy complications in women with a mechanical valve compared to women with a tissue valve

	OR	95%CI	adjusted OR*	95%CI
Hospital admission for cardiac reason	3.3	(1.6-6.6)	3.7	(1.8-7.9)
Thrombotic event**	8.7	(1.1-67)		
Hemorrhagic event	5.5	(2.4-12)	6.2	(2.6-15)
Miscarriage	12.2	(2.9-51)	11.0	(2.6-47)

*adjusted for baseline characteristics: maternal age, nulliparity, signs of heart failure and atrial fibrillation; since there were 35 cases for miscarriage this OR was adjusted for nulliparity, signs of heart failure and atrial fibrillation
**due to limited number of events, no adjusted OR could be determined

DISCUSSION

In this large contemporary study of 212 women with a MHV, maternal mortality was 1.4%, pregnancy loss was 18.4%, valve thrombosis occurred in 4.7% of the pregnancies and hemorrhagic complications in 23.1%. Overall, serious complications occurred in over 40% of pregnancies in women with a MHV, which is significantly higher compared to other groups of cardiac patients. Anticoagulation regimes varied widely but none proved to be superior in all respects, however, regimes that included VKA use were associated with a lower live birth rate.

Pregnancy outcomes

The maternal mortality rate for women with a MHV in this Registry is 1.4%, a 30 to 200-fold increase when compared to the normal pregnant population (depending on the country from which the normal data were drawn). MVT is the most feared complication and occurred in 4.7% of pregnancies and was associated with 20% mortality. This is consistent with the current literature, although the mortality and MVT rates vary in previous studies[5,13-16]. We found a relatively high percentage of hemorrhagic complications (23%) compared to other studies where rates of hemorrhage varied between 6 and 23%[5,13,15,17]. Fetal loss, on the other hand, occurred in 18.4% of all pregnancies, which is less frequent than expected, varying in literature from 24 to 65%[5,13-15,17,18]. This might reflect the reduction in VKA use in the past few years or that women who lost their child in the first trimester may have been underreported in our study.

Developed versus emerging countries

The outcome of pregnancy in emerging and developed countries was quite comparable, regarding maternal and fetal survival and heart failure events. However, patients in developed countries were more frequently admitted to hospital and had more hemorrhagic complications. Hospital admission is expensive and rates might be influenced by financial factors and local facilities. The higher rate of hemorrhage was marked, which is just partly explained by the higher Cesarean section rate in developed countries, and may be related to anticoagulant use.

The high frequency of preterm CS is an important observation. The current guidelines[9] suggest that Cesarean sections should be performed only for obstetric reasons, unless a patient is using VKA in the pre-delivery phase. This is relevant for an emergency CS, which, intriguingly, was not performed more frequently in developed countries.

Anticoagulation

In the previous literature, heparin, and specifically UFH, was associated with an increased thrombotic risk[5]. Closer examination of our data shows that 50% of the MVTs occurred dur-

ing the first trimester and that these five patients were being treated with heparin. MVT did not occur in any patients on VKA in the first trimester. Although not statistically significant, these data are striking. In considering the balance of risk between valve thrombosis and hemorrhage, it is clear that MVT was the more serious complication, associated with an increase in both maternal and fetal mortality, whereas hemorrhage was not associated with such serious sequelae.

The risk of miscarriage and late fetal death was clearly increased in women receiving VKA in the first trimester and in those receiving VKA throughout pregnancy. Although we found no difference in miscarriage rates between women receiving low and high dose VKA, there is one promising study showing that fetal loss might be lower in women who require a low VKA dosage to achieve effective anticoagulation[19]. This may be important for women with new generation aortic mechanical valves, with potentially less need for aggressive anticoagulation. However, more data are clearly warranted.

The current anticoagulant regimes differ considerably; despite this there is no clear evidence in support of one approach over another. The choice is often driven by physician experience and preference and sometimes by economic factors, forcing a choice for the less expensive UFH. Although several regimes have been recommended and advised by different guidelines, our data do not suggest that one regime is definitively superior. Our study is particularly relevant as it reports the current treatments used in 40 different centers across the world. Despite the breadth of the study, it is still not possible to recommend a uniform approach for all patients. Due to the limited numbers of patients treated with aspirin, it is not possible to conclude whether the addition of aspirin is of any benefit. Conversely, it appears that the addition of aspirin to other forms of anticoagulation is associated with an increased risk of hemorrhage. If the risk of MVT or other thromboembolic complications were to be reduced by the addition of aspirin, then the greater risk of hemorrhage may be deemed to be acceptable, however as yet, there is no evidence of this.

Our results indicate a stark choice between a lower rate of thrombosis but a much higher rate of fetal loss when women remain on VKA in the first trimester, and a probable higher thrombosis rate (including MVT) but less fetal loss if they are switched to heparin for the first trimester. This decision can only be made by the mother with the aid of careful counseling. It is possible that frequent monitoring of peak and trough anti-Xa levels or activated partial thromboplastin time will mitigate the risks involved and make the switch to heparin the preferable course. Whichever regime is chosen, it is clear that this is a dangerous situation, which demands that anticoagulant control should be as near to perfect as possible[20,21].

Choice of valve type in women of childbearing age

As previously shown, patients with tissue valves experienced less morbidity and less fetal loss than patients with mechanical valves during pregnancy[22,23] and this should be discussed with women before valve replacement. Currently, the superior durability of a mechanical

valve often dominates the discussion[7], but consideration should be given to a bioprosthetic valve, which would be safer in pregnancy and which could be replaced with a mechanical valve when it fails. However, if the availability of cardiac surgery is limited, then it may not be possible to offer women two valve replacements. Of course valve repair, when feasible, would be the best option.

Study limitations

This study, as in all registries, provides an insight into the current situation for pregnant women with a mechanical valve. Although it is one of the largest studies, the sample size is still limited.

The prospective nature of this study should prevent from selection bias. However, participation on voluntary basis can always introduce selection bias, which should be kept in mind while interpreting our results.

The outcome of pregnancy in a normal population has been provided to illustrate differences; however, as the percentages vary widely throughout the world, extrapolation needs to be done with caution. In addition, the relative contribution of individual countries to this Registry needs to be considered, however, the numbers of patients from different countries are too low for statistical analysis. Despite this, we have been able to show differences between emerging and developed countries in this and in a previous publication[3]. We aim to provide a global perspective, which, with local studies, will be invaluable in the development of future guidelines.

Conclusions

Patients with a MHV are at increased risk of maternal and fetal mortality and morbidity, particularly thrombotic and hemorrhagic complications during pregnancy. Half of the MVTs occurred in the first trimester and all of these on some form of heparin, while the use of VKA was associated with miscarriage and fetal death. Current anticoagulation regimes differ widely and, when considering both the outcome for both mother and fetus, none is clearly superior. The outcome of pregnancy in patients with a tissue valve is less hazardous, especially for the fetus. Women with a MHV should be counseled about the potential consequences of pregnancy and receive extensive guidance and care throughout pregnancy, delivery and the postpartum period, from a specialized multidisciplinary team.

Online Supplementary Information

Figure S1 Complications and anticoagulation

REFERENCES

1. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
2. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.
3. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
4. Elkayam U, Goland S. The search for a safe and effective anticoagulation regimen in pregnant women with mechanical prosthetic heart valves. *J Am Coll Cardiol* 2012; **59**(12): 1116-8.
5. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; **160**(2): 191-6.
6. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg* 2009; **137**(1): 82-90.
7. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. *J Am Coll Cardiol* 2005; **46**(3): 403-10.
8. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**(22): 2438-88.
9. European Society of G, Association for European Paediatric C, German Society for Gender M, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**(24): 3147-97.
10. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.
11. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010; **375**(9726): 1609-23.
12. Fund IM. World Economic Outlook - Recovery Strengthens, Remains Uneven. Washington; April 2014.
13. Ashour ZA, Shawky HA, Hassan Hussein M. Outcome of pregnancy in women with mechanical valves. *Tex Heart Inst J* 2000; **27**(3): 240-5.
14. Mazibuko B, Ramnarain H, Moodley J. An audit of pregnant women with prosthetic heart valves at a tertiary hospital in South Africa: a five-year experience. *Cardiovasc J Afr* 2012; **23**(4): 216-21.
15. Nassar AH, Hobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM. Pregnancy outcome in women with prosthetic heart valves. *Am J Obstet Gynecol* 2004; **191**(3): 1009-13.
16. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000; **107**(2): 245-53.
17. Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. *BJOG* 2012; **119**(8): 1008-13; discussion 12-3.
18. Samiei N, Kashfi F, Khamoushi A, et al. Pregnancy outcome after mechanical mitral valve replacement: a prospective study. *J Tehran Heart Cent* 2012; **7**(3): 117-20.
19. De Santo LS, Romano G, Della Corte A, et al. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation, a pilot obser-

vational study on a comprehensive pre-operative counseling protocol. *J Am Coll Cardiol* 2012; **59**(12): 1110-5.

20. McLintock C. Anticoagulant choices in pregnant women with mechanical heart valves: balancing maternal and fetal risks--the difference the dose makes. *Thromb Res* 2013; **131 Suppl 1**: S8-10.
21. Goland S, Schwartzenberg S, Fan J, Kozak N, Khatri N, Elkayam U. Monitoring of anti-xa in pregnant patients with mechanical prosthetic valves receiving low-molecular-weight heparin: peak or trough levels? *J Cardiovasc Pharmacol Ther* 2014; **19**(5): 451-6.
22. Heuvelman HJ, Arabkhani B, Cornette JM, et al. Pregnancy outcomes in women with aortic valve substitutes. *Am J Cardiol* 2013; **111**(3): 382-7.
23. Lawley CM, Algert CS, Ford JB, Nippita TA, Figtree GA, Roberts CL. Heart valve prostheses in pregnancy: outcomes for women and their infants. *J Am Heart Assoc* 2014; **3**(3): e000953.

PART III

Aortic disease

CHAPTER 10

Aorta pathology and Pregnancy

Iris M. van Hagen
Jolien W. Roos-Hesselink

Best Pract Res Clin Obstet Gynaecol. 2014 May;28(4):537-50

ABSTRACT

In addition to the hemodynamic changes in pregnancy, hormones also induce changes in the aortic wall. Women with diseases like Marfan syndrome, Ehlers-Danlos or other aortic abnormalities, have an increased risk of complications during pregnancy. Counseling and risk assessment prior to pregnancy is mandatory for all women with known aortic disease. Proper information should be provided about the risks of morbidity and mortality during pregnancy as well as information on the risks for the fetus, including the potential recurrence of disease in the offspring. Evaluation of past medical and family history, the aortic size prior to conception and any increase in size before and during pregnancy is essential to try and estimate the risk of aortic dissection. If the aorta is dilated, prophylactic repair prior to pregnancy may be indicated. In some cases elective surgery during pregnancy may be warranted. In patients with a severely dilated ascending aorta, caesarian section is at the moment the advised mode of delivery.

INTRODUCTION

In young women the occurrence of an aortic complication is fortunately rare, with a reported incidence in the general female population under 45 years of age of 0.4 per 100.000 person years [1]. When acute aortic dissection (AOD) occurs in a person under the age of 40, it is frequently caused by an underlying disorder such as Marfan syndrome (MFS) or a bicuspid aortic valve (BAV). In this young-age group aortic dissection has a mortality rate of 22%, which is similar to the mortality rate in those over 40 years old [2].

In pregnancy, there are hemodynamic adaptations that influence the vascular system, including the aorta. The major cause of maternal mortality in the United Kingdom between 2006 and 2008 was cardiac disease, with 2.31 deaths per 100.000 maternities. Although the incidence of aortic dissection is low, it was one of the most important causes of cardiac death [3]. A challenging situation exists for patients at risk of aortic complications who contemplate pregnancy. Moreover, some patients may have AOD during pregnancy as the first presentation of their aortic disease. High risk patients with known aortopathy reaching reproductive age should be counseled about the risks of pregnancy. They should be referred to a tertiary center for the purpose of surveillance during pregnancy and management of delivery.

GENERAL RECOMMENDATIONS AND GUIDELINES

Taskforces have made great efforts to provide recommendations on this important topic [4,5]. The two most recent provide helpful advice on how to manage women with aortopathy, but prospective studies are needed to assess and provide better data to support the recommendations. The Registry of Pregnancy And Cardiac diseases (ROPAC) is currently the largest worldwide prospective study on pregnancy in patients with cardiac disease and includes women with aortopathy. The registry is still ongoing [6].

EFFECT OF PREGNANCY ON THE AORTA

The aorta is subject to structural and functional changes throughout pregnancy. Cardiac output, heart rate and circulating volume increase, causing the aortic size to increase. The aortic size is also related to hemodynamic conditions and varies in dimension with conditions such as preeclampsia [7]. The hormonal changes in pregnancy influence connective tissue, changing the microstructure of the medial layer. Analysis of histopathology of the tunica media reveals hypertrophy and hyperplasia of smooth-muscle cells and fragmentation of reticulin which normally surrounds elastic fibers [8]. Subsequently, elastic fibers lose their organized structure, changes which are most notable in late pregnancy.

The above effects of pregnancy on the aorta explain why pregnancy itself is thought to be a risk factor for acute aortic dissection, although this topic is subject to debate and contradictory reports exist. A population based study in Sweden reported on pregnancy related AOD, being responsible for 60% of all AOD in young women with a 25-fold increased risk of dissection during pregnancy [9], however another population based report in Austria demonstrated no increase in risk of aortic dissection [1]. In these population based studies the difference in reported outcomes and risk of AOD might be related to different observation periods (1987-2007 versus 1994-2004) and the small absolute total numbers of dissections (29 versus 15). It is however clear that patients with an increased risk of aortic dissection are those with connective tissue diseases such as Marfan syndrome, Ehlers-Danlos and other genetic conditions pre-disposed to developing thoracic aneurysms and aortopathy. Aortic abnormalities in the context of bicuspid aortic valves will be reviewed elsewhere.

PRE-CONCEPTIONAL COUNSELING

Every patient at increased risk of aortic complications, including patients with known Marfan syndrome, Ehlers-Danlos syndrome (EDS), Loeys-Dietz syndrome (LDS) or familial thoracic aorta dissection syndrome (FTAAS), should be counseled prior to pregnancy. Preferably, counseling should be done once a female patient reaches reproductive age. Maternal and fetal risks should be discussed, as well as recurrence risk of the disease in the offspring and of the possible effect of medication use. It is also important that patients are made aware of the value of CT and MRI imaging of the aorta prior to pregnancy, because the results if abnormal may mean that pregnancy is inadvisable or elective aortic surgery is warranted [4,5]. The risk of aortic dissection is most likely due to a combination of pregnancy effects, pre-existance of an abnormal aortic wall and an increased aortic size at baseline. Hypertension is a significant risk factor in a healthy patient affected by an aortic dissection, but is less common in younger patients suffering from aortic dissection during pregnancy [2].

PRENATAL DIAGNOSIS

The recurrence risk of Marfan, Ehlers-Danlos and Loeys-Dietz syndrome is 50% in the offspring, due to an autosomal dominant inheritance pattern in all of these conditions. If the disease-causing mutation in a family has been identified, then prenatal testing is possible using chorion villus sampling or amniocentesis (cell culture) providing information on the presence or absence of the mutation [10,11]. However, in Marfan syndrome the mutation does not predict the severity of the clinical disease spectrum and moreover sampling is associated with a 1% risk of miscarriage. Foetal echocardiography is therefore an alternative lower

risk diagnostic tool looking for atrioventricular valve regurgitation and dilatation of the aortic root and pulmonary artery [12]. However, this technique is not 100% predictive.

SPECIFIC DISEASES

Marfan

Marfan syndrome is a connective tissue disorder with an autosomal dominant inheritance pattern, with an incidence of 2-3 per 10.000 in the general population. The mutation affects the Fibrillin gene (*FBN-1*), the gene encoding extracellular matrix protein or glycoprotein fibrillin-1 on chromosome 15. In patients with Marfan syndrome, approximately 75% have a family history; the other quartile have a sporadic or de novo mutation. There is recent evidence that excessive signaling of TGF-β (transforming growth factor B) is also associated with Marfan syndrome and these findings might play a key role in future treatment strategies [13,14].

The mutation of *FBN-1* causes a decrease in the amount of elastin and also loss of the organized structure of elastin itself [15]. The subsequent weakness of the supportive tissue affects the cardiovascular system (aorta, AV valves and conduction system), skeletal system, eyes and the dural sac of the spinal cord). Since there are more than a 1000 different mutations known, the diagnosis is based on a combination of clinical criteria and genetic findings as described by Loeys et al, in the revised Ghent nosology. Other important factors to be taken into account include a family history of AOD, aortic root aneurysm, ectopia lentis, an identifiable *FBN-1* mutation or a combination of systemic manifestations [16]. Cardiovascular involvement is present in 80% of cases with aortic dilatation, aortic regurgitation and mitral or tricuspid valve prolapse with or without regurgitation all being seen. Cardiac complications are the main cause of morbidity and mortality although life-expectancy has improved dramatically in the past two decades, mainly due to the treatment with elective cardiac surgery.

Maternal risk

Numerous retro- and prospective reports on the maternal outcome of pregnancy in patients with Marfan syndrome is available. **Table 1** presents an overview of the reported rates of aortic dissection [17-24]. The outcomes vary, partly because treatment has changed over the years. More women are treated with beta blockers or undergo elective aortic root replacement prior to pregnancy. In addition, some studies included only women with known Marfan syndrome, while others retrospectively included those diagnosed during pregnancy when they presented with a complication (aortic dilatation or dissection). Subsequently, it seems that nowadays the dissection rate is relatively low.

Table 1 Aortic events* in pregnancy of women with Marfan syndrome

Study	Year	Design	Patients	Pregnancies	Dissections	Beta blocker†	Time of diagnosis Marfan
Pyeritz et al[17]	1981	retrospective	26	105	0	Unknown	Unknown
Rossiter et al[18]	1995	prospective	21	45	2	Part of the cohort	All before pregnancy
Lipscomb et al[19]	1997	retrospective	36	91	4	Part of the cohort	Partially during pregnancy
Lind et al[20]	2001	retrospective	38	78	5	None	Partially during pregnancy
Meijboom et al[21]	2005	prospective	23	33	0	Part of the cohort	All before pregnancy
Pacini et al[22]	2009	retrospective	85	160	6	None	All before pregnancy
Donnelly et al[23]	2012	retrospective	69	199	0	Part of the cohort	Partially during pregnancy
Omnes et al[24]	2013	prospective	18	22	1	Major part of cohort	All prior to pregnancy

*Aortic event: aortic dissection, progressive dilation, elective surgery

†Beta blocker = beta blockers used throughout entire pregnancy

The first large report (retrospective study) on maternal risks was published by Pyeritz [17], who demonstrated a low risk of dissection during pregnancy in women with MFS. Since this was the first large study of its kind, the recommendations in this article have long been accepted into clinical practice to guide management, whereby pregnancy is discouraged when the aortic diameter exceeds 40-45 mm. These recommendations were further supported by 2 reports in the nineties: when the aortic diameter is smaller than 40mm the risk of dissection is approximately 1% in what was the first prospective study [18], while an aortic root diameter exceeding 40mm was associated with a 10% risk of aortic dissection [19].

More recent studies, one of which was prospective, demonstrated a low risk of AOD if the aortic diameter was less than 45 mm [21,23]. A low risk was also confirmed in a recent, smaller prospective study [24] describing patients managed according to the French guidelines. From these studies it would appear that the risk of aortic dissection is higher in patients not previously diagnosed before pregnancy and therefore were not managed according to the guidelines. This highlights the importance of recognition of the disease signs and its early diagnosis along with family screening programs for genetic disorders.

Aortic diameter growth during pregnancy

The aortic diameter is known to increase during pregnancy particularly in a hypertensive state [7]. Progressive aortic dilatation and dissection outside pregnancy is predicted by the aortic diameter itself [25-27]. Several studies have focused on the potential growth of the aorta during pregnancy in Marfan patients. Rossiter prospectively observed 21 women with Marfan syndrome during 45 pregnancies and compared them to a control group of non-pregnant Marfan patients. The aortic diameter did not increase in size faster in the pregnant group [18] but an important limitation of this study is that the reason for not embarking on pregnancy in the control group was not documented, so selection bias might be introduced with potentially more severe disease manifest in the non-pregnant group.

Meijboom described 33 pregnancies in women with Marfan syndrome with an aortic root diameter equal to or smaller than 45mm [21]. Their control group consisted of 22 age-matched female childless Marfan patients. No evident aortic root growth was reported when compared to the control group, apart from a mildly increased growth of the aortic root during long-term follow-up, in the patients who had a diameter of the root equal to or more than 40 mm at baseline.

A similar comparative study [28] divided Japanese pregnant patients with Marfan into an event group and a non-event group. Aortic dilatation of more than 60mm in any part of aorta or dissection were considered events. The aortic diameter increased by 0.41 mm per month in the event group, versus 0.05mm ($P<0.005$) in the non-event group. The study did not report however on long-term outcome, i.e. whether the diameter decreased after pregnancy.

The largest study by Donnelly et al compared patients with Marfan in 199 pregnancies with nulliparous Marfan patients [23]. An increase of 3 mm in aortic diameter was seen during pregnancy. Post-pregnancy the diameter decreased, but without full recovery during follow-up, up to 5 years, post-delivery.

In these 4 studies the evidence for an increase in aortic diameter is contradictory. Drawing firm conclusions is also made difficult because of a variable use of beta blockers and different follow-up duration. However there is some suggestion that aortic diameter growth could be partially irreversible.

Long term outcome

Life expectancy in Marfan patients has substantially increased and was up to 72 years in 1995. Although large series are still scarce, the literature shows that use of the current guidelines confers a favorable outcome in pregnancy in MFS, however evidence on long term outcome is needed. Donnelly et al found an increase of risk over the longer term (average about 5 years) with death, aortic dissection, severe symptomatic aortic regurgitation and need for urgent surgery defined as adverse outcomes in their study. Predictors of these outcomes are summarized in Table 2 [23].

Table 2 Risk factors for long term outcome after pregnancy in women with Marfan syndrome

Associated factors with long term adverse outcome:	Odds ratios
Aortic size	1.3 (1.11-1.61)
Number of pregnancies	1.5 (1.15-1.97)
Prospective care	0.1 (0.05-0.39)
Medication	0.3 (0.14-0.92)
Aorta>4cm	3.8 (1.11-13.3)
Independent correlates:	
Initial aortic size	1.8 (1.07-3.07)
Rate of aortic change (log)	7.4 (1.32-41.22)

Modified from: Donnelly et al[23]

Obstetric and fetal outcome:

The miscarriage rate in the normal population ranges from 10-20% before 20 weeks gestation. This rate can be higher in MFS with some patients experiencing habitual abortions [29]. An important cause of fetal and neonatal morbidity and mortality is prematurity, which is the result of premature rupture of membranes (PROM). PROM occurs more often in Marfan patients: approximately 5% has been reported. There is a strong suggestion that if the fetus has connective tissue disease the integrity of the membranes is weakened causing a greater risk of preterm rupture [30]. Small-for-gestational-age is also seen more frequently, with the frequent use of beta blockers implicated [17]. It appears that the obstetric outcome

of patients diagnosed with Marfan after pregnancy, is no different from those with known Marfan syndrome [29].

Ehlers-Danlos

The syndrome of Ehlers-Danlos is an autosomal dominant inherited disease. It is however more rare than Marfan syndrome with an incidence of approximately 1:5.000 [31]. The Villefranche classification consists of six different types: classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia and dermatosparaxis EDS [32]. The disease is characterized by hypermobility of large joints, hyperelastic skin, tissue fragility, easy bruising and poor wound healing. The vascular type is the most severe form of the syndrome. It is associated with a mutation in the gene for type III procollagen, 50% of which is a de novo mutation. This type of EDS involves the cardiovascular system and features like hypermobility and hyperelasticity are less frequently seen. Patients suffering from the vascular type have an increased risk of aortic dissection, often not preceded by aortic dilation. Surgery is difficult due to the features associated with the disease, such as tissue fragility. There is also an increased risk of uterine rupture and hemorrhage peripartum. Consequently pregnancy is high risk with a peripartum mortality of 12% reported due to arterial or uterine rupture [33].

Turner

Turner syndrome occurs in 1 per 2000 female births [34] and is caused by complete or partial monosomy for the X chromosome. It is characterized by short stature and premature ovarian failure, but also associated with a variety of congenital heart diseases and aortic pathology. Cardiovascular and aortic complications are the main reason for premature mortality in women with Turner syndrome. The highest prevalence of AOD is seen in women aged 20 to 39. No information on previous gravidity was available in this study [35]. The risk of aortic dissection appears to be elevated by approximate 100-fold in TS [36], which might be partly related to the higher incidence of a bicuspid valve present in 20-30% of patients, as well as coarctation of the aorta (found in 12% of cases). In addition aortic arch abnormalities are described in up to 50% of patients. A recent cardiac magnetic resonance (CMR) imaging study of 102 Turner patients found an association between the aortic diameter and aortic growth with coarctation and bicuspid aortic valve [37]. The aortic dilatation in TS tends to involve the ascending aorta. Specific echo views are needed to image this region but CMR or CT can also assess this region along with the whole aorta so are useful assessment tools. It is important that all aortic measurements are adjusted for body surface area. One study of 158 TS patients with a follow-up duration of 3 years showed 3 aortic dissections occurring in women all with a preexisting aortic diameter of larger than 25 mm/m2 and an abnormal aortic valve [38].

Infertility due to premature ovarian failure is an important clinical feature in Turner patients, although some mosaic Turner patients may be fertile. Subsequently, patients often

seek assisted conception with oocyte donation. There is limited data on the long-term cardiovascular risks associated with these treatments [39,40]. A review of reported cases of AOD revealed a 58% mortality rate in Turner patients. Specifically 7 AOD during pregnancy have been described, causing 6 maternal deaths [41]. Two retrospective national studies reported on mortality outcome in pregnancy. A French study showed 2 AOD, both fatal, in 93 pregnancies resulting from oocyte donation. Patients had not been treated using the recommended guidelines [42]. More recently no AOD were reported in 124 deliveries in TS patients in Denmark [43]. The exact incidence of AOD in pregnancy is not accurately defined, but mortality rate is definitely increased. Overall maternal mortality during pregnancy is estimated at 2% [44].

Other aortic syndromes

Other less common syndromes with a potential high risk for aortic dissection are Loeys-Dietz syndrome, Aneurysm-Osteoarthritis Syndrome (AOS) and Familial Thoracic Aortic Aneurysm and Dissection. The number of women with these syndromes contemplating pregnancy is unknown, but they are all associated with a high risk of dissection.

Loeys-Dietz syndrome is caused by mutation of the genes *TGFBR1* or *TGFBR2* and shows some overlap with other syndromes of thoracic aortic aneurysm and dissection, such as vascular Ehlers-Danlos and Marfan syndrome. It is characterized by arterial tortuosity, hypertelorism and bifid uvula, along with a large range of other features [11]. The mean age of death is 26 years, due to the vascular complications. Pregnancy has been reported in a few case reports [45,46]. In addition Loeys et al described 21 pregnancies in 12 women with LDS. During pregnancy or postpartum there were 4 AOD and two uterine ruptures [47].

Thoracic aneurysms resulting from *SMAD3* mutations have been recently described often presenting with early-onset osteoarthritis, named Aneurysm-Osteoarthritis Syndrome. It is a spectrum consisting of arterial aneurysms, dissections and tortuosity, accompanied by skeletal, craniofacial and cutaneous features. The mutations are located on chromosome 15q22.2-24.2 and are allied with the TGF-β pathway [48,49]. AOS appears to be an aggressive phenotype, with AOD occurring in vessels with even smaller diameters than Marfan syndrome. With regard to the aortic size where there is increased risk of AOD it is similar to LDS where AOD can occur even with normal aortic root dimensions [49]. Pregnancy outcomes have not been reported yet.

Familial Thoracic Aortic Aneurysm and Dissection syndrome is associated with a variety of gene mutations, and there is little data on pregnancy outcomes in this condition, they are however high risk and should be managed in the same way as other fragile aortic syndromes [5].

FOLLOW-UP

For all patients with aortopathy or fragile aorta's blood pressure control must be optimal. Monthly review with echo evaluation of the aortic root diameter each trimester and prior to delivery is recommended. If the aortic arch or thoracic aorta is at risk MRI should be used. It is safe in the second and third trimester of pregnancy [50]. Computed tomography should be avoided during pregnancy because of radiation exposure.

The frequency of echocardiography will depend upon the nature of the underlying aortopathy and baseline aortic root size. If the aortic diameter is larger than 40 mm, or there is progressive aortic dilatation, a history of surgery or previous AOD it is justifiable to perform echocardiography every 4 to 8 weeks. If there is rapid progressive aortic dilatation, a diameter exceeding 50 mm or aortic valve regurgitation, surgery during pregnancy may need to be considered. If the foetus is viable a caesarian section delivery should be undertaken prior to surgical intervention. The definition of rapid is not clear, but we would suggest aortic growth of more than 3-5 mm as significant [4,5].

MEDICATION

Retarding or preventing aortic dilatation is very important in patients with a fragile aorta. Current guidelines recommend using beta blockers as there is some evidence that beta blockers reduce aortic growth in pregnant Marfan patients [7]. Beta blockers might contribute to slowing aortic root absolute growth and a reduced rate of complications such as aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure and death. Although it should be noted that evidence is limited and controversial [51]. More research is needed to support the current use of beta blockers during pregnancy.

Easterling et al [7] found evidence for the benefit of atenolol in this perspective. However atenolol appeared to have an adverse fetal outcome, causing intrauterine fetal growth restriction [52]. Other common side effects of beta blockers are fetal bradycardia and hypoglycemia. Propranolol can also be considered as it decreases both aortic growth and risk of dissection [53]. Adverse effects in general are less common with propranolol or metoprolol so they are preferred for use in pregnancy[54].

In non-pregnant EDS patients a randomized controlled trial using celiprolol has been published. Celiprolol was given to 25 patients and outcomes compared with a control group of 28 patients, taking no medication. The trial showed a definite benefit of celiprolol with an incidence of arterial events in 20% of treated patients, versus 50% in the control group. No data exists with regards to the use of celiprolol in pregnancy in this patient population [55]. If beta blockers are used, the fetus will need more frequent growth scans to detect intrauterine growth restriction.

Some authors state, beta blockers should be given in such dosage, that heart rate is minimized to a resting heart rate of below 60 beats per minute, or at least a decrease of 20% [12]. However, again no good data are available during pregnancy and the negative fetal effects of beta blockers must also be considered. Goland et al report on the excretion of beta blockers in breast milk and found the effects on the infant were not significant, unless there is a diminished hepatic function.

In MFS there is evidence that angiotensin-converting enzyme (ACE) inhibitors [56] and angiotensin receptor blockers (ARBs) are beneficial both reducing aortic growth [57,58], the latter due to the inhibitory effect on TGF-β. Currently both these drugs are contra-indicated during pregnancy, because of potential adverse effects for the fetus, including congenital malformations, intrauterine growth restriction, oligohydramnios and renal failure. A recent study however, has shown that ACE-inhibitors and ARBs, when used in the first trimester were not major teratogens and hypertension per se was as important in determining fetal outcome and not necessarily the medication [59]. It is therefore suggested by the authors in this particular paper that these medications are relatively safe and can be continued until pregnancy is confirmed.

The treatment of acute AOD is emergency surgery with adjunctive medical therapy to lower blood pressure. Medical therapy includes the use of intravenous beta blockers such as labetalol or metoprolol with additional hydralazine if needed [5,12].

