Adult Congenital Heart Disease with Focus on Pregnancy

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Aquarel: Caren van Herwaarden: "Een wetenschapper werkt naar een uitkomst en zoekt wegen daarnaar toe, een kunstenaar volgt een weg zonder te weten waar die naar leidt. " *www.cvanherwaarden.com*

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Adult Congenital Heart Disease with Focus on Pregnancy

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Cardialysis

"Nobody has ever measured, even poets,
how much a heart can hold."

Zelda Fitzgerald

A

Chapter 1 | Introduction

INTRODUCTION

Congenital heart disease

The prevalence of Congenital Heart Disease (CHD) has been described to be 8,2 per 1000 live births in European countries.(1) Congenital heart disease is a collective term for a large number of different diagnoses with different anatomical substrate, complexity and prognosis. The most common subtypes that we encounter are: ventricular septal defect (VSD 2.6 per 1000 live births), atrial septal defect (ASD 1.6 per 1000 live births), persistent arterial duct (PDA 0.9 per 1000 live births), pulmonary stenosis (PS 0.5 per 1000 live births), tetralogy of Fallot (TOF 0.3 per 1000 live births), coarctation of the aorta (0.3 per 1000 live births), transposition of the great arteries (TGA 0.3 per 1000 live births) and aortic stenosis (0.2 per 1000 live births).(1)

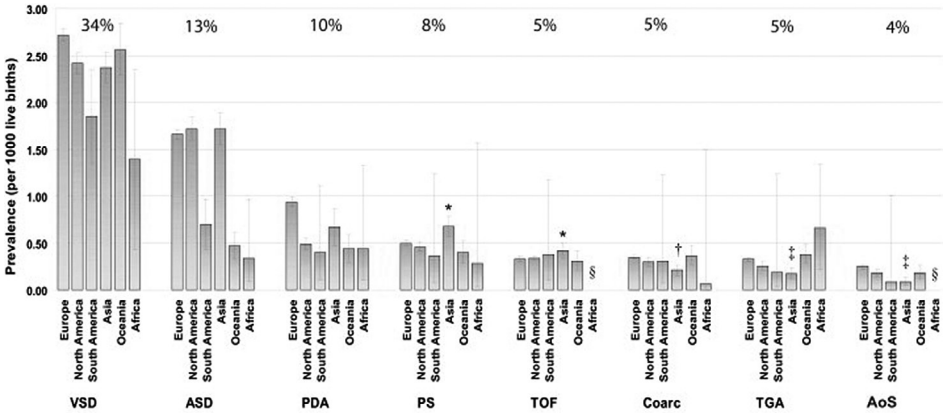


Figure 1. Birth Prevalence of CHD SubtypesReported birth prevalence of the 8 most common CHD subtypes per continent. Distribution of subtypes within total CHD is mentioned as percentages above bars. AoS = aortic stenosis; ASD = atrial septal defect; Coarc = coarctation; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Until the 1950's survival was very poor, with half of the patients that needed treatment, dying in the first decade of live. First cardio-thoracic surgery consisted of shunts from the aorta to the pulmonary artery to improve oxygenation and thereby survival of patients. The first successful corrective surgery of a patient with tetralogy of Fallot was done in 1954 in Minnesota.(2) Further advance of surgery was dependent of the development of cardiopulmonary bypass machines in the same time period. The first successful open heart procedure utilizing the heart lung machine was performed by John Gibbon on May 6, 1953 in Philadelphia.(3)

Since then survival rate has dramatically improved and nowadays 95% of all congenital heart disease patients reach adulthood.(4) Corrective surgery can be performed even in the very complex diagnoses, such as a univentricular heart. Besides improvements in cardiothoracic surgery there have also been major advances in anaesthesia, intensive care and specialist (paediatric) cardiologic care. Consequently, even more patients with CHD reach adulthood, creating a completely new and steadily growing patient population: patients with grown-up congenital heart disease (GUCH).(5)

First results of corrective surgery were very promising, with high survival rates and low complication rates in the first decade of life. Surgeons and cardiologists felt early optimism, but late complications became apparent in the second and third decade of life. Late complications include ventricular dysfunction, need for re-intervention, arrhythmias, heart failure and sudden death.(4) Surgical approaches have therefore been modified over the years to try and decrease these late complications. For instance in patients with transposition of the great arteries first an atrial switch operation was performed (Mustard or Senning procedure), which was later changed to an arterial switch procedure.(6) In the first cohorts of patients operations were performed at a later age, for instance patients with tetralogy of Fallot were originally operated at the age of 4-10 years. Nowadays operations are performed at the age of 4 month and even some centres have tried and operated them earlier.(7)

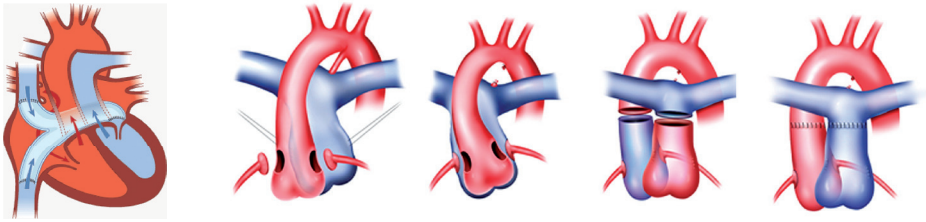


Figure 2. A Mustard operation **B** Arterial switch operation

Patients care in adult congenital heart disease

The type of care needed changes with patients growing up. Parents of the patients started to have questions related to participation in school and physical exercise, on work and sports. Determining safe levels of physical activity for children and adolescents with congenital heart disease is challenging. In the beginning both parents and doctors were very careful and restrictive. Evidence for making recommendations was limited and based on expert opinion and estimated risks of sudden cardiac death with activity. Nowadays, most jobs are

considered to be safe for most patients. Participation in sports and regular physical exercise have well documented beneficial effects on fitness, psychological well-being, confidence and social interaction as well as on the later risk of acquired cardiac disease. Counselling patients with question concerning sports include an appreciation of the type of energy expenditure involved in different sports and teaching of a method to enable the patient to limit his or her activities. The European guidelines advice to perform social exercise to a level of comfort, but not to attempt competitive sports in most situations.(8) Yet, still considerations are made per patient individually.(9)

The way patients evaluate their health can be a major determining feature for their well being. Previously, poor as well as good subjective states of health have been reported in adults with congenital cardiac malformations. In a large cohort study of congenital heart disease patients were compared to healthy peers. This study showed that congenital heart disease patients felt more impaired in physical functioning. But these patients reported less problems with work or social activities as a result of emotional problems.(10)

Pregnancy in congenital heart patients

Like women without heart disease, also women with heart disease have a desire to become pregnant. Originally, many women with cardiac disease were advised not to become pregnant, since it was considered to be a too large hemodynamic burden. Some of these women became pregnant nonetheless. Hereby providing evidence and experience that it was possible and a whole new field of cardiology arose.(11,12,13)

Pregnancy is known to impose a major hemodynamic burden and the risk of developing complications is clearly increased as compared with the normal population.(14) In addition to the hemodynamic impact, pregnancy is also a hypercoagulable state with a higher thrombotic risk.(15) The combination of hormonal and hemodynamic changes during pregnancy will also affect the vascular wall with a higher risk of arterial/aortic dissection. Furthermore, it is not clear whether pregnancy causes an irreversible deterioration in cardiac function.(16) Finally, maternal cardiac disease will also influence fetal outcome (17).

Although the prevalence of heart disease is relatively low in pregnant women, it is the most important cause of maternal mortality. Acquired conditions like aortic dissection, peripartum cardiomyopathy and acute coronary syndrome cause the highest maternal mortality rates. Some of these conditions may not be diagnosed before pregnancy.(18) Most patients with congenital heart disease are already diagnosed and treated for cardiac disease at a young age offering ample opportunity for timely counselling. It is very important to counsel women at a young age, preferably before they become sexually active, to avoid women with a high risk becoming pregnant before being counselled.(19)

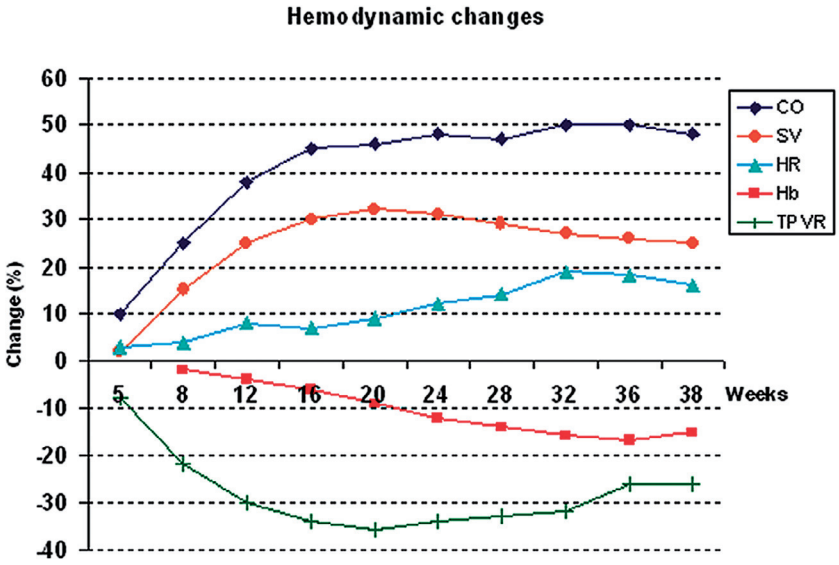
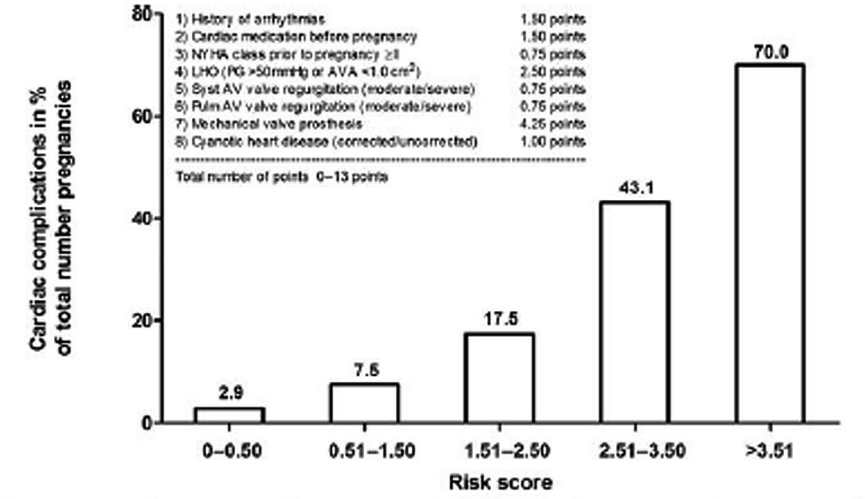


Figure 3. Hemodynamic changes: Hemodynamic changes in pregnancy. CO Cardiac output, SV stroke volume, HR heart rate, Hb blood levels haemoglobin, TPVR total peripheral vascular resistance.

Nowadays, also patients with complex heart disease, such as univentriculair heart disease, are now consulting cardiologists for advice about pregnancy. During counselling the following subjects are discussed: the use of cardiac medication, maternal risk for complications, fetal risk for adverse event and recurrence risk for congenital heart disease. In addition to the risks for mother and fetus, also life expectancy of the mother should be discussed with both future parents in case of complex congenital heart disease with a history of heart failure, severely diminished systemic ventricular function or other complications. To aid in this decision process some risk scores have been developed defining independent predictors of maternal cardiovascular complications. Siu was the first to publish a predictor model in 2001. In his landmark study New York Heart Association class, previous cardio-vascular event, left ventricular outflow obstruction and impaired systemic ventricular function were predictors for cardiovascular events.(20) Khairy showed that smoking, pulmonary valve regurgitation and impairment of the pulmonary ventricular function can be additional predicators.(17) The ZAHARA investigators showed that also a mechanical valve is a strong predictor for adverse events.(21) Recently, the adapted World Health Organisation (WHO) risk classification was developed in which the type and severity of the underlying heart disease are the main determinants.(22)

Heart failure has important implications for pregnancy, causing maternal morbidity and even mortality. It may also have negative impact on fetal outcome, increasing the incidence of fe-



Number of pregnancies at risk	828	280	126	58	10
Percentage of total population	63.6	28.1	6.1	1.4	0.8

Figure 4. The modified risk score for cardiac complications during completed (>20 weeks of gestation) pregnancies in women with congenital heart disease (expressed as % of the total number of completed pregnancies). AV, atrioventricular; AVA, aortic valve area; LHO, left heart obstruction; NYHA, New York Heart Association; PG, peak gradient; Pulm, pulmonary; Syst, systemic.

tal mortality, premature birth and low birth weight.(17) In congenital heart disease patients, data on HF during pregnancy are lacking. Labour and delivery are considered a particularly risky period due to the additional fluid overload in this period (23).

The pre-pregnancy plan should detail which medication must be discontinued, lowered in dose or continued during pregnancy. Most experience with medication use is gained in patients with either pregnancy induced hypertension or pre-eclampsia.(24) Many drugs have been proven to be fetotoxic, others showed teratogenic effects.(25) Some drugs are considered save and are commonly used in pregnancy, for other drugs there is a clear lack of information.(26)

Fetal outcome

The outcome of the child is dependant of the complexity of maternal heart disease. The most frequent complications include premature delivery, children small for gestational age and increased perinatal mortality.(17,21)

Recurrence risk for an offspring to have a congenital heart defect varies among the specific cardiac defects but the overall recurrence risk for non-mendelian inherited congenital heart defects lies between 3-15%.(27) For autosomal dominant defects, such as Marfan syndrome, the recurrence risk is 50%.(28)

The CARPREG study, the ZAHARA 1 study and the study by Khairy et al defined several risk factors for fetal complications, including NYHA class>II, left heart obstruction, cyanosis, and mechanical valve prosthesis.(17,20,21) Smoking and twin pregnancies have a negative impact on birth weight. In addition, medication use during pregnancy may have a direct adverse effect on the baby.

There have been studies on growth in preterm and small children. These studies showed that most children show catch-up growth within the first year.(29,30) Children who do not show catch-up growth are at risk for short stature and neurodevelopment disorders.(31) So far there is no study on growth of children from mothers with heart disease.

Research in congenital heart disease

There is still a lack of knowledge in adult cardiology with regards to long-term outcome after surgical correction of congenital heart disease and a lack of standards for the management of these special patients. Despite the lack of randomized trials in this field, there is growing experience and observational data. Even an expert consensus based on large clinical experience, nonrandomized studies, retrospective data and registries should be helpful to support cardiologists taking care of adult congenital heart disease and should raise the quality of patient care.

Aims and objectives of this thesis

In this thesis we wanted to investigate the outcome of congenital heart disease patients operated at young age and compare the results of the first group operated in the first surgical decade with the patients operated in the second decade of cardiac surgery. Surgical techniques, post operative care and psychological guidance of both children and parents have improved over time. By comparing two cohorts of patients operated upon in different time periods, we expected to find an improvement in cardiac and psychological outcome. We were hoping to find differences in survival, re-intervention rate, ventricular and valvular function and exercise capacity. In addition we studied quality of life and behaviour functioning. Information on the differences of the surgical cohorts could help us improve patient management. In case we would have found a reduction of adverse outcome the frequency of out patients clinic visit might have been reduced. If different long-term complications would have been present it would have help us to focus on these problems during patient contact

in the future. In addition, surgical techniques might benefit from these long-term outcome data.

Most studies in the field of pregnancy and heart disease described small series or retrospective cohorts. Only a few prospective studies were available and indeed randomised controlled trials are absent. There still is a demand for randomised trials on the use of medication. In addition there were few studies focussing on the neonatal outcome and child development. In the Registry On Pregnancy And Cardiac disease (ROPAC) we have started to collect patient data from all over the world to get insight in patient care in pregnancy and heart disease. The objectives of this large registry were to learn more about the optimal mode of delivery, the impact of medication use and to gain insight in the most prevalent complications during pregnancy and in the first six months thereafter. This information was largely missing in literature on pregnancy and heart disease. Most of our manuscripts could be seen as hypothesis forming, which might form the base for a randomised controlled trial in the future. Furthermore we collected data on the growth of the children of the patients from the ZAHARA study, known as the KIMAHA (Kinderen van Moeders met een Aangeboren HartAfwijking/children of mothers with a congenital heart disease) study. With this study we want to study growth in children of mothers with congenital heart disease. This was the first study focussing on the children. A healthy child is one of the main goals of treatment during pregnancy. With this study we studied a new approach to the long terms effects of heart disease in pregnancy.

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B

Part I Adult congenital heart disease

Chapter 2

Long-term outcome and quality of life after arterial switch operation. A prospective study with a historical comparison.

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Aim

To describe the long-term cardiological and psychological results of our first surgical cohort of arterial switch operation (ASO) patients and compare the results with our earlier series of Mustard patients.

Methods

Twenty-four survivors of ASO operated in our centre (1985-1990) were evaluated by ECG, echocardiography, MRI, exercise-testing, 24-hour Holter-monitoring and health-related quality of life questionnaire. The result were compared with 58 adult Mustard patients who were evaluated in 2001 using the same study-protocol.

Results

ASO was performed at a median age of 13 days and Mustard operation at 2 years. Median follow-up was 22 (range 20-25) and 25 years (22-29), respectively. After ASO survival was better ($p=0.04$). The event-free survival after 22 years was 77% after ASO versus 44% after Mustard ($p=0.03$). Good systemic ventricular function was present in 93% after ASO versus 6% after Mustard ($p<0.01$). Exercise capacity in ASO was 85% of predicted, compared to 72% in Mustard patients ($p=0.01$). Aortic regurgitation was found in 21% of in ASO versus 16% in Mustard patients. Arterial switch patients versus Mustard patients reported significantly better quality of life and less somatic complaints.

Conclusion

The progression made in surgical treatment for transposition of the great arteries from Mustard to ASO has had a positive impact on survival, cardiac function, exercise capacity, and also self-reported quality of life and somatic complaints. Longer follow-up is warranted to monitor aortic regurgitation.

Keywords

Arterial switch, Mustard operation, long-term outcome, survival, quality of life

INTRODUCTION

Complete transposition of the great arteries (TGA) is one of the most common cyanotic congenital heart diseases.(1) Until three decades ago, atrial repair (Mustard or Senning) was the only surgical option. Long-term follow-up showed considerable ongoing mortality and morbidity mainly caused by progressive right systemic ventricular failure.(2)

Nowadays, the arterial switch operation (ASO),has become the established surgical correction.(3) Operative survival after arterial switch in the current era is good, with a operative mortality rate of 5% to 6%.(4-5) Mid- and long-term follow-up studies are also encouraging, however the oldest survivors of ASO at most centres are young adults.(6-10) The aim of this study was to describe the long-term cardiac outcome and quality of life in our first surgical cohort of arterial switch patients and compare the results with the outcome data of our series of Mustard patients.

METHODS

Study protocol

Simple TGA was defined as TGA without concomitant abnormalities or minor concomitant abnormalities (atrial septal defect, ventricular septal defect not requiring surgical patch closure or a persisting arterial duct); others were defined as complex TGA. Major events were defined as death, cardiac transplantation, re-intervention (surgery or catheter intervention), pacemaker implantation or hospital admission for arrhythmia, endocarditis or heart failure.

The protocol included physical examination, 12-lead electrocardiography (ECG), 24-hour Holter monitoring, echocardiography, cardiac Magnetic Resonance Imaging (MRI), bicycle exercise test, N-terminal pro-Brain Natriuretic Peptide measurements (NT pro BNP) and quality of life assessment (short form 36). The results of the ASO group were compared with patients after Mustard procedure operated between 1973 and 1980, who were studied in 2001 after a comparable follow-up at a comparable age, using the same protocol except for MRI and NT pro BNP measurements.(2,11)

Echocardiography: Transthoracic two-dimensional echocardiography studies were performed using the iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands). Systemic ventricular systolic function was visually graded as normal, moderate or poor. Left ventricular end-systolic dimension and left ventricular end-diastolic dimension were measured using the standard parasternal long axis. Diastolic function was obtained by measurements of transmitral inflow pattern. Valvular stenosis and regurgitation severity were graded according to current guidelines.(12-13) Body surface area (BSA) was derived with the DuBois formula and aortic diameter was corrected for BSA.(14) Aortic root dilatation at the sinuses of Valsalva was defined as an aortic root diameter ratio above the upper limit of 1,3 of predicted.

MRI: MRI was performed using a Signa 1.5 Tesla MR imaging system (General Electric, Milwaukee, WI, USA). The CMR studies were analyzed on a Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA), equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole.(15)

Exercise capacity: Maximal exercise capacity was obtained using bicycle ergometry. The exercise capacity measured was indexed for age, sex and body height, standardized for the Dutch population.

NT-pro Brain Natriuretic Peptide: Peripheral venous blood was collected from each patient and analysed using the electrochemiluminescence immunoassay kit (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany). NT-proBNP <15 pmol/L was defined as normal.

Short form 36 (SF 36) Health-related quality of life was assessed using the Dutch SF 36.(16) Higher scores indicate a better quality of life. Effect sizes were expressed in terms of Cohen's d, (small effects: d<0.3., medium effects: 0.3<d<0.8, large effects:d>0.08). The scores of the arterial switch patients were compared to the Mustard patients and also to an age- and gender-specific Dutch population sample.(17)

Behavioural/Emotional Problems were assessed using a screening list for psychopathology: the Adult Self-Report (ASR) (Achenbach & Rescorla, 2003) and its previous version (Young Adult Self-Report (YASR) (Achenbach, 1997), respectively. Age-equivalent Dutch population data on the ASR (n=938) was derived from Vanheusden et al.(18) For historical comparisons, 88 common items of the ASR and YASR were used.

Patients

Between 1985 and 1990, 75 consecutive patients underwent successfully ASO in our institute. Forty-five patients were referred from other countries in Europe and could not be traced for adequate follow-up. Baseline characteristics and survival data of all other 30 patients were obtained by chart review and by contacting the civil registry. Twenty-nine (Dutch) survivors were invited to participate in this follow-up study in 2009. Institutional board review was obtained (NL26121.078.08) and participating patients provided informed consent. Five patients refused to participate, thus this cohort comprised 24 patients.

Control groups

In 2001 an extensive study of Mustard patients was performed with survival data available in all 91 patients and 58 patients participated in the in-hospital protocol. These 58 patients serve as the Mustard control group. The results of these Mustard patients were described previously in detail and are presented in the tables.(2)

The scores of the SF 36 and the Adult Self-Report were compared to the Mustard patients and also to Dutch population sample. Additionally, for comparison of echocardiographic measurements we studied 23 gender- and age matched healthy controls.

Statistical methods

Continuous data are presented as mean with standard deviation and were compared with the Student-T or Mann-Whitney test. Discrete variables are presented in absolute numbers and percentages and were analysed using the chi-square or Fischer's exact test and Mann-Whitney test for ranked discrete data. Cumulative survival rates were calculated with the Kaplan-Meier method and the Tarone-Ware test was used to compare the ASO and Mustard patients. The level of significance was $p < 0.05$ (2-sided). The data were analyzed with the SPSS version 16.0 software (SPSS Inc, Somers, NY).

RESULTS

Baseline characteristics of the 30 patients after ASO are shown in table 1. Thirteen patients had complex TGA (43%), of which 2 patients with hypoplastic right ventricle (1 with hypoplastic aorta). Lecompte's manoeuvre was applied in 70% of cases; the main reason not to apply the Lecompte's manoeuvre was side to side position of the aorta and pulmonary artery. The coronary pattern was left anterior descending artery and circumflex from the left coronary sinus and right coronary artery from the right coronary sinus in 50% of the patients; all other had various other coronary patterns.

Table 1. Baseline characteristics of arterial switch population and Mustard population.
All data are number of patients (%) IVS intact ventricular septum VSD ventricular septal defect DORV double outlet right ventricle.

	ASO 30	Mustard 58	p value
Male	17 (57)	40 (69)	0.26
Age at operation	13 days	2 years	<0.01
Rashkind septostomy	12 (40)	41 (71)	<0.01
Simple TGA	17 (57)	22 (38)	0.1
With IVS	16 (53)		
With VSD without patch	1 (4)		
Complex TGA	13 (43)	36 (62)	
TGA with VSD with patch	7 (23)		
TGA with DORV and/or aortic pathology	6 (20)		

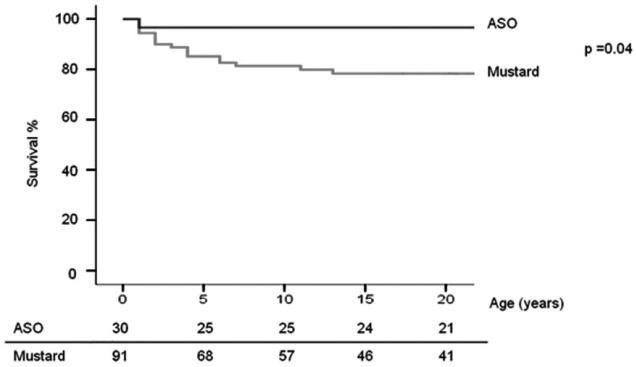


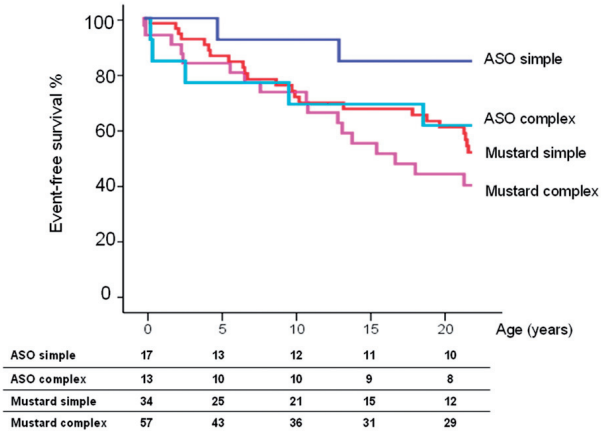
Figure 1. Cumulative survival after transposition of the great arteries. ASO: patients with Arterial Switch Operation studied in 2009, Mustard: Patients after Mustard operation, studied in 2001.

Survival

One patient with hypoplastic right ventricle and hypoplastic aorta died at 18 months of age, no specific cause could be identified by autopsy. Overall cumulative survival rate of the arterial switch patients was 97% at 25 years after operation while in Mustard patients this was 77% (Figure 1).

Re-interventions

Twelve re-interventions were performed in 6 arterial switch patients, mainly for pulmonary artery stenosis: reoperation (n=7), balloon dilatation (n=3) and 1 reoperation for residual ASD and VSD. One patient with complex TGA suffered from ventricular tachycardia (VT) at age 19, treated by ablation and Implantable Cardioverter Defibrillator (ICD) implantation. No interventions for neo-aortic regurgitation or coronary obstruction or hospital admission for heart failure were necessary. At 22 years follow-up the overall event-free survival was 77% in arterial switch patients versus 44% in Mustard patients p=0.03.(Figure 2) Event-free survival was 88% for simple TGA and 62% for complex TGA for patients who underwent ASO (p=0.15). In complex TGA patients there were 0.036 events per patient year, this was 0.006 events per patient year in simple TGA patients.



ASO simple	17	13	12	11	10
ASO complex	13	10	10	9	8
Mustard simple	34	25	21	15	12
Mustard complex	57	43	36	31	29

Figure 2. Event free survival after transposition of the great arteries. Events were defined as re-intervention, heart failure or arrhythmias.

Follow-up study

Twenty-four arterial switch patients participated in our in-hospital prospective follow-up study with a median age at follow-up of 22 years (IQR 20-24), of which 63% was male.

(24 hours) ECG monitoring

All 24 patients were in sinus rhythm at follow-up. One patient needed anti-arrhythmic medication and received an ICD. Voltage criteria for left ventricular hypertrophy or dilatation were found in 47%. Nineteen patients had Holter-monitoring. In 3 patients, non-sustained VT's were documented, of which 2 had VTs shorter than 10 beats. None of the arterial switch patients had supraventricular arrhythmias.

Echocardiographic findings

Echocardiography was performed in 23 of the 24 arterial switch patients. Mild or moderate neo-aortic regurgitation was present in 17% and 4%, respectively while no severe neo-aortic regurgitation was found. Mild neo-aortic stenosis was observed in one patient. Increased peak flow velocity (>2.0 m/s) was found across the pulmonary artery in 43% of the patients, the highest velocity found was 3,8 m/s. By detailed inspection of the images, it was concluded that anatomical deformities were responsible for 50% of obstructions; while surgery related obstruction (suture line or Lecompte's manoeuvre) was responsible for the other 50%. Mild pulmonary regurgitation was found in 42%, severe pulmonary regurgitation in 4%.

Systemic ventricular function was judged to be normal in 93% and no diastolic dysfunction was found. Mean fractional shorting was 37%, which was comparable with the healthy controls (Table 2).

Table 2. Echocardiography findings in arterial switch patients.
Echocardiography: All data are mean ± standard deviation. ASO patients with Arterial Switch Operation, LVESD Left ventricular end-systolic dimension, LVEDD left ventricle end-diastolic dimension, FS fractional shortening, IVSED end-diastolic thickness of the interventricular septum, LVPWED end-diastolic thickness of the posterior wall, E early component of the transmitral inflow pattern, A late component of the transmitral inflow pattern, DET deceleration time of E.

Echocardiogram	ASO 23	Controls 23	p-value
LVEDD mm	52 ± 6	49 ± 4	0.09
LVESD mm	32 ± 5	29 ± 3	0.06
FS %	37 ± 7	38 ± 5	0.35
IVS ED mm	9 ± 1	9 ± 1	0.93
PW ED mm	8 ± 1	8 ± 1	0.48
Aortic sinus mm	33 ± 6	26 ± 3	< 0.01
Aortic sinus ratio	1.1 ± 0.15	0.9 ± 0.08	< 0.01
E m/s	0.9 ± 0.3	0.8 ± 0.2	0.06
A m/s	0.4 ± 0.1	0.4 ± 0.1	0.21
E/A ratio	2.3 ± 0.9	2.2 ± 0.5	0.65
DET msec	193 ± 51	202 ± 30	0.47

Physical capacity

Results are presented in table 3. Two patients needed medication; the patient with the ICD received beta-blockers, another patient was treated with ACE-inhibitors because of moderate LV dysfunction.

Twenty patients underwent exercise testing. No arrhythmias occurred. One patient had a rate depended right bundle branch block during exercise and 3 patients (20%) showed ST alterations (downslope ST depression > 2 mm), but with additional testing no coronary artery obstruction was found (2 MIBI scans and CT angiogram).

Table 3. Overview outcome after surgery for transposition of the great arteries.
ASO = arterial switch operation, Mustard = Mustard correction.

	ASO (2009)	Mustard (2001)	p- value
NYHA class I	100%	24%	< 0.01
Sinus rhythm	100%	63%	< 0.01
Sinus node disease	0%	43%	< 0.01
Normal systemic ventricular function	93%	4%	< 0.01
Maximum heart rate reached during exercise testing	89%	84%	0.12
Exercise tolerance % of expected	88%	72%	0.03
Exercise capacity below 85 % of predicted value	53%	76%	0.05

MRI

Magnetic resonance imaging was performed in 13 arterial switch patients (54%). Reasons for not participating in the MRI were: claustrophobia(5), refused(5) and ICD(1). The mean ejection fraction measured with MRI was 66% for the left ventricle and 62% for the right ventricle. One patient had a left ventricle ejection fraction of 41%. The neo-aortic root had a mean diameter of 39 mm (range 30 to 49 mm), 44% of the patients had a neo-aortic root diameter of more than 40 mm.

NT-proBNP

NT-proBNP was measured in 18 arterial switch patients. Mean NT-proBNP was 10,1 pmol/L ± 12,2. Three patients had an elevated NT-proBNP level, of which 2 patients (21.4 and 23.3 pmol/L) had normal LV function. Their exercise capacity was 82 and 84% of predicted. The patient with the ICD had a moderate LV dysfunction and a NT-proBNP level of 52, 2 pmol/L.

Quality of life

Eighteen patients completed the quality of life questionnaires. Outcomes are presented in figure 3. Arterial switch patients scored better than the normal Dutch population on the scales physical functioning, vitality and role limitations due to emotional problems ($p < 0.01$). Compared to Mustard patients, arterial switch patients scored better in the sub domains physical functioning ($p<0.01$), general health perceptions ($p=0.04$) and vitality ($p=0.04$). All differences showed medium effect size.

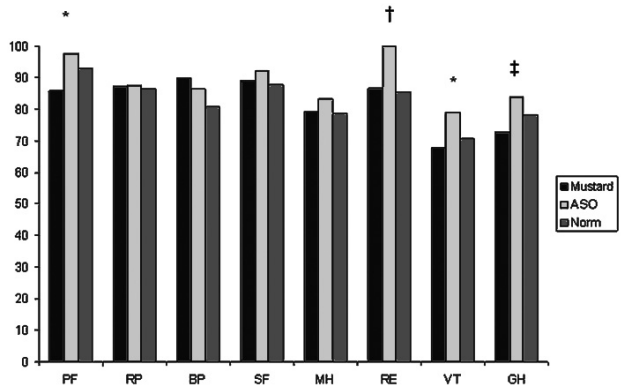


Figure 3. Quality of life: SF 36
PF Physical Functioning, RP role limitations due to physical health problems, BP bodily pain, SF social functioning, MH general mental health, RE role limitations due to emotional problems, VT vitality, GH general health perceptions, ASO: patients with Arterial Switch Operation, Mustard: Patients after Mustard operation, Norm: normal Dutch population matched for sex and age (20) * significant difference between ASO versus Mustard and versus Norm † significant difference between ASO versus Norm ‡ significant difference between ASO versus Mustard.

Table 4. Differences in mean behavioural/emotional problems scale scores between ASO patients and Mustard patients.
[a] Data on behavioural/emotional problems was available in 17 arterial switch patients and 55 Mustard patients
ASR = Adult Self-Report

	Problems Scores		
ASR scales	Switch (n=17)[a] M (SD)	Mustard (n=55)[a] M (SD)	p-value
Anxious/Depressed	4.1 (4.3)	5.9 (5.2)	0.19
Withdrawn	1.9 (2.0)	3.1 (2.6)	0.90
Somatic Complaints	2.3 (3.3)	3.6 (3.1)	0.04
Thought Problems	1.8 (2.4)	2.0 (2.1)	0.45
Attention Problems	3.4 (2.1)	3.5 (2.4)	0.98
Aggressive Behavior	1.9 (1.8)	2.8 (2.3)	0.15
Rule-Breaking Behavior	2.4 (1.8)	2.8 (2.3)	0.95
Intrusive	2.0 (2.2)	2.3 (2.0)	0.48
Internalizing Problems	8.4 (8.8)	12.6 (9.1)	0.05
Externalizing Problems	6.4 (4.0)	7.8 (5.3)	0.47

Behavioural/Emotional Problems

Data was available on 17 arterial switch patients and is presented in table 4. Overall, behavioural/emotional functioning was good. There was no significant difference between the arterial switch patients and the normative data from the Dutch general population on any of the ASR scales (data not shown). Arterial switch patients had significantly less somatic complaints than the Mustard patients (p=0.04).

DISCUSSION

This study describes the outcome of a small cohort of arterial switch patients. However, this group represent a good sample of the whole surgical cohort and was studied extensively, including MRI and psychological outcome. This study offers the possibility of a historical comparison with outcome after Mustard operation, because a large cohort of Mustard patients was studied with the same follow-up protocol after a comparable period of time in our institution before.

Twenty-two years after arterial switch operation excellent survival, low morbidity and favourable quality of life was found and outcomes are significantly better than after Mustard correction. Lessons from the past taught us that one should be careful with early optimism: where first results of the Mustard operation were reported to be good, major problems became apparent in adult life, of which most significant the failing capacity of the right ventricle

to sustain the systemic circulation.(2,19) Until now few studies have been published on the outcome after ASO in adulthood. Until now results are favourable.(5-8) Therefore, optimism about the outcome after arterial switch operations seems justified.

Our results show that both survival and event-free survival of TGA patients has dramatically improved with the introduction of ASO, as was expected and hoped for. In this study we compared the outcome of the two surgical techniques used in patients with TGA, as both cohorts are based on the planned follow-up of consecutive operated patients and not random patients seen at an outpatient clinic. Furthermore, both groups are studied in a similar designed long-term follow-up study using the same instruments for a medical and psychological assessment.

In our cohort of arterial switch patients there was a relatively high percentage of complex TGA. Survival was clearly better than after the Mustard and comparable with other studies after ASO with a lower percentage of complex TGA.(4, 5, 6) However, in complex arterial switch patients the event rate per patient year was considerably higher than in the simple patients. Especially pulmonary artery stenosis was common in these patients.

Clinical condition and ventricular function

Arterial switch patients were in good clinical condition 22 years after surgery, whereas only 24% of the Mustard patients were in NYHA class I. The inferior condition of the Mustard patients may be caused by the impaired systemic (right) ventricular function.

At long-term follow-up 93% of arterial switch patients in our study had normal systemic (left) ventricular function. The feared deterioration of the ventricular function late after arterial switch operation, related to coronary artery abnormalities, was not observed. However, in one patient a diminished left ventricular function was found (ejection fraction 41% using MRI) without a good explanation. Also diastolic function parameters were found to be normal in this small sample of patients.

Surprisingly, we found a reduced exercise capacity in arterial switch patients compared to the normal Dutch population (although better than Mustard patients).(19) This reduced exercise capacity was not exclusively found in patients with diminished left ventricular function or significant right ventricular outflow tract obstruction. The reduced levels of physical activity may be caused by overprotection of parents during childhood. In addition lack of training or self esteem have been described in literature, as cause for this diminished exercise capacity.(20) Ischemia was also suggested and in our study; three patients showed ST segment changes, however additional evaluation excluded coronary pathology. Giardini et al described reduced exercise capacity in young patients after ASO, but none showed ischemic electrocardiographic during exercise.(21) Finally, chronotrope incompetence may play a role.(22)

The development of arrhythmias was rare and sinus rhythm with normal conduction is maintained long-term after ASO, while after Mustard procedure there is a high incidence of

supraventricular arrhythmias and sinus node dysfunction. Only one arterial switch patient with complex TGA and moderate LV function underwent ICD implantation for ventricular tachycardia, he also had a mildly elevated NT-pro BNP. This was also seen in two other patients, who did not have a diminished LV function. More data on biomarkers as a predictor of adverse outcome is warranted.(23)

Valvular abnormalities

From other studies we know that neo-aortic regurgitation may become a problem later in life.(24) Our results confirm the presence of mild to moderate neo-aortic regurgitation in 21% of the patients, none of them has yet required re-intervention and non showed severe regurgitation.

Some degree of neo-aortic root dilatation is almost universal and several studies have shown serial increases in neo-aortic root diameter.(24) We found in 44% of the ASO patients a neo-aortic root of more than 40 mm. Early data suggest that neo-aortic dilatation may stabilize in adulthood, but follow-up is too short to be certain.

The main indication for re-intervention in ASO patients was pulmonary artery stenosis, as was the case in the study by Oda et al.(7) In our study nearly half of the arterial switch patients had a residual gradient across the pulmonary artery or pulmonary valve and some may need additional re-interventions in the future, warranting further close monitoring.

Health-related quality of life and behavioural/emotional problems

Self-reported physical functioning and vitality was better in arterial switch patients compared to normative data.(17) This is remarkable, since exercise capacity was reduced. Overestimation of physical functioning compared to actual exercise test results, has also been found by Gratz et al. (25). Noteworthy, behavioural/emotional functioning was as good as in the normal population.(18)

Compared to the Mustard group (26), arterial switch patients scored more favourable on physical functioning, general health and vitality, which confirms results of Muller et al.(8) In addition they had less self-reported somatic complaints.(27) These findings are of utmost importance since subjective wellbeing influences costs of medical and also other care.

Study limitations

As with many studies on congenital heart disease patient numbers are small in this study. Furthermore, we realize that a direct comparison between the results of Mustard and arterial switch patients in the same era would be the best possible study design. However, this is not feasible as nowadays all our TGA patients undergo an arterial switch operation. The study design, using the same tests after a comparable follow-up period and at the same age, seems the second best option. The two groups differ in several aspects: not only have surgical treatment feasibilities and age at repair changed, but anaesthetic techniques and neonatal

care have improved. Both groups were the first cohort of patients using that specific surgery, therefore results of more recent patients may be slightly different. Although patients were lost of follow-up due to foreign citizenship, the cohort described represents all arterial switch patients still under regular follow-up.

CONCLUSION

Long-term follow-up after arterial switch operation shows excellent survival, low morbidity and favourable quality of life and is clearly better when compared to the outcome after Mustard operation. Good cardiac function is the norm after ASO. However, results indicated lower than expected exercise capacity, the ongoing risk of developing important neo-aortic root dilatation with neo-aortic regurgitation. Re-interventions for pulmonary artery problems did occur. Careful systematic clinical follow-up is warranted to monitor these patients further.

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Chapter 3

Long-term outcome of surgery for tetralogy of Fallot: comparison between two historical cohorts.

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ABSTRACT

Aim

To describe differences in cardiological and psychological outcome after surgical correction of Tetralogy of Fallot (ToF) over time.

Methods

Survivors of ToF surgery performed in our centre: between 1980-1990 (ToF80) and between 1969-1980 (ToF70) were followed and evaluated 20-30 years after the initial correction in hospital. The study included ECG, echocardiography, exercise-testing, 24-hour Holter-monitoring and health-related quality of life questionnaire.