ELECTIVE INTERVENTION PRIOR TO OR DURING PREGNANCY

For any patient with an aortopathy or fragile aorta syndrome imaging of the whole aorta is recommended prior to pregnancy. Elective surgical aortic root replacement in non-pregnant patients is of significantly lower risk with a 30 day mortality of 1.5% compared to 11.7% in an emergency procedure [26]. Exact numbers for surgical mortality in pregnant patients are lacking, but repair should preferably take place outside pregnancy.

Current guidelines advise elective aortic root replacement in Marfan patients if the aortic diameter exceeds 50 mm or 45 mm if there is a family history of aortic dissection. If pregnancy is considered, conception probably should be dissuaded until pre-pregnancy prophylactic surgery is performed. If there are additional risk factors such as a family history of AOD or for those with Loeys Dietz syndrome [11], some authors suggest the threshold for intervention should be less at an aortic diameter of 40 mm. In other patients pre-pregnancy surgery can be deliberated if the diameter exceeds 50mm, for instance in patients with a bicuspid aortic valve. In particular in Turner patients the diameter has to be adjusted for body surface area. Current guidelines advise prophylactic surgery in a diameter of larger than 27 mm/m[24,5]. General recommendations are summarized in **Table 3**. It must be borne in mind that prophylactic surgery before conception does not lower the risks of AOD to the

Table 3 Indications pre-pregnancy surgery and Caesarian section[4,5]

Syndrome	Indication Pre-pregnancy Elective Surgery	Indication Caesarian Section
Marfan	≥ 45 mm	≥ 45 mm
Ehlers-Danlos	≥ 45 mm	all
Turner	≥ 27 mm/m2	≥ 27 mm/m^2
Loeys-Dietz	≥ 45 mm	≥ 45 mm
AOS	≥ 45 mm	≥ 45 mm
Others like associated BAV	≥ 50 mm	≥ 45 mm

AOS = Aneurysm-Osteoarthritis Syndrome
BAV = Bicuspid Aortic Valve
Level C evidence applicable for all recommendations

level of the normal population [4] and indeed there is no absolute safe diameter in patients with a fragile aorta. In addition, the risk of surgery in patients with Turner and especially Ehlers-Danlos syndrome is higher due to tissues being generally more friable with poor wound healing. A decision to proceed to surgery must therefore carefully be considered and the balance of risks discussed with the patient.

If the aortic size increases rapidly during pregnancy or if the root is over 50mm at presentation a multidisciplinary team should plan further management, depending on the underlying diagnosis, progression in aortic size and the viability of the child. If the fetus is viable, a caesarian section prior to cardiac surgery should be considered. Exact timing and sequence of delivery and thoracic surgery has not been specified yet. If cardiac surgery is going to be performed with the fetus in situ, the patient needs to be informed of the risks. Pomini states that hypothermia can induce uterine contractions and reduce placental blood flow, while rewarming can provoke uterine contractions and premature labor [60]. It is therefore advised that cardiopulmonary bypass is undertaken in normothermic conditions, left lateral decubitus position, while monitoring fetal heart rate and tocometry. Furthermore a higher pump flow is needed to maintain placental perfusion [61]. In anticipation of a possible preterm delivery, corticosteroids should be administered to accelerate fetal lung maturation [62].

MANAGEMENT OF AORTIC DISSECTION DURING PREGNANCY

There are several reports of a successful maternal outcome in AOD in pregnancy, although a publication bias of successful cases may exist. Zeebregt et al reported on the management and outcome of 6 patients presenting with acute AOD in pregnancy. Four presented with type A dissection, and two patients had undergone emergency caesarian section delivery immediately followed by thoracic surgery, with a favorable outcome for both mothers,

although only 1 infant survived. Two women had cardiac surgery performed with the fetus in situ: one had caesarian section (CS) delivery 5 days after repair and the other had CS 16 weeks after repair. Both infants survived. Two women with type B AOD were managed medically without surgical intervention and survived but in both cases, the fetus's died from asphyxia. The authors suggested that based on their reported outcomes, management should be individualized taking into account the gestational age of the fetus [63]. A review of literature overall [64] shows that outcomes have improved in the past few decades.

In a more recent review, Goland reported pregnancy complications in MFS. Of the patients described, 18 had a type A AOD during pregnancy. One fetus died before surgery and there was one maternal death post cardiac surgery, with subsequent death of the fetus as well [12]. A combined maternal and fetal death occurred in a patient having aortic repair with the fetus in utero [65].

The management of acute aortic dissection should follow the current guidelines for thoracic aortic disease [5], where emergency surgery is indicated for type A dissection. The management of acute type A AOD in pregnancy poses more of a challenge as both mother and fetus are at risk but in most cultures the health of the mother is prioritized over that of the unborn infant and this determines the management strategy. Reported maternal and fetal mortality after surgical repair of type A dissection is improving, however rates are difficult to estimate as the literature consists of case reports and small series. Acute type B AOD during pregnancy (**Figure 1**) is usually managed medically with blood pressure control, unless there is a state of malperfusion or aortic rupture [4,5].

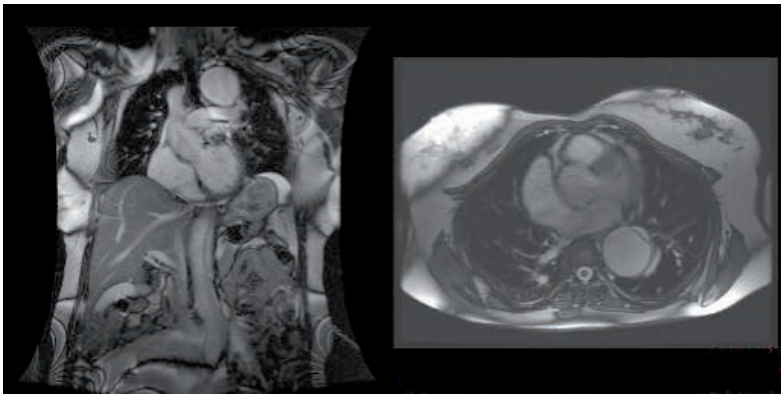


Figure 1 Type B dissection during pregnancy in Marfan syndrome

DELIVERY

Patients with dilatation of the aorta should deliver in a center with cardiothoracic surgery. In general, vaginal delivery is appropriate in selected low risk patients with an aortic diameter

less than 40mm. Epidural anesthesia and forceps or ventouse to assist the second stage is recommended. The optimal mode of delivery is not clear if the aortic root diameter is between 40 and 45mm: in the European guidelines a class IIa indication is given for a vaginal delivery and IIb for caesarian section [4]. If the aorta is exceeding 45mm or if there is a severe aortic valve regurgitation, a caesarian section is advised. However, this is not based on solid data, but merely on expert opinion. An advantage of caesarian section is the possibility to plan the operation during working hours with all possible experts available. In addition caesarian section is advised in all patients with vascular EDS to limit the risk of uterine rupture [4,5].

Epidural anesthesia can be more difficult in Marfan patients due to the presence of dural ectasia. This is caused by altered elastin composition of the dural sac. It is often asymptomatic, but will impede epidural anesthesia techniques [66]. If a lumbosacral MRI has not been performed prior to delivery a lumbar spine ultrasound may be helpful in guiding epidural catheter placement.

A recent retrospective study on the anesthetic management of delivery in 15 Marfan patients, reported on neuraxial and general anesthesia. The authors state there is no evidence to support superiority of general anesthesia with opioids to titrated (combined) spinal-epidural anesthesia, however the final decision regarding mode of analgesia should be made based upon the experience and expertise of the anaesthetist involved in the care of the patient [66].

SUMMARY

The management of the patients with aortopathy and a fragile aorta is challenging and these conditions are all high risk in pregnancy. Pre-conceptional counseling is the first very important step making the patient aware of the risks of aortic dissection, based on both type of aortic disease or genetic predisposition, family history as well as the aortic diameter. Frequent follow-up is needed during and after pregnancy to evaluate aortic size. Cardiologists, obstetricians, cardiothoracic surgeons and anesthesiologists should collaborate closely with a consensus on best management on an individualized case by case basis. Maternal and fetal outcomes are improving with better medical and surgical care and more adherence to guidelines. Nevertheless, there is a necessity for more research as current series are small. Multi-national and multi-centre prospective studies with adherence to the guidelines would supply us with more detailed and accurate information about and how to improve outcomes, risk and prognosis. Also, the advantages and disadvantages and dosage of medical therapy should be the focus of future research.

REFERENCES

1. Thalmann M, Sodeck GH, Domanovits H, et al. Acute type A aortic dissection and pregnancy: a population-based study. *Eur J Cardiothorac Surg* 2011; **39**(6): e159-63.
2. Januzzi JL, Isselbacher EM, Fattori R, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004; **43**(4): 665-9.
3. Wilkinson H, Trustees, Medical A. Saving mothers' lives. Reviewing maternal deaths to make motherhood safer: 2006-2008. *BJOG* 2011; **118**(11): 1402-3; discussion 3-4.
4. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
5. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010; **121**(13): e266-369.
6. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
7. Easterling TR, Benedetti TJ, Schmucker BC, Carlson K, Millard SP. Maternal hemodynamics and aortic diameter in normal and hypertensive pregnancies. *Obstet Gynecol* 1991; **78**(6): 1073-7.
8. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83**(4): 336-41.
9. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. *Eur J Obstet Gynecol Reprod Biol* 2010; **149**(1): 120-1.
10. Pepin MG, Byers PH. Ehlers-Danlos Syndrome Type IV. In: Pagon RA, Adam MP, Bird TD, al e, editors. Seattle: University of Washington; 1993-2013.
11. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. In: Pagon RA, Adam MP, Bird TD, al e, editors. Seattle (WA): University of Washington; 1993-2013.
12. Goland S, Barakat M, Khatri N, Elkayam U. Pregnancy in Marfan syndrome: maternal and fetal risk and recommendations for patient assessment and management. *Cardiol Rev* 2009; **17**(6): 253-62.
13. Mizuguchi T, Collod-Beroud G, Akiyama T, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. *Nat Genet* 2004; **36**(8): 855-60.
14. Pearson GD, Devereux R, Loeys B, et al. Report of the National Heart, Lung, and Blood Institute and National Marfan Foundation Working Group on research in Marfan syndrome and related disorders. *Circulation* 2008; **118**(7): 785-91.
15. Roos-Hesselink JW, Duvekot JJ, Thorne SA. Pregnancy in high risk cardiac conditions. *Heart* 2009; **95**(8): 680-6.
16. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010; **47**(7): 476-85.
17. Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981; **71**(5): 784-90.
18. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995; **173**(5): 1599-606.

19. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997; **104**(2): 201-6.
20. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. *Eur J Obstet Gynecol Reprod Biol* 2001; **98**(1): 28-35.
21. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJ. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. *Eur Heart J* 2005; **26**(9): 914-20.
22. Pacini L, Digne F, Boumendil A, et al. Maternal complication of pregnancy in Marfan syndrome. *Int J Cardiol* 2009; **136**(2): 156-61.
23. Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012; **60**(3): 224-9.
24. Omnes S, Jondeau G, Detaint D, et al. Pregnancy outcomes among women with Marfan syndrome. *Int J Gynecol Obstet* 2013; **122**(3): 219-23.
25. Sutsch G, Jenni R, von Segesser L, Turina M. Predictability of aortic dissection as a function of aortic diameter. *Eur Heart J* 1991; **12**(12): 1247-56.
26. Gott VL, Greene PS, Alejo DE, et al. Replacement of the aortic root in patients with Marfan's syndrome. *N Engl J Med* 1999; **340**(17): 1307-13.
27. Nollen GJ, Groenink M, Tijssen JG, Van Der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. *Eur Heart J* 2004; **25**(13): 1146-52.
28. Katsuragi S, Ueda K, Yamanaka K, et al. Pregnancy-associated aortic dilatation or dissection in Japanese women with Marfan syndrome. *Circ J* 2011; **75**(11): 2545-51.
29. Meijboom LJ, Drenthen W, Pieper PG, et al. Obstetric complications in Marfan syndrome. *Int J Cardiol* 2006; **110**(1): 53-9.
30. Anum EA, Hill LD, Pandya A, Strauss JF, 3rd. Connective tissue and related disorders and preterm birth: clues to genes contributing to prematurity. *Placenta* 2009; **30**(3): 207-15.
31. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers-Danlos syndromes and Marfan syndrome. *Best Pract Res Clin Rheumatol* 2008; **22**(1): 165-89.
32. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998; **77**(1): 31-7.
33. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**(10): 673-80.
34. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab* 2006; **91**(10): 3897-902.
35. Gravholt CH, Landin-Wilhelmsen K, Stochholm K, et al. Clinical and epidemiological description of aortic dissection in Turner's syndrome. *Cardiology in the Young* 2006; **16**(5): 430-6.
36. Bondy CA. Aortic dissection in Turner syndrome. *Curr Opin Cardiol* 2008; **23**(6): 519-26.
37. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH. Prediction of aortic dilation in Turner syndrome - enhancing the use of serial cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2013; **15**(1): 47.
38. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation* 2007; **116**(15): 1663-70.
39. Udell JA, Lu H, Redelmeier DA. Long-term cardiovascular risk in women prescribed fertility therapy. *J Am Coll Cardiol* 2013; **62**(18): 1704-12.
40. Roos-Hesselink JW, Johnson MR. Does fertility therapy hamper cardiovascular outcome? *J Am Coll Cardiol* 2013; **62**(18): 1713-4.

41. Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. *J Med Genet* 2007; **44**(12): 745-9.
42. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab* 2011; **96**(2): E260-7.
43. Hagman A, Kallen K, Bryman I, Landin-Wilhelmsen K, Barrenas ML, Wennerholm UB. Morbidity and mortality after childbirth in women with Turner karyotype. *Hum Reprod* 2013; **28**(7): 1961-73.
44. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril* 2003; **80**(3): 498-501.
45. Gutman G, Baris HN, Hirsch R, et al. Loeys-Dietz syndrome in pregnancy: a case description and report of a novel mutation. *Fetal Diagn Ther* 2009; **26**(1): 35-7.
46. Kunishige H, Ishibashi Y, Kawasaki M, Yamakawa T, Morimoto K, Inoue N. Surgical treatment for acute type A aortic dissection during pregnancy (16 weeks) with Loeys-Dietz syndrome. *Gen Thorac Cardiovasc Surg* 2012; **60**(11): 764-7.
47. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006; **355**(8): 788-98.
48. van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat Genet* 2011; **43**(2): 121-6.
49. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol* 2012; **60**(5): 397-403.
50. Rossi A, Cornette J, Johnson MR, et al. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. *J Cardiovasc Magn Reson* 2011; **13**: 31.
51. Gersony DR, McClaughlin MA, Jin Z, Gersony WM. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: a meta-analysis. *Int J Cardiol* 2007; **114**(3): 303-8.
52. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; **12**(6): 541-7.
53. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994; **330**(19): 1335-41.
54. Livingstone I, Craswell PW, Bevan EB, Smith MT, Eadie MJ. Propranolol in pregnancy three year prospective study. *Clin Exp Hypertens B* 1983; **2**(2): 341-50.
55. Ong KT, Perdu J, De Backer J, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. *Lancet* 2010; **376**(9751): 1476-84.
56. Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005; **95**(9): 1125-7.
57. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006; **312**(5770): 117-21.
58. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC, 3rd. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008; **358**(26): 2787-95.
59. Moretti ME, Caprara D, Drehuta I, et al. The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. *Obstet Gynecol Int* 2012; **2012**: 658310.
60. Pomini F, Mercogliano D, Cavalletti C, Caruso A, Pomini P. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg* 1996; **61**(1): 259-68.

61. John AS, Gurley F, Schaff HV, et al. Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg* 2011; **91**(4): 1191-6.
62. Houston L, Tuuli M, Macones G. Marfan syndrome and aortic dissection in pregnancy. *Obstet Gynecol* 2011; **117**(4): 956-60.
63. Zeebregts CJ, Schepens MA, Hameeteman TM, Morshuis WJ, de la Riviere AB. Acute aortic dissection complicating pregnancy. *Ann Thorac Surg* 1997; **64**(5): 1345-8.
64. Immer FF, Bansi AG, Immer-Bansi AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003; **76**(1): 309-14.
65. Sakaguchi M, Kitahara H, Seto T, et al. Surgery for acute type A aortic dissection in pregnant patients with Marfan syndrome. *Eur J Cardiothorac Surg* 2005; **28**(2): 280-3; discussion 3-5.
66. Allyn J, Guglielminotti J, Omnes S, et al. Marfan's syndrome during pregnancy: anesthetic management of delivery in 16 consecutive patients. *Anesth Analg* 2013; **116**(2): 392-8.

CHAPTER 11

Wish to conceive and concerns to develop cardiovascular complications during pregnancy in patients with Turner syndrome

Iris M. van Hagen
Anthonie L. Duijnhouwer
Marianne J. Ten Kate-Booij
Ramon H. M. Dykgraaf
Johannes J. Duvekot
Elisabeth M. W. J. Utens
Jolien W. Roos-Hesselink

J Psychosom Obstet Gynaecol. 2016 Sep 1:1-8

ABSTRACT

Introduction Turner syndrome (TS) is associated with subfertility and infertility. Nevertheless, an increasing number of women become pregnant through oocyte donation. The wish to conceive may be negatively influenced by the fear of cardiovascular complications. The aim was to investigate the wish to conceive and the concerns about cardiovascular complications during pregnancy in women with TS.

Methods The patient association for TS invited all members of ≥18 years old (n=344) to complete a specifically developed, disease-specific questionnaire, including questions about fertility, wish to conceive, attempts and concerns. Results were compared with previously published results of this questionnaire in women with congenital heart disease.

Results The questionnaire was completed by 89 women (median age 30.1 years, Q1–Q3=22.9–39.4). Of them, 51% had 45, X0-monosomy and 38% had ≥1 cardiac abnormality. Seventeen women (19%) had attempted to become pregnant and 12 of them succeeded to become pregnant. Women who had not undertaken attempts to conceive (81%), considered themselves mainly too young or had no partner. Of the total sample, 58% were concerned about the influence of pregnancy on their cardiovascular status. This was higher (75%) in the sample of women with TS and cardiac abnormalities, than in women with congenital heart disease from a previously published cohort (21%), ($p<.001$). There were no differences in concerns about pregnancy complications between women with TS who respectively had or had not attempted to become pregnant.

Discussion Women with TS, especially those with cardiac abnormalities, show serious concerns about the risks pregnancy may have. Patients should be timely counseled and specifically asked about their concerns. Psychosocial care should be provided when necessary.

INTRODUCTION

Turner syndrome (TS) is caused by a partial or total monosomy of the X-chromosome. One in 2000 live born girls is affected[1,2]. TS is characterized by short stature, webbed neck and gonadal dysgenesis. The phenotype varies considerably and some women have barely dysmorphic features. Awareness of TS from several disciplines has increased in the past decades and in the Netherlands it resulted in a multidisciplinary approach which is now part of standard care[3]. Cardiac or aortic abnormalities are present in 30–40% of women with TS[1,4,5]. Pregnancy in women with TS is an important challenge due to the gonadal dysgenesis, which may lead to premature ovarian failure. Only a small minority of women with TS is able to conceive spontaneously. Nevertheless, since oocyte donation became available, pregnancy became possible for a larger group of these women. The risk of complications during pregnancy in women with TS is suggested to be increased, in particular the risk of aortic dissection[6]. Pregnancy is assumed to decrease the integrity of the aortic wall[7]. The loss of structure may have deleterious consequences in women with an aortic syndrome and associated preexistent wall abnormalities. Several reports have described aortic dissection during pregnancy in patients with TS[8,9]. It is important to address this when counseling these women. So far, it is unknown how many women with TS are hesitant to become pregnant due to their knowledge about this specific cardiovascular risk during pregnancy.

The wish to conceive and concerns regarding pregnancy are rather unexplored and neglected field. Whether one wants to have children or not and concerns in this domain, are crucial subjects in a woman's life. The surplus value of this study is that by gaining more specific knowledge on essential themes, counselling of women with TS can be attuned more to these women's wishes.

Since the past two decades the possibility to conceive increased and evolved in this group of women, the present study aims to investigate how many women with TS have a wish to conceive and how many actually undertake attempts to conceive. Also, the concerns and fear for cardiovascular complications during pregnancy are assessed.

METHODS

This is a cross-sectional observational study organized together with the Dutch patients association for women with TS ("Turner Contact Nederland"). All adult women with TS, who were the members of the association, were approached by the association in November 2014. After giving informed consent, participants received a questionnaire. The medical status of all participants was checked to retrieve data on karyotype, cardiac abnormalities and conception or pregnancy outcomes. Institutional review board approval was obtained

(MEC-2014–457). The study was conducted according to the Declaration of Helsinki (version October 2013).

Data

A validated questionnaire about concerns and fear for potential pregnancy complications in this specific group is lacking. Hence, we based our questionnaire as much as possible on an existing questionnaire for patients with congenital heart disease, with published data[10]. Questions are presented in the results section. The karyotypes were subdivided into the seven groups commonly used in the literature[11]: monosomy, mosaic, isochromosomes, deletions, polyploidy, ring chromosomes and Y material.

Statistical analysis

Age, karyotypes and cardiac abnormalities are described. Concerns and fears were analyzed for age groups, karyotypes and presence versus absence of cardiac abnormalities. We compared women younger than 25 years of age with women over 25, because we hypothesized that the younger group may have been influenced by the rapid increase in the Netherlands of well organized and multidisciplinary care and the availability of oocyte donation in the past 10 years in particular. Continues variables were checked for normality and presented as mean with standard deviation, or as median with first and third quartile (Q1–Q3). Categorical variables are presented as frequencies and percentages, and compared using chi-squared tests providing a p value. The p values smaller than .05 was considered significant. The Bonferroni method was used to correct for multiple hypothesis testing, for each subgroup (corrected α=.05/n, with n=number of hypotheses tested). All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Of the total 344 women with TS invited for this study, 104 women (30%) responded and gave informed consent. The questionnaire was completed by 89 women (86%). Median age was 30.1 years (Q1–Q3=22.9–39.4; range 18.0–65.7 years). Patient characteristics including bicuspid aortic valve, aortic dilatation and coarctation are presented in **Table 1.** One or more of these anomalies were presented in 28 women (37.8%). Nine women had other cardiac abnormalities: partial anomalous pulmonary venous return (n=4), abnormal origin of the right subclavian artery (n=2), corrected persistent arterial duct (n=1), right descending aorta and persistent left superior vena cava (n=1), dextroposition (n=1).

Table 1 Patient characteristics

		n = 89	%
Age (median, Q1-Q3)		median = 30.1	Q1-Q3=22.9-39.4
Cardiac abnormalities* (total)		28	37.8
Bicuspid aortic valve**		20	28.6
Aortic dilatation		9	12.2
Coarctation		6	8.1
Other		9	12.2
Karyotype***			
	Monosomy	37	51.4
	Mosaic	9	12.5
	Isochromosomes	11	15.3
	Deletions	3	4.2
	Polyploidy	7	9.7
	Ring chromosomes	1	1.4
	Y material	4	5.6

*Cardiac abnormalities: unknown in 15 (16.9%) of patients.
**Valve morphology unknown in 19 (21.3%) of patients.
***Karyotype: unknown in 17 (19.1%) of patients.

Fertility and wish to conceive

The majority of the responders had been told by their physician that they probably needed oocyte donation to conceive (**Table 2**). Seventeen women (19.1%) were told they were infertile (median age of 22.6 years, Q1–Q3: 19.6–46.6, range: 18.5–62.6). Eleven patients did not know their fertility status (median age of 22.1 years, Q1–Q3: 19.1–41.3, range: 18.0–65.7).

Seventeen patients (19.1%) had attempted to become pregnant. The reason for not trying to get pregnant in the remaining 72 patients, as shown in **Table 3,** was in the majority their young age and the fact that they felt a child would not (yet) fit into their lives. Patients that reported their young age as a reason for not trying to get pregnant (n=28), had a median age of 21.1 years (Q1–Q3: 19.0–22.9, range 18.0–26.4). Three patients (3.4%) did not have a wish for a child at all.

Table 2 Fertility

Patients awareness of their fertility:		
If I would like to attempt pregnancy, then I would be dependent of an oocyte donation.	49	55.1%
I might have natural hormone production and thus I have a chance to conceive spontaneously.	12	13.5%
Doctors told me I could not get pregnant at all.	17	19.1%
I do not know about my fertility.	11	12.4%

Table 3 Pregnancy attempts

	n	%
Pregnancy attempt	17	19.1
No pregnancy attempt	72	80.9
Reason for no pregnancy attempts		
Too young	18	20.2
Children do not fit (yet) into my life	14	15.7
Too young and combination of other reasons	10	11.2
Rather not by oocyte donation	6	6.7
Never tried due to small chances	5	5.6
Never had a partner, too old	5	5.6
For a medical reason I should not get pregnant	4	4.5
No partner yet	3	3.4
No desire to have children	3	3.4
Aims to start reproductive therapy	2	2.2
Other reasons	1	1.1
Unknown	1	1.1
Total	89	

Of the 17 women, who had attempted to become pregnant, 14 women had been treated with assisted reproductive therapies. Five women failed to become pregnant, of whom two were still trying to get pregnant. Eventually, 12 women became at least once pregnant, which resulted in seven miscarriages before 20 weeks, one therapeutic abortion because of anencephaly, and eight live births. Preconception cardiac screening was performed in 12 of the 17 women; two patients had not been screened (in one of them it was 20 years ago) and in three patients TS had not been diagnosed at the time of their first attempt to conceive.

Concerns regarding pregnancy and cardiac complications

The results of the concerns questionnaire were available for 87 patients and are shown in **Figure 1:** more than half of the patients had concerns about the influence of pregnancy or delivery on their cardiovascular status. **Figure 2** shows the presence of concerns in TS women with cardiac abnormalities compared to those without. There were no significant differences in the concerns of women with and without pregnancy attempts. Women younger than 25 years of age (n=31) seemed to have more concerns about the heredity of TS (36% versus 13%, p=.013), but less concerns about not having enough energy for raising a child (29% versus 55%, p=.022) and fewer concerns about a negative influence of pregnancy on their mental health (13% versus 36%, p=.023). After correction for multiple hypothesis testing (p<.0033 considered significant), none of these results were significantly

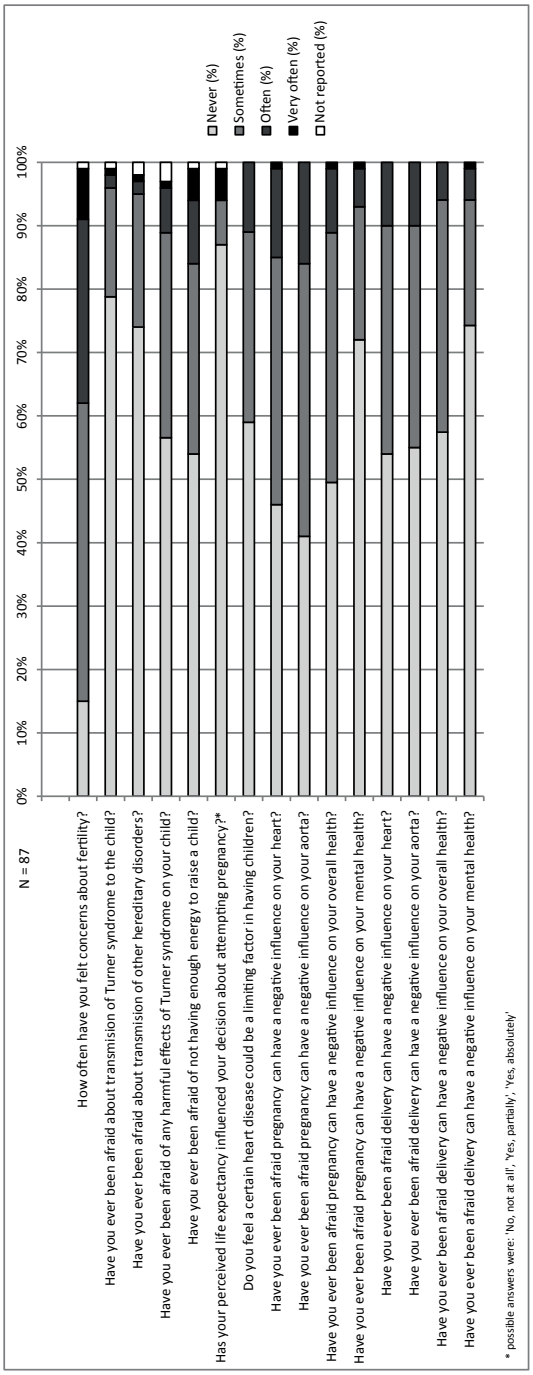


Figure 1 Concerns about pregnancy experienced by Turner patients.

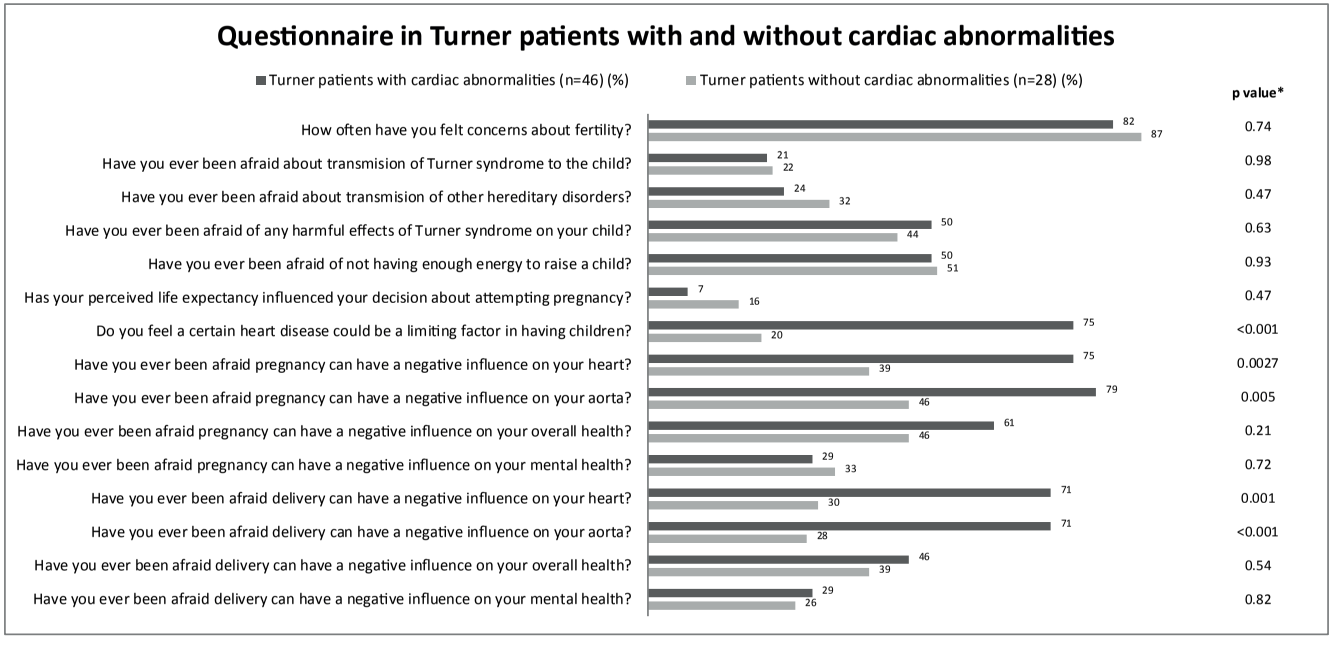


Figure 2 Concerns about pregnancy in Turner patients with cardiac abnormalities compared to Turner patients without cardiac abnormalities.
**p value of significance after Bonferroni's correction: p<.00333*

different. No significant differences were found in the answers to the questionnaire between patients with (n=37) versus without monosomy (n=34).