Results

Survival at 25 years after successful surgery was 93% for ToF70 and 98% for ToF80 (p=0.22). Pulmonary valve replacement for pulmonary regurgitation was performed more often in the ToF80 patients (p=0.030). Right ventricular dysfunction was found in 7.2% ToF70 and in 15.6% ToF80 (p=0.11),and left ventricular end-diastolic diameters were 49 mm and 45 mm (p = 0.008) respectively. Mean aortic sinus diameter was 37mm in ToF70 and 33mm in ToF80 (p=0.001). Aortic regurgitation was present in 21.1% and 7.5%, respectively (p<0.001). There was no difference in exercise capacity and quality of life between the ToF70 and ToF80 patients. ToF patients of both cohorts scored lower compared to healthy controls with respect to general health, but higher on social functioning and experienced less behavioural problems such as anxiety and aggression.

Conclusion

Compared to patients operated on in the 70's, patients from the 80's showed less aortic root dilatation, aortic regurgitation and a smaller end diastolic left ventriclular diameter, indicating an improvement of the left side of the heart. However, surprisingly pulmonary valve replacement was needed more often in patients who were operated in the 80's.

Keywords

Tetralogy of Fallot, survival, long-term outcome, quality of life, left and right ventricular dysfunction.

ABBREVIATIONS

Body surface area	(BSA)
Electrocardiography	(ECG)
Left ventricle	(LV)
Linearised Occurrence Rates	(LOR)
Pulmonary valve replacement	(PVR)
Pulmonary regurgitation	(PR)
Right ventricle	(RV)
Right Ventricular Outflow Tract	(RVOT)
Short Form 36	(SF 36)
Tetralogy of Fallot	(ToF)

INTRODUCTION

Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart disease. (1) Late outcomes after ToF repair are reported good with regard to survival. However, a considerable proportion of patients develop late complications or have residual lesions.(2,3,4) The surgical technique for right ventricular outflow tract (RVOT) reconstruction frequently distorts the pulmonary valve causing pulmonary regurgitation (PR) or residual stenosis. Late pulmonary valve replacement is often needed.(2,4,5) In addition concern exists regarding the fate of the left ventricle dysfunction, aortic valve regurgitation, aortic dilatation and arrhythmias.(6,7)

A detailed description of the time-related instantaneous hazard or risk of death, re-operation and pulmonary valve replacement (PVR), is required to assess the long-term outcome into adulthood for children operated for ToF. These late hazards are probably multifactorial. There has been consistent progress in treatment strategy, both with regard to patient selection and surgical techniques. In the 1970's patients often first had a palliative shunt, followed by corrective surgery with a right ventricular (RV) incision at around 4 years of age. In the 1980's surgeons attempted to avoid RV incision and shunts, the latter by operating earlier. The use of the transannular patch became more common in the 80s. In the 90's surgeons tried to avoid transannular patches, to decrease the reoperation rate for pulmonary valve dysfunction. (8) The impact of these developments on late outcome has not been studied.

Age at operation and new techniques may also influence psychological outcome. In a study by Knowles et al. patients with ToF reported lower functional health status then their healthy siblings, but quality of life and life satisfaction were comparable.(9)

We analysed clinical and psychological outcome of patients who underwent surgical correction for ToF in our institute between 1980 and 1990, and compared the results with previously reported outcome of patients who underwent surgical correction for tetralogy

of Fallot in our institute between 1969 and 1980. Assessment was done in a similar manner, enabling comparison of the two decades.

METHODS

Patients

The study population includes patients with ToF without major concomittant abnormalities such as pulmonary atresia with aorto-pulmonary collaterals or absent pulmonary valve.

The long term outcome of our first cohort of patients operated for ToF between 1969-1980 has been described extensively, previously.(2) Survival data were available in all of the 140 of the operated patients and in 2001 90 patients (64%) participated in the in-hospital protocol , as define below. Baseline characteristics of the patients who participated did not differ from the patients who did not participate. The data of these 90 patients studied and described in 2001, will be referred to as the ToF70 group. (2)

Between 1980 and 1990, 105 consecutive patients underwent surgical correction for ToF in our institute. Survival status was obtained in all patients. All survivors (n=95) were invited to participate in our study in 2010 using the same study protocol as used in ToF70. In total 82 patient (78%) participated. This group will be referred to as the ToF80 group. Institutional board approval was obtained (NL26121.078.08) and participating patients provided written informed consent.

Quality of life and behavioural problems assessment scores (the Short form 36 (SF 36) and the Adult Self-Report) of the ToF80 were not only compared with the ToF70 group, but also with the normal Dutch population adjusted for age and sex.(10)

Study protocol

The study protocol in both ToF70 and ToF80 included physical examination, 12-lead electrocardiography (ECG), 24-hour Holter monitoring, echocardiography, bicycle exercise test, and quality of life assessment (SF 36 and Adult Self-report).

Events: Events were defined as any cardiac intervention (either surgical or catheter intervention), arrhythmia requiring treatment or heart failure.

Echocardiography: Transthoracic two-dimensional echocardiography studies were performed using the iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands). Chamber quantification, valvular function, systolic and diastolic function were assessed according to the current recommendations. (11,12i) Left and right ventricular function were assessed by eyeballing as this method was used in 2001 by the same echo-technician as at that time. Body surface area was defined using the DuBois formula, aortic diameter was corrected for body surface area. Aortic root dilatation was defined as the diameter at the

sinuses of Valsalva ratio above 1.3 of the predicted diameter by the formula described by Roman. (13ROMAN)

Exercise capacity: Maximal exercise capacity was obtained using bicycle ergometry. The exercise capacity measured in Watts and was indexed for age, sex and body height, standardized for the Dutch population.

Quality of life was assessed by the Dutch SF 36, for which good reliability and validity have been proven.(14) Higher scores indicate a better quality of life. Mean scale scores of patients were compared between the cohorts ToF70 and ToF80.

Behavioural/Emotional Problems were assessed using a screening questionnaire for psychopathology, using the Adult Self-Report (ASR) for the ToF80 patients and its previous, parallel version the Young Adult Self-Report (YASR) for the ToF70 patients (Achenbach, 1997, 2003). Age-equivalent Dutch normative data on the ASR (n=1211) was derived from Vanheusden et al.(15) For the historical comparison between the ToF80 and T0F70 patients, only the 88 identical and overlapping items of the ASR and YASR were used.

Statistical methods

Continuous data were presented as mean with standard deviation and were compared with the Student-T or Mann-Whitney test. Discrete variables were presented in absolute numbers and percentages and were analysed using the chi-square or Fischer's exact test. Cumulative survival rates were calculated with the Kaplan-Meier method and the Tarone-Ware test was used to compare the two cohorts of patients. In a Cox-regression model (multivariable stepwise upward method) we evaluated era of operation (ToF70 or ToF80), right ventricular incision, age at operation < 2 years, transannular patch and prior palliative shunt as potential predictors for pulmonary valve replacement for pulmonary regurgitation. The level of significance was $p < 0.05$ (2-sided). The data were analyzed with the SPSS version 16.0 software (SPSS Inc, Somers, NY).

RESULTS

Baseline characteristics

Baseline characteristics and surgical data are shown in Table 1. Age at operation was lower in ToF80 compared to ToF70 ($p<0.001$). Prior shunt and RV incision were more prevalent in ToF70 ($p<0.001$). A transannular patch was more often used in ToF80 ($p= 0.001$).

Survival

In the ToF70 cohort the 30 days mortality was 14%. Late mortality in this group concerned 6 patients (TOF70 mortality linearised occurrence rates (LOR) 0.0024%/patient year).(2) The early (30 days) mortality was 8% in the ToF80 cohort ($p=0.098$). At 6 months of age 1 patient

Table 1. Characteristics from surgical correction of Tetralogy of Fallot.

	ToF70	ToF80	p value
Number of patients	140	106	
Male (n (%))	85 (61%)	64 (61%)	1.00
Prior palliative shunt (n (%))	49 (35%)	13 (12.4%)	<0.001
Blalock	20 (14%)	5 (4.8%)	0.015
Waterston	27 (19%)	8 (7.6)	0.010
Age at operation (median, IQR)	4.5 (0-6.5)	1.7(0-5.1)	<0.001
Transannular patch (n (%))	95 (68%)	85 (81%)	0.022
Right ventriculotomy (n (%))	138 (98.6%)	87 (83%)	<0.001
Follow up time (years, SD)	24.3 (4.7)	23.3 (2.6)	0.90

died due to ventricular tachycardia (recorded on Holter monitoring). In addition one patient died at the age of 22 due to endocarditis and liver failure after percutaneous pulmonary valve implantation for severe pulmonary regurgitation (mortality LOR 0.00098%/patient year). Late survival at 25 years after successful surgery (excluding early mortality) was 96% (95%CI 92%-100%) for ToF70 and 98% (95%CI 95%-100%) for ToF80 (p=0.24). Overall late cumulative survival after successful surgery of both cohorts is shown in Figure 1.

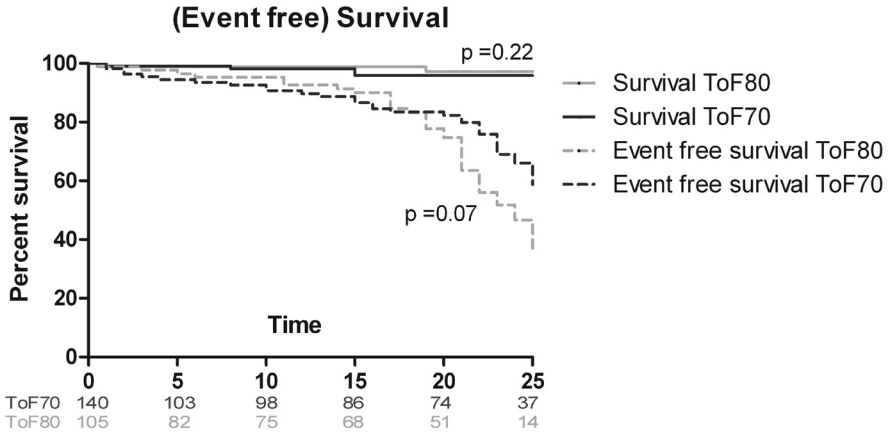

Figure 1. (Event free) Survival after successful surgery

Re-interventions

Event-free survival at 25 years after successful surgical correction was 63% (95%CI 53%-73%) for ToF70 and 52% (95%CI 41%-63%) for ToF80 (p=0.072) as shown in Figure 1. In the ToF70 the most frequently found re-intervention was homograft replacement for pulmonary regurgitation (n=22; LOR 0.010%/patient year) followed by closure of a residual VSD (n= 9;

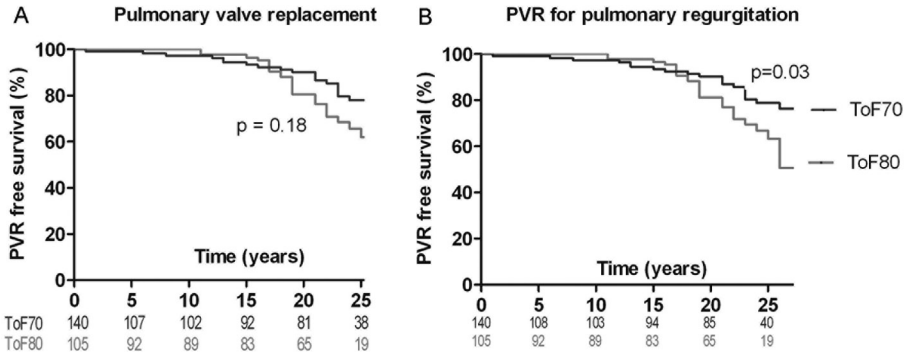

Figure 2a. Pulmonary valve replacement free survival for both pulmonary regurgitation and pulmonary stenosis

Figure 2b. Pulmonary valve replacement free survival for pulmonary regurgitation

LOR 0.0041%/patient year), relief of RVOT obstruction (n=8; LOR 0.0036%/patient year) and pacemaker implantation (n=5; LOR 0.0023%/patient year). Finally, one internal cardioverter-defibrillator was implanted.(2) In the ToF80 cohort the most frequently found complication was also homograft replacement for pulmonary regurgitation (n=29; LOR 0.0178%/patient year) followed by closure of a residual VSD (n= 8; LOR 0.0049%/patient year), relief of RVOT obstruction (n=6; LOR 0.0037%/patient year), an aortic valve replacement (n=1; LOR 0.0006%/patient year) and pacemaker implantation (n=1; LOR 0.0006%/patient year). In addition 2 aortic valve implantations were performed for severe aortic regurgitation (LOR 0.0012%/patient year). Two patients underwent a percutaneous pulmonary valve implantation in pulmonary position for severe homograft dysfunction. Pulmonary valve replacement free survival at 25 years after surgery is shown in Figure 2. In the Cox regression the use of a transannular patch was the only predictor for pulmonary valve replacement for pulmonary regurgitation (p=0.021), while era of operation (ToF70 or ToF80), right ventricular incision, age at operation < 2 years, or prior palliative shunt were not.

Clinical function state

The mean follow up duration after corrective surgery of patients was 24.3 ±4.7 years in ToF70 and 23.3 ±2.6 years in ToF80 (p=0.903). At last follow-up most patients were in NYHA class I in both groups; respectively 80% in ToF70 and 91% in ToF80 (p=0.104). More patients in ToF70 reported having had shortness of breath at some time after surgery 52% versus 10% in ToF80 (p<0,001).

(24 hours) ECG monitoring

Electrocardiography was performed in 90 ToF70 patients and 82 ToF80 patients. Mean QRS duration was 136 msec ± 33 and 136 ± 30 (p=0.97), respectively. Duration of the QRS was longer than 180 msec in 9.4% of ToF70 and 7,2% of ToF80 (p= 0.61). At follow-up 92% of

patients in ToF80 were in sinus rhythm versus 84% in ToF70 (p=0.14). Holter monitoring was performed in 70 ToF70 patients and 65 ToF80 patients. Supraventricular tachycardias were found in 2.7% of ToF70 and 14% of ToF80 (p=0.012). Non-sustained ventricular tachycardias were documented in 13% of ToF70 patients and 4.6% of ToF80 patients (p=0.12); only one of the ToF80 patients had a ventricular tachycardia longer than 10 beats.

Echocardiographic findings

Table 2 presents the echocardiographic data of the two groups. Left ventricular (LV) dysfunction was found in 10% in ToF70 and 4.9% in ToF80 (p=0.20), while RV dysfunction was found in 7% and 15.6% (p=0.12), respectively.

Table 2. Echocardiography.
All data are mean (± standard deviation) unless indicated otherwise. LVESD Left ventricular end-systolic dimension, LVEDD left ventricle end-diastolic dimension, FS fractional shortening, IVS ED end-diastolic thickness of the interventricular septum, LVPW ED end-diastolic thickness of the posterior wall, LA left atrium dimension, E early component of the transmitral inflow pattern, A late component of the transmitral inflow pattern, DET deceleration time of E.

	ToF70 (n=75)	ToF80 (n=81)	p value
Number of patients	75	81	
LVEDD (mm(SD)))	49 (6.4)	45 (7.9)	0.008
LVESD (mm (SD))	34 (5.3)	33 (6.7)	0.22
FS (%(SD))	30 (6.8)	31 (8.2)	0.89
IVS ED (mm (IQR))	10 (7-13)	8 (6-10)	<0.001
PW ED (mm (IQR))	10 (7-13)	9 (7-11)	0.071
LA (mm (SD))	37 (7.4)	36 (7.2)	0.77
Aortic sinus (mm (SD))	37 (6.3)	33 (6.0)	0.001
Aortic ratio	1.23 (0.20)	1.09 (0.19)	<0.001
Aortic ratio > 1,3	34	10	0.001
E/A ratio (SD)	2.1 (0.8)	1.9 (0.7)	0.046
DET (msec (SD)	177 (39)	193 (60)	0.10
Tricuspide regurgitation (mild to moderate) %	62	78	0.037
Tricuspide regurgitation (severe) %	2.8	6.3	045
Pulmonary regurgitation (moderate) %	34	53	0.017
Pulmonary regurgitation (severe) %	53	32	0.007
Mitral regurgitation (moderate) %	39	13.8	<0.001
Aortic regurgitation (moderate) %	21.1	7.5	<0.001
Aortic stenosis %	5.4	3.8	0.71
Pulmonary stenosis %	49	52	0.70

Exercise capacity

Exercise testing was performed in 73 ToF70 patients and 68 ToF80 patients. Mean exercise capacity was 82% of the expected value in ToF70 and 81% in ToF80 (p=0.55). Respectively 56% and 60% patients performed below 85% of the predicted value (p=0.57).

Quality of life

Outcomes of the SF 36 are presented in Figure 3. No difference was found on any of the SF-36 scales between the ToF70 and ToF80 patients.

Compared to normative data, ToF80 patients scored higher on mental health (p<0.001) and social functioning, (p<0.0001) but lower on general health (p<0.01) and vitality (p<0.0001).

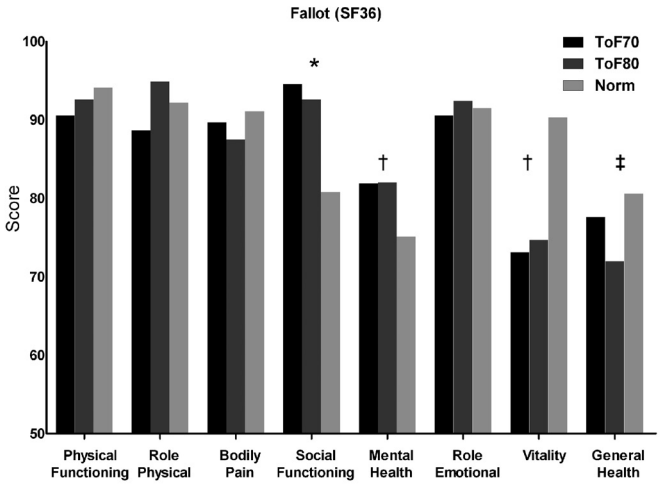

Figure 3. Mean SF-36 scale scores for the ToF70, ToF80 and normative group.
* ToF70 and ToF 80 versus norm p<0.001, † ToF70 and ToF 80 versus norm p<0.0001 , ToF 80 versus norm p<0.01

Behavioural/Emotional Problems

Regarding behavioural and emotional problems no significant differences were found between the ToF70 and ToF80 patients.

Compared to the normative group, ToF80 patients scored better on the scales anxious/depressed, attention problems, aggressive behaviour, internalizing and externalizing problems, as shown in Table 3.

Table 3. Differences in mean behavioural/emotional problems scale scores between ToF70 patients, ToF80 patients and the norm group

	Problem scores				
	ToF70 (n=72)	ToF80 (n=41)	norm (n=1211)		
ASR scales	M (SD)	M (SD)	M (SD)	p-value[a]	p-value[b]
Anxious/Depressed	4.5 (4.5)	4.3 (4.7)	6.1 (6.1)	0.84	0.022
Withdrawn	2.3 (2.1)	2.3 (2.4)	2.9 (2.7)	0.95	0.19
Somatic Complaints	3.2 (3.1)	2.7 (3.0)	2.9 (3.2)	0.45	0.77
Thought Problems	1.7 (2.2)	1.6 (2.1)	1.8 (2.1)	0.78	0.56
Attention Problems	3.0 (2.2)	3.0 (2.3)	6.1 (4.7)	0.98	<0.001
Aggressive Behavior	2.2 (2.5)	2.2 (1.8)	4.2 (4.1)	0.95	<0.001
Rule-Breaking Behavior	2.1 (2.3)	2.3 (2.3)	2.8 (2.8)	0.63	0.21
Intrusive	1.8 (1.7)	1.8 (1.6)	1.9 (1.9)	0.88	0.54
Internalizing Problems	9.9 (8.5)	9.3 (7.5)	11.9 (10.5)	0.89	0.042
Externalizing Problems	6.1 (5.4)	6.2 (4.7)	9.0 (7.2)	0.71	0.001

ASR = Adult Self-Report
a p value ToF70 versus ToF80
b p value ToF80 versus norm

DISCUSSION

This study provides a historical comparison of late outcome after surgical correction for ToF. Two large cohorts of ToF patients operated in the 70's and in the 80's were studied, using the same standardized follow-up protocol after a comparable period of time in the same institution. There was a trend towards a decrease of early mortality rate while the hazard of late death for adults with repaired ToF is low. The late mortality rate was not statistically different between both cohorts, although survival did show a positive trend.

Morbidity

Pulmonary valve regurgitation is a frequent late complication after ToF correction.(4) The relationship between the type of corrective surgery and long-term effects of the resulting PR has received considerable interest. In particular the use of transannular patching as a possible cause of PR and long-term morbidity has been suggested.(16) There have been contradicting reports about the influence of a transannular patch on the need for PVR. De Ruiter et al described an increase in right ventricular dilatation and need for PVR. On the other hand Hickey et al did not demonstrate more PR or ventricular dilatation after the use of a transannular patch.(5,17) With the shift towards earlier corrective surgery, more transannular patches were implanted in the ToF80 cohort of our study. In our study, the only factor associated with the increased need for re-operation for PR was the use of a transannular patch.