Table 4 shows the results of the comparison of the questionnaires of the TS women with cardiac abnormalities in our cohort with the questionnaires of another cohort of women with congenital heart disease[10]. The table shows that women with TS and cardiac abnormalities had more concerns than women with congenital heart disease regarding pregnancy risks, also related to the possible negative influence on their heart (75% versus 21%, p<.001).

Table 4 Concerns about pregnancy in Turner patients (with cardiac abnormalities) compared to other patients with congenital heart disease

	Turner patients with cardiac/ aortic disease	CHD patients*	p value**
N = 87	(%)	(%)	
Have you ever felt concerns about fertility?	82	26	<0.001
Have you ever been afraid of any harmful effects of your disease on your child?	50	37	0.17
Have you ever been afraid of not having enough energy to raise a child?	50	11	<0.001
Do you feel a certain heart disease could be a limiting factor in having children?	75	22	<0.001
Have you ever been afraid pregnancy can have a negative influence on your heart?	75	21	<0.001
Have you ever been afraid pregnancy can have a negative influence on your overall health?	61	21	<0.001
Have you ever been afraid delivery can have a negative influence on your heart?	71	28	<0.001
Have you ever been afraid delivery can have a negative influence on your overall health?	46	22	0.005

*Percentages of CHD patients extracted from: Opic et al, 2013 *Int J Cardiology.*

** p value of significance after Bonferroni correction: p=0.00625

DISCUSSION

In this study, we explored the wish to conceive and the concerns of cardiovascular complications during pregnancy in women with TS. Pregnancy had been attempted by 19.1% of all women, while only 3.4% had no wish for a child at all. More than half of all women with TS have or have had concerns about the influence of a potential pregnancy on their cardiovascular health. In women with TS and cardiac abnormalities this percentage was as high

as 75%. Women with TS and cardiac abnormalities also had much more concerns regarding pregnancy and possible complications, than women with congenital heart disease.

Cardiovascular risks of reproductive therapy and Turner syndrome

Awareness of cardiovascular pregnancy risks in women with TS has evolved since 2003, when a study reported an estimated 2% risk of maternal mortality[6] in pregnancy after oocyte donation. This percentage, however, was based on equivocal extrapolation of data. In the following 10 years, several papers were published containing retrospective data on pregnancy complications reporting aortic dissection rates during pregnancy of 0% (0/9; 0/13; and 0/18)[12-14], 0.8% (1/122)[9] and 2.2% (2/93)[8]. Most of these patients conceived through oocyte donation. In a national study that might have partially overlapped with one of these studies, one aortic dissection was found in 202 pregnancies (0.5%), where the majority conceived spontaneously[15]. Outside pregnancy, the presence of aortic dilatation, a bicuspid aortic valve and hypertension are risk factors for aortic dissection in women with TS[16]. However, also in the absence of these factors and with a normal diameter of the aorta, dissection has been reported. Hence, women with TS without aortic dilatation still need to be informed about these risks: not only about the risk of dissection but also about other pregnancy complications, like hypertension and early onset preeclampsia. A large Scandinavian study has shown the substantial risk of hypertensive complications during pregnancy in women with TS, who conceived by oocyte donation[9]. In 35% of these patients, pregnancy induced hypertension or preeclampsia occurred, which might be both related to TS and oocyte donation.

Since cardiac screening of women with TS prior to conception is advocated by the European Society of Cardiology guidelines[17], several studies have reported on the number of preconceptionally screened patients, which ranged from 37.6% to 48.7% [6,8,9]. Apart from those that received the diagnosis of TS after pregnancy attempts or pregnancy, cardiac screening was performed in almost all women who attempted pregnancy in our cohort, except for one patient who delivered in 2009 and one patient who tried to become pregnant in the nineties.

Fertility and counseling

Fertility issues and TS are closely connected, and the majority of women in our cohort do seem to be informed about their situation. However, 12.4% of (mainly younger, median age 22 years) patients did not know whether they are fertile or not. In a previous study, non-disclosure or partial disclosure of the TS diagnosis or associated infertility appeared to be a common strategy of physicians toward their patients, mostly in consensus with the patient's parents[18]. Withholding such important information may induce fear, isolation and depression[18,19]. However, in recent research it seemed that mainly parents of very young children had barriers to communicate about fertility[20]. Overprotective parents of the child with an

(cardiac) anomaly influences the evolvement of body image and self-esteem, and parents should be guided in how to communicate with their child about reproductive matters[21].

Patients with sex development disorders were previously reported to have difficulties with social interaction and impaired cognition, fewer experiences with sexual relationships and lack of initiative to finding a partner[22-24]. Talking about these subjects may help to lower the thresholds for entering a relationship. Also, early puberty induction may optimize their psychosocial development[25,26]. When fertility is discussed, a patient should also be informed about her risks of pregnancy complications. Timing of this additional information should not be delayed to adult age. Although adolescents with TS are generally older when they become sexually active[27], the age of onset of sexual intercourse decreases in the general population, and this may also happen in young patients with TS. In patients with congenital heart disease the (perceived) level of information regarding sexual activities and pregnancy seems to be deficient[10]. In Marfan syndrome, where the risk of aortic dissection during pregnancy is much better documented, women reported not having started a family partly because of the chances for an affected child, but also because of worries for personal health in 30% of the study cohort[28]. An increase in consciousness in reproductive decision-making was reported, similarly to some other genetic counseling populations. The authors do emphasize that this may also bring induce an undesired increased psychological burden.

Education about fertility and cardiovascular risks in women with TS by cardiologists and gynaecologists should be adequately timed, and when necessary follow-up by a psychologist should be offered.

Anxiety and pregnancy

The women in this study seem to have much more concerns about pregnancy and delivery risks, particularly when they have a cardiac abnormality, than women with congenital heart disease assessed by the same questionnaire. The female patients in the reference cohort were older (median age 39) than in our study cohort, which could partly explain the fact that patients were less worried about pregnancy complications.

Women were older and hence, might remember fewer concerns. However, comparing patients younger than 25 years to those older than 25, revealed no significant differences. Also, fertility is less of an issue in women without TS, which should be taken into account when interpreting our results.

It remains unknown if the difference between the two cohorts is due to information provided during counseling, or if this is associated with an underlying anxiety disorder or symptoms, which are known to be more common in women with TS[1]. Furthermore, a previous study described that women with congenital heart disease who thought they were unable to bear a child, often had expressions of self-hate and a feeling of inadequacy as women[21]. Regardless of the underlying cause, during pregnancy, stress symptoms have shown to be

associated with adverse pregnancy outcomes[29-31]. Thus, the presence of anxiety symptoms does warrant extra psychosocial care.

Clinical implications

Young women with TS, should be adequately informed about fertility issues, but also about the risks of pregnancy, irrespective of conceiving by spontaneous conception or oocyte donation[32-34]. After full disclosure of risks, women should be offered not only psychosocial support regarding subfertility or infertility, but also regarding fear or concerns of pregnancy complications since this might influence their pregnancy outcome as well.

Limitations and future perspectives

Since a validated questionnaire about this topic was not available from literature, we derived questions from a questionnaire already used in a cohort study of women with congenital heart disease[10]. We added questions focusing on the aorta and also on mental health. The questions were based on literature and clinical experience of experts in this field (JR;EU). However, since this is the first study using this questionnaire, future studies are needed to replicate our findings.

The initial response rate was quite low, which is probably related to the fact that people were approached through a nonmedical institution by airmail, so not in person, and first had to give their consent before questionnaires were sent. Since, we do not have data from nonresponders, we do not know to what extent a potential selection bias may have influenced our results. Overall, the age of women in our cohort was quite low, given the fact that all age categories are represented within the patient society. The topic of research is probably most appealing for women of young age who are considering their options of starting a family. Although this might induce a selection bias, the risk of recall bias is subsequently lower.

Finally, we did not report the medical fertility status, as opposed to the perception about fertility of women with TS in our cohort. It would be interesting to know whether there is a discrepancy between fertility and perceived fertility.

Conclusion

In this cohort, half of the women with TS currently or previously experienced fears and concerns about cardiac or aortic complications during pregnancy. This holds particularly for women with a cardiac abnormality. Information about these risks should be given, and psychosocial support during fertility and pregnancy counseling should be provided without restraint.

ACKNOWLEDGEMENTS

We would like to thank the board of the Dutch Association of Turner Patients for their support in approaching Turner women in this study and their help in conducting the questionnaire.

REFERENCES

1. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351**(12): 1227-38.
2. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab* 2006; **91**(10): 3897-902.
3. Syndroom N-VMnT. Klinische richtlijn Turner Syndroom. The Netherlands; 2012.
4. Gotzsche CO, Krag-Olsen B, Nielsen J, Sorensen KE, Kristensen BO. Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. *Arch Dis Child* 1994; **71**(5): 433-6.
5. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH. Prediction of aortic dilation in Turner syndrome - enhancing the use of serial cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2013; **15**(1): 47.
6. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril* 2003; **80**(3): 498-501.
7. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83**(4): 336-41.
8. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab* 2011; **96**(2): E260-7.
9. Hagman A, Loft A, Wennerholm UB, et al. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod* 2013; **28**(6): 1598-609.
10. Opic P, Roos-Hesselink JW, Cuypers JA, et al. Sexual functioning is impaired in adults with congenital heart disease. *Int J Cardiol* 2013; **168**(4): 3872-7.
11. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome--integrating cardiology, genetics, and endocrinology. *Endocr Rev* 2012; **33**(5): 677-714.
12. Bodri D, Vernaeve V, Figueras F, Vidal R, Guillen JJ, Coll O. Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. *Hum Reprod* 2006; **21**(3): 829-32.
13. Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertil Steril* 2011; **95**(7): 2251-6.
14. Alvaro Mercadal B, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner's syndrome and partial X monosomy. *Hum Reprod* 2011; **26**(8): 2061-8.
15. Hagman A, Kallen K, Barrenas ML, et al. Obstetric outcomes in women with Turner karyotype. *J Clin Endocrinol Metab* 2011; **96**(11): 3475-82.
16. Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. *Circulation* 2012; **126**(18): 2220-6.
17. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
18. Sutton EJ, Young J, McInerney-Leo A, Bondy CA, Gollust SE, Biesecker BB. Truth-telling and Turner Syndrome: the importance of diagnostic disclosure. *J Pediatr* 2006; **148**(1): 102-7.
19. Freedman B. The roles and responsibilities of the ethnics consultant. Hagerstown: University Publishing Group; 2000.

20. King JE, Plamondon J, Counts D, Laney D, Dixon SD. Barriers in communication and available resources to facilitate conversation about infertility with girls diagnosed with Turner syndrome. *J Pediatr Endocrinol Metab* 2015.
21. Gantt LT. Growing up heartsick: the experiences of young women with congenital heart disease. *Health Care Women Int* 1992; **13**(3): 241-8.
22. Ediati A, Faradz SM, Juniarto AZ, van der Ende J, Drop SL, Dessens AB. Emotional and behavioral problems in late-identified Indonesian patients with disorders of sex development. *J Psychosom Res* 2015; **79**(1): 76-84.
23. Ediati A, Juniarto AZ, Birnie E, Drop SL, Faradz SM, Dessens AB. Body image and sexuality in Indonesian adults with a disorder of sex development (DSD). *J Sex Res* 2015; **52**(1): 15-29.
24. Hong DS, Dunkin B, Reiss AL. Psychosocial functioning and social cognitive processing in girls with Turner syndrome. *J Dev Behav Pediatr* 2011; **32**(7): 512-20.
25. Lagrou K, Froidecoeur C, Verlinde F, et al. Psychosocial functioning, self-perception and body image and their auxologic correlates in growth hormone and oestrogen-treated young adult women with Turner syndrome. *Horm Res* 2006; **66**(6): 277-84.
26. Carel JC, Elie C, Ecosse E, et al. Self-esteem and social adjustment in young women with Turner syndrome--influence of pubertal management and sexuality: population-based cohort study. *J Clin Endocrinol Metab* 2006; **91**(8): 2972-9.
27. Boman UW, Moller A, Albertsson-Wikland K. Psychological aspects of Turner syndrome. *J Psychosom Obstet Gynaecol* 1998; **19**(1): 1-18.
28. Peters KF, Kong F, Hanslo M, Biesecker BB. Living with Marfan syndrome III. Quality of life and reproductive planning. *Clinical Genetics* 2002; **62**(2): 110-20.
29. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *Am J Obstet Gynecol* 1993; **169**(4): 858-65.
30. Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. *Health Psychol* 1992; **11**(1): 32-40.
31. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychol* 1999; **18**(4): 333-45.
32. Udell JA, Lu H, Redelmeier DA. Long-term cardiovascular risk in women prescribed fertility therapy. *J Am Coll Cardiol* 2013; **62**(18): 1704-12.
33. Roos-Hesselink JW, Johnson MR. Does fertility therapy hamper cardiovascular outcome? *J Am Coll Cardiol* 2013; **62**(18): 1713-4.
34. Practice Committee of American Society For Reproductive M. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. *Fertil Steril* 2012; **97**(2): 282-4.

CHAPTER 12

Cardiovascular complications during pregnancy in patients with Turner Syndrome

Iris M. van Hagen
Khalid Elghoul
Anthonie L. Duijnhouwer
Elisabeth M.W.J. Utens
Marianne J. Ten Kate-Booij
Ramon H.M. Dykgraaf
Johannes J. Duvekot
Jolien W. Roos-Hesselink.

Submitted

ABSTRACT

Background and aims Turner syndrome (TS) is typically associated with subfertility and infertility due to gonadal dysgenesis, but an increasing number of women with TS do get pregnant since the introduction of oocyte donation. Cardiac anomalies and aortopathy are present in a significant part of women with TS, and they are at increased risk of aortic dilatation and dissection. Therefore, we aimed to describe outcome of pregnancy in women with TS in our centre, with specific focus on cardiovascular outcome.

Methods This study included a retrospective cohort of women with Turner syndrome. All women who have a genetically proven diagnosis of Turner syndrome and have visited the obstetric or cardiac outpatient clinic at Erasmus Medical Centre, Rotterdam, between 2000 and 2015 were included in this study.

Results Data from 165 adult women who were diagnosed with Turner Syndrome were collected. Of them, 45 (27.3%) attempted to get pregnant at least once: 22 women had successful attempts (74 conceptions ending in 31 full-term pregnancies) and 23 women had no conception. No aortic dissection was reported. One patient had aortic dilatation, but no significant aortic growth during pregnancy. Pregnancy induced hypertension occurred in 10%, pre-eclampsia in 15% and HELLP in 10% of the patients who had a full-term pregnancy. One women had an uneventful pregnancy after aortic root replacement.

Conclusion In our cohort of women with TS no major aortic complications occurred. However, hypertensive complications and miscarriage seems prevalent.

INTRODUCTION

Turner syndrome (TS) is characterised by a partial or complete monosomy of the X-chromosome, with a wide variety in genotype and phenotype[1]. TS is typically associated with subfertility and infertility due to gonadal dysgenesis, but an increasing number of women with TS do get pregnant since the introduction of oocyte donation. Cardiac anomalies and aortopathy are present in a significant part of women with TS, and they are at increased risk of aortic dilatation and dissection[2]. How this influences pregnancy outcome, and more importantly how to deal with the wish for assisted reproductive therapy wish in this group of women remains subject of debate[3]. More data on the topic is clearly warranted, with the aim to better inform women with TS and a pregnancy wish, and to support present and future guidelines on TS and pregnancy.

Guidelines on pregnancy in Turner syndrome are not very well specified, mainly due to the fact that there are limited data. In other aortic syndromes such as Marfan syndrome, guidelines advice to consider prepregnancy prophylactic surgery in case of aortic dilatation[4]. But little data exists to ensure that this approach leads to a safe course of pregnancy without subsequent type B aortic dissection. An alarming series report described adverse pregnancy outcome in Loeys-Dietz syndrome (which is also often characterised by aortopathy) after prophylactic aortic surgery[5].

Therefore, we aimed to describe outcome of pregnancy in women with Turner syndrome in our centre, with specific focus on cardiovascular outcome, and specifically aortopathy.

METHODS

This study included a retrospective cohort of women with Turner syndrome. All women (>18 years) who have a genetically proven diagnosis of Turner syndrome and have visited the obstetric or cardiac outpatient clinic at Erasmus Medical Centre, Rotterdam, between 2000 and 2015 were included in this study. The medical status of all participants was checked to retrieve data on karyotype, cardiac abnormalities and conception or pregnancy outcomes. Institutional review board approval was obtained (MEC-2014-457).

Data

Data collection included: patient characteristics, pregnancy attempts, pregnancies and deliveries. Data were retrieved from electronic medical files by the first author. Patient characteristics included age at diagnosis of TS and of congenital heart disease, age at the time of conception, age at the time of this study, karyotype, growth hormone, puberty induction, cardiac screening, cardiac abnormalities and prior cardiac interventions. Pregnancy data included type of conception (spontaneous or assisted reproductive therapy - ART), miscar-

riage, therapeutic abortion, live births, pregnancy induced hypertension, pre-eclampsia, aortic dimensions, aortic dissection

A successful attempt was defined as an achieved conception, regardless of outcome such as miscarriage or live birth. Karyotypes were subdivided into seven groups[6]: monosomy, mosaic, isochromosomes, deletions, polyploidy, ring chromosomes, Y material.

Imaging data were collected for patients who conceived. Only those with images before and after pregnancy derived from the same modality (i.e. echocardiography before and after pregnancy, or magnetic resonance before and after pregnancy) were selected for graphical representation in this study.

Statistical analysis

A flowchart of included patients is provided. Patient characteristics are described. Women with successful pregnancy attempts and those with failed attempts are compared. Spontaneous conceptions are compared to conceptions induced by ART. Full term pregnancies will be described in detail, in particular in case of prior aortic surgery. Data from the general population in literature[7-11] are provided, but do not allow for statistical comparison.

Continuous data are presented as median and first to third quartile (Q1-Q3) as appropriate, and comparisons were made using Wilcoxon signed rank tests. Categorical data are presented as frequencies and percentages, and compared using chi-squared tests. P-values below 0.05 were considered significant. All analyses were performed with SPSS version 21.0(IBM Corp., Armonk, NY).

RESULTS

Total cohort

Data from 165 adult women who were diagnosed with Turner Syndrome were collected (**Figure 1**). Of these women, 45 (27.3%) had reported at least one pregnancy attempt to their physician. Women who did not report any pregnancy attempts (n=120) were generally younger at the time of this study (28 years versus 39 years, $p<0.001$) but also at the time of their diagnosis (9 years versus 14 years, $p<0.001$), than those who did report a pregnancy attempt. There were more women with a monosomy in the group that did not report a pregnancy attempt than those who did (56% versus 33%, $p=0.003$).

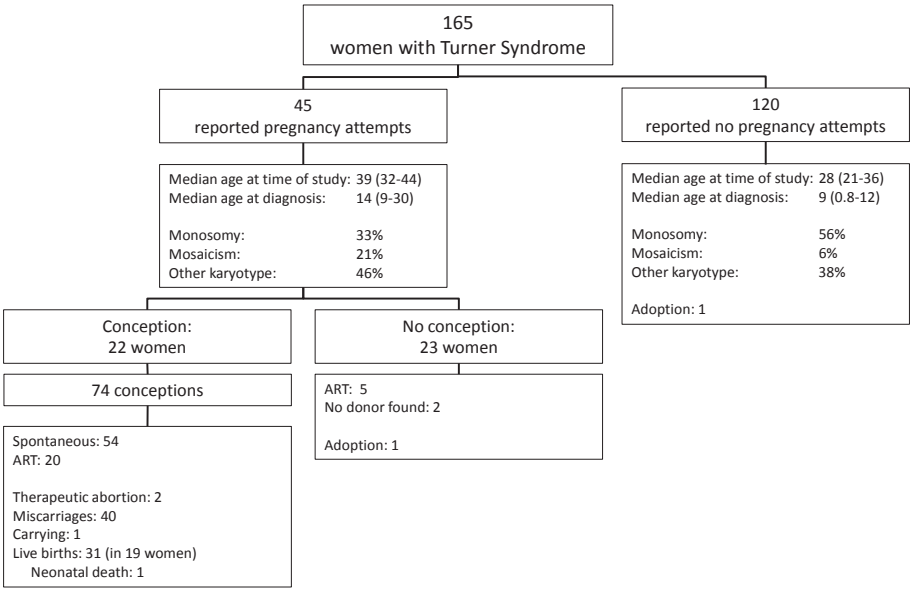


Figure 1 Flowchart
ART= assisted reproductive therapy

Pregnancy attempts

Table 1 shows the baseline characteristics of the women with at least 1 pregnancy attempt. There were 22 women with successful attempts (ending in conception) and 23 women with no conception. Karyotype was not significantly different overall (p=0.35). But there seemed to be more women with mosaicism in the group with successful attempts (35.0% versus 5.3%). Women with successful attempts had their diagnosis of Turner Syndrome more often during or after conception or fertility issues (50.0% versus 13.0%, p=0.008).

Women who did not receive puberty induction were more likely to have a successful attempt than women who did receive puberty induction (68.8% versus 25.0%, p=0.009). Growth hormone did not significantly contribute to the chance of success or failure: 56% of women without growth hormone had a successful attempt, versus 30% of women with growth hormone treatment (p=0.11).

Table 1 Women who attempted pregnancy

	Women with successful attempts		Women with failed attempts		
	n=22		n=23		p value
Median age at the time of the study (Q1-Q3)	41.1	(35.5-45.0)	34.7	(30.0-42.0)	0.09
Median age at diagnosis (Q1-Q3)	24.2	(8.3-35.5)	12.8	(7.2-21.9)	0.17
Karyotype, %					0.23
Monosomy	5	25.0%	8	42.1%	
Mosaic	7	35.0%	1	5.3%	
Isochromosomes	2	10.0%	3	15.8%	
Deletions	3	15.0%	3	15.8%	
Polyploidy	3	15.0%	2	10.5%	
Ring chromosomes	0	0.0%	1	5.3%	
Y material	0	0.0%	1	5.3%	
Diagnosis					0.008
before pregnancy attempts, %	10	50.0%	20	87.0%	
at or after the time of attempts, %	10	50.0%	3	13.0%	
Cardiac or aortic abnormality	4	21.1%	5	23.8%	1.00
BAV	2	10.5%	5	23.8%	0.41
Aortic dilatation	2	10.5%	2	9.5%	1.00
Coarctation	2	10.5%	1	4.8%	0.60
Other	3	15.8%	2	9.5%	0.65
Cardiac or aortic intervention	3	15.8%	1	4.8%	0.33
Growth hormone	6	40.0%	14	66.7%	0.11
Puberty induction	5	31.2%	15	75.0%	0.009

BAV = bicuspid aortic valve, Q1-Q3 = first to third quartile

Conceptions

Of the women who had at least one conception (n=22), 13 were screened by a cardiologist ; 4 women had their TS diagnosis after pregnancy; 3 had no screening or follow-up at all despite their diagnosis of TS (2 with low-level mosaicism); 2 had their first cardiac screening years after diagnosis and conception. Of the 13 women that were screened, 11 received cardiac follow-up during pregnancy, and 2 did not.

In total, 74 conceptions were achieved, by 22 women. **Table 2** shows the outcome of conceptions conceived either spontaneously (n=54) or through ART (n=20). Spontaneous conceptions were mainly achieved by women with mosaicism, and by women with deletion

Table 2 Conceptions: spontaneous versus ART

	Conceptions				
	Spontaneous		ART		
	n=54		n=20		p value
Median age at conception (Q1-Q3)	31.0	(26.5-35.0)	32.9	(28.3-39.0)	0.48
Number of previous pregnancies (Q1-Q3)	3	(2-5)	1.5	(1-4)	0.059
Pregnancy outcome:					0.48
Miscarriage	29	53.7%	11	55.0%	
Therapeutic abortion	2	3.7%	0	0.0%	
Live births	23	42.6%	8	40.0%	
Carrying	0	0.0%	1	5.0%	

ART= assisted reproductive therapy, Q1-Q3 = first to third quartile

or polyploidy. Outcome was quite similar, with 42.6% life births in spontaneous conceptions and 40.0% in conceptions achieved with ART.

Thirty-one conceptions ended in full term pregnancies in 19 women, shown in **Table 3.** Five of these women had a cardiac anomaly when they became pregnant: 1 patient required a mitral mechanical valve 7 years before conception (because of mitral valve regurgitation); 1 patient had a partial anomalous pulmonary venous return (PAPVR) but no other anomalies; 1 patient was diagnosed with TS 18 years after pregnancy and she appeared to have coarctation, a small perimembranous ventricular septal defect and a persistent left sided vena cava superior; 1 patient became pregnant while having a bicuspid aortic valve with aortic dilatation (40 mm); 1 patient became pregnant two years after ascending aortic surgery (case report below).

Table 3 Full term pregnancies

	Full term pregnancies		
	n= 31	%*	Normal
Median age at conception(Q1-Q3)	31.0	(26.0-35.0)	
Conceived by ART	8	25.8%	
Karyotypes			
Monosomy	4	12.9%	
Mosaic	17	54.8%	
Isochromosomes	1	3.2%	
Deletions	3	9.7%	
Polyploidy	3	9.7%	

Table 3 Full term pregnancies (continued)

	Full term pregnancies		
	n= 31	%*	Normal
Ring chromosomes	0	0.0%	
Y material	0	0.0%	
unknown	3	9.7%	
Turner syndrome known before pregnancy	18	58.1%	
Maternal mortality[a]	0	0.0%	<0.01%
Pregnancy induced hypertension[b]	2	10.0%	2.5%
Pre-eclampsia[c]	3	15.0%	3.8%
HELLP[d]	2	10.0%	<1.0%
Pregnancy duration, median (wks)	39	(38-40.5)	
Induced vaginal delivery	3	11.5	
Spontaneous vaginal delivery	17	65.4	
Primary caesarean section	3	11.5	
Secondary caesarean section	3	11.5	
Neonates	33		
Birth weight[e], median (gr)	3285	(2975-3495)	3454
Small for gestational age (<10th percentile)	2	8.3%	10.0%
Neonatal death[a]	1	3.2%	0.4%
Congenital anomaly	2	8.0%	

**Frequencies are presented as percentages of valid cases.*
Obstetric complications unknown in 11 cases; small for gestational age unknown in 7; congenital anomalies unknown in 6; birth weight and pregnancy duration unknown in 10.
[a]Europeristat, [b]Drenthen 2007, [c]Abalos 2013, [d]Stone 1998 Jama, [e]Jaddoe 2008

Caesarean section was planned in 3 patients: one had breech presentation; one had preeclampsia; and one had an aortic diameter of 44mm in the presence of a bicuspid aortic valve. A secondary CS was performed because of fetal distress in two, and failure to progress in one patient. Mode of delivery was unknown in 5 pregnancies.

One patient had a baby with atresia ani and maldevelopment of scrotum. Another patient had a baby with cheilognathopalatoschisis.

Cardiovascular complications

No aortic dissections were reported. One patient had aortic dilatation, but no significant growth during pregnancy. Hypertensive complications during pregnancy are shown in Table 3; one of these patients had pre-existent mild hypertension.

In four patients, echo data were present before and after pregnancy(and during pregnancy in some of them). The course of aortic dimensions are presented in **Figure 2.**

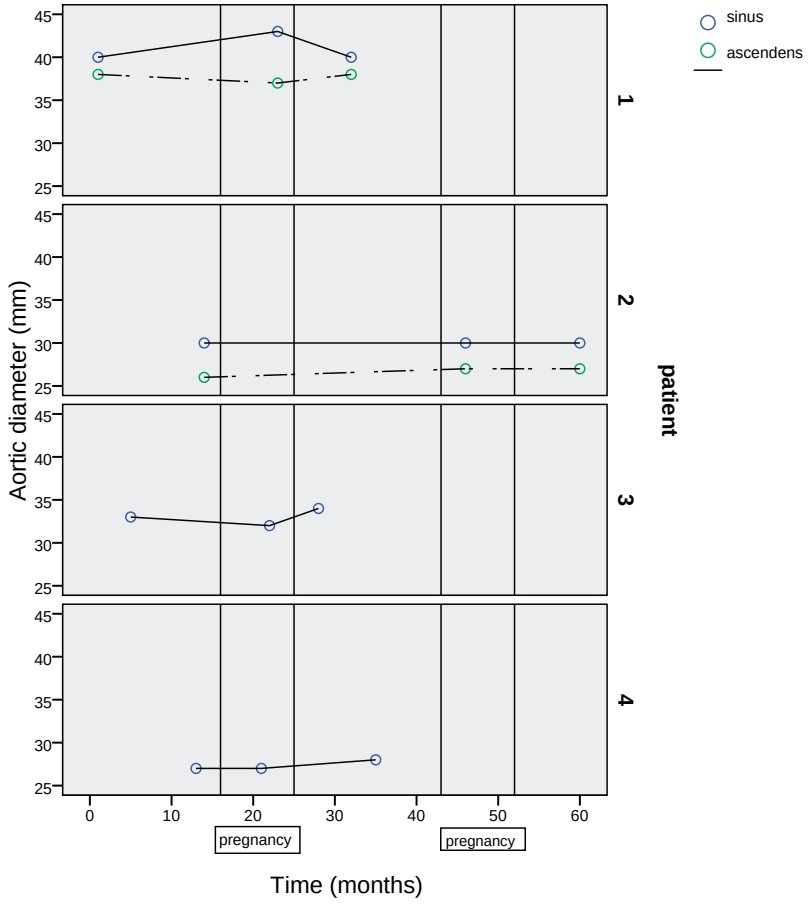


Figure 2 Aortic diameters on echocardiography

Case report of pregnancy after thoracic aortic surgery

The patient was a 32-year-old woman who had been diagnosed with Turner Syndrome at the age of 11 after growth failure. Karyotyping revealed a monosomy 45,X in all investigated blood cells. The patient was treated with growth hormone and estradiol. First cardiac evaluation one year after diagnosis showed a bicuspid aortic valve and mild aortic regurgitation. At age 15, a dilated ascending aorta was noticed on echocardiogram with a diameter of 38 mm. At age 18, the ascending aorta diameter was 35 mm, which further dilated to 40 mm at the age of 25. The patient decided to opt for egg cell donation four years later and hormone therapy was initiated in the form of estradiol and medroxyprogesterone. The patient consulted a cardiologist and a cardiac and thoracic MRI showed an ascending aortic diameter of 47 mm, mild aortic regurgitation and a mild prolapse of the mitral valve. The patient was advised to delay pregnancy until after replacement of the ascending aorta. She underwent a supracoronary replacement of the ascending aorta. The sinus was not found to be dilated and the aortic valve was left in place. One year after aortic surgery, the egg cell donation procedure was continued. The patient was confirmed to be pregnant at the age of 32. She received a total of three single donor embryos transfers: one fresh embryo transfer and two frozen embryo transfers. The second frozen embryo transfer resulted in pregnancy. An echocardiogram at 26 weeks of gestation showed a stable cardiac status and good functioning of the aortic graft. The ascending aortic diameter remained stable at 31 mm. The patient reported no complaints. At 41 weeks of gestation, labour was induced using prostaglandin and oxytocin because of postterm pregnancy, and secondary caesarean section was required due to foetal distress. She gave birth to a boy of 4510 grams without congenital defects. Postpartum course was uneventful. Upon cardiac evaluation three months postpartum, the patient reported good recovery. Echocardiographic evaluation two and three years postpartum showed a stable aortic diameter and mild aortic regurgitation. First postpartum CT scan of the thoracic aorta was performed three years postpartum and confirmed stable diameters.

DISCUSSION

In this single centre cohort of women with Turner syndrome, no severe aortic complications occurred during or directly after pregnancy. Some women experienced hypertensive events, as expected based on literature. We presented a unique case of a woman with Turner syndrome who became pregnant after aortic root replacement. The pregnancy was uneventful and aortic diameters were stable years after delivery.

Pregnancy and aortic complications

The aortic wall is subject to change during pregnancy. In post-mortem histopathology of the aorta in pregnant women, fragmentation of reticulum fibers and less corrugated elastic fibers were found in the intima media[12]. This leads to the hypothesis that pregnancy may lead to aortic dilatation or even rupture. Many case reports and series have been published, although restrained by low numbers and selection bias. Patients derived from these reports presumably overrepresent those with an unusual presentation of their disease[13]. An early review of literature did not reveal pregnancy as a risk factor. Also, only two out of 346 women in the largest registry of aortic dissections, were pregnant[14]. The registry could not reveal pregnancy as a risk factor, while aortic syndromes were the most important risk factor for aortic dissection in young women[15]. However, in a population based cohort, a clear increased risk of aortic dissection existed in pregnant women compared to their non-pregnant peers[16].

Whether pregnancy further increases the risk of aortic dissection in patients with Turner Syndrome, although often suggested, has not yet been determined. Two case series described the dramatic course of aortic dissection in TS women; some of them were pregnant[2,17]. However, these findings might also be attributed to the fact that aortic dissection generally occurs at young adult age. Both research groups reported a mean age of approximately 30-35 years at the time of aortic dissection in Turner syndrome.

Similar to our study, all studies on the incidence of aortic dissection during pregnancy in patients with Turner Syndrome were retrospective and one should be very cautious to draw any conclusion, as a high risk of selection and publication bias exists. The majority of pregnancies was conceived through assisted reproductive therapy[18-23]. Regardless of the risk being increased in pregnancy or not, aortic dissection is a potential devastating event and the most important cause of cardiovascular maternal mortality in the general population[24]. It requires a systematic approach of pregnancy counselling and follow-up in women who are at increased risk of aortic dissection, and thus also for women with Turner Syndrome.

Evidence of other complications in Turner syndrome

In addition to the potentially increased risk of aortic dilatation and dissection, women with Turner syndrome are at increased risk of hypertensive complications: in a Scandinavian cohort pregnancy induced hypertension occurred in 14.5% and pre-eclamptic toxaemia in 20.5% of oocyte donation pregnancies[23]. In a Belgian report, pregnancy induced hypertension and pre-eclampsia have been reported in 17% and 23%, respectively, of oocyte donation pregnancies in Turner patients[20]. Pre-eclampsia and gestational hypertension in the general pregnant population are associated with several risk factors including nulliparity, older age, pre-existing diabetes, antiphospholipid antibodies and pre-existing hypertension[25]. Hypertension is more common in women with Turner syndrome, which may contribute to the higher incidence of hypertensive complications during pregnancy.

Prophylactic aortic surgery and pregnancy

Currently, little is known about the risk of pregnancy after aortic surgery. In the European guidelines, prepregnancy surgery is advised in women with Marfan syndrome and a dilated ascending aorta (>45 mm in their case), and surgery should be considered in women with a bicuspid aortic valve and a diameter greater than 50mm or 27 mm/m^2. However, a recent report described 3 cases of pregnancy in women with Loeys Dietz syndrome after aortic surgery and 2 of them suffered from aortic dissection shortly after delivery[5]. It is unknown whether this risk is isolated to syndromes such as Loeys Dietz, or whether we should be reluctant also to perform prophylactic surgery in women with Turner syndrome, or even no specific aortic syndrome at all. In our cohort, one woman underwent prepregancy aortic root replacement, without subsequent problems during or after pregnancy. In retrospect, it may have been useful to plan delivery at 38 or 39 weeks, to prevent the additional risk of prolonged pregnancy and of delivery in the presence of macrosomia. More studies are definitely required to support the current guidelines on pregnancy in women with aortic disease.

Cardiovascular management of pregnancy

Prior to conception, all women with Turner syndrome should be screened for cardiac anomalies. Also, the risk of aortic dissection needs to be determined, just as outside pregnancy. Risk factors that have been found are: aortic dilatation, bicuspid aortic valve, hypertension, repaired or unrepaired coarctation, and history of aortic dissection[2,26]. The aortic size index should be evaluated by imaging of the aorta prior to conception, either with CT or MR. During pregnancy, at least one echocardiogram should be made (for instance at 20 weeks of gestation) to evaluate the aortic dimensions. If the aortic size index before pregnancy exceeded 2.0 cm/m^2, regular assessment is advised with an interval of 4 to 12 weeks. An MRI is indicated in case of aortic dilatation or an increase of dimensions, and also may be considered if echocardiographic images are not sufficient. Gadolinium is not routinely used because it crosses the placental borders and the consequences for the fetus are unclear.

Vaginal delivery is the preferred mode of delivery in every patient. Fetal adverse outcome is more frequently encountered in women with a caesarean section compared to women with a vaginal delivery[27]. Specific evidence is lacking in patients with aortic disease or even Turner syndrome and associated aortopathy. Based on expert opinion, in patients with a dilated aorta, i.e. an aortic size index of greater than 2.7 cm/m2, a caesarean section is recommended, to prevent of large haemodynamic differences causing aortic wall stress[4].

During the first six months after pregnancy careful evaluation and imaging is also indicated, as aortic dilatation and dissection may still occur in the postpartum period.

Limitations

This study is limited by its retrospective nature and by the low number of included patients. The latter is difficult to overcome, as the number of women with Turner syndrome getting pregnant, is quite low and increasing slowly in the past decades since oocyte donation came available. Selection bias remains hard to prevent, with probably a large number of women with Turner syndrome being cared for in peripheral hospitals or not visiting a clinic at all. These women presumably have a milder phenotype of Turner syndrome. Large prospective multicentre and multinational studies are definitely required to investigate the absolute risk of aortic problems and maternal mortality in women with Turner syndrome[3].

Conclusion

This study aimed to determine the risk of cardiovascular complications in women with Turner syndrome. In our retrospective cohort no major complications occurred. One women had an uneventful pregnancy after aortic root replacement. Larger cohorts are required to study incidence of aortic and hypertensive complications in more detail.

REFERENCES

1. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351**(12): 1227-38.
2. Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. *Circulation* 2012; **126**(18): 2220-6.
3. Lin AE, Karnis MF, Calderwood L, et al. Proposal for a national registry to monitor women with Turner syndrome seeking assisted reproductive technology. *Fertil Steril* 2016; **105**(6): 1446-8.
4. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
5. Braverman AC, Moon MR, Geraghty P, Willing M, Bach C, Kouchoukos NT. Pregnancy after aortic root replacement in Loeys-Dietz syndrome: High risk of aortic dissection. *American Journal of Medical Genetics Part A* 2016; **170**(8): 2177-80.
6. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome--integrating cardiology, genetics, and endocrinology. *Endocr Rev* 2012; **33**(5): 677-714.
7. EURO-PERISTAT. The European Perinatal Health Report 2010.
8. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007; **49**(24): 2303-11.
9. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013; **170**(1): 1-7.
10. Stone JH. HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets. *JAMA* 1998; **280**(6): 559-62.
11. Jaddoe VW, Troe EJ, Hofman A, et al. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. *Paediatr Perinat Epidemiol* 2008; **22**(2): 162-71.
12. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83**(4): 336-41.
13. Oskoui R, Lindsay J, Jr. Aortic dissection in women < 40 years of age and the unimportance of pregnancy. *Am J Cardiol* 1994; **73**(11): 821-3.
14. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation* 2004; **109**(24): 3014-21.
15. Januzzi JL, Isselbacher EM, Fattori R, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004; **43**(4): 665-9.
16. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. *Eur J Obstet Gynecol Reprod Biol* 2010; **149**(1): 120-1.
17. Gravholt CH, Landin-Wilhelmsen K, Stochholm K, et al. Clinical and epidemiological description of aortic dissection in Turner's syndrome. *Cardiology in the Young* 2006; **16**(5): 430-6.
18. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril* 2003; **80**(3): 498-501.
19. Bodri D, Vernaeve V, Figueras F, Vidal R, Guillen JJ, Coll O. Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. *Hum Reprod* 2006; **21**(3): 829-32.

20. Alvaro Mercadal B, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner's syndrome and partial X monosomy. *Hum Reprod* 2011; **26**(8): 2061-8.
21. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab* 2011; **96**(2): E260-7.
22. Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertil Steril* 2011; **95**(7): 2251-6.
23. Hagman A, Loft A, Wennerholm UB, et al. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod* 2013; **28**(6): 1598-609.
24. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
25. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010; **376**(9741): 631-44.
26. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation* 2007; **116**(15): 1663-70.
27. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, et al. Is a planned caesarean section in women with cardiac disease beneficial? *Heart* 2015; **101**(7): 530-6.

CHAPTER 13

Pregnancy in women with *SMAD3* mutation

Iris M. van Hagen
Denise van der Linde
Ingrid M.B.H. van de Laar
Laura Muiño Mosquera
Julie De Backer
Jolien W. Roos-Hesselink

Accepted in *JACC*. 2017

Women with genetic aortic disease, such as Marfan syndrome, are at increased risk of pregnancy complications, in particular aortic dissection[1]. Aneurysms-Osteoarthritis Syndrome (AOS) is an autosomal-dominant syndrome caused by *SMAD3* mutations, and is characterized by arterial aneurysms and tortuosity in combination with osteoarthritis. There is a lack of data about the cardiovascular risks of pregnancy in women with *SMAD3* mutation. Therefore, we collected data on the pregnancies of patients with *SMAD3* mutation followed in our centers.

We included all women with a *SMAD3* mutation that were previously enrolled in a prospective cohort study[2]. Data regarding pregnancy were collected retrospectively, both through the medical file and by interview. In two patients, with a recent pregnancy, aortic dimensions measured with echocardiography or computed tomography before, during and after pregnancy were available.

Seventeen women with *SMAD3* mutation had 34 pregnancies. Two of them had two pregnancies after they were diagnosed with *SMAD3* mutation. At the time of diagnosis, osteoarthritis and orthopedic lesions were present in all but one patient, and vascular anomalies present in at least 12 of the 17 patients. Mean age at first conception was 26 years (SD±3.6;range 22-33 years). There were 6 miscarriages in 4 women (23.6%). Twenty-eight pregnancies ended in live births, including two twins. No maternal mortality and no aortic dissection occurred. One patient developed pregnancy induced hypertension and preeclampsia, and another patient reported gestational diabetes. Hydronephrosis occurred in one other patient. At least 4 patients reported to have experienced severe pregnancy related pain in the pelvic area (24%). One patient had intrauterine growth restriction, resulting in a baby small-for-gestational age.

Three caesarean sections (CS) were performed. One woman delivered by secondary CS due to failure to progress, and two women had a planned CS: one was performed for breech position, and the other was planned at 35 weeks because of increasing aortic diameters (Patient 2, **Figure 1**). No uterine rupture was reported. One neonate had lower urinary tract obstruction, and another baby was reported to have a cleft palate. No postpartum hemorrhage or other complications were reported.

No major cardiovascular complications occurred postpartum. Imaging before and after pregnancy is shown in **Figure 1**.

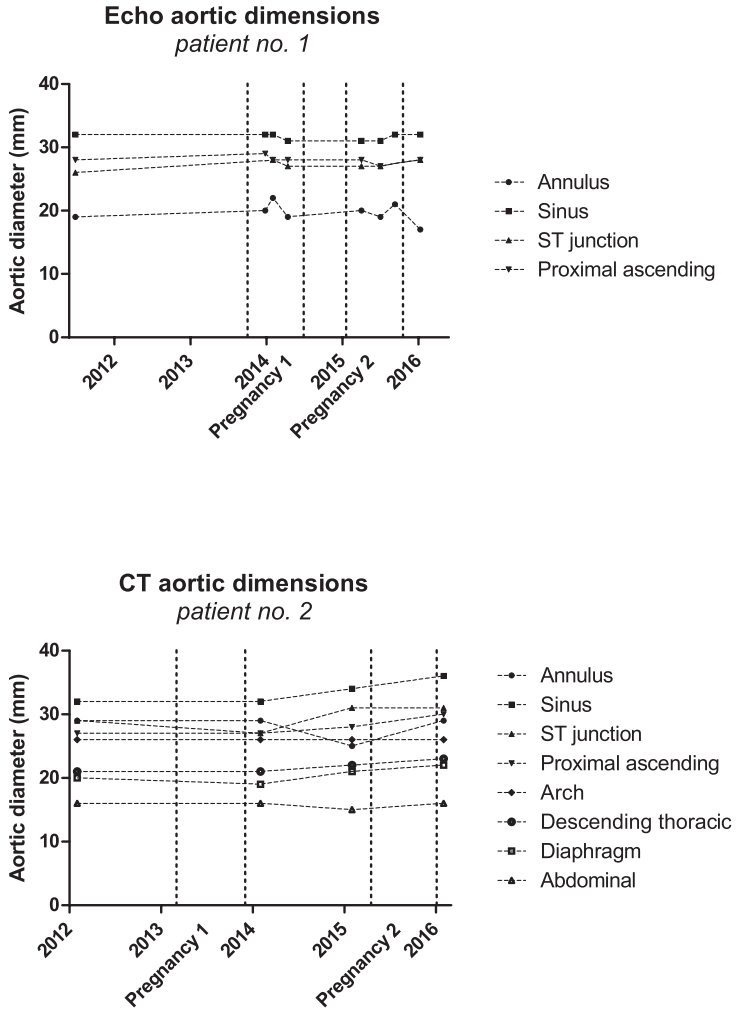


Figure 1 Aortic dimensions in two patients with *SMAD3* mutation.
Two women had been pregnant twice after being diagnosed with SMAD3 mutation. The evolvement of their aortic dimensions are shown in this figure. ST = sinotubular

COMMENT

Pregnancy not only induces hemodynamic changes, with a 30-50% increase of cardiac output and 10% increase in heart rate, but it may also influence the integrity of the aortic wall . This is suggested to be due to hormonal changes, that affect in particular the matrix profile resulting in decreased artery stiffness[3]. As AOS due to *SMAD3* mutations is an ag-

gressive aortic syndrome, concern exists around pregnancy in these patients. The current study describes 34 pregnancies in 17 women. No clear increased risk of aortic dissection or obstetric complications in these women was found. Conclusions of our results are limited by the retrospective nature of this study, with a risk of survivor bias, and the limited amount of patients included. Therefore, large prospective studies are warranted. In two patients with multiple aortic measurements, we observed no clear changes in Patient 1, while in Patient 2 the dimensions at the level of the sinus of Valsalva showed a tendency to increase. Future research must focus on aortic growth to further determine whether pregnancy has an effect on aortic diameters and poses women to an increased risk of aortic dissection. Finally, uterine rupture was not observed, but a number of patients spontaneously reported severe pain in the pelvic area, suggesting a link with pelvic joint pain.

This report, in combination with existing evidence on aortic syndromes caused by mutations in genes involved in the TGF-beta pathway like Loeys-Dietz, can provide guidance for preconception counseling and management of pregnancy in patients with *SMAD3* mutation. The guidelines on pregnancy and cardiovascular disease advise preconception surgery in women with *SMAD3* mutation, when the aorta is ≥45mm[4]. Further management during pregnancy includes strict blood pressure control. CS in women with an aortic diameter >45mm and vaginal delivery with epidural anesthesia when the aorta is <40mm is advised. Between 40 and 45mm bot strategies could be considered. We feel that these recommendations can be adapted to women with *SMAD3* mutation. In our series only 1 woman had a CS because of a dilated aorta. In the patients with vaginal delivery no aortic complications occurred.

In conclusion, in the absence of prospective studies, our retrospective study shows no adverse outcome for pregnancy in women with *SMAD3* mutation. However, counseling about the potential increased risk of pregnancy-related aortic complications remains warranted. In addition, pelvic joint pain might occur more often in these patients.

REFERENCES

1. Immer FF, Bansi AG, Immer-Bansi AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003; **76**(1): 309-14.
2. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol* 2012; **60**(5): 397-403.
3. Natoli AK, Medley TL, Ahimastos AA, et al. Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloproteinase expression. *Hypertension* 2005; **46**(5): 1129-34.
4. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.

PART IV

Cardiomyopathies and Pulmonary hypertension

CHAPTER 14

Pregnancy in women with hypertrophic cardiomyopathy: data from the European Society of Cardiology initiated Registry of Pregnancy and Cardiac disease (ROPAC)

Sorel Goland
Iris M. van Hagen
Gabby Elbaz-Greener
Uri Elkayam
Avraham Shotan
Waltraut M. Merz
Sibel C. Enar
Ilshat R. Gaisin
Petronella G. Pieper
Mark R. Johnson
Roger Hall
Alexander Blatt*
Jolien W. Roos-Hesselink*.

Submitted

ABSTRACT

Aims We report the maternal and fetal outcomes at birth and after 6 months in a cohort of pregnant women with hypertrophic cardiomyopathy (HCM).

Background Although most women with HCM tolerate pregnancy well, there is an increased risk of obstetric and cardiovascular complications.

Methods All pregnant women with HCM entered into the prospective worldwide Registry of Pregnancy and Cardiac disease (ROPAC) were included in this analysis. The primary endpoint was a major adverse cardiovascular event (MACE), which included death, heart failure (HF), thromboembolic event and arrhythmia. Baseline and outcome data were analysed and compared for patients with MACE versus without MACE and for patients with obstructive HCM versus non-obstructive HCM.

Results Sixty pregnant women (mean age 30.4±6.0 years) with HCM (41.7% obstructive) were included. No maternal mortality occurred in this cohort. In 14 (23%) patients at least one MACE occurred: 9 (15.0%) HF and 7 (12%) an arrhythmia (6 ventricular and 1 atrial fibrillation). MACE occurred most commonly during the 3rd trimester and postpartum period. In total, 3 (5.0%) women experienced fetal loss. Women with MACE had a higher rate of emergency Caesarean delivery for cardiac reasons (21.4% vs. 0%, p=0.01). No significant differences in pregnancy outcome were found between women with obstructive and non-obstructive HCM. NYHA functional class of ≥ II and signs of HF before pregnancy, were associated with MACE.

Conclusions Although most women with HCM tolerated pregnancy well, cardiovascular complications were not uncommon and predicted by pre-pregnancy status facilitating pre-pregnancy counselling and targeted antenatal care.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease and has a prevalence of 2% in the general population. The widespread use of echocardiography and genetic screening for HCM has led to a growing number of young women diagnosed with HCM where most of them desire pregnancy. HCM in the non-pregnant state is associated with an increased risk of sudden cardiac death, arrhythmia and heart failure and the pregnancy-associated changes in the cardiovascular system may exacerbate these risks, although their impact on maternal hemodynamics is not well understood. During pregnancy, there is an initial fall in peripheral vascular resistance occurring predominantly during the 1st and 2nd trimesters. This results in an increase in cardiac output of around 50% due to the combination of a greater stroke volume and higher heart rate[1]. The increase in blood volume and consequently of left ventricular size offsets the adverse effect of the fall in peripheral vascular resistance on the LVOT gradient. In addition, enhanced LV contractility and higher heart rate with a shortened diastolic filling time, could exacerbate or precipitate heart failure and may not be well tolerated. Moreover, at the time of delivery, the auto-transfusion from the contracting uterus into the systemic circulation and stress related tachycardia during delivery and early postpartum, may lead to clinical deterioration. Despite these potential complications, it appears that most women with HCM tolerate pregnancy well. Previous studies report widely differing rates of cardiovascular complications, varying between 2 and 48%. However, most of the reports are retrospective or include small case series and may suffer from selection bias including more severe cases[2-7].

This prospective study aims to provide information on the outcome of pregnancy in a cohort of pregnant women with HCM recruited to the observational, contemporary, worldwide Registry of Pregnancy and Cardiac disease (ROPAC). Such information may be helpful in pre-pregnancy counseling of women with HCM and identifying women at high-risk of an adverse outcome.

METHODS

ROPAC is an ongoing prospective and worldwide registry initiated in 2007 by the European Society of Cardiology working groups on valvular heart disease and on congenital heart disease[8]. All consecutive pregnant women with structural heart disease, aortic pathology or pulmonary hypertension were included; non-structural heart diseases such as lone arrhythmic disease were excluded. Data were prospectively collected, and centers could also retrospectively include all consecutive patients up to 6 months before study entry. For this interim analysis, pregnancies in women with hypertrophic cardiomyopathy who were included in the study from 2007 up to 2014 were selected.

Data

The patient characteristics collected at baseline (before pregnancy) included age, ECG rhythm, diagnosis, risk factors for cardiovascular disease (smoking, diabetes, hypertension), previous interventions, medication, parity, obstetric history and facultative echocardiographic parameters. Follow-up was available for all patients up to one week after delivery; in addition follow-up at 6 months was available for part of the cohort. Patient characteristics and events were reported by the individual sites and did not undergo centralized adjudication. However, all events were predefined in the case report form.

Definitions

HCM was defined "by the presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions"[9]. The diagnosis HCM was confirmed if one or more left ventricular (LV) myocardial segments showed a thickness of ≥15 mm on echocardiography, cardiac resonance imaging or computed tomography. Obstructive HCM was defined as "an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mm Hg at rest or during physiological provocation such as Valsalva maneuver, standing and exercise" (2014 ESC guidelines[9]). These diagnostic features were confirmed in each patient by the local cardiologist. LVOT gradient was not collected as separate variable, and therefore could not be analyzed.

The **primary endpoint** was a major adverse cardiovascular event (MACE), collected up to 1 week after delivery, including maternal death, heart failure (HF), thromboembolic events, and supraventricular or ventricular tachyarrhythmia. **Heart failure** was defined was defined according to ACC/AHA guidelines as a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) and signs (of fluid retention, such as edema, or rales) on physical examination as judged by the treating cardiologist[10]. The heart failure episode was only registered when signs or symptoms of HF were present which required new treatment, change of treatment or hospital admission. A **ventricular tachyarrhythmia** (VTA) was defined as three or more consecutive ventricular beats with a mean rate of more than 100 beats per minute; however, only clinically relevant VTA (when the patient had physical complaints, needed treatment for VTA or when the patient had more than 100 consecutive beats) was included. Other endpoints of interest were hospitalization for a cardiac reason, a Caesarean delivery for a cardiac reason, birth weight, small for gestational age (birth weight $<10^{th}$ percentile), miscarriage (<24 weeks), fetal death (≥24 weeks), neonatal death, termination of pregnancy and preterm birth (<37 weeks).

Baseline and outcome data were analyzed for the total group; patients with and without MACE were compared and those with obstructive HCM compared to those with non-obstructive HCM.

Statistical analysis

Continuous variables are presented as mean and standard deviation, or as median and quartiles where appropriate. Differences were assessed with Student's t-test. Categorical variables are presented as percentages and differences were assessed using Chi-square tests. Predictors of MACE were identified by performing univariable logistic regression analyses. The number of events (n=15) did not allow for multivariable regression analysis. Statistical tests were considered significant if a p-value was less than 0.05 (two-sided). All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Sixty pregnancies in women with hypertrophic cardiomyopathy were included, from 28 centers in 19 countries; the majority were from countries with an advanced economy (n= 49, 81.7%). Mean age was 30.4 (±6.0) years and 30 (50.0%) were nulliparous. All pregnancies were singleton. Baseline characteristics are presented in **Table 1**. Twenty-five patients (41.7%) were reported to have an obstructive hypertrophic cardiomyopathy. Eight patients (13.3%) had had a prior intervention (3 patients had undergone septal myectomy, 1 patient had had an alcohol septal ablation, 1 patient surgical repair of the mitral valve had been performed, and in 3 patients there had been an unspecified intervention). In 4 patients (6.7%) an implantable cardioverter-defibrillator (ICD) was implanted.

During pregnancy, 29 patients were treated with cardiac medication (48.3%); 24 were taking a beta-blocker (40.0%), five a calcium-antagonist (8.3%), four diuretics (6.7%), and three antiarrhythmic medications (5.0%).

Table 1 Baseline characteristics of women with hypertrophic cardiomyopathy with and without MACE

	All women with HCM		Women with obstructive HCM		Women with non-obstructive HCM			Women with MACE		Women without MACE		
	n= 60		n= 25 (41.7%)		n= 35 (58.3%)		p-value	n= 14 (23.3%)		n= 46 (76.7%)		p-value
Age, years	30.4	(±6.0)	30.4	(±5.4)	30.3	(±6.5)	0.98	31.7	(±6.2)	29.9	(±6.0)	0.33
Nullipara	30	50.0%	10	40.0%	20	57.1%	0.19	8	57.1%	22	47.8%	0.54
Living in an emerging country	11	18.3%	4	16.0%	7	20.0%	0.75	5	35.7%	6	13.0%	0,11
Hypertension	8	13.8%	1	4.0%	7	21.2%	0.12	4	30.8%	4	8.9%	0.066
Diabetes	2	3.3%	1	4.0%	1	2.9%	1.00	1	7.1%	1	2.2%	0.42
Current smoking	3	5.8%	1	4.5%	2	6.7%	1.00	0	0.0%	3	7.7%	0.56
NYHA class							0.44					0.001
NYHA I	40	66.7%	16	72.7%	24	68.6%		5	35.7%	35	81.4%	
NYHA II	16	26.7%	5	22.7%	11	31.4%		9	64.3%	7	16.3%	
NYHA III	1	1.7%	1	4.5%	0	0.0%		0	0.0%	1	2.3%	
NYHA IV	0	0.0%	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Signs of heart failure at baseline	5	8.6%	2	8.7%	3	8.6%	1.00	4	28.6%	1	2.3%	0.010
Episode of atrial fibrillation at baseline	1	1.7%	0	0.0%	1	2.9%	1.00	0	0.0%	1	2.2%	1.00
Intervention or ICD	11	18.3%	8	32.0%	3	8.6%	0.039	1	7.1%	10	21.7%	0.43
Cardiac medication	33	55.0%	16	64.0%	17	48.6%	0.23	8	57.1%	25	54.3%	0.85
Betablocker	29	48.3%	15	60.0%	14	40.0%	0.13	7	50.0%	22	47.8%	0.89
Calcium antagonist	2	3.3%	0	0.0%	2	5.7%	0.51	1	7.1%	1	2.2%	0.42
Antiarrhythmic	1	1.7%	1	4.0%	0	0.0%	0.42	0	0.0%	1	2.2%	1.00
Diuretic	2	3.3%	1	4.0%	1	2.9%	1.00	2	14.3%	0	0.0%	0.051

Table 1 Baseline characteristics of women with hypertrophic cardiomyopathy with and without MACE (continued)

	All women with HCM		Women with obstructive HCM		Women with non-obstructive HCM			Women with MACE		Women without MACE		
	n= 60		n= 25 (41.7%)		n= 35 (58.3%)		p-value	n= 14 (23.3%)		n= 46 (76.7%)		p-value
ACE inhibitor	2	3.3%	0	0.0%	2	5.7%	0.51	2	14.3%	0	0.0%	0.051
Obstructive cardiomyopathy	25	41.7%						4	28.6%	21	45.7%	0.26
Mitral regurgitation (mild to moderate)	21	35.6%	9	36.0%	12	35.3%	0.96	5	35.7%	16	35.6%	1.00
RVSP >30 mmHg	5	8.6%	2	8.3%	3	8.8%	1.00	3	21.4%	2	4.5%	0.085
Median IVS, mm (Q1-Q3) *(missing in: 17 cases)*	18	(14-25)	19	(16-27.5)	18	(13-25.5)	0.65	18	(17-27)	18.5	(13-25)	0.52
Median LVPW, mm (Q1-Q3) *(missing in: 19 cases)*	12	(10-14)	12	(11-15.5)	12.5	(10-14)	0.45	14	(11-16)	12	(10-14)	0.23

HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; IVS = intraventricular septum; LVPW = left ventricle posterial wall; MACE = Major Adverse Cardiac Event; na = not applicable; NYHA = New York Heart Association functional class; RVSP = right ventricular systolic pressure; Q1-Q3 = first to third quartile.

Maternal outcome

No maternal mortality occurred in this cohort. In 14 patients, at least one MACE occurred (23.3%, **Figure 1);** 9 developed HF (15.0%), 6 patients had a ventricular tachyarrhythmia (10%), and 1 patient had atrial fibrillation (1.7%). Two patients had two major adverse cardiac events: one developed both HF and ventricular tachycardia at five weeks of gestation and one developed HF at gestational age 23 weeks followed by a ventricular arrhythmia at 32 weeks. The timing of the first MACE was mainly in the third trimester (n=6) or postpartum (n=4) (**Figure 1**).

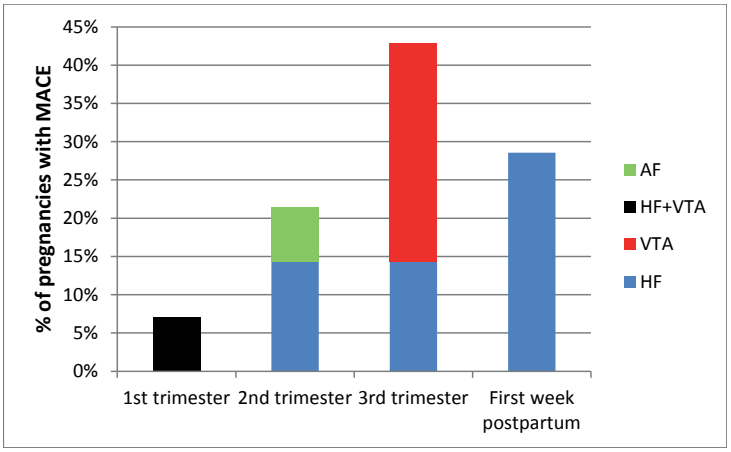


Figure 1 Timing and type of first Major Adverse Cardiac Event during pregnancy in women with hypertrophic cardiomyopathy

No maternal mortality or thromboembolic events occurred.

AF= atrial fibrillation; HF= heart failure; MACE= Major Adverse Cardiac Event; VTA= ventricular tachyarrhythmia

In **Table 2**, the management of patients who suffered a MACE during pregnancy is presented. Before the event, four patients were taking a beta-blocker and in another four patients, a beta-blocker had been stopped. After the event, 9 of 14 started or continued a beta-blocker, in some in addition to diuretics or antiarrhythmic medication. One patient with a ventricular tachyarrhythmia in the third trimester had an ICD implantation two days postpartum.

Results of the univariable analysis for MACE are shown in **Table 3**. NYHA functional class of ≥ 2 and signs of HF before pregnancy were significantly associated with MACE. The number of events was too small to allow for multivariable analysis.

Table 2 Description of MACE and medical management

Patient	MACE	Timing event	Timing second event	Medication before pregnancy	Medication changes before event	Medication changes after event	Intervention
1	HF+VTA	23+2	32+0			Betablocker + antiarrhythmic started	
2	HF+VTA	5+6	5+6	Betablocker and calcium antagonist	Betablocker and calcium antagonist stopped		
3	VTA	35+0		Betablocker stopped			
4	VTA	38+3					
5	VTA	40+1			Betablocker started	Betablocker continued	
6	HF	2 days pp		Betablocker started, ACE-i stopped		Betablocker continued	
7	HF	1 day pp		Betablocker	Betablocker stopped		
8	HF	1 day pp				Betablocker and diuretic started	
9	HF	27+3		Betablocker	Calcium antagonist started	Betablocker changed and diuretics started	
10	HF	32+6		ACE-i stopped	Calcium antagonist started	Betablocker started	
11	VTA	34+5				Betablocker started	ICD implanted 2 days pp
12	HF	24+5				Betablocker started	
13	HF	7 days pp		Betablocker	Betablocker stopped		
14	AF	23+6		Betablocker and diuretic		Betablocker and diuretic increased	

ACE-i=Angiotensin converting enzyme receptor inhibitor, AF=atrial fibrillation, HF=heart failure, ICD=implantable cardioverter defibrillator, MACE=major adverse cardiovascular event, pp=postpartum, VTA=ventricular tachyarrhythmia

Table 3 Univariable analysis of predictors of MACE during pregnancy in women with hypertrophic cardiomyopathy

Predictors of MACE			
	OR	95%CI	p-value
Nulliparity	1.46	(0.44-4.86)	0.54
Hypertension before pregnancy	4.56	(0.96-21.7)	0.057
NYHA class >1	8.55	(2.26-32.4)	0.002
Signs of heart failure	17.2	(1.73-171)	0.015
Obstructive cardiomyopathy	0.48	(0.13-1.74)	0.26
Mitral regurgitation	1.01	(0.29-3.52)	0.99
RVSP>30 mmHg	5.73	(0.85-38.6)	0.073
Septum thickness	1.03	(0.95-1.12)	0.48
LV posterior wall thickness	1.15	(0.94-1.42)	0.18

CI = confidence interval; NYHA = New York Heart Association functional class; OR= odds ratio; RVSP = right ventricular systolic pressure.