Our centre follows a rather selective policy towards pulmonary homograft replacement. (2,18,19) The indication for pulmonary homograft replacement nowadays consists of severe pulmonary valve regurgitation with a combination of symptoms, a reduction in exercise capacity over time, a decrease in right ventricular function or an indexed RV volume on MRI of > 150 ml/m^2. Over time there have not been essential differences in policy or indication for PVR in our centre. However, there has been an increase in the use of magnetic resonance imaging, which has become a standard diagnostic tool in the follow-up of Fallot patients. The use of MRI may have influenced the decision making concerning PVR and this may explain some of the differences found between both cohorts. However, in our centre the decision making for PVR is never done on the basis of MRI measurements only.

An unexpected finding was the trend towards increased right ventricular dysfunction in the ToF80 cohort, which may also be related to the frequent use of transannular patches with longstanding pulmonary regurgitation. In the 90s there was a tendency to avoid transannular patching and surgical correction was performed at an even earlier (neonatal) age.(8) Nowadays this very early intervention has been abandoned by most surgeons. It will be very interesting to study the additional impact of further changes in surgical technique on long-term reoperations rate and right ventricular function.

LV dysfunction significantly influences late prognosis in ToF patients.(20) In contrast to the unexpected negative findings on the right side of the heart, improvements in relation to the left side were noted in the 80's cohort. Positive effects on LV dimensions were observed, which may be explained by the corrective operation performed at younger age in the 80's. In addition less aortic regurgitation and aortic dilatation were found in this cohort. The question remains whether the aortic dilatation is the cause or rather the result of aortic regurgitation. Grotenhuis et al. hypothesised that aortic dilatation and regurgitation could be the cause for LV dysfunction.(21) Tan et al. showed post-mortem histological changes of the aortic root (as in Marfan and bicuspid valve patients) which may contribute to the aortic root dilatation and thereby regurgitation. (Tan23, Kalra3) In addition to morphological changes of the aorta another explanation could be found in flow patterns. Niwa et al. speculated that the use of prior palliation, with high aortic flow, is responsible for the increased aortic dilation with secondary aortic regurgitation. (22)

Clinical condition

Most patients were in NYHA class I and QRS duration was comparable in the two cohorts. QRS duration has been described to be a predictor of arrhythmias. (8,24) In the ToF80 more patients had supra ventricular tachycardias on holter monitoring, which may be associated with the RV dysfunction. (3) Short runs of ventricular tachycardia were found in both cohorts. In these patients thorough evaluation of the hemodynamic state and additional testing was done. Although most patients were able to exercise until an acceptable maximum heart rate,

both cohorts showed exercise capacity of around 80% of predicted. This is comparable with the exercise capacity mentioned in the literature between 77%-89%. (25,26)

Health-related quality of life

As quality of life and behavioural/emotional functioning showed the same results in the ToF70 and ToF80 patients, no clear improvements over time could be observed. Compared to the normal population ToF patients scored lower on general health and vitality.(27) This could indicate patients are aware of the disease in daily life. On the other hand they scored higher on social sub domains, thereby indicating they did not feel to be emotionally withheld because of this disease. This is in line with previous studies, for instance by Hickey et al. who showed SF-36 scores were significantly below normal for physical domains in 840 adults ToF patients(5) This appreciation of social functioning was confirmed by the results of the Adult Self-Report, in which we found less anxiety or internalizing problems and aggressive or externalizing problems.(18) The lower prevalence of behaviour problems may be due to the fact that these patients show a "response shift"". A respons shift is described in patients who have survived surgical correction and often had multiple hospital admissions. To cope with this major life event they have consequently developed a better coping mechanism. This may lead to a better subjective quality of life.(28)

Study limitations

In 2001 MRI was not performed routinely and also the modern echocardiographic measurements, such as speckle tracking and 3D, were not available yet. Since we could not compare these techniques, we did not include these techniques in this study. The echocardiographic left ventricular end systolic diameter may not be valid in all patients, considering the paradoxal septal deviation, therefore LV end systolic diameter and fractional shortening should be seen in this light. Exercise testing was done without maximum VO2, which would have been optimal. This study is an observational non-randomised trial; therefore conclusions should be drawn with care.

CONCLUSION

In 2001 we studied patients with ToF operated between 1968-1980, in the current study we repeated the protocol 10 years later in patients operated between 1980-1990. This study demonstrats that with an earlier stage surgery, there is a trend towards a diminished early mortality rate and late survival remained good. Although the left ventricle seems to be better protected by surgery at younger age. By avoiding the extensive use of a transannular patch, the need for reoperations may further decrease. Overall, quality of life was good with no significant differences between the two cohorts.

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Chapter 4

Long-term psychosocial outcome of adults with complex congenital heart disease: a historical comparison

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ABSTRACT

Objective

Making a historical comparison on the long-term psychosocial outcome of cardiothoracic surgery during childhood.

Methods

Adult patients operated for Tetralogy of Fallot or Transposition of the Great Arteries between 1980-1990 (recent sample) were compared with patients operated ten years earlier (historical sample). Also, atrial switch and arterial switch patients within the recent sample were compared. Psychosocial functioning was measured using standardised, validated psychological questionnaires.

Results

Although the recent sample of patients overall shows a favorable quality of life, impairments were found in income, living conditions, relationships, offspring and occupational level. Compared to the historical sample, the recent sample showed no significant improvements on psychosocial functioning, except for a better educational level. The amount of educational problems (such as learning difficulties) was still high compared to normative data. Recently operated patients with Transposition of the Great Arteries scored significantly better on the Short Form-36 vitality scale ($p=0.02$) compared to historical patients with Transposition of the Great Arteries.

Conclusions

Despite improvements in medical treatment over the past decades, hardly any change was found in psychosocial outcome of the recent patient sample compared to the historical patient sample. Especially the percentage of patients needing special education and showing learning problems remained high, while income was low compared to normative data.

Keywords

Transposition of the great arteries, Tetralogy of Fallot, quality of life, historical comparison, congenital heart disease

INTRODUCTION

The dramatically improved long-term survival of children born with congenital heart disease has resulted in a new and growing population of adults with congenital heart disease.[1,2] This has raised interest in the quality of life of adult congenital heart disease patients.

Adults with congenital heart disease differ from the general population by medical status and medical history, and have specific psychosocial needs and problems.[3] It has been shown that young adults with congenital heart disease obtained a lower educational and occupational level compared to normative reference groups.[4] Furthermore, as to subjective health status, patients experienced more limitations in physical functioning.[5]

Since 1980, many aspects of diagnostic, surgical and medical treatment of congenital heart disease have improved, supposedly resulting in less physiological stress on the patient. Our hypothesis is that improvements in cardiological outcome may also specifically result in more favorable long-term psychosocial outcome. To the best of our knowledge this study is the first to test this hypothesis using two cross-sectional samples of all adult congenital heart disease patients (matched for age and cardiac diagnosis), comparing results over a 10-year period.

The objective of this study was three-fold: 1) to investigate the psychosocial outcome of adults operated recently (between 1980 – 1990) for Tetralogy of Fallot or Transposition of the Great Arteries, 2) to compare those outcomes with a matched historical cohort (operated between 1968 – 1980), and 3) to make a comparison within the recent Transposition of the Great Arteries group between patients operated with the Mustard procedure versus the arterial switch procedure.

MATERIALS AND METHODS

Study design

In this cross-sectional single center study psychosocial outcome of a recent versus a historical patient sample was compared using a comparable age-range (20-37) and comparable cardiac diagnostic groups: Transposition of the Great Arteries and Tetralogy of Fallot.

Assessment procedure

For both the recent and historical sample, the institutional ethical committee on human experimentation approved the research protocol. In both studies, patients were approached uniformly and signed informed consent before participating. All patients were medically examined by a cardiologist in our center. The semi-structured interview and psychological

questionnaires were completed in our hospital. In both samples data collection took place in the same standardized way.

Recent patient sample

Out of 185 selected patients, 19 patients died, 45 patients were lost to follow-up and 6 patients were living abroad. Of the remaining 115 elegible patients, 36 refused to participate resulting into 79 participating patients. Five patients were not able to complete all questionnaires. Thus the overall response rate was 69%.

The recent congenital heart disease sample (n=79) consisted of all consecutive surviving patients with either Transposition of the Great Arteries (n=31) or Tetralogy of Fallot (n=48), who underwent their first open heart surgery for congenital heart disease in our center between 1980 - 1990, and were younger than 15 years at the time of surgery. At follow-up (2010), all patients were between 20 and 35 years of age. Of the 31 patients with Transposition of the Great Arteries, 18 patients underwent arterial switch surgery (58%) and 13 patients underwent a Mustard or Senning procedure (42%). All patients with Tetralogy of Fallot had a complete correction and in 74% a right-ventricular outflow tract patch was inserted. The median follow-up time of this group was 24.2 years (22.7 – 26.5).

Historical comparison

Historical patient selection

The 362 congenital heart disease patients that have been included in the historical patients sample has been described in detail previously.[4] These patients were all operated for congenital heart disease between 1968 and 1980 in our center, and were evaluated medically and psychosocially in 2000/2001. Out of this population, we excluded 230 patients because of non-comparable diagnosis (ASD, VSD and PS). A total of 22 patients did not fill in the questionnaires we need for the historical comparison, and 3 patients were excluded because of mental retardation, resulting in 107 eligible patients.

Matching procedure

The mean age of the 107 eligible patients was significantly higher than the selection made in the recent sample. We therefore stratified by congenital diagnosis (ToF and TGA) and removed the oldest patients until age was not significantly different anymore (ToF p=0.09, TGA p=0.33). This resulted into 88 included patients (ToF N=53, TGA N=55). Both groups were comparable on gender (ToF p=0.7, TGA p=0.9).

Instruments and normative data

The psychological examination consisted of the following instruments:

Biographical characteristics, such as nationality, living conditions, marital status, offspring, educational- and occupational status were assessed by a semi-structured interview.[6] Normative data were extracted from multiple tables, which were all derived from a variety of (very) large samples of the Dutch population, so that representativeness for the average Dutch situation was warranted (Netherlands Central Bureau of Statistics).[7] For some tables sample sizes were not provided by the CBS. Also, the sample sizes of the reference groups vary between different tables. To prevent confusion, these sample sizes were not included in the tables. Where possible, normative data were stratified by sex and age. Data tables used were:

Subjective health status was assessed by the Short Form-36.[8] Good reliability and validity for the Dutch Short Form-36 has been reported.[9] Normative data were derived from a nation wide, population based Dutch health status survey.[9]

The Satisfaction with Life Scale was has been proven psychometrically sound to be used in patients with congenital heart disease.[10] Normative data was derived from a large general population sample.[10]

The Linear Analogue Scale was used to assess self-perceived quality of life. This instrument has been proven valid, reliable and responsive for the congenital heart disease population.[10] Normative data was derived from a large general population sample.[10]

Statistical analyses

In order to make the comparison between the historical and the recent sample, both datasets of the recent and historical congenital heart disease samples was categorized according to the age and gender categories of normative groups. For categorical characteristics, proportions of patients are presented in percentages.

P-values were calculated on the basis of 95% confidence intervals. Because of the skewed nature of the data, Mann-Whitney-U tests were used to assess difference in outcome (Short Form-36, Satisfaction With Life Scale and Linear Analogue Scale) between diagnostic groups within the recent congenital heart disease sample. Pearson Chi-square tests were used to test for differences in distributions of gender and cardiac diagnoses between both patient samples. If cell values were less than 5, the Fisher exact test was used. The statistical package IBM SPSS Statistics for Mac version 19.0 (Release 19.0.0) was used. Figures were made using GraphPad Prism version 6.0a for Mac, GraphPad Software (Released July 18, 2012), La Jolla California USA.

RESULTS

Recent sample versus normative data

Biographical characteristics (Table 1, Figure 1 and 2)

Patients with congenital heart disease were living less often independently ($p<0.0001$), and were less often married or had a stable relationship compared to normative data ($p<0.01$). Patients with congenital heart disease were less likely to have children compared to normative data, stratified by age and gender categories ($p<0.0001$) (Figure 1).

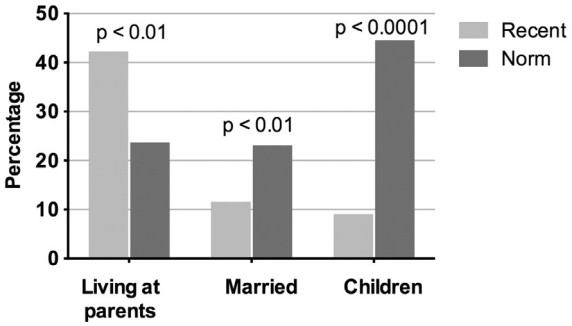

Figure 1: Biographical data
Figure 1 shows the comparison on three different biographical variables between the recently operated patients with congenital heart disease (shown in red) and a normative group (shown in green).
Living at parents = proportion of people still living at their parents; mother/father or both
Married = the proportion of people that are married
Children = the proportion of people that have one or more children.
p-values were calculated by chi-square tests

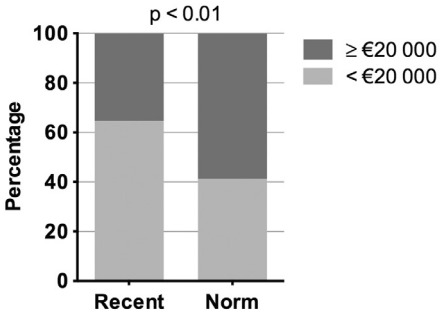

Figure 2: Comparison on income between the recently operated congenital heart disease group and the normative group
Figure 2 shows the comparison on income between the recently operated congenital heart disease group and a normative group (matched on age and gender). Shown in red is the proportion of the group that earns < €20 000, shown in green is the proportion of the group that earns ≥ €20 000

Patients with congenital heart disease obtained a similar educational level compared to normative data, except for females aged 25 to 35 years, who less often had higher education ($p<0.05$, not listed in the Table). As to occupation, recent patients with congenital heart disease less often had an academic occupational level ($p<0.01$), and more often had a lower occupational level ($p=0.02$) compared to normative data.

Considering employment, remarkably, patients with congenital heart disease who had a paid job were less frequently working part-time ($p<0.01$) and more often working full-time compared to normative data. There was no effect of gender as to working part-time versus full-time. Congenital heart disease did not appear to be the reason for working part-time in the majority of patients (80%). Regarding income, patients with congenital heart disease earned significantly less compared to the general Dutch population ($p<0.01$) (Figure 2). Finally, patients with congenital heart disease showed a significant higher percentage of sick leave compared to the general Dutch population (7% vs. 4.4%). This effect was mainly found in arterial switch patients.

Quality of Life (Table 2)

Subjective health status: Compared to normative data, the recent congenital heart disease sample obtained less favorable results on bodily pain, vitality and general health scales. Patients with congenital heart disease more often experienced bodily pain ($p=0.05$) and as to vitality, reported to feel more worn out and tired ($p<0.0001$). Patients scored their general health as significantly lower and believed it was likely to get worse over time ($p<0.01$). Also, the recent sample obtained more favorable scores ($p<0.0001$) on social functioning, indicating less interference from physical or emotional problems in attending social activities. Recent patients reported a better general mental health compared to normative data ($p<0.0001$).

Compared to normative data (Figure 3) the recent Tetralogy of Fallot group obtained more favorable scores on social functioning ($p<0.0001$) and mental health ($p<0.001$). Less favorable scores for the recent Tetralogy of Fallot group were obtained on the vitality scale ($p<0.0001$) and general health scale ($p<0.01$).

The recent Mustard group obtained more favorable scores compared to normative data, on social functioning ($p<0.0001$), mental health ($p=0.02$), role emotional ($p<0.0001$), and less favorable on physical functioning ($p=0.01$) and vitality ($p=0.04$) (Figure 4)

Within the recent sample, no differences were found between patients with Tetralogy of Fallot and patients with Transposition of the Great Arteries. When comparing Mustard and arterial switch patients within the recent sample, two differences were found: arterial switch patients reported better physical functioning compared to patients operated with the Mustard procedure ($p<0.01$). This indicates that arterial switch patients feel less limited in performing physical activities compared to patients operated with the Mustard procedure.

Table 1. Medical and biographical characteristics of the recent and historical sample compared to normative groups (in percentages).

Table legend:

* Normative data was derived from the Netherlands Bureau of Statistics 2010. Normative data on daily activities was not available and is therefore not displayed in the table.

Fallot = patients with Tetralogy of Fallot; TGA = patients with transposition of the Great arteries; Switch = patients with arterial switch (subgroup of TGA); Mustard = patients with Mustard correction (subgroup of TGA); Part-time is working < 36 hours a week; Fulltime is working ≥ 36 hours a week.

[a] significant difference Switch versus Mustard

[b] significant difference in ToF versus TGA

[c] all patients that do not live together with a partner

[d] persons living in institutions for mentally handicapped are excluded

[e] Only persons that have a paid job and are between 25 and 35 years of age are included

[f] Sick-leave percentage was used instead of number of days on sick-leave, since the number of hours a person works a week (full-time/part-time) might vary considerably. P-values could not be calculated since data on standard deviations or ranges were missing for the normative groups. P-values for the historical comparison were calculated using Mann-Whitney U tests because of the skewed nature of the data.

Age
Gender (male)
NYHA-class
I
II
III
Daily activities
Attending education [a]
Paid job [a,b]
Combination above [b]
Looking for work
Long-term sick leave
Volunteer unpaid work
Mentally handicapped
Housewife/man
Other
Living conditions
Parents
Independently
Institution
Marital status
No stable relationship [b,c]
Cohabitants
Married [a]
Divorced
Offspring
No children
≥1 children
Educational attainment [d]
Lower
Average
Higher
Educational problems
Special education
Doubled a class
Learning difficulties

Recent versus normative data							Historical comparison		
ToF	TGA			Total	* Norm	Total ConHD vs Norm p-value	Historical N=88	Recent N=61	Historical vs recent p-value
	Total	Switch	Mustard						
N=48	N=31	N=18	N=13	N=79	N~				
28.5±3.5	26.1±2.7	24.0±1.2	26.7±1.6	27.5±3.4			26.8±4.0	26.4±3.1	0.5
66.7	67.7	66.7	69.2	67.1			66.7	67.2	0.9
95.8	92	91.7	92.3	94.5			28.9	95.7	<0.001
4.2	8	8.3	7.7	5.5			53.3	4.3	<0.001
							17.8	-	<0.001
									0.4
14.6	29	44.4	7.7	20.3	-	-	9.3	13.1	0.4
64.6	38.7	16.7	69.2	54.4	-	-	67.3	65.6	0.8
4.2	22.6	27.8	15.4	11.4	-	-	3.7	6.6	0.4
2.1	0	0	0	1.3	-	-	4.7	1.6	0.3
4.2	0	0	0	2.5	-	-	3.7	3.3	0.9
2.1	0	0	0	1.3	-	-	0.9	1.6	0.7
8.3	9.7	11.1	7.7	8.9	-	-	3.7	8.2	0.2
0	0	0	0	0	-	-	1.9	0	0.3
0	0	0	0	0	-	-	4.7	0	0.09
34	54.8	66.7	38.5	42.3	23.7	<0.01	31.8	34.4	0.7
57.4	45.2	33.3	61.5	52.6	75.6	<0.0001	65.4	59	0.4
8.5	0	0	0	5.1	0.7	0.1	2.8	6.6	0.2
59.6	80.6	88.9	69.2	67.9	51.5	<0.01	47.7	60.7	0.1
27.7	9.7	11.1	7.7	20.5	25.5	0.3	24.3	24.6	1
12.8	9.7	0	23.1	11.5	23.1	<0.01	26.2	14.8	0.09
							1.9	-	0.3
87.2	96.8	100	92.3	91	55.5	<0.0001	79.4	88.5	0.13
12.8	3.2	0	7.7	9	44.5		20.6	11.5	
16.7	14.3	25	10	15.9	17.9	0.7	48.1	24	0.004
53.3	57.1	75	50	54.5	43	0.1	33	52	0.02
30	28.6	0	40	29.5	39.1	0.2	18.9	24	0.5
25	16.7	16.7	16.7	21.8	3.5		34.6	23.3	0.1
45.8	43.3	50	33.3	44.9				43.3	
43.8	30	22.2	41.7	38.5				43.3	

Table 1. Medical and biographical characteristics of the recent and historical sample compared to normative groups (in percentages). *(Continued)*

Occupational level [d]				
Elementary				
Lower				
Average [b]				
Higher [b]				
Academic				
Duration of employment [e]				
Part-time				
Full-time				
Male				
Part-time [a]				
Full-time [a]				
Female				
Part-time				
Full-time				
Reason part-time work				
Heart sole reason				
Heart a reason				
Heart no reason				
Income				
< €20000				
≥ €20000				
Sick-leave [f]				
Sick-leave compared to collegues				
More				
Equal				
Less				

Recent versus normative data							Historical comparison		
ToF	TGA			Total	* Norm	Total ConHD vs Norm p-value	Historical	Recent	Historical vs recent p-value
	Total	Switch	Mustard				N=88	N=61	
N=48	N=31	N=18	N=13	N=79	N~				
3.6	0	0	0	2.5	5.6	0.2	5.4	2.3	0.4
35.7	41.7	50	40	37.5	19.5	0.02	40.5	39.5	0.9
50	16.7	50	10	40	40	1	32.4	37.2	0.6
7.1	41.7	0	50	17.5	24.1	0.3	16.2	16.3	1
3.6	0	0	0	2.5	10.7	<0.01	5.4	4.7	0.9
16.7	18.2	50	11.1	17.1	33.8	<0.01	24	15.9	0.3
83.3	81.8	50	88.9	82.9	66.2		76	84.1	
9.1	11.1	50	0	9.7	12.8	0.6	10.2	6.3	0.5
90.9	88.9	50	100	90.3	87.2		89.8	93.8	
37.5	50	0	50	40	56.9	0.3	50	41.7	0.6
62.5	50	0	50	60	43.1		50	58.3	
12.5	0	0	0	6.7	-	-	27.8	14.3	0.5
25	0	0	0	13.3	-	-	5.6	28.6	0.1
62.5	100	100	100	80	-	-	66.7	57.1	0.7
63.6	66.7	80	60	64.6	41.3	<0.01	44.6	61.9	0.1
36.4	33.3	20	40	35.4	58.7		55.4	38.6	
7	7.1	13.4	3.6	7	4.4		12.1	5.1	0.1
7.9	28.6	30	27.3	15.3	-	-	13.9	11.6	0.7
34.2	47.6	50	45.5	39	-	-	33.3	34.9	0.9
57.9	23.8	20	27.3	45.8	-	-	52.8	53.5	0.9

Table 2. Mean scale scores of the recent sample and normative data on instruments.
Table legend:
ConHD = all ConHD patients (ToF & TGA combined). Norm = normative data for the general Dutch population corrected for age and sex where possible.
ToF = patients with Tetralogy of Fallot; TGA = patients with Transposition of the Great Arteries, including arterial switch patients and patients operated with the Mustard procedure.
Switch = patients with arterial switch operation; Mustard = patients operated with the Mustard procedure.
The SF-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status

	Norm vs ConHD					ToF vs TGA					TGA				
	ConHD		Norm			ToF		TGA			Switch		Mustard		
	n=74		n=1742			n=44		n=30			n=17		n=13		
	x	sd	x	sd	p	x	sd	x	sd	p	x	sd	x	sd	p
SF-36															
Physical functioning	92.8	11.3	94.1	13.2	0.3	92.6	13.5	93.0	7.1	0.3	96.5	5.2	88.5	6.9	<0.01
Role function phyisical	93.2	16.2	92.2	22.3	0.6	94.9	12.7	90.8	20.2	0.6	86.8	23.6	96.2	13.9	0.2
Bodily pain	86.7	18.7	91.1	15.1	0.05	87.5	17.2	85.5	20.9	0.8	85.8	21.0	85.2	21.5	1.0
Social functioning	92.7	12.2	80.8	14.5	0.000	92.6	11.8	92.9	13.0	0.8	90.4	15.6	96.2	7.9	0.4
Mental health	82.6	13.5	75.1	15.6	0.000	82.0	12.6	83.5	14.8	0.5	82.6	16.4	84.6	13.0	0.8
Role function emotion	95.0	17.2	91.5	15	0.08	92.4	21.4	98.9	6.1	0.1	98.0	8.1	100.0	0.0	0.4
Vitality	76.9	16.2	90.3	24.6	0.000	74.7	18.2	80.2	12.3	0.4	79.1	11.2	81.5	13.9	0.4
General health	74.9	17.5	80.6	14.7	<0.01	72.0	17.0	79.1	17.7	0.1	84.1	15.9	72.7	18.5	0.05
SWLS	27.6	4.8	25.8	4.6	<0.01	27.5	5.1	28.3	3.7	0.7	29.1	3.1	27.4	4.2	0.5
LAS	80.2	9.0	77.1	8.9	0.02	80.1	9.7	80.3	8.0	0.9	82.2	6.5	77.9	9.3	0.1

Arterial switch patients reported better general health compared to patients operated with the Mustard procedure (p=0.05).

On the Satisfaction with Life Scale, the recent patients with congenital heart disease showed more favorable scores compared to normative data (p<0.01). No difference was found for patients with Tetralogy of Fallot versus patients with Transposition of the Great Arteries or arterial switch versus patients operated with the Mustard procedure.

On the Linear Analogue Scale, the recent congenital heart disease sample rated their quality of life significantly higher compared to normative data (p=0.02). No difference was found for patients with Tetralogy of Fallot versus patients with Transposition of the Great Arteries or arterial switch versus patients operated with the Mustard procedure.

Recent sample versus historical sample

Medical background. The age at first treatment differed between the recent and historical sample (Recent: median = 0.8(0.5–1.8) years. Historical: median = 1.5(0.6–4.2) years, p=0.02).

Table 3. Differences in mean behavioural/emotional problems scale scores between ToF70 patients, ToF80 patients and the norm group.
ASR = Adult Self-Report
a p value ToF70 versus ToF80
b p value ToF80 versus norm

	Problem scores				
	ToF70 (n=72)	ToF80 (n=41)	norm (n=1211)		
ASR scales	M (SD)	M (SD)	M (SD)	p-value[a]	p-value[b]
Anxious/Depressed	4.5 (4.5)	4.3 (4.7)	6.1 (6.1)	0.84	0.022
Withdrawn	2.3 (2.1)	2.3 (2.4)	2.9 (2.7)	0.95	0.19
Somatic Complaints	3.2 (3.1)	2.7 (3.0)	2.9 (3.2)	0.45	0.77
Thought Problems	1.7 (2.2)	1.6 (2.1)	1.8 (2.1)	0.78	0.56
Attention Problems	3.0 (2.2)	3.0 (2.3)	6.1 (4.7)	0.98	<0.001
Aggressive Behavior	2.2 (2.5)	2.2 (1.8)	4.2 (4.1)	0.95	<0.001
Rule-Breaking Behavior	2.1 (2.3)	2.3 (2.3)	2.8 (2.8)	0.63	0.21
Intrusive	1.8 (1.7)	1.8 (1.6)	1.9 (1.9)	0.88	0.54
Internalizing Problems	9.9 (8.5)	9.3 (7.5)	11.9 (10.5)	0.89	0.042
Externalizing Problems	6.1 (5.4)	6.2 (4.7)	9.0 (7.2)	0.71	0.001

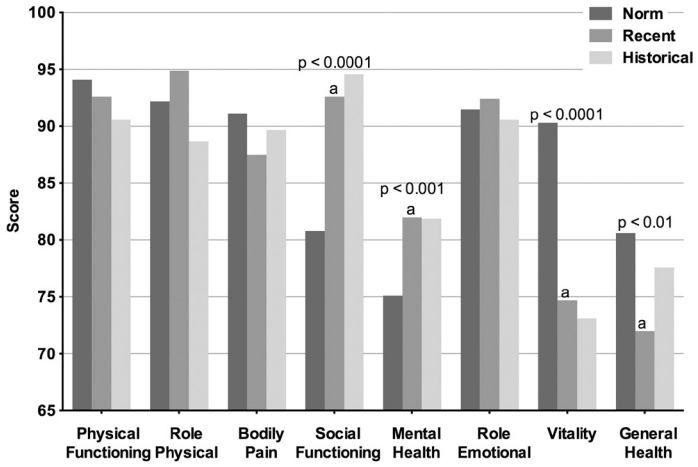

Figure 3: Comparison between normative data, recently operated Tetralogy of Fallot patients and historically operated Tetralogy of Fallot patients.
Figure 3 shows the comparison on the Short Form-36 scale for the recent patients with Tetralogy of Fallot (shown in red) versus the historical patients with Tetralogy of Fallot (shown in orange) and a normative group (shown in green). The Short Form-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status.
a = Significant difference between the normative group and the recently operated congenital heart disease group

The difference in age at treatment was also observed in recent patients with Tetralogy of Fallot versus historical patients with Tetralogy of Fallot patients (median = 1.2(0.5–2.4), respectively 2.8(1.2-4.8) p=0.07), and recent patients operated with the Mustard procedure versus historical patients operated with the Mustard procedure (median = 0.5(0.2-0.7) respectively 0.7(0.4-2.3) p=0.002). No significant difference was found on the number of surgeries using a right-ventricular outflow tract patch between the recent sample (74%) versus the historical sample (77%) (p=0.7).

Biographical characteristics (Table 1). A trend was observed showing that the recent patients with congenital heart disease less often had a relationship (p=0.1), and were married less often (p=0.09) compared to the historical sample. Recent patients with congenital heart disease obtained a significantly higher educational level compared to the historical sample. Both recent and historical sample showed a comparable high amount of special education , 35% for the historical group and 23% for the recent group (p=0.1).

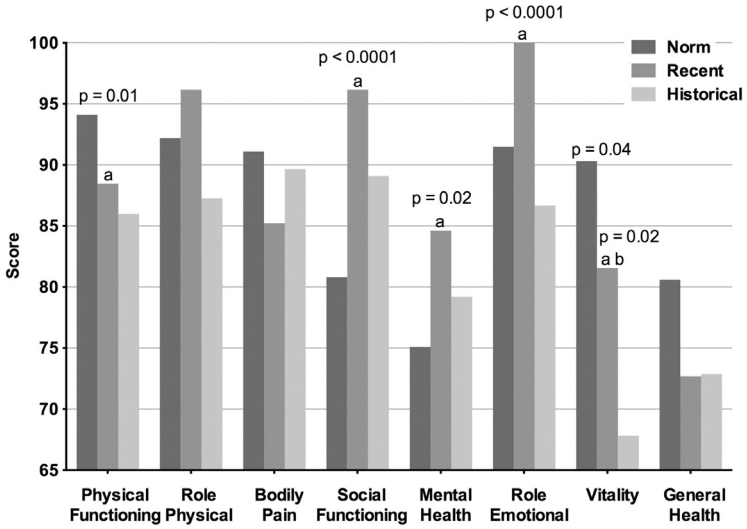

Figure 4: Comparison between normative data, recently operated patients operated with the Mustard procedure and patients historically operated with the Mustard procedure.
Figure 4 shows the comparison on the Short Form-36 scale for the recent patients operated with the Mustard procedure (shown in red) versus the historical patients operated with the Mustard procedure (shown in orange) and a normative group (shown in green). The Short Form-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status.
a = Significant difference between the normative group and the recently operated congenital heart disease group
b = Significant difference between the recently operated congenital heart disease group and the historically operated congenital heart disease group.

Quality of life (Figure 3 and 4)

Diagnostic groups. Figure 3 shows no differences between recent versus historical patients with Tetralogy of Fallot on any of the Short Form-36 scales. Figure 4 shows that recent patients operated with the Mustard procedure obtained more favorable scores on the vitality scale of the Short Form-36 compared to historical patients operated with the Mustard procedure (p=0.02). The other non-significant differences, except for general health, all pointed in the same direction of a better outcome for recently operated patients with Transposition of the Great Arteries.

DISCUSSION

Although the recent sample of patients with congenital heart disease overall shows a favorable quality of life, impairments were found on living conditions, relationships, offspring, occupational level, and also the income of patients with congenital heart disease is still lower than expected. Compared to the historical sample, the recent sample showed no significant improvements on psychosocial outcome, except for a better educational level.

To our knowledge, this is the first published psychosocial study making a historical comparison on long-term psychosocial outcome between a recent and historical sample of adult patients with congenital heart disease. To ensure that both samples were comparable, patients with the same diagnoses and same age-range were selected. Clinically relevant areas of psychosocial functioning were investigated, using internationally standardized assessment instruments.

Recent sample versus normative data

Biographical outcome

Although a few older studies showed similar patterns on living less independently and lower offspring rates, our recent findings still show an impressive impact on living conditions in our complex ConHD population.[11-16] The relatively young age of this patient sample cannot be the sole reason for these findings, since the same categories for age and sex were used in comparing our patient data with normative data. The low amount of offspring might be explained by the high amount of patients working fulltime, but it can also be the other way around, that patients less often have children and thus keep on working fulltime. The recent sample obtained a lower occupational level and was earning a significantly lower income compared to the general Dutch population. Our present findings on living conditions, marital status and occupational level all point in the same direction of being less independent and having a lower socio-economic status for patients with congenital heart disease. A delayed process of gaining autonomy and striving for independence might explain the differences in

biographical outcome and occupational level. Our findings support previous research from Kovacs, Kokkonen and Paavilainen, Utens and Simko et al.[3,11,17,18] Furthermore, overprotectiveness from parents may play a role in the delayed process of gaining autonomy.[19] The way in which the physician informs the parents may play a role in overprotectiveness as well.

The recent patients with congenital heart disease reported a higher amount of sick leave compared to the general Dutch population. Surprisingly, when asked about sick leave, the majority of patients with congenital heart disease reported to be less often sick compared to their colleagues. This findings points towards a gap between objective and subjective sick leave. Van Rijen explained a similar phenomenon by "denial", social desirability or overcompensation by the patients with congenital heart disease.[4]

Recent patients with congenital heart disease still experience more educational related problems compared to normative groups. The percentage of patients requiring special education in the recent congenital heart disease sample was 24%, which is almost seven times as high as compared to normative data (3.5%). Also, 45% of our patients reported having repeated a class and 39% experienced learning difficulties. Although normative data on these two categories was not available, we assume that this is higher than in the general population.[20,21] Possible explanations for these findings are the underlying cardiac diagnoses with frequent periods of cyanosis, cardiac surgery and school absences due to hospitalizations. These unfavorable findings may be explained neuropsychological impairments in patients with surgical corrected congenital heart disease, which have been reported in reviews.[20,21] Besides pre-operative factors (genetics, structured brain injury, severity of disease), preoperative- (e.g. deep hypothermic circulatory arrest, pH-management during cooling, hemodulation) and postoperative factors (e.g. number of operations, clinical and EEG seizures), also school absenteeism may contribute to learning problems. Also genetic patterns such as the 22q11 deletion can play a role.[20,21]

Quality of life

Our recent sample reported a quality of life which was comparable or even better than that of normative groups on three different instruments (Short Form-36, Satisfaction With Life Scale, Linear Analogue Scale). Our results are in line with previous studies, in which a good quality of life for patients with Tetralogy of Fallot and patients operated with the Mustard procedure has been reported.[10,14,22-24]

On the Short Form-36 social functioning scale, recent patients with congenital heart disease obtained a more favorable outcome compared to normative data. Previous studies have shown that a favorable social functioning has a protective role against a low quality of life.[25,26] The favorable self-reported social functioning on the Short Form-36 scale could therefore be protecting our patients from a low quality of life.

Recent sample versus historical sample

Biographical outcome

The educational level of the recent sample was significantly better than that of the historical sample. This might be explained by improved social acceptance of congenital heart disease over time, stimulating patients to get the same educational levels compared to normative data. Despite this improvement, the need for special education was comparable in both samples and high compared to the general population.

The historical sample showed a higher amount of sick leave compared to normative data. This finding was also seen in the recent sample.

Quality of life

Recent patients with Tetralogy of Fallot obtained comparable scores on all Short Form-36 scales compared to historical patients with Tetralogy of Fallot.

The only significant difference found between the recent and historical patients operated with the Mustard procedure was the improved Short Form-36 vitality score for current patients. Although not significant, improvements were found on role limitations due to physical and emotional health, bodily pain, social functioning and mental health. These findings all pointed towards a better psychological functioning for patients operated with the Mustard procedure over time.

Role of Mustard versus arterial switch surgical procedures

Our data showed comparable psychosocial functioning for patients operated with the Mustard procedure versus the arterial switch patients. Within the present sample, arterial switch patients scored more favorable results on two Short Form-36 scales, namely physical functioning and general health. These findings are in line with Görler et al., who found no significant difference between Mustard and switch patients, but did describe a tendency towards a better result of the arterial repair group in general health perceptions and role limitations due to emotional problems.[27] Loup et al. found that patients operated with the Mustard/Senning procedure patients showed significantly lower scores on vitality and the psychological functioning Short Form-36 scales.[28] These findings indicate that arterial switch patients feel less limited in performing physical activities and evaluate their personal health as being better compared to patients operated with the Mustard procedure. Despite these improvements, the overall quality of life was not affected as reported on the Satisfaction With Life Scale and the Linear Analogue Scale.

Clinical implications

The more dependent life-style and high amount of special education are prominent in patients with congenital heart disease. Patients still score less favorable on vitality and general

health compared to normative data. These findings provide a solid argument for offering routinely applied comprehensive and multidisciplinary psychosocial care.

When looking at the historical picture, some improvements over time can be seen, especially for patients operated with the Mustard procedure on the quality of life instruments.

Limitations

The patients included in this study either had Tetralogy of Fallot or Transposition of the Great Arteries and all these patients were followed in a tertiary academic medical center. The obtained results therefore, may not be representative for all patients with congenital heart disease.

Future research

Future research should aim to investigate the relationship between a lower occupational level and a lower income in patients with congenital heart disease, and what interventions can be implemented to decrease these impairments in socio-economic status. Also the low offspring rate and low independence should be studied further. In addition, the relation between psychological characteristics and quality of life should be investigated in more depth. A large cohort is advisable to avoid underpowered conclusions.

CONCLUSION

This article presents a comparison between psychosocial problems encountered in patients with congenital heart disease, operated between 1980 and 1990, to those of patients with congenital heart disease operated between 1968 and 1980.

Despite evident improvements in treatment, hardly any changes were found in psychosocial outcome. The recent patients with congenital heart disease sample showed a favorable quality of life, despite several psychosocial impairments as to relationships, offspring, lower occupational level and lower income. When comparing psychosocial outcome of the recent congenital heart disease sample with the historical congenital heart disease sample, no significant better outcome for the recent congenital heart disease sample were observed.

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C

Part II Pregnancy in women with heart disease

Chapter 5

Pregnancy and delivery in cardiac disease

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ABSTRACT

Although its prevalence is relatively low in pregnant women, heart disease is the most important cause of maternal mortality. Problems may arise due to hemodynamic burden and the hypercoagulable state of pregnancy. Heart disease may be congenital or acquired. In developed countries, the former composes the biggest part of women with heart disease. Patients with unrepaired lesions, cyanotic lesions, diminished systemic ventricular function, complex congenital heart disease, left ventricular outflow tract obstruction, pulmonary hypertension, or mechanical valves are at highest risk of developing complications during pregnancy.

All patients with known cardiac disease should preferably be counseled before conception. Pre-pregnancy evaluation should include risk assessment for the mother and fetus, including medication use and information on heredity of the cardiac lesion. Management of pregnancy and delivery should be planned accordingly on individual bases. The types of complications are related to the cardiac diagnosis, with arrhythmias and heart failure being most common. Treatment options should be discussed with the future parents, as they may affect both mother and child. In general, the preferred route of delivery is vaginal. The optimal care for pregnant women with heart disease requires multidisciplinary involvement and is best concentrated in tertiary centers.

KEYWORDS

Pregnancy; Heart disease; Counseling; Delivery; Fetal outcome

INTRODUCTION

Epidemiology

In the developed world many women with congenital heart disease are reaching childbearing age and wish to become pregnant.

While congenital heart disease is more often encountered than acquired disease in pregnant women, it seems associated with a lower risk. Acquired conditions such as aortic dissection, peri-partum cardiomyopathy, and acute coronary syndrome (ACS) cause the highest maternal mortality rates) (1,2). Pregnancy increases the risk of having an ACS three- to four-fold (3). The overall incidence of pregnancy related ACS is reported to be between 2.7 and 6.2 per 100,000 deliveries and this figure is increasing, probably due to changes in lifestyle, higher prevalence of obesity, and older age at pregnancy (3,4). In the developing world, rheumatic heart disease remains the most common pathology (5).

Physiological changes in normal pregnancy

Major hemodynamic changes take place during pregnancy. Total peripheral vascular resistance (TPVR) is reduced and blood volume and cardiac output are increased around 50% (6). During labor and delivery, cardiac output is further increased as a result of uterine contractions and maternal effort (6). After delivery, most changes are rapidly reversed in the first 2 weeks with further normalization toward preconception values after 3-12 months. Figure 1 shows the hemodynamic changes. However, some structural changes might never completely be reversed.

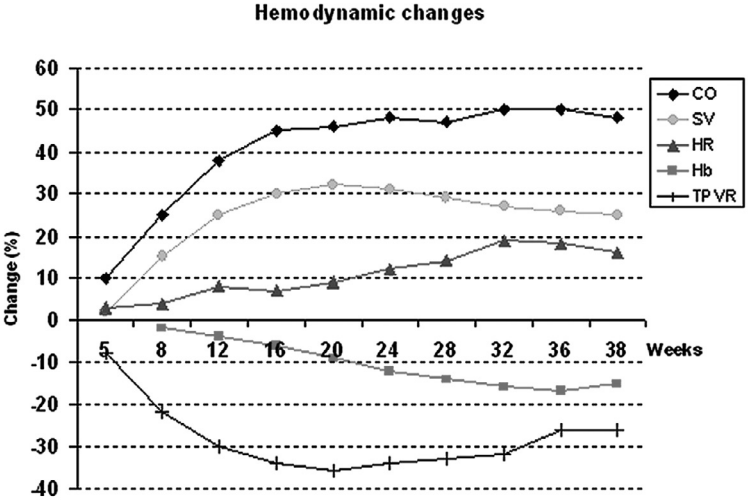

Figure 1. Hemodynamic changes in pregnancy. CO, cardiac output; SV, stroke volume; HR, heart rate; Hb, hemoglobin; TPVR, total peripheral vascular resistance.