Obstetric and fetal outcome

Table 4 shows the obstetric and fetal outcome for the total HCM group and for women with MACE versus those without MACE. Three fetal losses occurred; 1 miscarriage and 2 fetal deaths after 24 weeks. The miscarriage occurred at 23 weeks and the growth-restricted fetus was suspected of a mitochondrial cardiomyopathy. In the patient who had developed HF and a ventricular tachyarrhythmia at 5 weeks, intrauterine fetal death occurred at 29 weeks of gestation. One patient with pre-existing permanent atrial fibrillation, was treated with disopyramide, digoxin and unfractionated heparin and had an intrauterine fetal death at 27 weeks. Pregnancy duration in women with MACE was significantly shorter than in women without MACE. An emergency Caesarean delivery for a cardiac reason was performed in three of the 14 women with MACE: in 2 after HF (of whom one also had a ventricular tachyarrhythmia) and in 1 after atrial fibrillation.

Five neonates (8.3%) were diagnosed with an inherited hypertrophic cardiomyopathy: 3 babies of women with non-obstructive HCM (8.6%) (in 1 of these 3, fetal loss at 23 weeks occurred), and 2 of the women with obstructive HCM (8.0%).

Obstructive and non-obstructive HCM

No significant differences in pregnancy outcome were found between women with obstructive and non-obstructive HCM. The data are presented in Table 5.

Table 4 Obstetric and fetal outcome of pregnancy in the presence of hypertrophic cardiomyopathy, in women with and women without MACE

	All women with HCM	Women with MACE	Women without MACE	
	n= 60	n= 14 (23.3%)	n= 46 (76.7%)	p-value
(pre-)eclampsia or HELLP	3 5.0%	2 14.3%	1 2.2%	0.13
Pregnancy-induced hypertension	0 0.0%	0 0.0%	0 0.0%	na
Postpartum haemorrhage	1 1.7%	1 7.1%	0 0.0%	0.23
Caesarean section	36 60.0%	12 85.7%	24 52.2%	0.031
Emergency CS for a cardiac reason	3 5.0%	3 21.4%	0 0.0%	0.011
Miscarriage <24 weeks	1 1.7%	0 0.0%	1 2.2%	1.00
Fetal death ≥24 weeks	2 3.3%	1 7.1%	1 2.2%	0.42
Termination of pregnancy	0 0.0%	0 0.0%	0 0.0%	na
Small-for-gestational age	9 16.1%	2 14.3%	7 16.7%	1.00
Preterm birth (<37 weeks)	14 24.6%	4 30.8%	10 22.7%	0.72
Low Apgar (<7)	6 11.1%	1 7.7%	5 12.2%	1.00
Pregnancy duration, weeks (Q1-Q3)	38.3 (36.9-39.1)	37.4 (34.6-38.3)	38.6 (36.9-39.9)	0.037
Birthweight, grams (Q1-Q3)	3000 (2500-3280)	2900 (2555-3228)	3045 (2488-3389)	0.56
Neonatal death, ≤1 week	0 0.0%	0 0.0%	0 0.0%	na

CS = Caesarean section; HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; MACE = Major Adverse Cardiac Event; na = not applicable; Q1-Q3 = first to third quartile

*2 patients with heart failure also developed a ventricular arrhythmia

Table 5 Outcome in women with obstructive and non-obstructive hypertrophic cardiomyopathy

	Women with obstructive HCM	Women with non-obstructive HCM	
	n= 25 (41.7%)	n= 35 (58.3%)	p-value
MACE*			
Maternal mortality	0 0%	0 0%	na
Heart failure	2 8.0%	7 20.0%	0.28
Supraventricular tachyarrhythmia	1 4.0%	0 0%	0.42
Ventricular tachyarrhythmia	1 4.0%	5 14.3%	0.39
Thromboembolic complication	0 0%	0 0%	na
Hospital admission	8 32.0%	13 38.2%	0.62
Cardiac hospital admission	4 16.0%	8 22.9%	0.51
(pre-)eclampsia or HELLP	0 0.0%	3 8.6%	0.26

Table 5 Outcome in women with obstructive and non-obstructive hypertrophic cardiomyopathy (continued)

	Women with obstructive HCM		Women with non-obstructive HCM		
	n= 25 (41.7%)		n= 35 (58.3%)		p-value
Postpartum haemorrhage	0	0.0%	1	2.9%	1.00
Caesarean section	14	56.0%	22	62.9%	0.59
Emergency CS for a cardiac reason	2	8.0%	1	2.9%	0.57
Miscarriage <24 weeks	0	0.0%	1	2.9%	1.00
Fetal death ≥24 weeks	1	4.0%	1	2.9%	1.00
Small-for-gestational age	4	16.7%	5	15.6%	1.00
Preterm birth (<37 weeks)	4	16.7%	10	30.3%	0.24
Low Apgar (<7)	5	21.7%	1	3.2%	0.073
Pregnancy duration, weeks (Q1-Q3)	38.6	(37.0-39.1)	38.1	(36.4-39.6)	0.70
Birthweight, grams (Q1-Q3)	3014	(2568-3258)	3000	(2420-3450)	0.80

CS = Caesarean section; HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; MACE = Major Adverse Cardiac Event; na = not applicable;
Q1-Q3 = first to third quartile
*2 patients with heart failure also developed a ventricular arrhythmia

Follow-up

Follow-up at 6 months was available in 49 of the 60 pregnancies (81.7%) and no maternal mortality occurred during follow-up. One patient, with non-obstructive HCM and good LV function prior to pregnancy, was found to have severe LV dysfunction with apical thrombus formation - along with signs and symptoms of overt HF - at 4 months after delivery with a gradual recovery of LV function after heart failure medication was started.

DISCUSSION

The results of our study demonstrate a favorable maternal and fetal outcome in the majority of women with HCM who tolerated pregnancy well without maternal mortality. At the same time, however, 23% of the patient still developed important MACE including HF and arrhythmias. In addition, women with cardiac complications had a shorter duration of pregnancy and higher rates of emergency cesarean delivery. Functional status and signs of HF prior to pregnancy were associated with these complications.

Mortality in pregnant women with HCM

The results of this study support data obtained from few retrospective studies reporting low mortality rate (0%-2%) related to pregnancy in women with HCM[4,11,12]. In the study by

Autore et al, 2 women (out of 100) with very high-risk profiles died during pregnancy. Both had been advised against becoming pregnant[4]. One had a septum thickness of more than 30 mm, a very high LVOT gradient and a poor functional class with deterioration during her previous pregnancies and the other had an extremely strong familial history of sudden death and had experienced prolonged runs of VT prior to death. A recent review presented the pooled analysis of 408 pregnancies including these two cases, which were the only deaths in the series, giving a maternal mortality rate of 0.5%[13]. It seems likely, if current recommendations[9] had been followed, that both of these deaths would have been prevented. Indeed, in our contemporaneous data, there was no maternal mortality, although at least 7 patients had a septal thickness of more than 30 mm.

MACE in pregnant women with HCM

A number of complications such as HF, arrhythmias, syncope and thromboembolic complications have been described in women with HCM during pregnancy. The rates of these vary from 15% to 48% depending on the study design and patient population[4,6,7,13]. In the most recent retrospective study by Lima et al, which included 52 women with HCM, the reported rate of MACE was 23% at time of delivery, which was significantly lower compared to women with peripartum or dilated cardiomyopathy[14]. In our contemporary registry, almost a quarter of pregnant women with HCM developed either HF or arrhythmia and most of these complications occurred during the 3rd trimester or postpartum, consistent with the reported literature.

Heart failure and timing of occurrence

Autore et al identified 98 survivors among 100 women with HCM (199 pregnancies)[4]. In their study, most of the patients were asymptomatic before pregnancy and clinical deterioration during pregnancy was uncommon. HF symptoms tended to worsen more often in those with LVOT obstruction (25% vs 11%), this difference however, was not statistically significant. In our registry, 15% of women experienced HF, mainly during the 3rd trimester, but there was no difference in pregnancy outcome between women with obstructive and non-obstructive HCM. These data are consistent with two other studies where the presence of LVOT obstruction had no influence on maternal outcome[5,6]. Avila et al compared 12 non-pregnant and 23 pregnant women with HCM, and found that similar to our findings, 30% of pregnant women experienced HF mainly during the 3rd trimester[6].

Arrhythmia

Recently, in a retrospective review of 27 pregnancies in 23 women with HCM, Tanaka et al reported a cardiovascular event rate of 48%; the vast majority involved an arrhythmia and occured during the third trimester[7]. In contrast, Avilla et al reported an arrhythmia rate of only 13% among 23 pregnant women with HCM, a rate lower than found in non-pregnant

women with HCM[6]. In a series of 8 high risk women with HCM who had an implantable cardioverter defibrillator (ICD), 2 patients had VT (1 sustained and 1 non-sustained) and 2 had SVT[15]. Notably, all events but one, which required anti-tachycardia rapid pacing, were detected by interrogation of the ICD without any intervention by the device. In a recent review of the existing literature Schinkel et al reported ventricular arrhythmias in 5% and supraventricular arrhythmias in 7% of the patients[13]. Similar to this review, in our registry we found that 11.7 % of patients developed arrhythmia, 10% ventricular tachyarrhythmia and 1.7% atrial fibrillation (1.7%). In one woman ICD-implantation was necessary because of studies reported episodes of palpitations and arrhythmia during pregnancy in women with HCM which were similar to those experienced before their pregnancy[5,6]. More information is needed in order to define the effect of pregnancy on the incidence and severity of arrhythmias in women with HCM.

Predictors of complications in pregnant women with HCM

Several studies reported that symptomatic women deteriorated more often during pregnancy than asymptomatic women with HCM[5-7]. In a large retrospective study (using questionnaires), Thaman et al described 271 pregnancies in 127 women with HCM and found that the majority (90%) of women with symptoms during pregnancy had been symptomatic before[7]. Similarly, Autore et al found that those who had symptoms prior to pregnancy were more likely to deteriorate then those who did not (42% vs. 4%)[4]. Tanaka et al identified the use of cardiac medication prior to pregnancy as a predictor of maternal complications in a retrospective study of 27 pregnancies in 23 women with HCM[7]. In line with ESC risk stratification guidelines[9], the results of our contemporary registry show that NYHA functional class of ≥2 and signs of HF prior to pregnancy are associated with the occurrence of MACE.

Obstetric and fetal outcome

Schinkel reported a 25% Caesarean section rate for predominantly obstetric indications and a 15% rate of spontaneous abortion 5% therapeutic abortions and a 2% stillbirth rate[13]. In our study , the most frequently observed fetal morbidity was premature birth (26%), followed by being small for gestational age (8%) and developing fetal bradycardia (3%). Another study described termination of pregnancy in 4 out of 27 pregnancies, all due to cardiovascular complications[7]. In our registry, pregnancy duration in women with MACE was significantly shorter than in women without MACE and emergency Caesarean delivery for cardiac reasons was performed in 3 women, all of whom had a MACE. Three fetal losses occurred, 1 in a woman with MACE, 1 in a woman with pre-existing atrial fibrillation and 1 due to a mitochondrial cardiomyopathy in the fetus itself. As in the current series, fetal mortality in all available reports is comparable with the general population[16] although it seems to

occur mostly in women with cardiac complications, emphasizing the need for appropriate follow-up and management of women after a MACE, including close fetal monitoring.

Conclusion

Over the last decades, considerable progress has been made in the diagnostic evaluation, risk assessment and clinical management in patients with HCM. Results of this contemporaneous, multicenter, prospective, worldwide registry showed that most women with HCM tolerated pregnancy well and there was no mortality. However, cardiovascular complications such as heart failure and arrhythmias were not uncommon and influenced fetal outcome and delivery. Functional status and signs of heart failure prior to pregnancy are important risk factors for cardiac complications in pregnant women with HCM. Pre-pregnancy counseling, close monitoring and optimal care are mandatory to prevent complications in women with HCM.

Limitations

Our study has a number of limitations mostly related to missing information such as the LVOT gradient and its changes during pregnancy. However, obstructive HCM was defined as the presence of an LVOT gradient >30 mmHg, so we could characterize the group of women with obstructive HCM. In addition, there was incomplete information regarding family history, syncope and arrhythmias prior to pregnancy. Despite these limitations, this prospective registry included a large number of women with HCM, managed according to on contemporary guidelines, providing important information related to the maternal and fetal outcome in women with HCM.

REFERENCES

1. Elkayam U, Goland S, Pieper PG, Silverside CK. High-Risk Cardiac Disease in Pregnancy: Part I. *J Am Coll Cardiol* 2016; **68**(4): 396-410.
2. Turner GM, Oakley CM, Dixon HG. Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy. *Br Med J* 1968; **4**(5626): 281-4.
3. Oakley GD, McGarry K, Limb DG, Oakley CM. Management of pregnancy in patients with hypertrophic cardiomyopathy. *Br Med J* 1979; **1**(6180): 1749-50.
4. Autore C, Conte MR, Piccininno M, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **40**(10): 1864-9.
5. Thaman R, Varnava A, Hamid MS, et al. Pregnancy related complications in women with hypertrophic cardiomyopathy. *Heart* 2003; **89**(7): 752-6.
6. Avila WS, Amaral FM, Ramires JA, et al. Influence of pregnancy on clinical course and fetal outcome of women with hypertrophic cardiomyopathy. *Arq Bras Cardiol* 2007; **88**(4): 480-5.
7. Tanaka H, Kamiya C, Katsuragi S, et al. Cardiovascular events in pregnancy with hypertrophic cardiomyopathy. *Circ J* 2014; **78**(10): 2501-6.
8. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
9. Authors/Task Force m, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**(39): 2733-79.
10. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; **53**(15): e1-e90.
11. Avila WS, Rossi EG, Ramires JA, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. *Clin Cardiol* 2003; **26**(3): 135-42.
12. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
13. Schinkel AF. Pregnancy in women with hypertrophic cardiomyopathy. *Cardiol Rev* 2014; **22**(5): 217-22.
14. Lima FV, Parikh PB, Zhu J, Yang J, Stergiopoulos K. Association of cardiomyopathy with adverse cardiac events in pregnant women at the time of delivery. *JACC Heart Fail* 2015; **3**(3): 257-66.
15. Schuler PK, Herrey A, Wade A, et al. Pregnancy outcome and management of women with an implantable cardioverter defibrillator: a single centre experience. *Europace* 2012; **14**(12): 1740-5.
16. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.

CHAPTER 15

Pulmonary Hypertension and Pregnancy Outcome: Data from the Registry Of Pregnancy And Cardiac Disease (ROPAC) of the European Society of Cardiology

Karen Sliwa
Iris M. van Hagen
Werner Budts
Lorna Swan
Gianfranco Sinagra
Maryanne Caruana
Manuel Vazquez Blanco
Lodewijk J. Wagenaar
Mark R Johnson
Gary Webb
Roger Hall
Jolien W. Roos-Hesselink, on behalf of the ROPAC investigators.

Eur J Heart Fail. 2016 Sep;18(9):1119-28

ABSTRACT

Aims To describe the outcomes of pregnancy in women with pulmonary hypertension.

Methods and Results In 2007 the European Registry on Pregnancy and Heart Disease was initiated by the European Society of Cardiology. Consecutive patients with all forms of cardiovascular disease, presenting with pregnancy, were enrolled with the aim of investigating the pregnancy outcomes. This sub-group of the cohort included 151 women with pulmonary hypertension (PH) either diagnosed by right heart catheterization or diagnosed as possible PH by echocardiographic signs, with 26% having pulmonary arterial hypertension (PAH), in 3 subgroups: idiopathic (iPAH), associated with congenital heart disease (CHD-PAH) or associated with other disease (oPAH); and 74% having PH due to left heart disease (LHD-PH, n=112). Maternal mean age was 29.2±5.6years and 37% were nulliparous. The right ventricular systolic pressure was <50mmHg in 59.6% of patients, 50-70 mmHg in 28.5% and >70mmHg in 11.9%. In more than 75% of patients, the diagnosis of PH had been made prior to pregnancy. Maternal death up to 1 week after delivery occurred in 5 patients (3.3%), with another 2 out of 78 patients who presented for follow-up (2.6%), dying within 6 months after delivery. Highest mortality was found in iPAH (3/7, 43%). During pregnancy, heart failure occurred in 27%. Caesarean section was performed in 63.4% (23.9% as emergency). Therapeutic abortion was performed in 4.0%. Complications included miscarriage (5.6%), fetal mortality (2%), premature delivery (21.7%), low birth weight (19.0%) and neonatal mortality (0.7%).

Conclusion Mortality in this group of patients with various forms of PH was lower than previously reported as specialised care during pregnancy and delivery were available. However, maternal and fetal mortality remains prohibitively high in women with iPAH, although this conclusion is restricted by limited numbers. Early advice on contraception, pregnancy risk and fetal outcome remains paramount.

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological condition often leading to debilitating symptoms and shortened overall life expectancy, due to narrowing of the pulmonary vasculature and often leading to right heart failure. Pregnancy in women with PH, including idiopathic pulmonary arterial hypertension (iPAH), PH associated with congenital heart disease (CHD-PAH) or PAH due to other conditions (oPAH), are known to be associated with a high maternal mortality - between 25-56%[1,2]. PH in pregnant women is a modified World Health Organization (WHO) Class IV indication and, therefore, pregnancy should be avoided[3]. Pregnancy outcome is poor with high rates of preterm delivery (85-100%), fetal growth restriction (3-33%) and fetal/neonatal loss (7-13%)[1,2,4]. However, despite the advice to avoid pregnancy[3,5] some women with PH choose to become pregnant or to continue with an unplanned pregnancy.

Due to absence of larger (>20 cases) prospective outcome studies on PH in pregnancy, many questions remain. The aim of this report was to investigate maternal and fetal outcomes in women with pulmonary hypertension including all subtypes of PH, according to the most recent guidelines [6] and to document the outcomes in the different subpopulations. The specific impact of comorbidities, type of anesthesia, mode of delivery and medication were evaluated, as well as the risk of developing heart failure and thrombotic events in the mother. The data were collected by the European Registry of Pregnancy and Cardiac Disease (ROPAC). This registry was initiated by the European Society of Cardiology in 2007. Consecutive patients with all forms of cardiovascular disease presenting with pregnancy were enrolled[7]. By 2014, 151 women with elevated pulmonary artery pressures, either diagnosed by right heart catheterization or diagnosed as possible PH by echocardiographic signs, were included.

METHODS

Study design

A detailed description of study design and data collection was previously reported[7]. ROPAC is an ongoing worldwide registry that includes all pregnant women with congenital and structural cardiac disease. Patients with arrhythmic disease in the absence of structural heart disease are excluded. Prospective inclusion of patients commenced in January 2008. This interim analysis concerns patients enrolled between January 2008 and April 2014.

For this study, outcomes of pregnancy were analysed for patients with PH. All patients with right ventricular systolic pressure (RVSP) >30 mmHg at rest, measured by echocardiography or right heart catheterization, were included. Patients with elevated RVSP due to outflow tract obstruction/pulmonary stenosis were excluded.

Data

Information was collected regarding age, parity, cardiovascular risk factors, type of heart disease, etiology of PH, previous interventions, New York Heart Association (NYHA) functional class, signs of heart failure, rhythm disturbance, medication, maternal or fetal mortality, cardiac events such as heart failure or arrhythmias, obstetric events such as preeclamptic toxaemia or postpartum haemorrhage, timing and mode of delivery, neonatal sex and birth weight and postpartum events. Follow-up data included vital status, cardiac events and neonatal status. Follow-up was available in all patients up to one week. If available, follow-up was reported up to six months.

Information on pulmonary hypertension was collected via the following ROPAC Registry website CRF variables: Under echocardiographic assessment the value of the peak velocity tricuspid regurgitation, as well as the right ventricular systolic pressure could be entered. Right ventricular systolic pressure could be entered via a tick box in the following categories of <30, 30-50, 50-70, 70-90 and more than 90 mmHg or unavailable. Amongst the parameters for the cardiac function the right ventricular function could be entered as normal, moderately impaired and severely impaired.

The question if full right heart catheterization confirming pulmonary hypertension via standard criteria was performed prior to pregnancy, could be answered with either a yes (26%) or no. No other parameters such e.g. cardiac output, pulmonary vascular resistance were collected in this data base.

Pregnant women were categorised based on the PH etiology as classified in the most recent consensus document[8]. Patients with PAH in case of iPAH, CHD-PAH or oPAH due to diseases such as connective tissue disease or vascular malformations were classified as group 1. Patients with PH due to left heart disease (LHD-PH) in case of left ventricular systolic dysfunction, valvular disease or congenital/acquired left heart inflow or outflow tract obstructions or congenital cardiomyopathies were classified as group 2. Other diagnoses mentioned in the consensus documents were not present in our study population.

Patients were stratified by RVSP level in three groups: RVSP 30-50 mmHg, 50-70 mmHg, and >70 mmHg.

Heart failure was defined according to ESC guidelines, as a clinical syndrome that is characterised by specific symptoms (dyspnea and fatigue) and signs (fluid retention, such as oedema, rales) on physical examination, as judged by the treating cardiologist. A heart failure episode during or after pregnancy was only registered when signs or symptoms of HF were present which required new treatment, change of treatment or hospital admission.

Statistical analysis

Baseline characteristics, as well as cardiac, obstetric and fetal outcome are presented for the total PH group. We compared baseline characteristics and outcome of PH in group 1 and group 2. Categorical data are presented as frequencies and percentages, and chi-square

tests were used for comparison. If there are less than five cases in a group Fisher's exact test was used. Normality of continuous data was checked with Kolmogorov-Smirnov tests and presented either as mean ± standard deviation, or as median and first and third quartiles (Q1-Q3) as appropriate. Differences between groups were assessed using Student's t tests or, in case of non-normality, using Mann Whitney tests. P values are considered statistically significant if less than 0.05 (2-sided test). All analyses were performed in SPSS 21.0 (IBM SPSS 21.0, SPSS Inc., Chicago IL, USA).

RESULTS

Baseline characteristics

In total 2966 pregnancies were enrolled in this interim analysis and 151 (5.1%) had PH (flowchart: *online supplemental Figure S1*). Of these women, 39 (26%) had PAH (**Table 1**). PAH was either idiopathic, associated with congenital heart disease or associated with other disease (e.g. connective tissue disease or vascular malformations). LHD-PH was present in 112 (74%) patients. LHD-PH was associated with valvular heart disease in 100 women and with cardiomyopathy in 12 women (**Table 1)**. Mean age of the 151 PH patients was 29.2±5.6 years and 56 of them (37%) were nulliparous. The majority (59.6%) had a mildly elevated RVSP between 30 and 50 mmHg. Further baseline characteristics are presented in **Table 2**.

In more than 75% of the patients the diagnosis of PH had been made prior to pregnancy. There were no differences between women diagnosed before and during pregnancy.

Management

Management of PH patients is presented in **Table 2**. In six women (4.0%), therapeutic abortion was performed because of the pulmonary hypertension in the mother. This occurred in two (28.6%) of the iPAH patients; three (10.7%) of the CHD-PH patients; none (0.0%) of the oPAH patients; and one (0.9%) of the LHD-PH patients (p=0.003).

There were 41 patients (27.2%) who were administered diuretics during pregnancy (34 were LHD-PH patients). Fourteen patients (9.3%) took digoxin during pregnancy (13 were LHD-PH patients). Four of these used digoxin temporarily (only one trimester).

During pregnancy nine patients received advanced PH medication (*online Table S1*) - all of them were given a phosphodiesterase type 5 inhibitor (PDE5-i). In addition, four of these nine patients were administered an endothelin-receptor antagonist (ERA), and three patients were given a prostacyclin analogue. One of these patients used all three. Of the patients on ERA, one patient developed a postpartum pulmonary embolism as well as heart failure, and one patient was reported to have a thromboembolic complication leading to temporary blindness for five days. Heart failure occurred in three other patients - all of whom were taking PDE5-i.

Table 1 Classification of pregnant women with pulmonary hypertension

Etiology of pulmonary hypertension		n	%
Group 1 (n=39, 25,9%)			
Idiopathic PAH		7	4.6%
PAH in Congenital heart disease			
	Eisenmenger syndrome	6	4.0%
	PAH in Left-to-right shunts	7	4.6%
	Post-operative PAH	15	9.9%
Other PAH		4	2.6%
Group 2 (n=112, 74.1%)			
Left heart disease			
	Valvular		
	Aortic stenosis	11	7.3%
	Aortic regurgitation	7	4.6%
	Mitral stenosis	54	35.8%
	Mitral regurgitation	26	17.2%
	Other valve disease	2	13.2%
	Cardiomyopathy		
	Dilated CMP	1	0.7%
	Hypertrophic CMP	2	1.3%
	PPCM	4	2.6%
	Myocarditis	2	1.3%
	other CMP	2	1.3%
	ccTGA, with systemic ventricle dysfunction	1	0.7%

ccTGA = congenitally corrected transposition of the great arteries, CMP = cardiomyopathy, PAH=pulmonary arterial hypertension, PPCM = peripartum cardiomyopathy.

Maternal Outcomes

Hospitalization was needed in 75 patients with 26 of them being admitted more than once. In 52 patients there was a cardiac reason for admission. Median timing of admission (known in 73% of cases) was 27 weeks (Q1-Q3 = 19.6 – 35.1). Admission for cardiac reasons occurred at a median of 25.1 weeks (Q1-Q3 = 19.2-31.2) and mainly for heart failure (42 patients).

No deaths occurred during pregnancy. Five women (3.3%) died peripartum up to one week after delivery. Another 2 (2.6%) of 78 women in whom follow-up was available died within six months after delivery. Details of maternal mortality are presented in **Table 3**. Death most commonly occurred in the group of iPAH (3/7, 43%), followed by patients with LHD-PH (3/112, 2.7%). One of the patients with CHD-PAH died (1/28, 3.6%). The five patients who died in the first week postpartum died shortly after a preterm spontaneous or induced delivery and cause of death was acute cardiac failure. In two patients this was induced by an infection (patient numbers 4 and 6) and in one patient by mechanical valve thrombosis (patient number 5). Two patients died during an intervention (abortion in patient number 2

Table 2 Baseline characteristics, management and outcome of pregnant women

		Group 1			Group 2	
	PH n=151	iPAH n=7	CHD-PAH n=28	oPAH n=4	LHD-PH n=112	*p value* of difference between 4 diagnostic groups
	n (%)	n (%)	n (%)	n (%)	n (%)	
Baseline characteristics						
Age, years (SD)	29.2 (±5.6)	29.9 (±7.2)	28.7 (±5.8)	32.3 (±5.0)	29.2 (±5.6)	0.69
Nulliparous	56 (37.1)	3 (42.9)	14 (50.0)	3 (75.0)	36 (32.1)	0.11
Diagnosis made*						0.36
Before pregnancy	88 (71.5)	4 (66.7)	21 (87.5)	2 (50.0)	61 (68.5)	
During pregnancy	35 (28.5)	2 (33.3)	3 (12.5)	2 (50.0)	28 (31.5)	
NYHA class						0.86
I	76 (51.0)	4 (57.1)	12 (42.9)	1 (25.0)	59 (53.6)	
II	47 (31.5)	2 (28.6)	10 (35.7)	2 (50.0)	33 (30.0)	
III	22 (14.8)	1 (14.3)	6 (21.4)	1 (25.0)	14 (12.7)	
IV	4 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	
Signs of heart failure	31 (20.5)	1 (14.3)	8 (29.6)	1 (25.0)	21 (18.9)	0.58
Right Ventricular Systolic Pressure						0.053
30-50 mmHg	90 (59.6)	3 (42.9)	12 (42.9)	3 (75.0)	72 (64.3)	
50-70 mmHg	43 (28.5)	2 (28.6)	9 (32.1)	1 (25.0)	31 (27.7)	
70-90 mmHg	8 (5.3)	0 (0.0)	2 (7.1)	0 (0.0)	6 (5.4)	
>90 mmHg	10 (6.6)	2 (28.6)	5 (17.9)	0 (0.0)	3 (2.7)	

Table 2 Baseline characteristics, management and outcome of pregnant women (continued)

		Group 1			Group 2	
	PH n=151	iPAH n=7	CHD-PAH n=28	oPAH n=4	LHD-PH n=112	*p value* of difference between 4 diagnostic groups
	n (%)	n (%)	n (%)	n (%)	n (%)	
Management						
Delivery, median weeks of pregnancy (Q1-Q3)	38.0 (37.0-39.0)	37.4 (32.1-38.6)	38.1 (36.1-39.3)	36.6 (34.6-38.8)	38.0 (37.0-39.0)	0.47
Mode of delivery**						
Vaginal	53 (35.8)	1 (20.0)	6 (24.0)	0 (0.0)	45 (40.9)	0.004
Caesarean Section	92 (63.4)	4 (80.0)	19 (74.0)	4 (100)	65 (59.1)	0.23
Emergency CS	22 (23.9)	0 (0.0)	2 (10.5)	1 (25.0)	19 (29.2)	0.29
General Anaesthesia during CS	21 (32.3)***	0 (0.0)	5 (33.3)	1 (33.3)	15 (34.1)	0.78
Antithrombotic therapy						
During pregnancy: Therapeutic	34 (22.5)	4 (57.1)	2 (7.1)	0 (0.0)	28 (25.0)	0.016
During pregnancy: Antiplatelet only	3 (2.0)	0 (0.0)	3 (10.7)	0 (0.0)	0 (0.0)	0.027
During pregnancy: Other	18 (11.9)	2 (28.6)	9 (32.1)	0 (0.0)	7 (6.2)	0.001
Calcium Channel Blokkers	6 (4.0)	3 (42.9)	0 (0.0)	0 (0.0)	3 (2.7)	0.003
Outcome						
Maternal Death						
During pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	na
Postpartum (<1 week)	5 (3.3)	2 (28.6)	0 (0.0)	0 (0.0)	3 (2.7)	0.35

Table 2 Baseline characteristics, management and outcome of pregnant women (continued)

		Group 1			Group 2	
	PH n=151	iPAH n=7	CHD-PAH n=28	oPAH n=4	LHD-PH n=112	*p value* of difference between 4 diagnostic groups
	n (%)	n (%)	n (%)	n (%)	n (%)	
Postpartum (>1 week; <6 months)	2 (2.6)****	1 (16.7)	1 (6.7)	0 (0.0)	0 (0.0)	0.057
Other complications						
Pulmonary thrombo-embolism	1 (0.6)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0.26
Other thrombo-embolic events	4 (2.6)	0 (0.0)	1 (3.6)	0 (0.0)	3 (2.7)	0.69
Heart failure	42 (27.8)	2 (28.6)	10 (35.7)	2 (50.0)	28 (25.0)	0.42
Postpartum haemorrhage	6 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.4)	0.75
Supraventricular tachyarrythmias	5 (3.3)	0 (0.0)	1 (3.6)	0 (0.0)	4 (3.6)	1.00
Ventricular tachyarrythmias	6 (4.0)	0 (0.0)	3 (10.7)	0 (0.0)	3 (2.7)	0.28
Pre-eclamptic toxaemia	2 (1.3)	1 (14.3)	0 (0.0)	0 (0.0)	1 (0.9)	0.17

*not reported in 28 cases, **not reported or not applicable in 6 cases, ***not reported in 27 cases ****Follow-up available in 78 cases

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; CS = Caesarean Section; iPAH, idiopathic pulmonary arterial hypertension; LHD-PH, pulmonary hypertension caused by left heart disease; NYHA, New York Heart Association; oPAH, pulmonary arterial hypertension associated with other disease; PH, pulmonary hypertension.

and hysterotomy in patient number 3). One of these seven patients reached term pregnancy and died 24 weeks after delivery of cardiogenic shock (patient number 1). One patient died of sudden death 24 weeks after therapeutic abortion performed because of maternal heart failure (patient number 7).

Some women suffered from thrombotic events. One patient, with a closed arterial duct, had a pulmonary embolism and four patients suffered from other thrombotic complications (prosthetic valve thrombosis, n=1; ischemic cerebrovascular event, n=3). The ischemic cerebrovascular events occurred in the presence of a mechanical aortic valve (n=1), mitral valve stenosis (n=1) and an unrepaired arterial duct.

Figure 1 shows the outcome of pregnancy in three different RVSP level groups: mildly, moderately and severely elevated RVSP. Maternal mortality at 6 months follow-up was significantly different in the three groups (0% in mild PH, 0% in moderate PH, 25% in severe PH). There were non-significant differences in the rate of low birth weight (<2500g) in the children of women with severe PH (p=0.09, **Figure 1**). However, in the analysis of the data by type of PH, more women with CHD-PAH and oPAH had babies with a birthweight of less than 2500g (**Figure 2**).

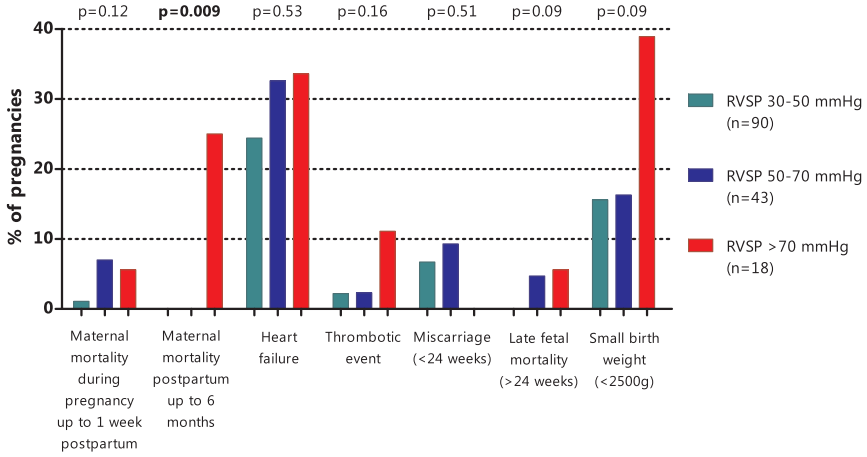


Figure 1 Outcome of pregnancy and level of RVSP

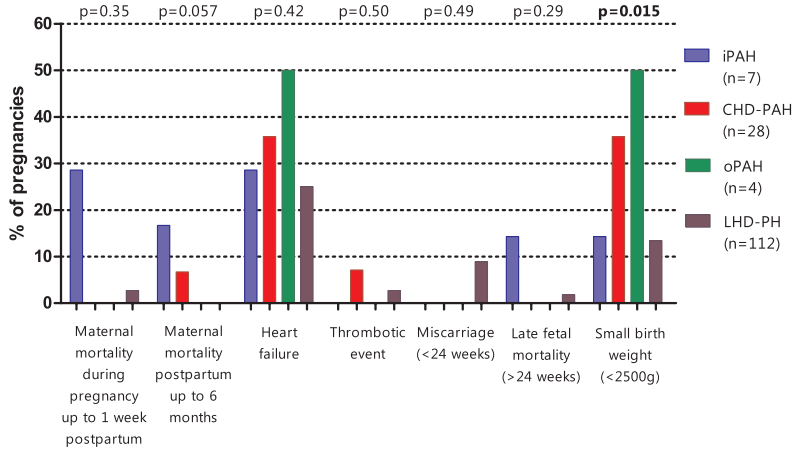


Figure 2 Outcome of pregnancy per PH group
iPAH, idiopathic pulmonary arterial hypertension; CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; oPAH, pulmonary arterial hypertension associated with other disease; LHD-PH, pulmonary hypertension caused by left heart disease.
Epilogue

Delivery

Details of delivery were reported in 145 patients (96.0%). Caesarean section (CS) was performed in 92 patients (63.4%) and it was initially planned in 83 of them (90.2%), mainly for cardiac reasons (65.1%). In ten patients a spontaneous start of labor was reported. Anesthesia was reported in 65 CS patients. In 21 patients (32.3%), CS was performed under general anesthesia and in 44 patients (67.7%), under local anesthesia. Emergency CS was reported in 21 patients, and in eight of them this was for cardiac reasons: heart failure or anticoagulation. Heart failure occurred in five (11.4%) patients after general anesthesia and in three (14.3%) patients after local anesthesia in the peripartum period and up to one week postpartum. Maternal death occurred in 2 patients (9.1%) after emergency CS, 2 patients (2.9%) died after planned non-emergency CS within one week after delivery and one patient died during therapeutic abortion (p=0.25, **Table 3**).

Vaginal delivery was performed in 53 patients (36.6%). Twenty-three patients (43.4%) had an induced vaginal labor. Heart failure peripartum or in the first week postpartum occurred in two (3.8%) patients after vaginal delivery and in 12 (13.0%) patients after CS (p=0.07). No maternal mortality within one week postpartum occurred in patients after vaginal delivery versus 4.3% in the CS group (p=0.19).

Table 3 Cases of maternal death

Patient	Region	Age	Diagnosis	Diagnosis known before pregnancy	Medical history	RVSP (mmHg)	Parity	Prepregnancy counseling	NYHA before pregnancy	Events during pregnancy	Pregnancy duration	Delivery	Fetal status	Timing maternal death	Cause of death	Additional details
1	Mediterranean	29	Idiopathic PAH	No		>90 (after delivery)	G1P0	No	I	Puerperal PET	39 wks	Induced vaginal delivery, epidural anesthesia	Alive	24 weeks postpartum	Oligoanuric cardiogenic shock	Treated with diuretics and vasoactive drugs
2	Mediterranean	23	Idiopathic PAH	Yes		50-70	G2P0A1	Yes	II		7 wks	Therapeutic abortion because of maternal condition	Abortion	During therapeutic abortion	Syncope during therapeutic abortion	Trial medication: Tadalafil and ambrisentan vs placebo
3	North Africa	17	Idiopathic PAH	Yes	Heart failure and PET in previous pregnancy	>90	G2P0A1	No	III	PET followed by heart failure at 28 weeks; IUFD	29 wks	Hysterotomy for IUFD under general anesthesia	Death	During 'delivery'	RV failure, shock during hysterotomy	Treated with diuretics and calcium antagonist
4	Mediterranean	35	Aortic and mitral mechanical valve; rheumatic disease; LV dysfunction	Yes	Heart failure in previous pregnancy	50-70	G3P2	Yes	II	Heart failure and pneumonia	24 wks	Induced labour, emergency CS for maternal shock under general anesthesia	Alive	5 days postpartum	Cardiac shock due to H1N1 pneumonia	Beta-blocker and diuretics, VKA throughout pregnancy
5	North Africa	17	Mitral mechanical valve; rheumatic disease	Yes	History of stroke	30-50	G1P0	Yes	I	Increased valve gradient	34 wks	Spontaneous labour, planned CS because of valve gradient	Alive	2 days postpartum	Mechanical valve thrombosis	VKA throughout pregnancy*, then treated with streptokinase, no surgery available

Table 3 Cases of maternal death (continued)

Patient	Region	Age	Diagnosis	Diagnosis known before pregnancy	Medical history	RVSP (mmHg)	Parity	Prepregnancy counseling	NYHA before pregnancy	Events during pregnancy	Pregnancy duration	Delivery	Fetal status	Timing maternal death	Cause of death	Additional details
6	North Africa	18	Aortic and mitral regurgitation, rheumatic	Yes		50-70	G2P1	Yes	II		33 wks	Spontaneous labour (PROM), emergency CS because of fetal distress	Death	2 days postpartum	Septic shock	Postpartum heart failure, PPH and persistant chest infecion with poor response to therapy
7	Africa	20	Eisenmenger, muscular VSD	Yes	Cyanosis <85%	70-90	G1P0	No	III	Ventricular arrhythmia, heart failure in 12th week	14 wks	Therapeutic abortion because of maternal condition	Abortion	24 weeks postpartum	Sudden death	

*(1st trimester anticoagulation unknown)

CS = Caesarean Section; G = gravida; IUFD = Intrauterin fetal death; LV = left ventricular; P = para; PET = preeclamptic toxaemia; PPH = postpartum haemorrhage; PROM = premature rupture of membranes; RV = right ventricular; VKA = vitamin K antagonist; VSD = ventricular septal defect.

Table 4 Fetal and neonatal outcome

		Group 1			Group 2	
	PH n=151	iPAH n=7	CHD-PAH n=28	oPAH n=4	LHD-PH n=112	*p value* of difference between 4 diagnostic groups
	n (%)	n (%)	n (%)	n (%)	n (%)	
Fetal complications						
Premature delivery (<37 weeks)	26 (21.7)	1 (25.0)	7 (29.2)	2 (50.0)	16 (18.2)	0.20
Low birth weight (<2500 g)	28 (19.0)	1 (14.3)	10 (35.7)	2 (50.0)	15 (13.4)	0.015
Miscarriage <24 weeks	10 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (8.9)	0.49
Fetal mortality > 24 weeks	3 (2.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (1.8)	0.29
Neonatal mortality < 1 week	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1.00

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; iPAH, idiopathic pulmonary arterial hypertension; LHD-PH, pulmonary hypertension caused by left heart disease; oPAH, pulmonary arterial hypertension associated with other disease; PH, pulmonary hypertension.

Fetal outcome

Fetal or neonatal death up to one week after delivery occurred in 14 pregnancies (9.3%). There were 20 neonates (13.8%) who were small for gestational age (**Table 4**). Of these, thirteen babies had a birthweight below 2500 grams. A birthweight below 2500 grams occurred in 28 (19.3%) neonates. Twenty-five of them were delivered by CS, which accounts for 27.2% of CS deliveries versus three (5.7%) of vaginal deliveries (p=0.002). Eight of these 25 were emergency Caesarean sections.

Six neonates (4.0%) were reported to have cardiac anomalies: one persistent ductus arteriosus; one, a combination of persistent ductus arteriosus and atrial septal defect; one, a combination of persistent ductus arteriosus, atrial septal defect and pulmonary stenosis; one hypertrophic cardiomyopathy; one pulmonary valve stenosis; one combination of total anomalous pulmonary venous return and atrial septal defect. Of these 6 neonates, 4 had a mother with LHD-PH (4 out of 99 live births in LHD-PH, 4%) and 2 had a mother with CHD-PAH (2 out of 25 live births in CHD-PAH, 8%). The atrial septal defect (ASD) was found in a mother with CHD-PAH that used a PDE5-i.

Six other neonates were reported to have the following non-cardiac anomalies: congenital hemophagocytic syndrome; hydrocele; respiratory distress syndrome; rhesus isoimmunization; wet lung.

Follow-up six months postpartum

In 78 patients (51.7%) follow-up at six months postpartum was available. Baseline characteristics of patients with and without follow-up are presented in *online supplemental Table S2*. Two of these patients (2.6%, **Table 2** and **Table 3**) died 24 weeks after delivery. Heart failure occurred in one of the patients who died, as well as in five other patients (7.8%) and two patients (2.6%) had an arrhythmic event.

In 22 patients (14.6%) echocardiography before and after pregnancy was available and no significant change in the RVSP category was found.

DISCUSSION

In this prospective, contemporary, international registry of 151 pregnant women with PH, the incidence of maternal cardiac and neonatal complications was high. However, with a maternal mortality for the entire group of less than 5%, the overall outcome was substantially better than previously reported. It is the first larger cohort including pregnant women with PH categorised according to the most recent consensus document. A clear distinction in maternal morbidity and mortality could be made between the different forms. PH due to left heart disease was the most common form of PH in this cohort and, to a large extent, caused by mitral valve disease or complicated peripartum cardiomyopathy.

PH due to left heart disease, classified as group 2 of the most recently updated classification on PH[8], is believed to be the most common cause of PH globally. Epidemiological studies of group 2 PH are less exhaustive than for the rarer causes of PH such as iPAH[9]. Group 2 PH is likely to be caused by passive downstream elevation in the left heart pressures (post capillary), but may progress to reactive changes of the pulmonary arteries (precapillary), leading to mixed PH[10]. For reasons unknown, only a certain proportion of patients progress to develop reactive pulmonary vasoconstriction, despite the presence of chronic heart failure. Our data show that the diagnosis of PH was made in the majority of cases prior to pregnancy, with more than 80% of women having no or minimal symptoms (NYHA FC I or II). We found a lower mortality in women with LHD-PH (3 of 112 cases) and CHD-PAH (1 of 28 cases) compared to a mortality of 43% (3 of 7 cases) in women with iPAH, with most of the deaths occurring postpartum. The latter deserves special attention as it implies that all women with PH should remain under close supervision for at least a week after having given birth. Heart failure occurred in almost 30% and arrhythmias were common. Forty-one patients received diuretics during pregnancy, but advanced PH therapy was only given to 9 cases (8 of 39 cases in group 1, predominantly with iPAH, and 1 of 112 cases in group 2).

Tabarsi and colleagues[11] recently reported their experience with Epoprostenol, the first approved therapy shown to improve morbidity and mortality in PAH, in a woman with severe PAH and right ventricular dysfunction. The outcome for this woman was satisfactory

up to 2 years post-delivery. However, the authors stress the importance of early contact with a highly experienced obstetrician in the course of a pregnancy and management by a multi-disciplinary team. This team will also prepare a delivery plan, balancing the advantages of vaginal birth (lower blood loss, lower risk of infection and thrombus formation) versus Caesarean section (better hemodynamic monitoring). The 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension[6], as well as the ESC guidelines on cardiac disease in pregnancy[3], state that pregnancy in all women with PH should be avoided or terminated early. Our data suggests that such advice should be focused on the high-risk subgroups, namely PAH. However, if pregnancy occurs very close expert follow-up is needed with at least monthly review. Serial echocardiography should be used to screen for right heart failure.

Altogether, little is known about the outcome of PH in the peripartum period. There are only 2 systematic overviews and selected case series (< 20 patients). The case series have mainly focused on PAH, e.g. the study by Xavier Jais et al[12] reporting on the outcome of 26 pregnancies in 13 participating centres, during a 3-year period. Three women (12%) died and one woman needed urgent heart-lung transplantation. Women with well controlled PAH and a low pulmonary vascular resistance in modern therapy had a better outcome in this cohort. A study by Weiss et al[2], reported on the pooled analysis of publications from 1978 through 1996, on a total of 125 cases, including 73 with Eisenmenger syndrome, 27 with primary arterial PH and 25 with secondary PH, with a mortality of 36%, 30% and 56% respectively. Of the total number of reported deaths (n=48), 20% occurred late (as late as several months post-delivery). Hemoglobin was only reported for 43 and pulmonary artery pressure (PAP) for 81 of the 125 patients. A more recent study by Bedard et al[1] summarised the findings from 73 pregnant patients with PAH, with 29 having iPAH, 29 CHD-PAH and 15 oPAH, with a 90-day reported mortality of 17%, 28% and 33%. More than two-thirds of the deaths occurred within the first month after delivery. Patients with PH-LHD were not included in this analysis. As most of the cases in this cohort came from individual case reports, mean pulmonary artery pressure (MPAP), when not reported, was approximated or echocardiographic data utilised, using the Bernoulli formula (MPAP=systolic PAP estimated by echocardiogram/4x2.4). In the study by Bedard[1], therapies for PAH were used during pregnancy and delivery in 72% of iPAH, 52% of CHD-PAH and 47% of oPAH. Patients receiving general anesthesia were four times more likely to die, compared to patients receiving regional anesthesia.

Recommendations for the management of pregnant women with PAH have been published recently in a state-of-the-art review[13]. However, this may not be applicable to pregnancy in women with other forms of pulmonary vascular disease as the use of PDE5 inhibitors and prostacyclin have not been investigated in those types of pregnancies[6].

Role of echocardiography in our cohort estimating the degree of PH

According to the 2015 ESC/ERS guidelines for the diagnosis of pulmonary hypertension [6], right heart catheterization is recommended as a Class IC indication in patients with pulmonary arterial hypertension. Right heart catheterization for patients with PH due to left heart disease has an IIB indication and is indicated only to support treatment decisions. Right heart catheterization would therefore not have been indicated in pregnant women in PH groups II-V. The challenges to diagnose the most frequent causes of PH have recently been summarised in a paper by Hoeper et al, *A global view of pulmonary hypertension* [14].

The recently published guidelines highlight also the use of echocardiographic probability of PH in symptomatic patients with a suspicion of PH. The authors of the guidelines preferred the use of peak tricuspid regurgitation velocity over the estimated PASP or RVSP. However, in the ROPAC data base peak tricuspid regurgitation velocity was only rarely entered by the investigators. It was not a mandatory field.

The majority of the women in the ROPAC registry had mildly to moderately elevated RVSP with more than 80% having a RVSP <70mmHg. Transthoracic echocardiography allows estimation of the RVSP from the velocity of the tricuspid regurgitation by adding the right atrial pressure[10]. This diagnostic module has led to widespread use and increased documentation of the burden of PH in patients with heart disease and its association with a high morbidity and mortality. PH is often a neglected issue and the importance of long-term follow-up has recently been highlighted[15].

A rationale for using echocardiography in the diagnosis of PH in patients from low-to-middle income countries, where RHC is often not available, has been summarised recently[16]. According to our knowledge, the impact of the haemodynamic changes of pregnancy on the measurement of the RVSP by echocardiography has not been formally evaluated. However, in more than 75% of patients the diagnosis of PH had been made prior to pregnancy using standard criteria.

Recommendations for the management of pregnant women with PAH have been published in the ESC/ERS guidelines for the treatment and management of PH [6]. Patients with PAH that choose to continue pregnancy should be treated with disease-targeted therapy. However, this may not be applicable to pregnancy in women with other forms of pulmonary hypertension as the use of PDE5 inhibitors and prostacyclin has not been investigated in these types of pregnancies. This may have been the reason why only 9 patients in our cohort have received PH medication during pregnancy.

Fetal complications and outcomes

Perinatal complications were common, with fetal or neonatal demise occurring in almost 10%. Further, a birthweight of less than 2500 gram occurred in one fifth of the babies, reflecting the high rates of growth restriction and preterm birth. The long-term impact of chronic maternal hypoxia on fetal outcome remains unknown, but fetal growth restriction is known

to programme increased rates of diabetes, heart disease and hypertension in later life[17]. Poor fetal growth has been noted in most reports relating heart disease with pregnancy outcome, with the combination of hypoxia and impaired cardiac output having the most deleterious effect.

Data about the pulmonary circulation during pregnancy and its influence on the placental flow is scarce. However, it is known that the mean pulmonary arterial pressure in a normal pregnancy does not change[18], while the pulmonary flow increases. This implies that the pulmonary vascular resistance has to decrease. In women with pulmonary hypertension, it is likely that there is a limited ability of the pulmonary vascular resistance to change throughout pregnancy and, hence, the pulmonary flow, might decrease. In a recent systematic review, cardiac output during pregnancy was significantly lower in women with heart disease and predicted a poor perinatal outcome (hypertension, pre-eclampsia, fetal growth restriction, stillbirth and placental growth abruption)[19]. However, although the poor pregnancy outcome may be a reflection of the limited cardiac output, it is also possible that other factors present in women with pre-existing heart disease may influence placental development, leading to poor pregnancy outcome. We found a high frequency of congenital heart disease in the newborn, which warrants further research.

Limitations

This registry, as most other registries, has numerous limitations such as incomplete (<5%) and biased data. Specifically the timing of diagnosis has not been reported in 25% of cases. This is a global registry with some centres having dedicated high-risk obstetric clinics and much higher volumes than others, which is likely to affect the outcome. In general, centres in ROPAC are typically tertiary centres with well-organised pregnancy clinics. Thus, all conclusions must be drawn with caution.

In addition, the diagnosis of PH was not made with heart catheterisation in all patients. As highlighted by others[14], many patients had echocardiographic diagnosis of probably PH because an invasive test would neither be feasible or indicated. The interpretation of our data must take into account that echocardiography as a diagnostic modality has limitations in PH.

This is a relatively large series of patients with PH, but mortality occurred in only a limited number of cases. Therefore, interpretation of mortality rates per subgroup should be done cautiously. In many countries patients are unable to return for 6-month follow-up visits due to financial constraint, e.g. having to pay for the clinic visit and all investigations and transport to the hospital. As late (6-month) follow-up was only reported in about 50% of the patients, the number of late deaths is likely to have been underestimated. Therefore only limited conclusion can be drawn from these data.

Conclusion

Despite the advent of a number of therapeutic options for patients with PH, pregnancy remains a substantial risk and commonly leads to heart failure. Mortality remains high, particularly in women with iPAH (although limited number of patients: 3/7, 43%). However, there are marked differences in the maternal and fetal outcome of women with iPAH, CHD-PAH, oPAH and LHD-PAH, which need to be highlighted and investigated further. Our data differ from previous systematic overviews and pooled cases series as we included all sub groups of PH including a high number of LHD-PH. As most deaths occurred postpartum, women should be kept in hospital for at least a week post-delivery and possibly longer, being monitored for arrhythmia, heart failure and uterine hemorrhage in particular. Vaginal delivery is usually the preferred mode of delivery. Pre-conception, women need to be counselled, not only about the risk to their health in the short and longer term, but also about the overall poor outcome for their children. However, if pregnancy occurs, close follow-up with a minimum of monthly visits and echocardiograms to screen for and treat right heart failure are essential. Larger, prospective, carefully conducted multi-centre studies in patients with PH are required to determine the exact pregnancy-related risk, the role of supportive care and advanced PH therapy, as well as predictors of outcome for each sub-group.

Online Supplementary Information

Figure S1 Flowchart of inclusion
Table S1 Pulmonary hypertension medication
Table S2 Characteristics of patients with and without follow-up

REFERENCES

1. Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009; **30**(3): 256-65.
2. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *Journal of the American College of Cardiology* 1998; **31**(7): 1650-7.
3. European Society of G, Association for European Paediatric C, German Society for Gender M, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**(24): 3147-97.
4. Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. *British journal of obstetrics and gynaecology* 1998; **105**(8): 921-2.
5. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart* 2006; **92**(10): 1520-5.
6. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal* 2015.
7. Johnson M, Gatzoulis M, Roos-Hesselink J. Pregnancy and heart disease: Time for a randomized controlled trial. *Int J Cardiol* 2013.
8. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology* 2013; **62**(25 Suppl): D34-41.
9. Dzudie A, Kengne AP, Thienemann F, Sliwa K. Predictors of hospitalisations for heart failure and mortality in patients with pulmonary hypertension associated with left heart disease: a systematic review. *BMJ open* 2014; **4**(7): e004843.
10. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation* 2012; **126**(8): 975-90.
11. Tabarsi N, Levy R, Rychel V, et al. Pregnancy among women with pulmonary arterial hypertension: a changing landscape? *International journal of cardiology* 2014; **177**(2): 490-1.
12. Jais X, Olsson KM, Barbera JA, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *The European respiratory journal* 2012; **40**(4): 881-5.
13. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. *J Am Coll Cardiol* 2015; **65**(18): 1976-97.
14. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *The Lancet Respiratory medicine* 2016.
15. Luscher TF. Pulmonary embolism and pulmonary hypertension: two issues often neglected in cardiology. *European heart journal* 2015; **36**(10): 581-3.
16. Thienemann F, Dzudie A, Mocumbi AO, et al. Rationale and design of the Pan African Pulmonary hypertension Cohort (PAPUCO) study: implementing a contemporary registry on pulmonary hypertension in Africa. *BMJ open* 2014; **4**(10): e005950.
17. Barker DJ, Gelow J, Thornburg K, Osmond C, Kajantie E, Eriksson JG. The early origins of chronic heart failure: impaired placental growth and initiation of insulin resistance in childhood. *European journal of heart failure* 2010; **12**(8): 819-25.

18. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial changes in pulmonary haemodynamics during human pregnancy: a non-invasive study using Doppler echocardiography. *Clinical science* 1991; **80**(2): 113-7.
19. Kampman MA, Bilardo CM, Mulder BJ, et al. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol* 2015; **46**(1): 21-8.

Epilogue

Discussion

SUMMARY

Cardiac disease is the most important cause of maternal mortality[1]. The overall maternal mortality rate declines, but there is a remarkable increasing trend for cardiac death during pregnancy and after delivery. This thesis investigated the risks of pregnancy in women with cardiac disease. The majority of the chapters is based on the global prospective Registry for Pregnancy And Cardiac disease (ROPAC), which was designed to study large groups of women with all sorts of heart disease, aortic pathology and pulmonary hypertension[2]. From previous studies we know that risk stratification is important to distinguish between those women at low, intermediate or high risk[3-5]. The guidelines for pregnancy and heart disease recommend to use the modified World Health Organization (WHO) risk classification[6]. It is based on expert opinion. Women are stratified by their cardiac lesion, systolic function and New York Heart Association (NYHA) classification. Women with a simple cardiac lesion such as a repaired atrial septal defect, are in class I which is associated with a low risk of morbidity and mortality, comparable to pregnant women without cardiac disease. Women in class IV (pulmonary arterial hypertension, NYHA class 3 or 4) have an extremely high risk and are advised to avoid pregnancy. The complication risk is thought to increase in modified WHO class II and III.

In **Chapter 1,** we validated the modified WHO risk classification, in the largest cohort to date and also in emerging countries for the first time. We showed that the modified WHO classification has a moderate discriminative power with a c-statistic of 0.71 and is therefore quite useful but there is room for improvement. First of all, there is a noteworthy incidence of events in WHO class I, assumed to be a group with no increased risk. Women in this group should not be told that the risk is negligible, and we need to further define which class-I-women have an elevated risk compared to their peers. The difference in accuracy of the tool in emerging and advanced countries is also remarkable. The event rate shows the expected gradual increase in advanced countries, while the event rate varies in emerging countries. This is partly explained by the different underlying diagnoses: predominantly congenital heart disease in advanced countries, and valvular heart disease in emerging countries. We added more clinical parameters to the modified WHO-risk tool. Adding atrial fibrillation and signs of heart failure to the risk tool enables a better prediction of risks, in particular in countries with an emerging economy, and we introduced a revised risk tool for clinical use. In **Chapter 2** it appeared that the modified WHO risk tool has a poor value for prediction of obstetric and fetal risks. It seems that the 'usual suspects' like multiple pregnancy and

preconception hypertension are better predictors to evaluate risks just like in other pregnant women. Twin pregnancy had a major influence on outcome (OR 6.4 for fetal/neonatal death; OR 5.0 for small-for-gestational age), but we do not know whether this influence is more distinct than in women without cardiac disease. It does raise the question how to deal with multiple pregnancy. A preventive approach is probably a sensible choice, by avoiding multiple embryo transfer and restrict ovulation induction. It is impossible, however, to prevent spontaneous multiple pregnancies. Reduction of multiple pregnancy just because of the presence of maternal cardiac disease seems a step too far, but definitely should be considered in case of deterioration of the mother's condition. Other associations found, were maternal complex congenital heart disease being predictive of fetal growth restriction, and more interestingly aortic disease being related to pre-eclampsia. These findings may help to better understand pathophysiology of pregnancy complications.

We investigated the impact of several specific complications: supraventricular and ventricular arrhythmia's. The results are described in **Chapter 3 and 4**. Fortunately, the incidence of arrhythmic complications was relatively low. Ventricular arrhythmias occurred in 1.4% of women and were associated with heart failure, but it is difficult to conclude on cause and effect based on the data we have. As previously described, heart failure indeed is a much bigger problem with an incidence of approximately 13%[7]. We found that most patients with ventricular arrhythmia had heart failure, but not all patients with heart failure developed ventricular arrhythmias. Patients with NYHA class 2 or higher were at highest risk. Clearly, efforts should be made to prevent ventricular tachyarrhythmia's, not only because of the maternal risks, but also because of the clear impact on fetal outcome, expressed as higher rates of preterm birth (36%), low birth weight (33%) and neonatal death (4.8%). While atrial fibrillation and flutter are considered quite benign events in the general population, we showed an alarming trend towards higher maternal death rate. In our large database of patients with structural heart disease we found an incidence of 1.3%. Atrial fibrillation and flutter were found mainly in patients with mitral valve disease and women with other left sided lesions, and occurred typically by the end of the second trimester. Heart failure and arrhythmias form the major complications during pregnancy.

Other potential hazardous situations during pregnancy such as acute coronary syndrome, aortic dissection or prosthetic valve thrombosis are discussed in **Chapter 5**.Women suffering from these life-threatening events often present 'de novo', and thus did not have preconception counselling, simply because they were not known to have a cardiac or aortic disease. We know from the "Confidential enquiries" in the United Kingdom, an obligatory registry of all maternal deaths, that these diseases are the most important cause of maternal cardiac mortality[1]. Doctors working in the emergency department should have knowledge of this specific high-risk group of patients. Practical flow charts are provided to assist in urgent treatment decision making.

We conclude part 1 of this thesis with a study describing the impact of socioeconomic factors on the outcome of pregnancy in women with cardiac disease. The results are presented in **Chapter 6.** While maternal condition appeared the main denominator of pregnancy outcome in women with heart disease, some socioeconomic influence cannot be denied. Access to advanced health care, with dedicated 'pregnancy and heart disease clinics', is not the norm in many countries and rural areas. Women may present at a later stage, because of costs but also because of their cultural background, with pregnancy providing a certain status. For instance, in Egypt it is so important to have children that women often do not mention their heart defect. Only when pregnancy is already in an advanced state or when severe problems arise, these women seek help, making early intervention (let alone prevention) very difficult. It is important to bear in mind the interregional differences in outcome, not only when interpreting the ROPAC results, but also when aiming for improvement of general maternal outcome.

Part II focusses on pregnancy in women with valvular heart disease. In **Chapter 7 and Chapter 8** we studied women with left-sided valve disease. We describe a cohort of 96 patients with moderate or severe aortic stenosis. The pregnancy related mortality rate was low in these women, compared to older studies. However, women with symptomatic severe aortic stenosis in our study had a considerable risk of developing heart failure (26%) throughout pregnancy. Probably at least some of them should have been treated pre-pregnancy anyway. It remains a difficult decision whether we should treat women with asymptomatic severe stenosis pre-pregnancy or not. Valve replacement introduces a new dilemma. In case of choosing a mechanical valve, we know pregnancy is a risky period when it comes to bleeding and thrombosis (see chapter 9). In case of choosing a bioprosthetic valve, we know this valve will deteriorate over time and another valve intervention will be unavoidable after 10-15 years. As we are discussing young patients they typically will need many reinterventions in that situation.

In Chapter 7, we have shown that women with rheumatic mitral valve disease, specifically those with severe mitral stenosis, are at very high risk of adverse outcome. This was not surprising, with the current guidelines advising to avoid pregnancy in those with a severe and symptomatic stenosis (heart failure in 36%). But the evidently increased risk of pregnancy in women with moderate mitral stenosis (heart failure in 23%), and even those with isolated significant regurgitation (heart failure in 23%), is a finding that needs closer attention in future recommendations: how to deal with women who are formally not an intervention candidate yet, but do have a pregnancy wish in the presence of moderate mitral stenosis? Does the risk of pregnancy outweigh the risk of early intervention or not? And what type of intervention is safest? Balloon dilatation during pregnancy was associated with an uneventful course of further pregnancy in most women.