In order to reduce blood loss around delivery, the production of tissue plasminogen activator (tPA), protein C and S is decreased and tPA inhibitor and factors V, VII, VIII, IX, X, XII and von Willebrand factor are increased, leading to a hypercoagulable state (7,8,9).

MANAGEMENT OF PREGNANCY IN WOMEN WITH HEART DISEASE

Pre-pregnancy counseling

Counseling after thorough evaluation should be offered to all women of reproductive age with known cardiac disease. This should preferably be done before conception or alternatively in early pregnancy (5). Risk for persistent deterioration of heart function may influence the choice whether to become pregnant. Pre-pregnancy evaluation should focus on identifying and quantifying risks for both mother and offspring. An exercise test (with VO2 max measurements) and echocardiogram provide essential information on pre-pregnancy cardiac status and reserve.

Life expectancy and ethical aspects of parenthood should also be discussed during the pre-pregnancy consultation. Genetics and inheritance will be of special interest in some patient groups (congenital heart disease, Marfan syndrome, and hypertrophic cardiomyopathy) (5). The advantages and disadvantages of medication should be discussed including teratogenicity. If necessary, drug schedules should be adapted. More information on medication in pregnancy can be found in Table 1.

Several risk stratification models have been described over the years. Siu et al. published the CARPREG risk score in 2001 mainly based on women with congenital and valvular heart disease. Significant predictors for adverse maternal and neonatal outcome were prior cardiac events (heart failure, transient ischemic attack, stroke before pregnancy or arrhythmia), baseline New York Heart Association (NYHA) functional class >II or cyanosis, left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak left ventricular outflow tract gradient >30 mmHg by echocardiography) and reduced systemic ventricular systolic function (ejection fraction <40%) (10). Khairy et al. found additional predictors for adverse outcome namely a history of smoking and severe pulmonary regurgitation (11). The ZAHARA investigators showed in a large retrospective cohort of women with congenital heart disease that a history of arrhythmic events or mechanical valve implantation are independent predictors for maternal and neonatal complications (12). The World Health Organization (WHO) developed a risk score based on cardiac pathology and co-morbidity. WHO class 1 indicates low risk, WHO class 2 indicates an intermediate risk, WHO class 3 indicates high risk, and WHO class 4 indicates a contraindication for pregnancy (Table 2) (13).

Table 1. Medication during pregnancy. Food and drug administration (FDA) classification: Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Medication	FDA	Information
Atenolol	D	Intrauterine growth restriction and premature birth
Other beta-blockers	C	Low birth weight, hypoglycemia, and bradycardia in the fetus
Angiotensin-converting enzyme inhibitors	D	High incidence fetal death and fetotoxic effect: renal failure, renal dysplasia
Amiodarone	D	Thyroid insufficiency
Angiotensin receptor blockers	D	High incidence fetal death and fetal renal failure
Aspirin	B	Low-dose aspirin is safe (large database)
Calcium channel antagonists	C	Diltiazem: an increase in major birth defects has been reported
Clopidogrel	B	The benefits of using clopidogrel in some high-risk pregnancies may outweigh the potential fetal risks
Digoxin	C	No reports of congenital defects, monitor serum levels
Loop diuretics	C	Hypovolemia can lead to reduced uterine perfusion
Low molecular weight heparin and unfractionated heparin	C	Factor Xa should by measured weekly, levels may fluctuate during pregnancy
Nitrates	B	Careful titration is advised to avoid maternal hypotension
Spironolactone	D	Potential anti-androgenic effects on the developing male fetus
Statins	X	Animal studies demonstrated increased skeletal abnormalities, fetal and neonatal mortality.
Thiazide diuretics	B	Hypovolemia can lead to reduced uterine perfusion

Table 2. Different diagnoses with corresponding risks categories and most encountered problems.

Type of heart disease	WHO categories	Most often encountered complications	Other important information
Congenital heart disease (corrected)			
Atrial septal defect	1	Arrhythmias (1%)	In uncorrected atrial septal defect higher risk of pre-eclampsia
Ventricular septal defect	1	Premature delivery (12%)	In uncorrected ventricular septal defect higher risk of pre-eclampsia
Atrio-ventricular septum defect	2 or 3	Arrhythmias (10%) / deterioration of atrio-ventricular valve regurgitation (17%)	Recurrence of congenital heart disease in up to 10%
Tetralogy of Fallot	2	Arrhythmias (6%)	Patients with severe pulmonary regurgitation are at risk for progressive right ventricular dilation
Coarctation of the aorta	2 or 3	Hypertensive disorders (11%)	Increased risk of aortic dissection
Transposition of the great arteries (Mustard/Senning)	3	Arrhythmias (22%) / Heart failure (11%)	Irreversible ventricular dysfunction in 10%
Fontan operation	3	Arrhythmias (16%) / Heart failure (4%)	In case of cyanosis risk for miscarriage
Eisenmengers syndrome	4	Heart failure (21%) / Maternal mortality up to 50%	Mainly in post-partum period (first 3 days)
Valvular heart disease			
Mitral stenosis	2 or 3	Heart failure (31%)/ Arrhythmias (11%)	Mainly in patients with mitral valve <1.5 cm^2
Aortic stenosis	2 or 3	Heart failure (3- 44%)/ Arrhythmias (6-25%)	Mainly in patients with an aortic valve <1.5 cm^2
Pulmonary stenosis	1	Right sided heart failure (9%)	Mainly in patients with moderate to severe pulmonary stenosis
Regurgitation lesions	1 or 2	Heart failure (7%) / Supra ventricular tachycardia (9%)	Mainly in patients with decreased cardiac function at baseline
Mechanical valves	3	Valvular thrombosis up to 10% maternal mortality up to 4%	Outcome depends on anticoagulation regimen used
Cardiomyopathy			
Peri-partum cardiomyopathy in current pregnancy	2 or 3	Severe heart failure at the end of pregnancy 100%, maternal mortality in 15%	Half of the patients have complete recovery of ventricular function
Peri-partum cardiomyopathy in previous pregnancy without abnormal ventricular function	2 or 3	Recurrence of heart failure (21%)	Ventricular function further decreases in some patients
Peri-partum cardiomyopathy in previous pregnancy with abnormal ventricular function	4	Recurrence of heart failure (44%) maternal mortality (20%)	Ventricular function further decreases in most patients

Table 2. Different diagnoses with corresponding risks categories and most encountered problems. *(Continued)*

Type of heart disease	WHO categories	Most often encountered complications	Other important information
Dilated cardiomyopathy	2 or 3	Heart failure (25%) arrhythmia's (19%)	Mainly in patients with abnormal ventricular function (left ventricular ejection fraction <45%) at baseline
Hypertrophic obstructive cardiomyopathy	2 or 3	Heart failure (28%)	Mainly in symptomatic patients at baseline, beta-blockers should be considered
Hypertrophic non obstructive cardiomyopathy	2 or 3	Low risk of heart failure	Mainly in symptomatic patients at baseline
Ischemic heart disease			
Before pregnancy	2 or 3	Recurrence risk unknown, heart failure in patient with reduce ventricular function	Increasing prevalence in recent decades
During pregnancy	Not applicable	Maternal mortality (9%)	Electrocardiographic changes and troponin are essential diagnostic tools
Peri-partum	Not applicable	High risk of coronary dissection (34%) Maternal mortality (18%)	Coronary dissection partly due to hormonal changes during the last trimester and hemodynamic burden
Aortic disease			
Marfan	2 or 3	Aortic dissection (1-10%)	High risk in patients with aortic diameter > 45 mm
Bicuspid aortic valve disease	2 or 3	Aortic dissection (<1%)	High risk in patients with aortic diameter > 50 mm
Turner's syndrome	3	Hypertensive disorders (67%) / Aortic dissection (5%)	Women with Turner's syndrome are often not fertile
Ehlers-Danlos	3 or 4	Maternal mortality (11,5%)	An increased risk of spontaneous uterine rupture
Pulmonary arterial hypertension	4	Maternal mortality (17-33%)	Mainly in post-partum period (first 3 days)

Complications during pregnancy

The type of complication depends on the specific cardiac pathology (Table 1). Arrhythmias and heart failure are the most common complications encountered (14).

Heart failure: All patients with heart failure during pregnancy should be admitted for bed rest. Medical treatment includes salt and fluid restriction, diuretics to limit the volume load, and antihypertensive therapy for afterload reduction. Angiotensin-converting enzyme (ACE) inhibitors can induce fetal anuria, pulmonary hypoplasia, and skull deformities especially when used in the second and third trimester. They are, therefore, contraindicated during pregnancy. However, in some specific situations the maternal benefits can outweigh the fetal risks and ACE inhibitors may be used for a short time (5,15).

Arrhythmias: The incidence of arrhythmias may be increased during pregnancy in women with heart disease. When drug therapy is deemed necessary, beta-blockers or digoxin are the preferred choice. The latter can be used in women with atrial fibrillation. Due to the increase in blood volume during pregnancy, higher doses are necessary to reach adequate blood levels. Electrical cardioversion is the treatment of choice for all drug-refractory maternal arrhythmias. It can be performed safely during pregnancy (16).
Bradyarrhythmias are uncommon and usually well tolerated. Pacemaker implantation may be necessary in selected patients whereby radiation should be kept to a minimum (17). Ectopic beats are often benign and also present in one-third of healthy pregnant women. Management mainly consists of reassurance. Supraventricular tachyarrhythmias are rare (17). Nakagawa et al. studied 11 patients with new-onset ventricular arrhythmia during pregnancy, 73% of these originated from the right ventricular outflow tract, post-pregnancy the arrhythmia disappeared completely in all patients (18).

Diagnosis in pregnancy

Identifying deterioration of an existing cardiac condition can be a diagnostic challenge as cardiopulmonary signs and symptoms reported during normal pregnancy closely mimic heart disease. In addition, acquired heart diseases often present acutely and catastrophically in women with no known pre-existing disease. Recognition of the acute presentation, immediate diagnostic examination, and appropriate management will improve their chances of survival (15).

Physical examination: In a healthy pregnant woman, normal findings include a mild increase in resting heart rate, a widened pulse pressure, peripheral edema, and a slight elevation of venous pressure. During the later stages of pregnancy there is a physiological fixed splitting of the second heart sound (S2). Systolic murmurs are common, secondary to the increased cardiac output. However, diastolic murmurs are unusual and therefore call for further evaluation (16).
Electrocardiogram: The electrocardiogram changes as a result of the upward shift of the diaphragm caused by the growing uterus. There is left axis deviation and in the third trimester Q waves in lead III and aVF and inverted T waves in leads III, V1, and V2 are seen (17).
Echocardiography: Trans-thoracic (and trans-esophageal) echocardiography is a safe, rapid, and useful diagnostic tool. In a normal pregnancy a significant increase in cardiac output, cardiac index, left ventricular end-diastolic volume, and left ventricular wall thickness is observed (17). Cardiac ultrasound is indicated in women with symptoms of cardiac disease as well as in women with established heart disease in order to monitor cardiac condition and valvular function (5). In patients with aortic dilatation, echocardiography should be done at 6-8 weeks intervals throughout the pregnancy until 6 months postpartum (15).

Imaging: Chest X-ray should be performed on indication (19). Magnetic resonance imaging (MRI) may be useful in complex heart disease and aortic pathology. MRI is considered to be safe from 12 weeks' gestation. Gadolinium contrast is best avoided (20).

Laboratory: For the diagnosis of ACS both creatinine kinase (CK) MB and troponin are used. During labor elevated CK and CK MB can be found due to uterine contractions. These levels normalize during the second day after labor (21). Troponin I is not elevated in normal pregnancy, as a result troponin I is the recommended laboratory test in pregnancy (22). However, troponin I serum levels can be elevated in patients with pre-eclampsia or a hypertensive crisis. It is not clear whether this is a sign of cardiac ischemia in these patients. Increased B-type natriuretic peptide levels are found during pregnancy in many pregnant women with heart disease. In the study by Tanous et al. B-type natriuretic peptide levels lower than 100 picograms per milliliter had a negative predictive value of 100% for identifying events during pregnancy. Therefore during pregnancy serial B-type natriuretic peptide levels could be helpful, specifically in excluding suspected adverse cardiac events (23).

Treatment during pregnancy

Medication: Table 2 shows the safety profile of commonly used cardiovascular drugs during pregnancy.

Interventional treatment: Indications for intervention may arise when cardiac function deteriorate during pregnancy or when a cardiac condition is either unknown or underestimated before pregnancy (24). In emergency situations, interventional procedures are justified. Ultrasound-guidance and abdominal shielding can help to limit fetal radiation exposure to acceptable doses. The uterus receives radiation scattered from the irradiated area, which is more important than the direct exposure (only 2%). The actual risk depends on the dose and stage of development of the fetus. Radiation doses to the fetus higher than 50 to 100 mGy place the child at risk for growth retardation, malformation, or miscarriage. For low doses to the fetus, the principal risk is radiation-induced cancer (stochastic effects) (19).

Cardiac surgery: Cardiac surgery during pregnancy should only be done if all other treatment modalities (medication and percutaneous intervention) have failed. Intraoperative hypotension and hypothermia, embolic complications, and placental hypoperfusion and preterm labor cause fetal mortality in 14% to 33% or severe morbidity in another 20% where maternal mortality is not much encountered. Severe maternal illness, total operative time, emergency surgery, necessity of revision, advanced maternal age, and gestational age are all associated with poorer outcome (25).

Fetal heart rate monitoring eventually combined with intermittent uterine and umbilical artery Dopplers reflect placental perfusion and should be used to guide bypass pump flow. However, one should take into account that fetal heart rate variability and movements will probably be depressed as a result of the central anesthetics and hypothermia. External tocolysis and clinical examination might reveal uterine contractions. Due to an increased risk of

malformations, surgery is best avoided in the first trimester. In the third trimester, the risks of prematurity should be balanced against the risks of surgery. Therefore European guidelines advise considering delivery before surgery after 28 weeks of gestation (26).

DELIVERY

Delivery team

Timing and mode of delivery should be discussed in advance in a multidisciplinary team consisting of at least an obstetrician, an anesthesiologist, and a cardiologist. The patient's preference should to be taken into account and she should be thoroughly counseled about the delivery plan and potential complications. A written record should be available at all times for all involved caregivers and should include plans to manage foreseeable complications.

Timing

In asymptomatic women in good condition, spontaneous delivery can be awaited. In women with complex lesions, severe cardiac dysfunction, heart failure, aortic dilatation, Eisenmenger syndrome, or mechanical valve switched to heparin, a planned delivery might be more appropriate. Maternal or fetal condition might warrant a planned delivery before 37 weeks.

Mode of delivery

The mode of delivery mainly depends on obstetric indication and the maternal hemodynamic condition. Vaginal delivery is preferred in women with adequate cardiac output. According to the European guidelines, primary Cesarean section should be considered for the patient on oral anticoagulants (OAC) in pre-term labor, in women with severe heart failure, aortic root diameter >45 mm, and patients with acute or chronic aortic dissection (5,27).

Vaginal delivery: Vaginal delivery is uncomplicated in most women with heart disease. Decreased blood loss, more rapid recovery, absence of abdominal surgery, and decreased thrombogenic risks are the most important benefit over Cesarean section. Adequate pain relief with epidural analgesia can help to attenuate the hemodynamic changes that accompany labor and delivery. It also allows controlled fetal descent to the pelvic floor by suppressing bearing down reflex. As such the need for bearing down effort with accompanying Valsava manoeuver is often reduced. Epidural catheters are contraindicated in women using anticoagulants. Alternatives like intravenous analgesia can be considered. Adequate measures to prevent a sudden fall in peripheral vascular resistance associated with epidural anesthesia should be taken in women with left ventricular outflow tract obstruction (28). Assisted vaginal delivery (by vacuum or forceps extraction) is recommended when excessive maternal efforts and prolonged labor are contraindicated. Cervical ripening using either

prostaglandins or mechanical methods and induction of labor with oxytocine are relatively safe in most women with cardiac disease (29).

Cesarean section: Cesarean delivery annihilates the hemodynamic changes associated with labor. It also often permits more appropriate invasive and non-invasive hemodynamic monitoring and management. However it increases the risk of venous thrombo-embolism, infection, and post-partum hemorrhage. Controlled loco-regional anesthesia is often possible and preferred. However some cases may warrant general anesthesia (30,31).

Post-partum period

Care should be given with intravenous bolus of oxytocine in the third stage of labor, as it might cause a sudden fall in cardiac output. Controlled intravenous infusion might be more appropriate. Also certain intravenous prostaglandins, used to prevent or treat post-partum hemorrhage can cause coronary vasospasms (such as sulprostone).

The volume shifts caused by auto-transfusion the first days after delivery have deleterious effects on patients with diminished left ventricular function. Several days of close monitoring for signs of heart failure is recommended in high-risk women (5). Prophylactic diuretics and ACE inhibitors may be indicated in high-risk patients with severe systemic ventricular dysfunction. A routine echocardiographic examination post-delivery in high-risk women is advisable, paying careful attention to the aortic root in women with Marfan syndrome or aortic valve disease. The risk of thrombo-embolic complications is further increased post-partum and anticoagulation should be adjusted accordingly (9).

In patients with low risk for heart failure and with normal ventricular function, a short observation period of several hours up to 48 hours post-partum might be sufficient. While lactation is possible in most women with heart disease, it might be contraindicated due to medication use, severely decreased effort tolerance, or risk of mastitis and bacteremia in some women. The use of diuretics can complicate the initiation of milk production.

Fetal outcome

Predictors Neonatal outcome is strongly correlated with maternal outcome. Similar to maternal risk factors, several predictors for neonatal outcome have been described such as baseline NYHA class >II or cyanosis, left heart obstruction, smoking during pregnancy, the use of oral anticoagulants during pregnancy, mechanical valve prosthesis, and multiple gestation. Cardiac surgery causes high fetal mortality during pregnancy (up to 30%) (23).

Monitoring Genetic counseling and invasive prenatal diagnosis should be offered women carriers of known genetic anomalies (e.g. Marfan syndrome, 22q11 deletions, familial cardiomyopathies, and arrhythmias). A second trimester ultrasound screening for fetal abnormalities with special focus on potential congenital heart defects is indicated in all women with congenital heart disease as the risk for congenital heart disease in the offspring is around 3-5% (5, 32). From 24 weeks' gestation, assessment of fetal growth and well-being should be

performed at regular intervals using clinical examination, ultrasound biometry and biophysical profile, uteroplacental and fetal Dopplers, and fetal heart rate monitoring as appropriate (33)

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Chapter 6

Hemodynamic adaptation to pregnancy in women with structural heart disease.

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ABSTRACT

Background

Many women with structural heart disease reach reproductive age and contemplate motherhood. Pregnancy induces and requires major hemodynamic changes. Pregnant women with structural heart disease may have a reduced cardiac reserve. There are no longitudinal data on cardiovascular adaptation throughout pregnancy in women with structural heart disease.

Methods

Thirty-five women with structural heart disease were included in a prospective observational trial. Maternal hemodynamics were assessed before conception, during pregnancy and 6 months postpartum by transthoracic echocardiography. Uteroplacental perfusion was analyzed by obstetric Dopplers. Longitudinal evolution over time was analyzed as well as the long term influence of pregnancy on cardiac function.

Results

Cardiac output (CO), stroke volume (SV), left ventricular mass (LV mass) and E/E' ratio significantly increased and ejection fraction (EF) and fractional shortening (FS) decreased during pregnancy. There was a statistically significant difference in EF, FS and E/E' ratio before and after pregnancy.

Conclusions

The characteristic pattern of hemodynamic adaptation to pregnancy is attenuated in women with structural heart disease. The pregnancy related volume load induces progression of diastolic dysfunction. Our data suggest a persistent reduction in systolic and diastolic cardiac functions after pregnancy in women with structural heart disease.

Keywords

Congenital, Heart, Pregnancy, Hemodynamic

INTRODUCTION

Normal pregnancy induces and requires a major cardiac adaptation. An initial arterial vasodilatation, early in pregnancy, triggers a rapid increase in blood volume, cardiac output and ventricular mass(1, 2). Most of these changes are reversed 6 months after pregnancy(3).

Advances in medical and surgical care of patients with structural heart disease have led to improved survival and outcome, especially in women with congenital and valvular heart disease. Many of these women reach reproductive age and experience their quality of life to be sufficient to consider pregnancy and motherhood. However, they are at increased risk for cardiac and obstetric complications(4-6). The hemodynamic changes can put a strain on their circulatory system and may induce cardiac complications such as heart failure or arrhythmia. Alternatively, their reduced cardiac reserve could prevent adequate adaptation, possibly leading to hypertensive disorders of pregnancy, fetal growth restriction or adverse fetal outcome.