In **Chapter 9**, pregnancies in the presence of a mechanical and/or bioprosthetic valve are described. Women with a mechanical valve had a dissatisfactory 58% chance of having an

uncomplicated pregnancy with a live child, while women with a bioprosthetic valve had a much better outcome. But the question remains whether there is a long-term deteriorating effect of pregnancy on bioprosthetic substitute functioning. Also, there is much room for improvement when it comes to anticoagulant treatment during pregnancy in the presence of a mechanical valve. Guidelines advice different strategies, with a switch to low-molecular-weight heparin or unfractionated heparin in the first trimester, and continuation of vitamin K antagonists in high-risk pregnancies[6]. In the second and third trimester, a vitamin K antagonist is recommended. As of 36 weeks it should be replaced with some sort of heparin to prevent major fetal bleedings during vaginal delivery. Currently, none of the reported strategies in our cohort appeared superior. Vitamin K in the first trimester was related with a high rate of fetal deaths in the second and third trimester, while the use of low molecular weight heparin seems to increase the risk of valve thrombosis. The newer direct thrombin inhibitors (such as apixaban) are not safe for prevention of mechanical valve thrombosis.

The effects of pregnancy on the aortic wall are delineated in **Chapter 10**, the first chapter of Part III. These effects generally do not lead to severe aortic problems in women without underlying aortic pathology, but women with an aortic syndrome such as Marfan, Loeys Dietz or Turner syndrome may be at increased risk of aortic dissection. An overview of literature is presented, with focus on specific etiologies, medical treatment and surgical approach during pregnancy.

Turner syndrome is characterised by a partial or total monosomy of the X-chromosome. It is associated with short stature, sub- or infertility due to gonadal dysgenesis, and cardiac and aortic anomalies. Pregnancy has been out of reach for the vast majority of women with Turner syndrome for decades due to infertility. But since oocyte donation has become available, the number of pregnancies in this group has expanded. In **Chapter 11**, we described pregnancy wish, reasons for not (yet) attempting pregnancy and number of attempts ending in conceptions. A significant number of women had (had) concerns about the risk of cardiovascular complications during pregnancy and delivery, which we feel deserves attention from treating physicians. In **Chapter 12** we show the outcome of pregnancy in women with Turner syndrome from our centre. We found that the number of miscarriages was high, but that the full-term pregnancies had a quite low cardiovascular event rate. However, much more research is required, given the fact that studies describing cardiovascular events in Turner syndrome, including ours, are limited by the lack of statistical power. A large multicentre global prospective registry such as ROPAC, with a focus on Turner syndrome an d(very) long-term follow-up, would be the only way to discover the exact aortic growth and incidence of aortic dissection related to pregnancy. While the same lack of statistical power issue plays a role in women with SMAD3 mutations, our report in **Chapter 13** is the first and largest case series describing pregnancy in this recently discovered genotype of patients with aggressive aortic pathology, associated with aneurysms and aortic dissection and rupture. No severe cardiovascular problems were found in 17 pregnancies in women

with SMAD3 mutations, almost all having at least some clinical findings of the phenotype (some several years after pregnancy), and this retrospective study can be seen as a starting point for further investigations in this group of women.

Chapter 14 shows the relatively favourable outcome of pregnancy in 60 women with hypertrophic cardiomyopathy. No maternal deaths occurred, but 15% of women suffered from heart failure and 10% had a ventricular tachyarrhythmia. Events occurred mainly during the 3rd trimester, and directly postpartum. Women with pre-pregnancy dyspnea or signs of heart failure were at highest risk. Surprisingly, no differences were found between women with obstructive disease and those with non-obstructive cardiomyopathy. However, the overall cardiac event rate of 23% should be definitely mentioned when counselling women with hypertrophic cardiomyopathy.

Pulmonary hypertension is a whole other story: as previously mentioned, pulmonary *arterial* hypertension (PAH) is a reason to avoid pregnancy according to the guidelines. We demonstrated in **Chapter 15** that the existing concerns about this group of patients is justified. But until now, little was known about the risk of pregnancy in women with elevated right ventricular systolic pressures due to left-sided heart disease. We studied a cohort of 151 with elevated right ventricular systolic pressures (RVSP), of whom 26% had PAH and 74% had pulmonary hypertension due to left-sided heart disease. Heart failure occurred in 36% and 25%, respectively. Maternal death occurred mainly in women with idiopathic PAH (3 out of 7: 43%), while the maternal mortality rate in left-sided heart disease was not zero either (2.7%). Women with severely elevated pressures (RVSP>90 mmHg) were at highest risk of maternal death, thrombotic events and delivery of a small baby (<2500gr), although low numbers prevented statistical significance. The results of our study imply that pulmonary hypertension due to left sided heart disease may carry a lower risk of pregnancy related events, but that they should be carefully counselled about the associated risks. It would be reasonable to distinguish between mildly, moderately and severely elevated right ventricular systolic pressures in future guidelines.

CONCLUSIONS AND FUTURE DIRECTIONS

Leading a 'normal' life is important to young women with heart disease, just as it is for their healthy peers, and pregnancy is one important aspect of that normal life. This thesis investigated the risk of pregnancy in women with several types of cardiac and aortic disease. Apart from some high risk groups, women with cardiac disease tolerate pregnancy reasonably well in the current era. The majority of young girls and women with heart disease can be reassured about these improving prospects, provided that we accurately search for the ones with a substantial higher risk.

Every woman with cardiac disease and a pregnancy wish, needs to be stratified and informed accordingly about her risk for adverse cardiac and fetal outcome. We recommend the use of the modified WHO classification, which we amended in Chapter 1 along with a risk chart that is easy to use in practice. But the advice and management plan is still a matter of individualized medicine. All women should therefore be evaluated before pregnancy, and in case of modified WHO class II or higher, this should be done in a multidisciplinary team of at least a cardiologist and obstetrician. Once a woman is pregnant, this multidisciplinary approach needs to be continued, with close collaboration with an anesthesiologist, who has expertise in the field of obstetrics and cardiac dysfunction. Other specialties should be involved with low threshold, such as a haematologist in case of therapeutic anticoagulation indications, or a pulmonologist in case of pulmonary arterial hypertension.

Young women with valvular stenosis will benefit in particular from close echocardiographic evaluation before preconception advise. We have shown the high risk of pregnancy complications, specifically in those with moderate or severe mitral stenosis. The imminent pregnancy wish of these women preferably is discussed in a team with valve intervention cardiologists and valve surgeons. A lower threshold towards intervention may be the result. However, whether the risk of pregnancy with valve stenosis outweighs the risk of valve surgery remains an important question. And in case of mechanical valve implantation, one should be aware of the risk of pregnancy complications in the presence of any anticoagulation strategy. Perhaps newer interventional approaches offer a solution: is there a future for trans-catheter valve replacement in these young women?

Several diagnosis groups need further investigation in the future, to determine whether women may tolerate pregnancy in the current era and to select clinical predictors or biomarkers to reveal the group that may be better off, avoiding pregnancy. Examples are ischemic heart disease, certain aortic syndromes (as explained later) and complex congenital heart disease with interventions such as Fontan circulation. Ischemic heart disease in pregnant women is quite rare but an expanding problem in young women, as a result of wealth-related epidemic issues such as smoking, obesity and increasing age at childbirth. Acute myocardial infarction during pregnancy is associated with high rates of maternal morbidity and mortality[8]. First and above all, coronary artery disease in young women should be prevented by all means. But there is also a need for further research about the therapeutic strategies in pregnant women: percutaneous coronary intervention is first choice. But little is known about the use of antiplatelet therapy such as ticagrelor and glycoprotein IIb/IIIa inhibitors such as eptifibatide. Their use in pregnant women and also the (hopefully improving) outcome of pregnancy in the presence of ischemic heart disease need to be studied in more depth.

It is only since a few decades that the life expectancy of children with complex congenital heart disease improves rapidly: the majority of patients with a Fontan circulation for instance now reach adulthood, and thus fertile age. Although fertility issues seem to be present,

some women with a Fontan circulation do get pregnant[9]. And it will be just a matter of time until we start to see the first reports about pregnancy in Fontan patients with hypoplastic left heart syndrome, a very complex entity. Current studies in Fontan are rather small and/or retrospective, and show a high miscarriage rate and significant cardiac event rate in the remaining women[10,11]. Prospective long-term follow-up studies are required to study the exact risks and the influence of pregnancy on these women's life expectancy.

Echocardiographic changes during pregnancy have been described by several studies, both in 'normal' pregnancies, as well as in women with structural heart disease[12-17]. Cardiac output increases up to 50% during pregnancy, but an even bigger impact has been described during delivery, as also depicted in Chapter 5, figure 1. It is a period of risk for developing heart failure, specifically in women with diminished left ventricular function, and close monitoring of hemodynamic parameters such as cardiac output would be desirable. Echocardiographic measurement of cardiac output has been validated in pregnant women[18]. But echocardiographic measurements during delivery are quite hard to achieve. Non-invasive cardiac output measurements have been proposed in this setting, but require validation studies during pregnancy and in particular during delivery. It would be very interesting to study this method in women with structural heart disease and a high risk of developing heart failure.

Also, long term effect of pregnancy on the structural abnormal heart needs further investigation. Clinical follow-up studies showed an increased event rate 1 year postpartum, mainly in women who experienced a cardiac event during pregnancy[19,20]. A prospective cohort study showed reduction of systolic and diastolic function after 6 months in women with cardiac disease[21]. Little is known about which underlying diagnosis carries the highest risk, and more importantly, whether it is related to more events later in life and reduces life expectancy of the mother. This may influence a patient's pregnancy wish and in selected cases maybe even the physician's advice regarding assisted reproductive therapy. Large prospective cohort studies with long-term echocardiographic follow-up are required.

In Chapter 2 we have shown an association between aortic disease and preeclampsia. Preeclampsia during pregnancy in general is predictive for cardiovascular disease in later life, with an increased risk of hypertension, ischemic heart disease, stroke and death[22,23]. It is suggested that this increased risk results from arterial changes, but others hypothesize that there is no causal relationship between preeclampsia and cardiovascular disease in later life, but that these women were predisposed anyway[24,25]. Still it poses us to the question: are women with pre-existent aortic disease, who develop pre-eclampsia during pregnancy, at much higher risk of aortic dissection well after pregnancy, at an earlier age, than their peers with an uncomplicated pregnancy? Would these women benefit from preventive strategies for preeclampsia such as low-dose aspirin therapy?

The additive risk of pregnancy in women with Turner syndrome when it comes to aortic dissection is very hard to determine. Available evidence comes from small cohorts, mainly

of retrospective nature. Of course these studies are the basis of future research. But single centers and nations are not able to collect numbers of patients large enough to draw firm conclusions about the exact risk of aortic dissection. There is a clear need of a large international collaboration[26]. Hopefully, a recent taskforce on new guidelines will accelerate such initiatives (expected in 2017). A research question we are eager to get an answer to is whether women with Turner syndrome can safely get pregnant, after prophylactic aortic surgery. Braverman and colleagues wrote an alarming report describing 3 cases of pregnancy after aortic surgery in Loeys-Dietz syndrome, ending up in a dissection in two cases[27]. Currently, we do not have much other evidence on pregnancy after aortic surgery, let alone in Turner syndrome. Also, we do not know whether pregnancy induces a significant increase of aortic dimension in Turner syndrome. It would be very interesting to know if these women benefit from beta-blockers, used to limit aortic growth rate in some forms of aortic aneurysms such as Marfan syndrome, and this needs further investigation both during and outside pregnancy.

While the goal of this thesis was to answer a lot of questions, undoubtedly it raised even more questions as mentioned in this chapter. And we could continue forever about topics that deserve or require attention: what are the risks of pregnancy in women with arrhythmic disease? What is the effect of preconception counselling in the different WHO classes? Is assisted reproductive therapy an option in women with a complex cardiac disease, that have an improved life expectancy in the current era of medical technologies? We are still at the beginning of elucidating this interesting research area. By shedding a light on these issues, young women with heart disease will have a chance to lead a life as close to normal.

REFERENCES

1. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
2. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
3. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001; **104**(5): 515-21.
4. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
5. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010; **31**(17): 2124-32.
6. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
7. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.
8. Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. *Circulation* 2014; **129**(16): 1695-702.
9. Zentner D, Kotevski A, King I, Grigg L, d'Udekem Y. Fertility and pregnancy in the Fontan population. *Int J Cardiol* 2016; **208**: 97-101.
10. Gouton M, Nizard J, Patel M, et al. Maternal and fetal outcomes of pregnancy with Fontan circulation: A multicentric observational study. *Int J Cardiol* 2015; **187**: 84-9.
11. Cauldwell M, Von Klemperer K, Uebing A, et al. A cohort study of women with a Fontan circulation undergoing preconception counselling. *Heart* 2016; **102**(7): 534-40.
12. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. *Br Med J (Clin Res Ed)* 1987; **295**(6607): 1169-72.
13. Robson SC, Dunlop W, Hunter S. Haemodynamic changes during the early puerperium. *Br Med J (Clin Res Ed)* 1987; **294**(6579): 1065.
14. Robson SC, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *Br J Obstet Gynaecol* 1987; **94**(11): 1014-27.
15. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
16. Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. *Curr Opin Obstet Gynecol* 2012; **24**(6): 413-21.
17. Kampman MA, Bilardo CM, Mulder BJ, et al. Maternal cardiac function, uteroplacental Doppler flow parameters and pregnancy outcome: a systematic review. *Ultrasound Obstet Gynecol* 2015; **46**(1): 21-8.
18. Cornette J, Laker S, Jeffery B, et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheters in severely ill pregnant women. A prospective comparative study and systematic review. *Ultrasound Obstet Gynecol* 2016.
19. Kampman MA, Balci A, Groen H, et al. Cardiac function and cardiac events 1-year postpartum in women with congenital heart disease. *Am Heart J* 2015; **169**(2): 298-304.

20. Tzemos N, Silversides CK, Colman JM, et al. Late cardiac outcomes after pregnancy in women with congenital aortic stenosis. *Am Heart J* 2009; **157**(3): 474-80.
21. Cornette J, Ruys TP, Rossi A, et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. *Int J Cardiol* 2012.
22. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; **335**(7627): 974.
23. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008; **156**(5): 918-30.
24. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. *Obstet Gynecol* 2009; **114**(5): 961-70.
25. Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? *Circulation* 2010; **122**(6): 579-84.
26. Lin AE, Karnis MF, Calderwood L, et al. Proposal for a national registry to monitor women with Turner syndrome seeking assisted reproductive technology. *Fertil Steril* 2016; **105**(6): 1446-8.
27. Braverman AC, Moon MR, Geraghty P, Willing M, Bach C, Kouchoukos NT. Pregnancy after aortic root replacement in Loeys-Dietz syndrome: High risk of aortic dissection. *American Journal of Medical Genetics Part A* 2016; **170**(8): 2177-80.

Nederlandse samenvatting

Voor jonge mensen met een hartafwijking is het belangrijk om een zo normaal mogelijk leven te leiden, net als hun leeftijdsgenoten zonder een hartafwijking. Zwangerschap is daar een onderdeel van. Maar zwangerschap vormt een belasting voor het hart: om de baarmoeder en het kind te kunnen voorzien van voldoende zuurstof en voedingsstoffen, neemt het bloedvolume sterk toe. Dat betekent dat het hart zo'n 50% meer bloed rond dient te pompen per minuut[1-3]. Een gezond hart kan deze fysiologische veranderingen aan. Maar een hart dat afwijkend is, kan zich niet altijd aanpassen. Daarnaast hebben de hormonale veranderingen tijdens de zwangerschap impact op de bloedvaten en kan zwangerschap leiden tot een hogere bloeddruk. Hartziekte (cardiovasculaire ziekte) vormt de belangrijkste oorzaak van moedersterfte[4]. Terwijl moedersterfte door andere oorzaken wereldwijd juist afneemt is er in de laatste decennia een toename van moedersterfte door cardiovasculaire ziekte[5]. Dit is een zorgwekkende trend, en het maakt onderzoek naar de risico's van zwangerschap in vrouwen met een hartafwijking noodzakelijk. Wie zijn de vrouwen met het hoogste risico, en moeten zij afgeraden worden om zwanger te worden? Wat zijn de risico's voor het kind als de moeder een hartafwijking heeft en wat gebeurt er als zij een complicatie doormaakt? Het doel van dit proefschrift is dan ook het inzichtelijk maken van de risico's van zwangerschap, middels de volgende onderwerpen:

- risico stratificatie voor de uitkomst van zowel moeder als kind
- incidentie en impact van complicaties zoals ritmestoornissen
- bestuderen van patiënten met een hoog-risico aandoening zoals een kunstklep
- invloed van socio-economische factoren op de uitkomst van zwangerschap in deze groep vrouwen
- bestuderen van de zwangerschapswens bij vrouwen met het syndroom van Turner

Het voornaamste gedeelte van dit proefschrift is gebaseerd op de Registry Of Pregnancy And Cardiac disease, de ROPAC studie[6]. Deze wereldwijde registratie werd in 2007 opgezet, door Professor Roger Hall uit Norwich, Verenigd Koninkrijk, en Professor Jolien Roos-Hesselink, uit Rotterdam, met als doel een grote groep vrouwen met een hartafwijking te verzamelen, en de uitkomst van hun zwangerschappen te bestuderen. Vrouwen met allerlei soorten structurele hartafwijkingen worden geïncludeerd. Tot op het moment van schrijven zijn er al meer dan 4000 vrouwen geïncludeerd, in meer dan 100 verschillende centra uit meer dan 60 verschillende landen.

In Deel I van dit proefschrift hebben we het voorkomen van verschillende acute hartproblemen (cardiale complicaties) bestudeerd. Welke vrouwen hebben het hoogste risico op een problematisch verloop van de zwangerschap? In de Europese richtlijnen wordt de gemodi-

ficeerde World Health Organization (WHO) risicoscore geadviseerd om het risico van een patiënte in te schatten[7,8]. Het is gebaseerd op de onderliggende diagnose (bijvoorbeeld een gerepareerd gaatje in het boezem tussenschot of een verhoogde druk in het longvaatbed). WHO klasse 1 houdt in dat er een laag risico bestaat op het ontwikkelen van een complicatie tijdens de zwangerschap, vergelijkbaar met het risico van zwangerschap bij een vrouw zonder hartafwijking. In klasse 2 en 3 loopt dat risico op, en in WHO klasse 4 worden vrouwen geplaatst met een ernstig verhoogd risico op complicaties en sterfte, hetgeen een reden is om hen absoluut af te raden om zwanger te worden. Deze classificatie is ontwikkeld op basis van expertise. Grote onderzoeken ontbraken tot op heden om de waarde van de classificatie aan te tonen middels statistische analyses. In **hoofdstuk 1** laten we zien dat de classificatie redelijk in staat is om het risico op een cardiale complicatie te voorspellen. Er zijn echter duidelijk verschillen in de voorspellende waarde in ontwikkelingslanden en in ontwikkelde landen. Tot op heden was er weinig bekend over de uitkomst en dus ook de voorspellers van uitkomst van zwangerschap in vrouwen met een hartafwijking uit ontwikkelingslanden. We stellen voor om een aantal klinische parameters aan de WHO risico classificatie toe te voegen, om de voorspelling nauwkeuriger te laten verlopen: met name in ontwikkelingslanden voorspelt het hebben van een boezemritmestoornis (fibrilleren) of tekenen van hartfalen vóór de zwangerschap in belangrijke mate het risico op een cardiale complicatie tijdens zwangerschap.

In **Hoofdstuk 2** gaan we op zoek naar de waarde van de WHO classificatie voor het voorspellen van obstetrische en foetale complicaties, zoals pre-eclampsie, laag geboorte gewicht en foetale sterfte. Het blijkt dat de WHO classificatie niet goed in staat is om deze uitkomsten te voorspellen. Zodoende gingen we op zoek naar voorspellers van specifieke complicaties in vrouwen in de ROPAC studie. Het blijkt bijvoorbeeld dat een complexe aangeboren hartafwijking bij de moeder veel vaker gepaard gaat met een te laag geboorte gewicht bij het kind, relatief tot de duur van de zwangerschap. Ook zien we dat pre-eclampsie vaker voorkomt bij vrouwen met een ziekte van de aorta. Dit zijn interessante bevindingen die ons in de toekomst wellicht ook meer inzicht kunnen bieden in het ontstaan van de betreffende complicaties. Een ander belangrijke associatie is tweelingzwangerschap: in onze studie eindigden deze zwangerschappen zorgwekkend vaak tot foetale sterfte, en het is de vraag of verlies van de foetus zelfs vaker voor komt dan in tweelingzwangerschappen in vrouwen zonder een hartafwijking. Maar hoe om te gaan met meerlingzwangerschappen in deze vrouwen? Het lijkt verstandig om in het geval van fertiliteitsbehandeling terughoudend te zijn met ovulatie inductie en met multipele embryo terugplaatsingen en de voorkeur te geven aan 'single embryo transfer'. Maar spontane meerlingzwangerschappen zijn moeilijk te voorkomen, en het lijkt een brug te ver om actief over te gaan tot reductie van de zwangerschap tot een eenling, enkel omdat het een zwangerschap betreft bij een vrouw met een hartafwijking. Maar in het geval dat de conditie van de vrouw ernstig achteruit dreigt te gaan, zal dit zeker overwogen moeten worden.

Hartfalen is een bekend probleem in patiënten met een hartafwijking: het hart is onvoldoende in staat om het bloed de aorta in te pompen, en doordat het daarin faalt, kan een patiënt last krijgen van longoedeem ('vocht achter de longen'), met kortademigheid en moeheid, en oedeem in de benen. Bij vrouwen met een hartafwijking komt het voor in 13% van de zwangerschappen, zoals collega dr. Ruys reeds beschreef in een eerder artikel over de ROPAC[9]. Het is één van de complicaties die we probeerden te voorspellen in hoofdstuk 1. In **hoofdstuk 3 en 4** gaan we op zoek naar het voorkomen van ritmestoornissen in de zwangerschap. Zowel supraventriculaire (boezem) als ventriculaire (kamer) ritmestoornissen komen gelukkig niet vaak voor: respectievelijk in 1.3% en in 1.4% van de zwangerschappen. Ventriculaire ritmestoornissen waren vaak geassocieerd met het optreden van hartfalen. Patiënten met kortademigheid voor de zwangerschap hadden het hoogste risico op een ventriculaire ritmestoornis. Verder blijkt dat vrouwen die een ritmestoornis hebben tijdens de zwangerschap, een hoger risico hebben op een slechte afloop: ze verliezen iets vaker hun baby, en er is vaker sprake van een laag geboorte gewicht. We moeten zo'n ritmestoornis dus zo goed mogelijk proberen te vermijden of in ieder geval zo vroeg mogelijk op te sporen. De behandeling is tijdens de zwangerschap lastiger dan buiten de zwangerschap omdat sommige medicijnen kwaad kunnen bij de baby. Van sommige medicijnen is dit goed uitgezocht, maar hier is duidelijk nog meer onderzoek nodig.

In **hoofdstuk 5** beschrijven we welke acute en potentieel levensgevaarlijke complicaties er op kunnen treden tijdens de zwangerschap, en vooral hoe daar het beste mee om gegaan kan worden. Voorbeelden zijn acuut coronair syndroom (dat is, in het ergste geval, een hartinfarct), aorta dissectie (een scheur in de grote lichaamsslagader) of kunstklep trombose (een stolsel op de kunstklep). Vrouwen die zich met zo'n complicatie presenteren, zijn vaak vooraf nog niet bekend met een/hun hartafwijking, en hebben daarom voorafgaand aan de zwangerschap ook geen consult met een cardioloog gehad om te spreken over de potentiele risico's van zwangerschap ten aanzien van het hart of de aorta. We weten van de 'Confidential enquiries' in het Verenigd Koninkrijk, een nationale verplichte registratie voor moedersterfte, dat deze hartproblemen de belangrijkste oorzaken zijn van moedersterfte[4]. Artsen op de spoedeisende hulp zouden zoveel mogelijk kennis in huis moeten hebben over deze specifieke groep risico patiënten om tijdig de diagnose te kunnen herkennen. Om snelle behandelingskeuzes mogelijk te maken, worden in hoofdstuk 5 flow diagrammen voor diagnostiek en behandelingsstrategie per diagnose aangeboden.

We besluiten Deel I van dit proefschrift met het bekijken van de invloed van socio-economische factoren op de uitkomst van zwangerschap in vrouwen met een hartafwijking. De invloed van dit soort factoren is nog onvoldoende onderzocht. Onze resultaten zijn weergegeven in **hoofdstuk 6**. Terwijl maternale conditie de belangrijkste noemer voor uitkomst van zwangerschap bleek, kan socio-economische invloed op de uitkomst in deze groep vrouwen niet ontkend worden. Toegang tot de juiste vorm van gezondheidszorg, met toegewijde 'zwangerschap en hartafwijkingen – klinieken', is niet de standaard in veel

landen en afgelegen gebieden. Vrouwen presenteren zich vaak in een later stadium, vanwege de kosten, maar ook vanwege hun culturele achtergrond, waarbij zwangerschap een vorm van status is. In Egypte bijvoorbeeld, is het dusdanig belangrijk om kinderen te krijgen, dat vrouwen vaak niet praten over hun hartafwijking. Alleen wanneer zwangerschap al in een ver gevorderd stadium is, of wanneer er serieuze problemen ontstaan, zoeken deze vrouwen hulp. En dat bemoeilijkt vroege interventie, laat staan preventie. Het is belangrijk om die interregionale verschillen in uitkomst in het achterhoofd te houden, niet alleen bij de interpretatie van ROPAC resultaten, maar ook wanneer men als doel heeft om de uitkomst van zwangerschap wereldwijd te verbeteren.

Deel II richt op zwangerschap in vrouwen met een hartklep afwijking. In **hoofdstuk 7** en **hoofdstuk 8** hebben we vrouwen bestudeerd met linkszijdige hartklep afwijkingen, te weten van de aortaklep (tussen de linker kamer en de aorta) en de mitralisklep (tussen de linker boezem en de linker kamer). We beschrijven een cohort van 96 vrouwen met matige of ernstige aortaklep stenose (vernauwing). Zwangerschap gerelateerde sterfte bij aortaklep stenose kwam in onze studie niet voor, en het voorkomen van sterfte is daarmee veel lager dan in oudere studies. Echter, vrouwen met symptomatische ernstige aortaklepstenose in onze studie hadden een aanzienlijk risico op het ontwikkelen van hartfalen: in 26% van de zwangerschappen. Een aantal van hen had waarschijnlijk reeds voor de zwangerschap al een indicatie om klepvervanging te ondergaan. Het blijft een moeilijke beslissing of we vrouwen met een asymptomatische ernstige klepstenose voor de zwangerschap moeten behandelen of niet. Klepvervanging neemt namelijk een nieuw dilemma met zich mee: moet de klep vervangen worden door een biologische of een mechanische kunstklep? Wanneer gekozen wordt voor een mechanische kunstklep, weten we dat zwangerschap een risicovolle periode is wat betreft bloedingen en trombose (stolselvorming op de kunstklep, zie ook hoofdstuk 9). Wanneer gekozen wordt voor een biologische kunstklep, dan weten we dat die klep niet veel langer dan 10-15 jaar mee gaat en dat in deze jonge populatie dus een klepvervanging na die periode onvermijdelijk is, hetgeen ook niet zonder risico is. Onze studie laat zien dat bij vrouwen met een matig tot ernstige aortastenose er wel complicaties optreden, maar deze waren goed te behandelen en er was gelukkig geen sterfte in onze groep. Dat ondersteunt het beleid om bij de meeste vrouwen niet eerder te gaan opereren vanwege een zwangerschapswens.

In hoofdstuk 7 laten we zien dat vrouwen met reumatische mitralisklep afwijkingen (door acuut reuma in de jeugd), en met name de vrouwen met mitralisklep stenose, een heel hoog risico hebben op een problematische zwangerschap. Dat kwam niet als een verassing, aangezien de huidige richtlijnen adviseren om zwangerschap te vermijden in het geval van ernstige en symptomatische stenose. Deze laatste groep ontwikkelde hartfalen in 36% van de gevallen in onze studie. Maar het evident verhoogde risico van zwangerschap in vrouwen met matige mitralisklep stenose (hartfalen in 23%) en zelfs in vrouwen met een

significante mitralisklep insufficiëntie (eveneens hartfalen in 23%), is een bevinding die meer aandacht behoeft in de toekomstige richtlijnen: hoe moeten we omgaan met de situatie waarin een vrouw formeel nog geen kandidaat is voor klepvervanging, maar die wel een zwangerschapswens heeft in de aanwezigheid van bijvoorbeeld een matige mitralisklep stenose? Weegt het risico van zwangerschap zwaarder dan het risico van een interventie die eerder dan noodzakelijk wordt verricht? En welk type interventie is het veiligst, zoals hierboven op een rij gezet? Tijdens de zwangerschap hadden 14 vrouwen in onze studie een ballon dilatatie ondergaan (verwijding van de klepvernauwing via de bloedbaan met een ballon). Dit was geassocieerd met weinig problemen gedurende het verdere verloop van de zwangerschap en lijkt dus veilig.

In **hoofdstuk 9** worden zwangerschappen beschreven bij vrouwen die een mechanische of biologische kunstklep hebben. Vrouwen met een mechanische kunstklep hadden slechts een teleurstellende 58% kans op een ongecompliceerde zwangerschap resulterend in een levend geboren baby, terwijl vrouwen met een biologische prothese een veel gunstigere uitkomst hadden. De vraag blijft of er op langere termijn sprake is van een snellere achteruitgang van het functioneren van zo'n biologische prothese. Tevens is er veel ruimte voor verbetering wat betreft de behandeling met anticoagulantia (sterke 'bloedverdunners') tijdens de zwangerschap. Bij mensen met een mechanische kunstklep moeten bloedverdunners (anticoagulantia) levenslang gebruikt worden in verband met het risico op stolselvorming op de mechanische kunstklep. Er zijn verschillende soorten anticoagulantia, bijvoorbeeld tabletten acenocoumarol ('oraal', vitamine K antagonisten) of subcutaan of intreveneus heparine (via de huid of de bloedbaan). De tabletten kunnen aangeboren afwijkingen bij de baby veroorzaken, maar zijn wel het veiligst voor de moeder. De spuitjes zijn veilig voor de baby, maar waarschijnlijk iets minder veilig voor de moeder en als er iets met de moeder gebeurt, heeft dit ook direct nadelige consequenties voor de baby. Richtlijnen voor zwangerschap in deze vrouwen adviseren verschillende strategieën, met een switch van orale naar subcutaan of intraveneus heparine in het eerste trimester, en voortzetten van de orale anticoagulantia gedurende het tweede en derde trimester. De switch wordt aanbevolen in verband met ernstige aangeboren afwijkingen bij de baby in geval van doorgebruik van orale anticoagulantia. Vanaf 36 weken zal er weer geswitcht moeten worden naar een subcutaan of intraveneus middel, om ernstige bloedingen bij het kind tijdens vaginale bevalling met name te voorkomen. In ons cohort bleek dat geen van de strategieën beduidend beter was. Wel bleek dat gebruik van het orale middel (vitamine K antagonist) in het eerste trimester, geassocieerd was met een hoog aantal foetale sterftes in het tweede en derde trimester, terwijl het gebruik van subcutaan heparine het risico op klep trombose leek te verhogen. De nieuwere orale middelen, zoals apixaban, hebben we niet onderzocht, maar zijn in het algemeen niet bruikbaar bij patiënten met een kunstklep omdat het niet veilig genoeg is om kunstklep trombose te voorkomen.