Timely counseling and specialized follow up by a dedicated team of cardiologists, obstetricians and anesthesiologists, with knowledge of the implications of structural heart defects as well as adaptive requirements of pregnancy, are therefore advised(7, 8).

While cardiac (mal)adaptation to pregnancy has mostly been studied in healthy women, women with hypertensive disorders or with growth restricted fetuses, there is hardly any longitudinal data on women with structural heart disease(9). As such most information comes from extrapolation of other patient groups(10-17).

Also, little is known on the degree of reversibility of hemodynamic adaptation and its effects on cardiac function after pregnancy(18, 19).

We therefore aimed to prospectively study longitudinal hemodynamic adaptation to pregnancy in women with structural heart disease and asses the influence of this cardiac adaptation on postpartum cardiac function.

METHODS

The prospective single center observational study was conducted from 2007 until 2010 in a joint collaboration by the departments of Cardiology and Obstetrics at the Erasmus MC. Women with inherited or acquired structural heart disease visiting the outpatient clinic of cardiology and/or obstetrics for preconceptional counseling or pregnancy during the study period were invited to participate. Women received an individualized, standard management by a multidisciplinary team consisting of dedicated cardiologists, obstetricians and anesthesiologists according to international guidelines.

Maternal and uteroplacental hemodynamics were assessed by transthoracic echocardiography and obstetric Dopplers. Maternal and pregnancy outcomes were assessed. Cardiac

measurements were performed before pregnancy, in each trimester of pregnancy and six months postpartum. Obstetric Doppler measurements of the uterine and umbilical artery were performed in the second and third trimesters. Preconceptional hemodynamics were investigated at inclusion or retrieved from a recent previous echocardiographic exam. Pre and post pregnancy measurements were performed irrespective of the menstrual cycle, method of anticonception and breast feeding status. The study was approved by the medical ethical committee of the Erasmus MC University Medical Centre of Rotterdam and all participants gave written informed consent. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology(20).

General outcomes

Demographics, cardiac diagnoses, obstetric outcomes and both maternal and obstetric complications were prospectively recorded. Post-partum hemorrhage (PPH) was defined as blood loss above 500 ml after vaginal delivery and 1000 ml after cesarean section(21).

Birthweight centiles, corrected for gestational age, maternal race, parity and fetal sex were derived from the Dutch national reference curves(22). A birthweight less than the 10th percentile, was considered as small for gestational age (SGA).

Hypertension (HT) during pregnancy was classified as either pre-existent (occurring before 20 weeks of gestation), gestational hypertension (de novo hypertension without proteinuria occurring after 20 weeks of gestation) or pre-eclampsia (hypertension in combination with proteinuria)(23).

Preterm delivery was defined as a delivery occurring before 37 weeks of gestation. Pregnancy loss was defined as a miscarriage before and intrauterine death from 20 weeks of gestation.

Echography:

Transthoracic echocardiography was performed using commercially available devices with sector transducers (SONOS 7500, Philips Medical Systems, Best, The Netherlands or iE33, Philips Medical Systems, Best, The Netherlands), according to the guidelines of the American Society of Echocardiography and, when necessary, adapted to the structural abnormality(24).

Diastolic and systolic volumes were computed from the left ventricular end systolic and end diastolic diameters (LVESD,LVEDD) using the Teicholz formula and fractional shortening (FS) and ejection fraction (EF) were calculated accordingly(25). Left ventricular mass (LVmass) was calculated using the Devereux formula(26). Left ventricular outflow tract diameter was obtained from the parasternal long access view and left ventricular outflow tract velocity time integral from the apical five chamber view. Stroke volume (SV) was calculated by multiplying left ventricular outflow area with left ventricular velocity time integral, cardiac output (CO) by multiplying stroke volume with heart rate. Diastolic function was assessed by pulsed

wave Doppler of the mitral inflow (E/A ratio) and tissue Doppler of the septal mitral annulus (E/E' ratio).

Obstetric Dopplers were obtained with commercially available ultrasound devices with curved array transducers (iU22, Philips Ultrasound Bothell, WA, USA and Voluson 730 Expert G.E, Medical systems, Zimpf, Austria). Pulsatility index of the umbilical artery (Umb PI) and mean pulsatility index of both uterine arteries (Uter PI) were obtained by color directed pulsed wave Doppler.

Statistical analysis

Continuous variables are displayed as means with a standard deviation (SD) and range, discrete variables are displayed as counts and proportions.

To investigate the longitudinal evolution over time of the individual cardiac and obstetric Doppler parameters and to account for the correlation in the measurements taken from the same patients, a repeated measurement analysis using linear mixed effect models' was performed (27). As the evolution of each parameter during pregnancy may not be linear, we used in our model specification second degree polynomials for both the fixed and random effects parts. The models' assumptions were validated using residual plots. The analysis was performed in the R statistical software (version 2.14.0, 2011-10-31) using package nlme (version 3.1-102). The significance level was set at 5% and no multiple testing corrections were applied.

Differences between pre-and post-pregnancy values were analyzed with an F-test. To assess whether the evolution during pregnancy predicted this pre-post pregnancy difference, the area under the longitudinal trajectory during pregnancy using a linear mixed effect models was computed and subsequently the association between this area and pre-post pregnancy difference was tested.

To investigate the association between fetal growth and cardiac adaptation, these areas were also correlated with adjusted birthweight centiles and evolution in uterine artery flow.

To assess the influence of the severity of cardiac condition and the occurrence of pregnancy complications on the longitudinal evolution of the parameters, the population was divided in two groups. For the severity of cardiac condition, the division was based on the WHO cardiac function classification (WHO classes 1-2 versus WHO classes 3-4)(28). For the occurrence of pregnancy complications, only those associated with maladaptation to hemodynamic changes were taken into account. As such the population was divided based on the occurrence of hypertension and/or small for gestational age fetuses (HT/SGA).

The same types of analysis as for the whole population were performed, allowing for differences in the average longitudinal evolutions per risk group. Likelihood ratio tests for differences in average longitudinal evolutions between both groups were calculated as well as differences between the pre-post pregnancy values. The effect of the severity of cardiac

condition on adjusted birthweight centiles and occurrence of complications was analyzed with a Wilcoxon test and Fisher's exact test respectively.

RESULTS

Thirty-five women with structural heart disease were invited to participate into the study. Thirty-two of them became pregnant and 29 reached a gestational age beyond the limits of viability (24 weeks). One woman had a spontaneous first trimester miscarriage, one woman miscarried after a septic episode following a first trimester reduction of a spontaneous triplet to a singleton pregnancy and one woman had an intrauterine death with signs of severe placental insufficiency at 20 weeks gestation.

Figure 1 represents an organogram of the study population. Table 1 offers details on diagnosis, previous cardiac interventions, the cardiac condition before pregnancy as well as the

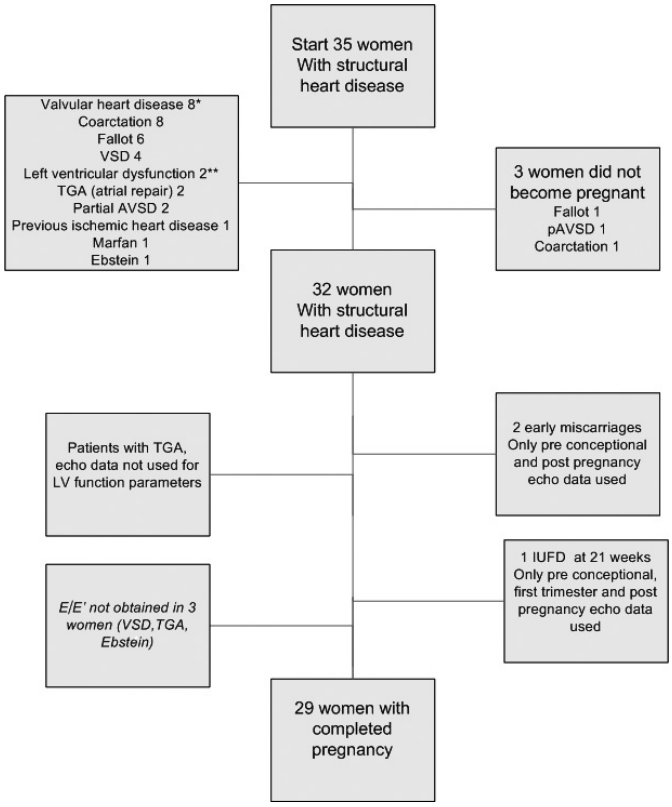

Figure 1. Organogram of the study population with details on cardiac diagnosis.
* Five women with mechanical aortic and/or mitral valve.
** One woman after previous chemotherapy and one woman with a dilated cardiomyopathy.

Table 1. Detailed information on type of structural heart disease, previous interventions, preconceptional cardiac condition and WHO group of the study population.
Abbreviations in order of appearance: WHO: WHO group, RHD: rheumatic heart disease, AVR: aortic valve replacement, MVR: mitral valve replacement, //: subsequent intervention, TV: tricuspid valve, AF: atrial fibrillation, AS: aortic valve stenosis, bicus AV: bicuspid aortic valve, MS: mitral valve stenosis, LV: left ventricle, MV: mitral valve, ACS: acute coronary syndrome, Ao asc: aorta ascendens, PS: pulmonary valve stenosis, MI: mitral valve insufficiency, LA: left atrium, DM: diabetes mellitus, RF: renal failure, Coarct: aortic coarctation, HT: hypertension, APVD: anomalous pulmonary venous drainage, ASD I: atrium septum defect type 1, Le-Ri shunt: left to right shunt, RV: right ventricle, TI: tricuspid valve insufficiency, VSD: ventricular septum defect, PODB: persistent open ductus of Botalli, PA: pulmonary artery, PV: pulmonary valve, TOF: tetralogy of Fallot, RA: right atrium, RV: right ventricle, PI: pulmonary valve insufficiency, AI: aortic valve insufficiency, ASD II: atrium septum defect type 2, DCM: dilated cardiomyopathy, CM: cardiomyopathy, TGA: transposition of the great arteries: pAVSD: partial atrioventricular septum defect, AMI: acute myocardial infarction, PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery, LAD: left anterior descendens coronary artery, RCX: ramus circumflexus.

Diagnosis	Interventions prior to pregnancy	Condition prior to pregnancy	WHO
RHD	St Judes AVR (2x), St Judes MVR // TV plasty (2x)	AF	3
RHD	St Judes MVR // St Judes AVR	AF	3
AS (bicus AV)	St Judes AVR	Aortic root dilatation 48 mm	3
MS (congenital)	St-Judes MVR	Good LV and MV function after previous valve thrombosis with ACS	3
AS (bicus AV)	Homograft	Ao asc 43 mm	2
PS	balloon dilatation	Mild PS	1
MI	No	Severe MI , dilated LA with DM and RF	1
Coarct, bicus AV	Patch // valvulotomy // Ross //stent recoarctation // Bentall	No rest coarct, no HT	3
Coarct , bicus AV	End to end anastomosis	Mild AS, no rest coarct, Ao asc 40 mm, no HT	2
Coarct, APVD	Subclavian flap	Mild rest coarct , no HT	2
Coarct, ASD I	End to end anastomosis // balloon dilatation	Mild rest coarct, HT, Le-Ri shunt over ASD and elevated RV filling pressures	3
Coarct, bicus AV, cervical arch	End to end anastomosis	Mild rest coarct, no HT, Ao asc 44mm	3
Coarct	End to end anastomosis	No rest coarct, no HT, moderate MI and TI	2
Coarct	End to end anastomosis	Mild rest coarct, HT	2
Coarct, bicus AV	End to end anastomosis // balloon dilatation	Mild rest coarct, HT, Ao asc 37 mm	2
Coarct, VSD, PODB	Subclavian flap, PA banding, closure PODB // PA debanding, PV plasty (2x), balloon dilatation recoarctation	Mild rest coarct, mild PS, no HT	2
VSD, subvalvular aortic membrane	Closure VSD (2x), resection subvalvular aortic membrane	Ao asc 41 mm	2
TOF	Closure VSD, transannular patch	Dilated RA and RV, mild PS and severe PI	3
TOF, atresia left PA	Closure VSD and PODB , transannular patch	Mild PS	2
TOF	Closure VSD, transannular patch // homograft for severe PI	Moderate PI	2

Table 1. Detailed information on type of structural heart disease, previous interventions, preconceptional cardiac condition and WHO group of the study population. *(Continued)*

Diagnosis	Interventions prior to pregnancy	Condition prior to pregnancy	WHO
TOF, atresia PA	Waterston // Rastelli // plasty for PS, closure VSD	Severe AI and moderate PI	3
TOF	Closure VSD, transannular patch // homograft	Mild PI	2
TOF	Blalock-Taussig //closure VSD, infundibulectomy 2x // balloon dilatation PV	Moderate PI	2
VSD	No	Mild Le-Ri shunt	2
VSD, ASD II	No	Mild Le-Ri shunt	2
VSD, double orifice MV	PA banding // PA debanding, closure VSD // MV plasty	Mild MI and PS	2
DCM (familial)	No	Mild LV impairment	2
CM (chemotherapy)	No	Dilated LV, mild LV impairment, mild MI	2
TGA	Senning	Mild RV impairment	3
TGA	Mustard	Mild RV impairment	3
pAVSD	Closure ASD, VSD, MV plasty	Moderate MI	2
pAVSD	Closure ASD (2x), VSD (2x), MV plasty (2x) and TV plasty	Moderate MI, dilated LA	2
AMI (inferioposterior)	PTCA RCA, stent LAD and RCX // PTCA LAD for restenosis	Mild LV impairment	3
Marfan syndrome	No	Aorta 39 mm	2
Ebstein anomaly	RV and TV plasty (Chauvaud), partial cavopulmonary shunt	AF, severe TI, RV impairment	3

WHO risk group classification for each women individually. Of the 32 included women, 85% had a congenital structural heart defect and 82% had a prior cardiac intervention. Fifty-six percent of women were nulliparous at inclusion. Mean age at delivery was 32 years (SD: 4.3 years, Range: 24 to 41 years) and mean BMI was 25 (SD: 3.9, Range: 18 to 34).

Major maternal (both cardiac and non-cardiac) and/or obstetric (miscarriage, fetal death, gestational hypertension, pre-eclampsia, SGA, PPH and major congenital abnormality) complications occurred in 62.5% of pregnancies. There was no significant difference in complication rate between the low risk (WHO 1-2) and high risk (WHO 3-4) groups.

Three women had pre-existent atrial fibrillation and 3 other women reported transient episodes of palpitations. There were no new arrhythmic complications during the study period. One woman developed a thrombosis of her prosthetic aortic valve (St-Judes) at 32 weeks, leading to heart failure and requiring postpartum valve replacement. Details of maternal and obstetric complications as well as obstetric outcomes are represented in Table 2.

The longitudinal profiles over time of the echocardiographic and uteroplacental parameters, starting before pregnancy until six months postpartum, are presented in Figure 2 and

Table 2.
Details of maternal and obstetric complications and outcomes.
* Excluding the intrauterine death at 21 weeks

Complications	N	%	WHO 1-2 (n)	WHO 3-4 (n)	remarks
			21	11	
Cardiac					
Valve thrombosis	1	3%	-	1	Aortic valve thrombosis leading to heart failure
Heart failure	1	3%	-	1	
Non-cardiac					
Kidney transplant	1	3%	1	-	Kidney failure during pregnancy in diabetic women with pre-existent kidney dysfunction necessitating postpartum dialysis and transplant
Sepsis	1	3%	1		After early reduction of a triplet pregnancy
Suicide attempt	1	3%	-	1	
Post partum depression	2	6%	1	1	
Pyelonefritis	1	3%	1		
Obstetric					
Pre-existent hypertension	3	9%	2	1	
Gestational hypertension	3	9%	3	-	
Pre-eclampsia	1	3%	1	-	
Preterm delivery	3	9%	1	2	$34^{3/7}$,$35^{1/7}$,$35^{6/7}$ weeks
Postpartum hemorrhage	8	25%	5	3	
Caesarean section	7	22%	6	1	
early miscarriage	2	6%	1	1	
Fetal-neonatal					
Intrauterine death	1	3%	-	1	At 21 weeks
Major congenital abnormality	1	3%	1	-	Trisomy 21 with duodenal atresia
NICU admission	3	9%	1	2	
SGA	6	18%	2	4	
Pregnancy outcomes	Mean	SD	WHO 1-2 (mean)	WHO 3-4 (mean)	Median	Min	Max
Gestational age (weeks)	39	2	39,175	38,011	39	$34^{3/7}$	$41^{6/7}$
Birth weight (gram)	3156	587	3319	2792	3255	1810	4100
Apgar 5 minute	9	1	9,40	9,56	10	8*	10

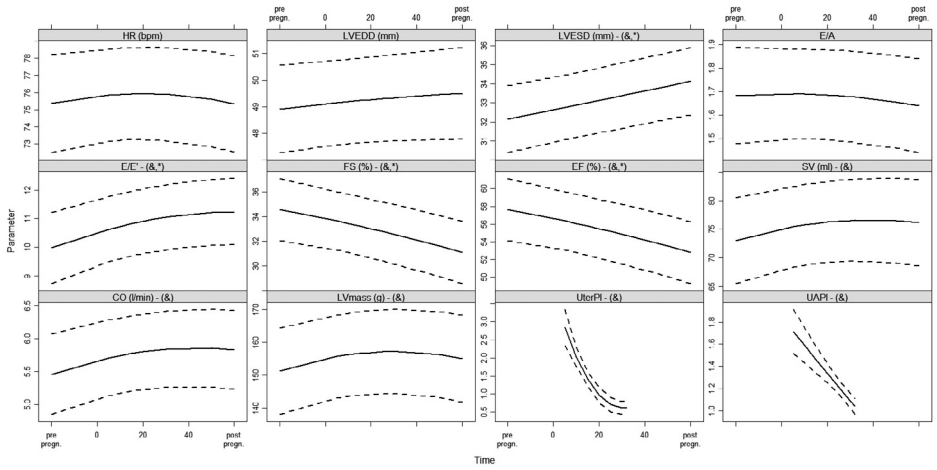

Figure 2.
Fitted longitudinal profiles of each parameters for the whole population. The dashed lines denote 95% point-wise confidence intervals. The symbol `&' denotes parameters for which there was a significant time effect, and the symbol `*' parameters for which there was a significant difference between pre- and post pregnancy measurements.

estimated regression coefficients in Table 3. A statistically significant linear evolution was observed towards a larger LVESD (P=0.001) and smaller FS (P=0.001) and EF (P≤0.001). E/E' ratio (P=0.008), SV (P=0.045), CO (P=0.028), LVmass (P=0.005) as well as uterine and umbilical artery PI (P≤0.001, P≤0.001 respectively) showed a statistically significant parabolic evolution (quadratic effect) with increase during pregnancy for the cardiac parameters and decrease for the obstetric Doppler indices.

There was a statistically significant increase in LVESD (P=0.001) and E/E' ratio (P=0.006) and decrease in FS (P=0.001) and EF (P=0.001) after pregnancy as compared to before pregnancy, however evolution during pregnancy was not predictive for this difference. Neither was it related to evolution in uterine artery flow nor with adjusted birthweight.

The influence of severity of cardiac structural defect based on WHO class on longitudinal evolution of the parameters is illustrated in Figure 3. There were no significant differences in average evolution over time between groups except for heart rate (LRT 9.78, P=0.021). Severity of structural heart defects only influenced heart rate on pre-post pregnancy difference. Adjusted birthweight centiles were significantly higher in the low risk group (WHO1-2) (median = 38: IQR 35,6) as compared to the high risk group (WHO3-4) (median = 14: IQR 24) (P = 0.04).

Thirteen women presented with pregnancy complications associated with hemodynamic maladaptation (HT/SGA). There were no significant differences in average longitudinal evolution of the parameters between patients with and without HT/SGA . The corresponding fitted average longitudinal evolutions are illustrated in Figure 4. There was a significant pre-post

pregnancy difference for the LVEDD (mean diff= -2.97 mm, P=0.031) between patients with and without HT/SGA.

Table 3.
Estimated regression coefficients per parameter for the for the whole population.