De effecten van zwangerschap op de aorta vaatwand hebben we beschreven in **hoofdstuk 10**, het eerste hoofdstuk van Deel III. Deze effecten leiden in principe niet tot ernstige problemen bij vrouwen zonder een onderliggende aortaziekte, maar vrouwen met een aorta syndroom zoals Marfan, Loeys Dietz of Turner syndroom hebben wel een verhoogd risico op een aorta dissectie (een scheur in de aorta). Een overzicht van de literatuur wordt gegeven in dit hoofdstuk, met de focus op specifieke aorta ziekten, farmacologische behandeling en chirurgische benaderingen tijdens de zwangerschap.

Turner syndroom wordt gekarakteriseerd door een partiële of totale afwezigheid van een X-chromosoom (monosomie). Het is geassocieerd met een korte gestalte, sub- of infertiliteit (verminderde/afwezige) vruchtbaarheid, en hart- en aorta afwijkingen. Zwangerschap was voorheen niet aan de orde voor het grootste deel van deze vrouwen. Maar sinds het mogelijk is zwanger te worden na ontvangst van eiceldonatie, is het aantal vrouwen met Turner syndroom dat zwanger wordt toegenomen. Natuurlijk zijn er nog niet veel Turner vrouwen zwanger en er speelt nog veel onzekerheid en angst. In **hoofdstuk 11** beschrijven we de zwangerschapswens, redenen om (nog) niet te proberen om zwanger te worden, en het aantal pogingen dat eindigt in een werkelijke zwangerschap. Een aanzienlijk aantal vrouwen had zorgen (gehad) rondom het risico op problemen van het hart en de aorta tijdens zwangerschap en bevalling, hetgeen duidelijk aandacht behoeft van de behandelende artsen die betrokken zijn bij de zorg rondom vrouwen met Turner syndroom. In **hoofdstuk 12** tonen we de uitkomst van zwangerschap in vrouwen met het Turner syndroom in ons centrum. Het aantal miskramen was hoog, maar bij de voldragen zwangerschappen, was er sprake van een relatief laag aantal cardiovasculaire complicaties. Echter, er is veel meer onderzoek noodzakelijk, aangezien de onderzoeken naar cardiovasculaire complicaties tijdens zwangerschap bij vrouwen met het Turner syndroom, inclusief onze studie, sterk beperkt worden door het kleine aantal patiënten dat geïncludeerd werd. Dit probleem geldt ook voor vrouwen met een SMAD3 mutatie: een recent ontdekte genetische afwijking waarbij patiënten een agressieve aorta ziekte ontwikkelen, geassocieerd met aneurysmata (verwijdingen van de aorta) en dissectie. De groep patiënten beschreven in **hoofdstuk 13** in de eerste serie van zwangerschappen in SMAD3 patiënten. Geen ernstige cardiovasculaire problemen werden gevonden in 34 zwangerschappen in 17 vrouwen met zo'n genmutatie, die bijna allemaal een klinische uiting van het syndroom hadden of hadden ontwikkeld (sommigen enkele jaren na de zwangerschap). Deze retrospectieve studie kan gezien worden als het startpunt voor verder onderzoek naar zwangerschap in deze vrouwen.

Hypertrofische cardiomyopathie is een aandoening waarbij de hartspier verdikt is, meestal door een genetische mutatie. Het wordt steeds vaker ontdekt op jonge leeftijd dankzij genetische screening. Over het algemeen wordt gedacht dat zwangerschap redelijk verdragen kan worden, maar er is tot op heden nog weinig onderzoek naar gedaan. **Hoofdstuk 14** toont de relatief gunstige uitkomst van zwangerschap in vrouwen met hypertrofische

cardiomyopathie. In onze studie was er geen sprake van maternale sterfte, maar 15% van de vrouwen ontwikkelde hartfalen en 10% had een ventriculaire ritmestoornis gedurende de zwangerschap. Deze problemen traden meestal op tijdens het derde trimester, en direct postpartum. Vrouwen met kortademigheid of tekenen van hartfalen voorafgaand aan de zwangerschap hadden het hoogste risico op een complicatie. Er waren geen verschillen tussen vrouwen met obstructieve hartziekte (een situatie waarbij de hartspier zo verdikt is dat het de uitstroom van het bloed belemmert) en vrouwen zonder obstructieve ziekte. Het is van belang dat een vrouw met hypertrofische cardiomyopathie en een zwangerschapswens op de hoogte is van het voorkomen van een cardiale complicatie in 23% van de gevallen.

Pulmonale hypertensie is een heel ander verhaal: zoals eerder benoemd is pulmonale arteriële hypertensie (PAH, een verhoogde druk in het longvaatbed) een reden om zwangerschap te vermijden. Echter de studies waarop dit advies is gebaseerd, zijn over het algemeen retrospectieve studies. In **hoofdstuk 15** tonen we dat de bestaande terughoudendheid gerechtvaardigd is. Maar tot op heden was er weinig bekend over het risico van zwangerschap in vrouwen met een verhoogde druk in de rechterkamer door linkszijdige hartziekte, hetgeen formeel gezien pulmonale hypertensie heet (omdat het niet arterieel bepaald is, maar primair een probleem van de linkerkant en dus het long veneuze vaatbed). In ons cohort hebben we 151 vrouwen met een verhoogde rechts druk (right ventricular systolic pressure, of RVSP) bestudeerd, van wie 26% PAH had en 74% verhoogde longdrukken door linkszijdige hartafwijkingen. Hartfalen kwam respectievelijk voor in 36% en 25% van de zwangerschappen. Maternale sterfte kwam met name voor bij vrouwen met PAH zonder duidelijke oorzaak (idiopathisch): 3 uit 7 patiënten, 43%. Echter onder vrouwen uit de tweede groep, met linkszijdige hartafwijkingen, kwam ook sterfte voor in 2.7% van de zwangerschappen. Vrouwen met ernstig verhoogde drukken (RVSP>90 mmHg) hadden het hoogste risico op sterfte, trombotische problemen en bevalling van een baby met laag geboortegewicht (<2500gr), hoewel één en ander niet statistisch significant was bij te lage aantallen. De resultaten van onze studie impliceren dat pulmonale hypertensie door linkszijdige hartafwijkingen wellicht een lager risico met zich mee brengt tijdens de zwangerschap dan in het geval van PAH, maar dat deze vrouwen zeker goed geïnformeerd moeten worden over de risico's. Het zou aan te bevelen zijn om in de toekomstige richtlijnen een duidelijk onderscheid te maken in adviezen voor vrouwen met mild, matig en ernstig verhoogde rechts drukken.

Het doel van dit proefschrift was om een aantal vragen te beantwoorden, maar er zijn nog zoveel vragen te beantwoorden. Wat zijn de risico's van zwangerschap in vrouwen met een ritmestoornis zonder onderliggende structurele hartafwijking? Wat is het effect van het preconceptioneel advies van artsen in de verschillende WHO klasses? Is fertiliteitsbehandeling een optie in vrouwen met een complexe aangeboren hartafwijking, die inmiddels een

langere levensverwachting hebben dan vroeger dankzij de verbeterde medische technologien? We staan aan het begin van de ontwikkeling van een zeer interessant onderzoeksgebied. Door deze vragen te beantwoorden krijgen jonge vrouwen met een hartafwijking steeds meer een kans hun leven op een zo normaal mogelijke manier te leiden. Voorop staat dat zij voorafgaand aan pogingen om zwanger te worden in ieder geval goed geinformeerd moeten worden over hun risico op problemen tijdens en na de zwangerschap. Goede informatie en een gedegen besluitvorming zullen bijdragen aan een veiligere situatie voor moeders met een hartafwijking en hun toekomstige kinderen.

REFERENTIES

1. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; **256**(4 Pt 2): H1060-5.
2. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992; **68**(6): 540-3.
3. Cornette J, Ruys TP, Rossi A, et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. *Int J Cardiol* 2012.
4. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118 Suppl 1**: 1-203.
5. Tanaka H, Katsuragi S, Osato K, et al. The increase in the rate of maternal deaths related to cardiovascular disease in Japan from 1991-1992 to 2010-2012. *J Cardiol* 2016.
6. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**(9): 657-65.
7. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *European Heart Journal* 2011; **32**(24): 3147-97.
8. Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. *J Fam Plann Reprod Health Care* 2006; **32**(2): 75-81.
9. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. *Heart* 2014; **100**(3): 231-8.

List of publications

1. **I.M. van Hagen**, D. van der Linde, I.M.B.H. van de Laar, J. De Backer, J.W. Roos-Hesselink. Pregnancy in women with *SMAD3* mutation. Accepted in *JACC*. 2017.

2. **I.M. van Hagen**, J. Cornette, M.J. Johnson, J.W. Roos-Hesselink. Managing cardiac emergencies in pregnancy. *Heart*. 2017 Jan 15;103(2):159-173.

3. S. Orwat, G.P. Diller, **I.M. van Hagen**, R. Schmidt, D. Tobler, M. Greutmann, M.R. Johnson, R. Hall, J.W. Roos-Hesselink, H. Baumgartner. Risk of Pregnancy in Moderate and Severe Aortic Stenosis: Results from a Multinational Registry (ROPAC). *J Am Coll Cardiol*. 2016 Oct 18;68(16):1727-1737.

4. **I.M. van Hagen,** T.A.L. Duijnhouwer, E.M.W.J. Utens, M.J. Ten Kate-Booij, R. Dykgraaf, J.J. Duvekot, J.W. Roos-Hesselink. Wish to conceive and concerns to develop cardiovascular complications during pregnancy in patients with Turner Syndrome. *J Psychosom Obstet Gynaecol*. 2016 Sep 1:1-8.

5. E. Ertekin, **I.M. Van Hagen**, A. M. Salam, T.P.E. Ruys, M.R. Johnson, J. Popelova, W.A. Parsonage, Z. Ashour, A. Shotan, J.M. Oliver, G.R. Veldtman, R. Hall, J.W. Roos-Hesselink. Ventricular tachyarrhythmia during pregnancy in women with heart disease: data from the ROPAC, a registry from the European Society of Cardiology. *Int J Cardiol*. 2016 Oct 1;220:131-6.

6. K. Sliwa, **I.M. van Hagen,** W. Budts, L. Swan, G. Sinagra, M. Caruana, M. Vazquez Blanco, L. Wagenaar, M.R. Johnson, G. Webb, R. Hall, J.W. Roos-Hesselink, on behalf of the ROPAC investigators. Pulmonary Hypertension and Pregnancy Outcome: data from the European Society of Cardiology initiated Registry of Pregnancy and Cardiac disease (ROPAC). *Eur J Heart Fail*. 2016 Sep;18(9):1119-28.

7. **I.M. van Hagen,** E. Boersma, M.R. Johnson, S.A. Thorne, W.A. Parsonage, P. Escribano Subías, A. Lesniak-Sobelga, O. Irtyuga, K.A. Sorour, N. Taha, A.P. Maggioni, R. Hall, J.W. Roos-Hesselink, on behalf of the ROPAC investigators and EORP team. Global cardiac risk assessment in the Registry Of Pregnancy And Cardiac disease: results of a registry from the European Society of Cardiology. *Eur J Heart Fail*. 2016 May;18(5):523-33.

8. **I.M. van Hagen**, J.W. Roos-Hesselink, P.T.E. Ruys, W. Merz, S. Goland, H. Gabriel, M. Lelonek, O. Trojnarska, W. Almahmeed, H.O. Balint, Z. Ashour, H. Baumgartner, H. Boersma, M.R. Johnson, R. Hall. Pregnancy in women with a mechanical heart valve: Data of the European Society of Cardiology Registry Of Pregnancy And Cardiac disease (ROPAC). *Circulation*. 2015 Jul 14;132(2):132-42.

9. A. Salam, E. Ertekin, **I.M. van Hagen,** J. Al Suwaidi, P.T.E. Ruys, M. Johnson, L. Gumbiene, A. Frogoudaki, K.A. Sorour, L. Iserin, M. Ladouceur, A.C.C. van Oppen, R. Hall, J.W. Roos-Hesselink. Atrial Fibrillation or Flutter during Pregnancy in Patients with Structural Heart Disease: data from the ROPAC. *JACC Clin Electrophys*. 2015 Aug; 1 (4): 284-92.

10. M.F. Hoes, **I.M. van Hagen**, F. Russo, D.J. van Veldhuisen, M.P. van den Berg, J.W. Roos-Hesselink, K.Y. van Spaendonck-Zwarts, P. van der Meer. Peripartum cardiomyopathy: Euro Observational Research Program. *Neth Heart J*. 2014 Sep;22(9):396-400.

11. **I.M. van Hagen**, J.W. Roos-Hesselink. Aorta pathology and pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2014 May;28(4):537-50.

12. **I.M. van Hagen**, J.W. Roos-Hesselink. Pregnancy in women with congenital heart disease. *SA Heart*. 2013;10(4):616-624.

Submitted manuscripts

13. A.T. van den Hoven, R. Saru, T. Duijnhouwer, K. Nieman, L. Demulier, D. Devos, **I.M. van Hagen,** J.W. Roos-Hesselink. Evaluation of PAPVR in patients with Turner Syndrome. *Submitted.*

14. W.M. van Everdingen, J. Walmsley, M.J. Cramer, **I.M. van Hagen**, B.W.L. de Boeck, M. Meine, P.A. Doevendans, F.W. Prinzen, J. Lumens, G.E. Leenders. Right ventricular dysfunction complicates prediction of response to cardiac resynchronization therapy by mechanical dyssynchrony parameters. *Submitted*.

15. **I.M. van Hagen**, S. Thorne, N. Taha, G. Youssef, A. Elnagar, H. Gabriel, Y. ElRakshy, B. Iung, M.R. Johnson, R. Hall, J.W. Roos-Hesselink. Pregnancy outcome in women with rheumatic mitral valve disease: results from the Registry Of Pregnancy And Cardiac disease (ROPAC) of the European Society of Cardiology. *Submitted*.

16. **I.M. van Hagen**, J.W. Roos-Hesselink, V. Donvito, C. Liptai, M. Morissens, D.J. Murphy, L. Galian-Gay, N.M. Bazargani, J. Cornette, R. Hall, M.R. Johnson. Incidence and predictors

of obstetric and fetal complications in women with structural heart disease: data from the Registry Of Pregnancy And Cardiac disease (ROPAC) from the European Society of Cardiology. *Submitted*.

17. S. Goland, **I.M. van Hagen**, A. Blatt, U. Elkayam, A. Shotan, W.M. Merz, S.C. Enar, I.R. Gaisin, P.G. Pieper, M.R. Johnson, R. Hall, J.W. Roos-Hesselink**.** Pregnancy in women with hypertrophic cardiomyopathy: data from the European Society of Cardiology initiated Registry of Pregnancy and Cardiac disease (ROPAC). *Submitted*.

18. **I.M. van Hagen**, S. Baart, R. Fong Soe Khioe, K. Sliwa, N. Taha, M. Lelonek, L. Tavazzi, A. Maggioni, M.R. Johnson, N. Maniadakis, R. Fordham, R. Hall, J.W. Roos-Hesselink. Influence of socioeconomic factors on pregnancy outcome in women with structural heart disease: data from ROPAC, an ESC registry. *Submitted*.

19. **I.M. van Hagen**, T.A.L. Duijnhouwer, E.M.W.J. Utens, M.J. Ten Kate-Booij, R. Dykgraaf, J.J. Duvekot, J.W. Roos-Hesselink. Cardiovascular complications during pregnancy in patients with Turner Syndrome. *Submitted*.

Book chapters

I.M. van Hagen, J.W. Roos-Hesselink. Care during pregnancy. In: Pregnancy and Congenital Heart disease. Springer International Publishing: M. Johnson and J.W. Roos-Hesselink (editors); 2017.

J.W. Roos-Hesselink, **I.M. van Hagen**. Management of Ischemic Heart Disease in Pregnancy. In: Heart Disease in Pregnancy. Cambridge University Press; Steer and Gatzoulis (Editors): 2016. Page 174-179.

PhD portfolio

Name	Iris M. van Hagen
Department	Cardiology
Research school	COEUR, Erasmus MC
PhD period	2013-2016
Title thesis	Risk of pregnancy in women with cardiovascular disease
Promotores	Prof. Dr. J.W. Roos-Hesselink
	Prof. Dr. M.R. Johnson
Date of thesis defense	April 18, 2017

PhD training (46 ECTS)

In-depth courses

2013-2016	COEUR research seminars and lectures, Rotterdam, The Netherlands
2013	Functional and applied cardiac anatomy, CVOI, Rotterdam, The Netherlands
2013	Cardiovascular Medicine, COEUR, Erasmus MC, Rotterdam, The Netherlands
2014	Echocardiography, congenital heart disease, Erasmus MC, Rotterdam, The Netherlands
2014	Women's Health, NIHES, Rotterdam, The Netherlands
2014	English Biomedical Writing, Erasmus MC, Rotterdam , The Netherlands
2014	Clinical Cardiovascular Epidemiology, COEUR, Rotterdam, The Netherlands
2015	Cardiovascular Imaging and Diagnostics, COEUR, Rotterdam, The Netherlands
2015	Atherosclerosis and Aneurysmal Disease, COEUR, Rotterdam, The Netherlands
2015	Congenital Heart Disease, COEUR, Rotterdam, The Netherlands

Other courses

2013	Biostatistical Methods I: basic principles, NIHES, Rotterdam, The Netherlands
2014	Basic course Clinical Investigators (BROK), Rotterdam, The Netherlands

2014	OpenClinica course
2014	Photoshop and Illustrator course
2015	Research Integrity, Erasmus MC, Rotterdam , The Netherlands

Teaching

2014	Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands
2013 - 2016	Lectures at research meetings at the department of congenital cardiology, Erasmus MC, Rotterdam, The Netherlands
2014	Supervising a 4th year medical student in performing medical research
2014	Supervising 3rd year medical students in writing a systematic review within a minor Congenital Heart Disease, Erasmus MC, Rotterdam, The Netherlands
2014	Lecture "Pregnancy in Turner Syndrome", Turner syndrome patient information day, Amersfoort, The Netherlands
2014	Lecture "Pregnancy with a mechanical valve", Patient information day, Rotterdam, The Netherlands
2015	Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands
2015	Lecture "Adult Congenital Heart Disease" for specialized nurses in training (January) , Erasmus MC, Rotterdam, The Netherlands
2015	Lecture "Pregnancy and Heart disease", COEUR course on Congenital Heart Disease, Erasmus MC, Rotterdam, The Netherlands
2015	Lecture "Adult Congenital Heart Disease" for specialized nurses in training (September), Erasmus MC, Rotterdam, The Netherlands
2015	Supervising 3rd year medical students in writing a systematic review within a minor Congenital Heart Disease, Erasmus MC, Rotterdam, The Netherlands
2015	Lecture "Pregnancy and Heart disease", Minor on Obstetric medicine, Erasmus MC, Rotterdam, The Netherlands

Symposia and conferences

Oral presentations

2014	Dutch Society of Cardiology (NVVC) Autumn congress Papendal, The Netherlands
2014	COEUR annual PhD day Rotterdam, The Netherlands
2015	Winter Meeting General Cardiology Davos, Switzerland
2015	Dutch Society of Cardiology (NVVC) Spring congress Noordwijkerhout, The Netherlands
2015	Abstract presentation, European Society of Cardiology (ESC) Congress London, United Kingdom
2015	Case presentation, European Society of Cardiology (ESC) Congress London, United Kingdom
2015	Dutch Society of Cardiology (NVVC) Autumn congress Papendal, The Netherlands
2016	Two abstract presentations, International congress on Cardiac Problems in Pregnancy Las Vegas, United States
2016	Dutch Society of Cardiology (NVVC) Spring congress Noordwijkerhout, The Netherlands
2016	Consensus Study Group Meeting for the Care of Girls and Women with Turner Syndrome Cincinnati, USA
2016	Two abstract presentations in Rapid Fire session, European Society of Cardiology (ESC) Congress, Rome, Italy

Invited oral presentations

2015	"Cardiology and pregnancy", CarvasZ symposium Ede, The Netherlands
2016	"Pulmonary hypertension and pregnancy", International congress on Cardiac Problems in Pregnancy Las Vegas, United States

Poster presentations

2014 European Society of Cardiology (ESC) congress
Barcelona, Spain

2014 American Heart Association (AHA) Scientific Sessions
Chicago, USA

Attended

2013 European Society of Cardiology (ESC) congress
Amsterdam, The Netherlands

2014 International congress on Cardiac Problems in Pregnancy
Venice, Italy

2014 Karel V symposium "Pulmonary atresia and ventricle septal defect"
Utrecht, The Netherlands

2014 ACHD symposium
London, United Kingdom

2015 Karel V symposium "Morbus Ebstein"
Utrecht, The Netherlands

2015 Aortapathology
Rotterdam, The Netherlands

Award

2016 Best oral presentation in 'General Cardiology', NVVC spring congress

Guideline involvement

2016 Task Force on Consensus document Turner Syndrome, Working group cardiovascular disease

About the author

Iris Maria van Hagen was born on May 11th 1985, in Eindhoven, the Netherlands. After graduating high school (St. Oelbert Gymnasium, Oosterhout), she started medical school at the Univerity of Utrecht. During her study, she was a board member of the Medical Students Congress (Medisch Interfacultair Congres) and spent two internships abroad (Paramaribo Surinam; Brisbane Autralia). In the final year of medical school she did a research internship at the department of cardiology (University Medical Centre Utrecht), followed by a clinical internship at the same department. After obtaining her Medical Doctor's degree, she started working as a resident (Anios) at the department of cardiology in the Meander Medical Centre Amersfoort and Haga Teaching Hospital, The Hague. In 2013, she started with the research project described in this thesis 'Risk of Pregnancy in Women with Cardiovascular Disease', supervised by Prof. Jolien Roos-Hesselink (Erasmus Medical Centre Rotterdam) and Prof. Mark Johnson (Imperial College London). During this PhD project, she had the opportunity to present her work on several national and international conferences and to publish manuscripts in peer reviewed international journals. She was involved in the writing of the international Turner Syndrome guidelines.

As of October 2016 , Iris is working as a resident at the department of cardiology at the Erasmus Medical Centre, Rotterdam. Outside work, she enjoyes to run and play field hockey. Iris is married to Wouter Liem.

Dankwoord

De totstandkoming en afronding van dit proefschrift was niet mogelijk geweest zonder de hulp of steun van velen: ik ben eenieder ontzettend dankbaar die mij op welke wijze dan ook gesteund heeft. Hierna volgen de namen van een aantal mensen die ik in het bijzonder wil bedanken. Voor iedereen die hier niet genoemd staat: dank, dank, dank!

Professor Roos-Hesselink, lieve Jolien: dankjewel, voor alles! Jij hebt mij zoveel kansen en ruimte gegeven om mij te ontwikkelen op het mooie vakgebied van de cardiologie rondom de zwangerschap. Zonder jou was dit proefschrift er letterlijk nooit geweest. Je bent een bevlogen professor, een gepassioneerd onderzoeker, een zeer toegankelijke mentor, kortom een fantastisch mens. Het kan niet anders dan dat er veel meer dan 24 uur in jouw dagen zit… Je hebt me het vak van het schrijven, het presenteren en het netwerken bijgebracht. Ik bewonder je om wat jij bereikt hebt, en ben je dankbaar voor het feit dat jij met zoveel enthousiasme de deuren opent voor mij en andere jonge onderzoekers en clinici. Ik hoop van harte dat we nog veel zullen samenwerken in de toekomst, en kijk daar nu al naar uit.

Professor Johnson, dear Mark: thank you so much for your support. It was a great pleasure working with you. Within your busy schedule, you always took time to provide us with important comments on the manuscripts. Your critical view on the data has often helped me to better understand our results. Also, your sophisticated English writing has definitely helped me to improve my 'Dunglish' . The brainstorm sessions between Jolien and yourself, that I joined a few times, absolutely amazed me. This is where research starts: two inspiring professors thinking 'out of the box'. It is a great honour to have you as a supervisor on my thesis, thank you.

Professor Hall, dear Roger: thank you, for starters, for having started the great project of ROPAC together with Jolien. I am so thankful for this unique project and the fact that you and Jolien have trusted me with the valuable database. Our joint project on the mechanical valves was a though one, but we managed to get it in Circ, and that would definitely not have been possible without your supervision and your expertise on valve disease. I enjoyed our meetings in Rotterdam and on congresses, and I am very honoured that you accepted to be part of the comittee at my thesis defence.

Leden van de leescommissie: Professor Dr. Takkenberg, Professor Dr. Steegers, Professor Dr. De Backer, ik wil u allen hartelijk danken voor het feit dat u in de leescommissie hebt willen plaatsnemen. Julie, het was prettig samenwerken op het gebied van aorta pathologie en ik hoop van harte op een vervolg in de toekomst. Professor Dr. van Rossum, hartelijk dank voor het plaatsnemen in de grote commissie.

Dr. Vriend, beste Joris: eigenlijk ben jij de aanstichter van dit boekje! Ik wil je hartelijk danken voor jouw vertrouwen en het feit dat je mij naar Jolien hebt verwezen. Het is een ware eer dat je in de grote commissie hebt plaats genomen.

To continue: I would like to thank all ROPAC investigators and co-authors worldwide: this thesis would not have been possible without you!

I would like to thank everyone at the EORP (EurObservational Research Programme) from the ESC, who has supported the ROPAC. Prof. Maggioni, Prof. Tavazzi, thank you for being a co-author on some of our papers. Your support for ROPAC is a great deal to us. Thierry Ferreira, Elin Folkkesson-leFranq, Viviane Missiamenou, Gerard Gracia, Sebastian Authier: thank you all for all your efforts, it was a great pleasure working with you. Elin, I already miss our email conversations! Thank you all for giving me a warm welcome at the EHH in 2014.

Ik wil graag de collegae van de gynaecologie bedanken: Dr. Duvekot en Dr. Cornette. Beste Hans en Jerome, dank voor jullie waardevolle input in de papers. Ik hoop dat we in de toekomst kunnen blijven samenwerken op dit boeiende gezamenlijke vakgebied.

Alle collegae bij de congenitale cardiologie: hartelijk dank voor de samenwerking, de gezamenlijke koffie en de mooie 'congenitale uitjes'. Dr. Maarten Witsenburg, Dr. Annemien van den Bosch, Dr. Judith Cuypers, Jackie, Celeste en Tineke: van jullie allemaal heb ik de afgelopen jaren veel geleerd. Celeste, dank voor je onvoorwaardelijke inzet voor patiënten, maar ook voor de logistiek van verschillende onderzoeken, en voor de lekkere bakseltjes!

Kamer Ba308: drie jaar promoveren op dezelfde kamer smeedt een band. Jannet, mijn eerste voorbeeld als kamer oudste, en wat voor één.. je bent echt vliegensvlug gepromoveerd en in opleiding gekomen, maar had en hebt desondanks altijd wel tijd voor een congresje of een borreltje, gezellig! John, een super harde werker, ik bewonder je om jouw doorzettingsvermogen en gedrevenheid. Een dag niet geknald.. Myrthe, wat hebben wij een hoop meegemaakt. NVVC congressen, Chicago, Barcelona, vrijmibo's, fietstochtjes, Rome, veel onvergetelijke events, en ook minder leuke dingen. Ik kijk met veel plezier terug op een fijne tijd. Ik vind het super knap dat je je hart bent gevolgd en wens je heel veel succes bij de radiologie. Dat er af en toe nog maar in de thee gelengeld mag worden ;) Allard, het moment dat je mevrouw van Hagen met 'u' aansprak staat me nog helder voor de geest. Je bleek geen groen studentje toen je tijdens je wetenschapsstage op de kamer kwam en wij al gauw doorhadden dat onze sportieve prestaties weinig voorstelden vergeleken met die van jou. Dank voor het onverwachte 'hazen' op dat pleuris eind lopen. Super veel succes in de komende drukke maar ongetwijfeld mooie jaren die je voor de boeg hebt. Vivan, we hadden elkaar nog niet eens ontmoet toen we, nog voor je eerste werkdag, al samen met Allard op de racefiets zaten op de Utrechtse heuvelrug.. Het was een voorbode van een paar super gezellige jaren. Hard werken is je middle name, maar er is altijd tijd om een biertje te todelen of een dansje te battelen, van Barcelona tot Davos, van de jkd tot Rome! Dank ook voor jouw luisterend oor. Ik weet zeker dat jij een supermooie carriere tegemoet gaat!

En natuurlijk de nieuwe Ba308 lichting: Roderick, Lidia en Lucia. Als ik de laatste maanden nog terug kwam op Ba308 voelde het als thuiskomen, dus dat is een goed teken! Ik wens jullie veel plezier en succes met jullie trajecten. Lucia, veel succes met het voortzetten van de ROPAC, ik heb er alle vertrouwen in dat het bij jou in goede handen is.

Graag wil ik alle vrienden en vriendinnen bedanken die hun interesse hebben getoond in mijn onderzoek. In het bijzonder Willemien, Renske, Irene en Sara: we zien elkaar niet zo vaak meer, maar het is fijn om elkaar te kunnen blijven volgen en onze medische hoogte- en dieptepunten met elkaar te kunnen delen! Floor, Lotte, Esther en Frederieke: dank voor jullie fijne vriendschap! Inge, dank voor jouw bijdrage aan de omslag, jouw creativiteit is van een uniek niveau! Lieve Heleen, je hebt geen idee van jouw onbewuste bijdrage aan dit boekje..

Mijn paranimfen, Irene en Carolien: wat ben ik blij dat jullie naast me zullen staan! Ik bewonder jullie allebei om jullie doorzettingsvermogen, om wat jullie bereikt hebben, maar ook om hoe jullie omgaan met voor- en tegenspoed in het leven. Meer dan eens waren jullie een luisterend oor voor mij en hebben jullie me gestimuleerd vooral te doen wat mijn hart me ingeeft: ontzettend bedankt en ik hoop dat we samen nog veel moois zullen meemaken!

An Hoo, Annelies, Marieke, Martijn, Jesper en Nicki: bedankt voor het feit dat ik me zo op mijn plek kan voelen in een warm nest. Ik heb me de afgelopen jaren enorm gesteund en gestimuleerd gevoeld om dit boekje te volbrengen. Jullie zijn een inspirerend voorbeeld voor me geweest. Annelies: nu jij nog, ik weet zeker dat het een prachtig werk gaat worden!

Lieve pap en mam: dank voor alle kansen die ik gekregen heb. Wat heb ik een geluk dat wij allemaal de kans en ook de vrijheid hebben gekregen te studeren en onszelf te ontplooien. Daphne, Carmen, Florian, Lucas, Maarten en Nienke: jullie zijn allen individueel een waar voorbeeld van wat je met hard werken kunt bereiken. De familie gelegenheden worden steeds 'drukker' bezocht, en het maakt me trots dat jullie mijn familie zijn. Dank voor jullie support!

Lieve Wouter, 'alles komt goed' is uitgekomen: dit boekje ligt voor je! Alles is reeds gezegd c.q. geschreven in september vorig jaar. Bedankt voor jouw belangrijkste bijdrage: Hakuna Matata!

Financial support for this dissertation was generously provided by:

European Society of Cardiology, EURObservational Research Programme
Actelion Pharmaceuticals Nederland B.V.
Roche Diagnostics Nederland B.V.
ChipSoft B.V.
Servier Nederland Farma B.V.

Leading a 'normal' life is important to young women with heart disease, just as it is for their healthy peers, and pregnancy is one important aspect of that normal life. This thesis investigated the risk of pregnancy in women with several types of cardiac and aortic disease. Apart from some high risk groups, women with cardiac disease tolerate pregnancy reasonably well in the current era. The majority of young girls and women with heart disease can be reassured about these improving prospects, provided that we accurately search for the ones with a substantial higher risk. We are still at the beginning of elucidating this interesting research area. By shedding a light on these issues, young women with heart disease will have a chance to lead a life as close to normal.