Parameter	Coef	Value	Std.Error	t-value	p-value
HR	Intercept	75.78	1.39	54.48	<0.001
	time	0.01	0.02	0.76	0.447
	time^2	−0.00	0.00	−2.02	0.046
LVEDD	Intercept	49.11	0.82	59.93	<0.001
	time	0.01	0.01	0.91	0.366
	time^2	−0.00	0.00	−0.43	0.667
LVESD	Intercept	32.63	0.88	37.02	<0.001
	time	0.02	0.01	2.50	0.014
	time^2	0.00	0.00	0.08	0.939
E/A	Intercept	1.69	0.10	16.98	<0.001
	time	0.00	0.00	0.06	0.954
	time^2	−0.00	0.00	−1.22	0.225
E/E'	Intercept	10.52	0.60	17.63	<0.001
	time	0.02	0.01	3.10	0.003
	time^2	−0.00	0.00	−2.96	0.004
FS	Intercept	33.84	1.23	27.56	<0.001
	time	−0.04	0.02	−2.15	0.034
	time^2	−0.00	0.00	−0.76	0.452
EF	Intercept	56.61	1.71	33.08	<0.001
	time	−0.05	0.02	−2.22	0.029
	time^2	−0.00	0.00	−0.74	0.460
SV	Intercept	75.03	3.68	20.38	<0.001
	time	0.08	0.05	1.75	0.084
	time^2	−0.00	0.00	−2.55	0.013
CO	Intercept	5.67	0.30	18.95	<0.001
	time	0.01	0.00	2.17	0.034
	time^2	−0.00	0.00	−2.73	0.008
LVmass	Intercept	155.01	6.55	23.65	<0.001
	time	0.14	0.08	1.84	0.069
	time^2	−0.00	0.00	−3.25	0.002
UterPI	Intercept	3.81	0.45	8.48	<0.001
	time	−0.21	0.04	−4.83	<0.001
	time^2	0.00	0.00	3.69	0.001
UAPI	Intercept	1.84	0.13	14.71	<0.001
	time	−0.03	0.00	−5.68	<0.001

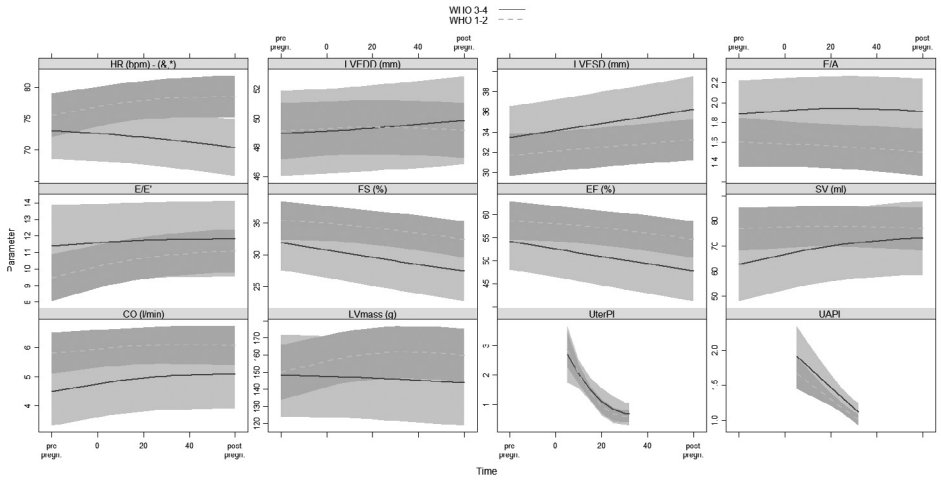

Figure 3.

Fitted longitudinal profiles for each parameter divided according to the severity of the cardiac condition. The dark gray area surrounding the dashed red line and lighter gray area surrounding the full blue line denote the 95% pointwise confidence intervals for the WHO1-2 group and WHO3-4 group respectively. The symbol '&' denotes parameters for which there was a significant difference in the average evolutions in time, and the symbol '*' parameters for which there was a significant difference between pre and post pregnancy measurements between groups.

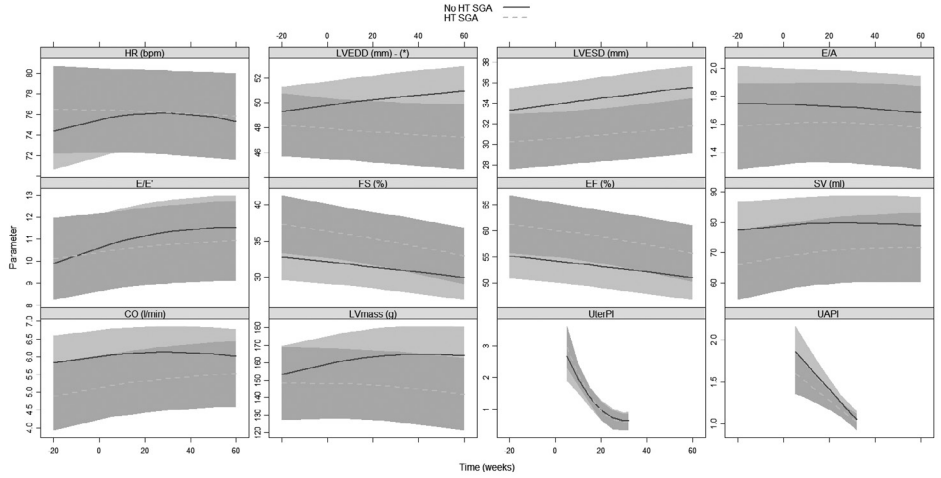

Figure 4.

Fitted longitudinal profiles for each parameter divided according to the occurrence of hypertension and/or small for gestational age fetus.

The dark gray area surrounding the dashed red line and lighter gray area surrounding the full blue line denote the 95% pointwise confidence intervals for the group with and the group without hypertension and/or small for gestational age fetus respectively. The symbol `*' parameters for which there was a significant difference between pre and post pregnancy measurements.

DISCUSSION

Our results offer an insight on both hemodynamic adaptation to pregnancy and long term influence of pregnancy on cardiac function in a population of women with structural heart disease. They show an attenuated cardiovascular adaptation with reduction in systolic function and progression of diastolic dysfunction during pregnancy, which persist 6 months after pregnancy.

We observed the characteristic significant increase in SV and CO, with steep rise in the first half and a more gradual plateau-like phase in the second half of pregnancy.

However, the magnitude of increase seems lower than in previously described normal pregnant populations and more comparable to the pattern observed in pregnancies complicated by growth restriction and pregnancies at high altitude(10, 11, 13-15, 29).

The pre-pregnancy LVmass was already elevated in our population, comparable to third trimester levels for normal healthy women(17). While somewhat attenuated, we still observed a statistically significant increase in LVmass during pregnancy.

Our data also showed a gradual decline in FS and EF due to an increase in LVESD, similar to normal pregnancy (17). While the absolute values persisted within normal ranges, the decline continued until six months postpartum leading to a statistically significant difference between pre- and post-pregnancy measurements.

These findings suggest a negative influence of pregnancy on systolic function in women with structural cardiac disease. Our data are in contrast to Uebing's findings who could not observe a deleterious effect pregnancy on left ventricular function(19). One could question the accuracy of EF and FS derived from the Teicholz formula in reflecting systolic function in pregnant women with structural heart disease. As most other echocardiographic volume estimations equally have intrinsic limitations, we believe that MRI analysis of systolic function is necessary to confirm our findings.

Normally the E/A ratio decreases with gestational age, as the importance of atrial contribution to ventricular filling increases along with HR towards the end of pregnancy (13, 17, 30). We observed a relatively constant E/A ratio and HR within normal ranges throughout pregnancy in our population. However, E/E' ratio, which was already elevated before pregnancy in our population, showed a further significant increase with gestational age. While the pattern is similar to normal pregnancy the absolute values were far above both normal and pre-eclamptic pregnancy values, clearly in the pathological range(11-13). Our findings suggest a progressive diastolic dysfunction in women with structural heart disease with advancing gestational age. In normal pregnancy, increased load is compensated by myocardial hypertrophy. Due to elevated baseline levels, the capacity for further expansion in LVmass seems reduced in our population. Increments in load therefore lead to elevation of filling pressures, as reflected by the E/E' ratio. The significant difference in pre-post-pregnancy E/E' ratio, indicates a persistent negative influence of pregnancy on diastolic function in women

with structural heart disease 6 months postpartum. Future studies should consider a longer postpartum follow-up to evaluate the transient or permanent nature of these changes.

To our knowledge this is the first study assessing diastolic function during and after pregnancy in women with structural heart disease. Our observations also highlight the importance of tissue Doppler in the longitudinal assessment of diastolic dysfunction during pregnancy. As important volume- and loading shifts occur along with gestational age, changes are best evaluated by a combined assessment of the pulsed wave mitral inflow Doppler and load independent tissue Doppler of the mitral annulus.

Not surprisingly, all these findings suggest a mildly reduced cardiac potential for adaptation to the normal requisites of pregnancy in women with structural heart disease. The maladaptation is partly comparable to that observed in women with growth restriction and gestational hypertension, however diastolic dysfunction is more severe(11, 31).

When assessing the influence of severity of cardiac disease on cardiac adaptation we observed a similar pattern betweenWHO1-2 and WHO3-4 groups. While the trend seems visually more pronounced for the severe group (WHO 3-4) in Figure 3, it failed to show statistical significance except for heart rate. Considering the known association between fetal growth restriction and hemodynamic maladaptation, the difference in adjusted birthweight centiles nevertheless emphasizes the impression of a reduced cardiac adapative potential in high risk groups (Figure 3) and thus requires further investigation in a larger population.

A similar effect is observed for the influence of HT/SGA in Figure 4. This suggests that the reduced cardiac reserve is probably intrinsic to the structural heart disease rather than caused by the relatively high prevalence of hypertensive complications and SGA in our population (40%).

While the incidence of cardiac complications was relatively low in our population, the overall complication rate was high (62.5%). Previous research has demonstrated that women with heart disease are also at increased risk for non-cardiac and obstetric pathology(4-6). Most hypertensive complications occurred in women with known risk factors such as aortic stenosis and coarctation(4). As expected, SGA infants occurred mostly in women with atrial repair of transposition of the great arteries and pulmonary stenosis spectra(32, 33). Of note is the occurrence of post-partum depression in 2 women and a suicide attempt during pregnancy in a third woman. One could imagine that the burden of cardiac disease adds to the normal psychological challenge which accompanies pregnancy and early motherhood.

A higher incidence of depression or psychiatric disturbances has not been described in women with structural heart disease. It merits attention in further prospective trials as both cardiac disease and suicide are the main causes of maternal mortality in the western world(34).

Data on hemodynamic adaptation in pregnancy in women with structural heart disease are scarce and have not been described in a longitudinal matter. Therefore comparison with other studies is very difficult. Lesniak et al. analyzed the evolution of echocardiographic parameters of various valvular conditions during pregnancy, describing slightly different patterns according to the specific valvular pathology(9).

The strength of our study lies in its prospective nature and longitudinal assessment of hemodynamic adaptation during pregnancy as well as in the observation of the influence of pregnancy on long term cardiac outcome.

The main weaknesses of our study are the relatively limited number of patients, the heterogeneity of structural heart diseases and the absence of a control group. Future prospective research should be multicentric in order to allow pathology specific pattern analysis. Where evolutions during pregnancy were compared with previously published populations of pregnant women, a matched control group would certainly be preferable, ideally with inclusion of preconceptional measurements.

In conclusion our results show an attenuated cardiovascular adaptation to pregnancy in women with structural heart disease. Our data indicate a reduction in systolic function and progression diastolic dysfunction during pregnancy, which persist 6 months after pregnancy.

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Chapter 7

Pregnancy in congenital heart disease: prospective validation and assessment of cardiovascular and offspring risk

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ABSTRACT

Background

Adequacy of prepregnancy prediction of cardiovascular and offspring risk associated with pregnancy in women with congenital heart disease (CHD) determines for a large part the efficacy of counseling prior to and management during pregnancy. The accuracy of the different risk assessment tools needs prospective validation and comparison.

Methods

In this prospective study, we included 183 women with CHD and determined the outcomes of 191 pregnancies. The ZAHARA I and CARPREG cardiovascular risk scores were calculated for each pregnancy, as was the total number of cardiovascular (TPc) or offspring risk predictors (TPo) from these and other studies combined. Pregnancies were also classified according to the modified World Health Organization (WHO) classification of maternal cardiovascular risk and according to disease complexity (DC).

Results

Maternal cardiovascular events occurred during 19 (9.9%) pregnancies. Offspring events occurred during 63 pregnancies (33.0%). Both cardiovascular and offspring event rate increased with higher risk scores, higher TPc or TPo, higher WHO class and greater DC. The highest area under the curve (AUC) for cardiovascular risk was achieved by the WHO class (AUC: 0.79). CARPREG and ZAHARA I offspring risk scores and TPo performed comparably in estimating offspring risk (AUC: 0.67, 0,66 and 0.68 respectively). A combination of different risk estimation systems resulted in a slightly higher AUC for both maternal and offspring risk.

Conclusion

The WHO classification is the best available individual risk assessment model for estimating cardiovascular risk in pregnant women with CHD. For the estimation of offspring risk, the total number of offspring risk predictors, the CARPREG risk model and the ZAHARA I risk model are equally predictive.

Keywords

Pregnancy, outcome, risk predictors, heart disease

INTRODUCTION

Pregnancy in women with structural congenital heart disease (CHD) is associated with increased maternal cardiac and offspring risk. Maternal cardiac risk consists mainly of arrhythmias and episodes of heart failure, whereas the offspring is mainly at risk of premature birth, small for gestational age and mortality.[1-8] The magnitude of cardiac and offspring risk depends on the underlying CHD and is attributable to the complexity of the heart disease and (residual) lesions such as valvular and ventricular dysfunction.[1,2,7] For the attending cardiologist, adequate risk assessment is essential to optimize prepregnancy counseling and pregnancy management.

Several classifications and risk scores are available to estimate the cardiac and offspring risk associated with pregnancy in women with CHD.[2,5,7,9,10] Risk assessment models developed by the CARPREG investigators and by our own ZAHARA research group provide quantification of maternal cardiovascular and offspring risk of pregnancy. Both identified independent predictors of maternal cardiovascular and offspring events, as described elsewhere in detail.[2,7] Both models attribute points to each predictor of maternal cardiovascular risk, thus attributing a certain cardiovascular and offspring risk to the pregnancy. Additional predictors were identified by Khairy et al.[5] The European Society of Cardiology guidelines for the management of heart disease in pregnancy advise to estimate maternal risk according to the modified World Health Organization (WHO) classification.[9,11] This classification integrates knowledge from the total body of literature and takes into account the underlying heart disease, ventricular and valvular function, as well as predictors identified by several studies. Patients are classified as low, moderate or high risk, or contraindication for pregnancy.[9,11] Because risk of pregnancy is associated with disease complexity, risk assessment may also be performed using a generally accepted disease complexity (DC) classification.[1,10,12] A prospective external validation and comparison of the abovementioned risk scores and risk assessment models has not been performed.

We therefore aimed in this prospective multicenter study to provide external validation of the CARPREG and ZAHARA I risk scores and to compare the different risk assessment models in order to identify the optimal assessment strategy for estimating the risk of cardiovascular and offspring events of pregnancy in women with CHD.

PATIENTS AND METHODS

Design and setting

The ZAHARA II project is an ongoing prospective observational multi-centre cohort study. The study design of the ZAHARA II study is published elsewhere; therefore we provide a comprehensive summary here.[13]

Inclusion and exclusion criteria

Pregnant women with structural CHD (≥18 years) followed in any of 8 participating tertiary centers who provided written informed consent were included in the study at 20 weeks gestation. Miscarriage or pregnancy termination prior to 20 weeks gestation was reason for exclusion, as were drugs and alcohol abuse.

Baseline characteristics

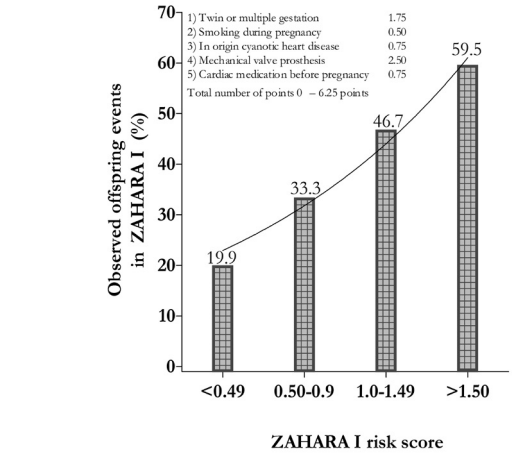
Baseline data recorded at the first prenatal visit at the cardiology outpatient clinic (at 20 weeks gestation) included: maternal age, obstetric history (including parity), underlying heart disease, prior interventions, cardiac sequelae, prior cardiovascular events, co-morbidity, prior and present cardiac status including ventricular and valvular function assessed according to the recommendations and guidelines of the EAE/ASE, use of medication, alcohol and smoking history.[14-17]

Risk assessment

Maternal cardiovascular and offspring risk of pregnancy was scored by 2 investigators who were ignorant of pregnancy outcome according to the foregoing risk assessment models using the baseline characteristics. Based on the presence of independent predictors, the ZAHARA I and CARPREG cardiovascular risk scores were calculated.[2,7] The ZAHARA I and CARPREG studies published predictors of offspring risk, but did not develop a risk score. Since we had full access tot the ZAHARA I data, we were able to calculate a ZAHARA I offspring risk score using identical methodology as previously described for the maternal risk score.[2] (Figure 1) We also developed an offspring risk score based on the predictors identified in the CARPREG study by using the exponent value of the OR from the independent predictors for offspring events published by the CARPREG investigators to weigh the risk factors and attribute points per risk factor.[7] No risk percentages per offspring risk point were available for this CARPREG offspring risk score. Additionally, the total number of (non-overlapping) predictors (TPo) (ZAHARA I, CARPREG and Khairy combined) of cardiovascular and offspring events were assessed. Patients were also classified according to the modified WHO classification of pregnancy risk and according to disease complexity (DC).[9,10]

Endpoints

We scored maternal cardiovascular and offspring events for each pregnancy according to the definitions used in the CARPREG and ZAHARA I studies. Primary cardiovascular events were: cardiovascular mortality, clinically significant (needing treatment) arrhythmia, clinically significant (needing treatment) heart failure, thrombo-embolic events (e.g. pulmonary embolism, valve thrombosis or deep venous thrombosis), vascular events (e.g. cerebrovascular accidents, myocardial infarction and dissection), need for urgent or invasive cardiovascular intervention up to 6 months post partum and endocarditis.[2,7] Secondary cardiac events were: NYHA class deterioration ≥2 points compared to baseline. Offspring events were: premature



Number of events	173	122	14	22
Pregnancies at risk	869	366	30	37
Percentage of total cohort (%)	66.7	28.1	2.3	2.8

Figure 1. The newly developed ZAHARA I risk score for offspring events during 1302 completed (>20 weeks gestation) pregnancies in women with congenital heart disease. Details on the ZAHARA I study can be found in reference 2.

delivery (delivery <37 weeks gestation), small for gestational age birth weight (<10th percentile), respiratory distress syndrome and/or sepsis; intracerebral (intraventricular) hemorrhage; recurrence of congenital heart disease and offspring mortality (demise in utero (>20 weeks gestation) till the first year postpartum).

Statistical analysis

We used SPSS (version 16.0, SPSS Inc., Chicago, Illinois, USA) and STATA (version 11.0, StatCorp LP, College Station, Texas, USA) for statistical analysis. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. Mean values and standard deviations were presented for normally distributed continuous variables. For non-normal distributed continuous variables median and ranges were computed. All P-values are two-sided. External validation of the CARPREG cardiovascular risk score and ZAHARA I cardiovascular and offspring risk scores were performed by plotting the expected versus observed event rates. We also calculated the area under the receiver-operating characteristic (ROC) curve (AUC) to compare the discriminative capacity of the different cardiovascular and offspring models. The best combination of risk assessment models was assessed by calculating the AUC following logistic models for the different test combinations. The p-value for the AUC results from the Chi^2 testing for random guess (AUC 0.5)). The goodness of fit of the model was assessed using the Hosmer-Lemeshow test.

Ethical Considerations

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The Medical Ethical Committee of all participating hospitals has approved the study. The Dutch Heart Foundation had no role in the design, data collection, analysis, interpretation, writing of the manuscript or the decision to submit for publication of this manuscript. The corresponding author has full access to all data and the responsibility for the submission of this manuscript for publication.

RESULTS

Overall, 201 women with structural CHD were asked to participate and 198 women gave informed consent (98.5%). Fifteen women were excluded: 9 women (4.5%) because of late (>12 weeks) spontaneous miscarriage and 6 women (3.0%) because of protocol violations (non-compliance (n=4) and moving abroad (n=2)). The remaining 183 women had 191 complete pregnancies (≥20 weeks of gestation). No women with cyanosis (oxygen saturation <90%), severe pulmonary hypertension or Eisenmenger syndrome were included. The baseline characteristics per pregnancy (n=191) are shown in Table 1.

Maternal cardiovascular events

The distribution of CHD and the primary and secondary cardiovascular events per CHD subtype are shown in Table 2. No maternal death occurred. Primary cardiovascular events were observed in 19 pregnancies (9.9%). Most frequent events were clinically significant arrhythmias (n=11), followed by heart failure (n=4) and thrombo-embolic events (n=4). Women with a history of arrhythmia (n=14) had 6 cardiovascular events, including 3 arrhythmias. One woman underwent pacemaker implantation because of atrioventricular block. Women with a mechanical valve prosthesis (n=11) had 6 cardiovascular events. Deterioration of NYHA functional class ≥2 points (secondary cardiovascular event) occurred in 38 pregnancies (19.9%).

Offspring events

Offspring events occurred in 66 children, corresponding to 63 pregnancies (33.0%). The distribution of offspring events per CHD subtype is shown in Table 2. Twenty-eight children (14.4%) were born prematurely (43% due to preterm labor), 29 children (14.9%) were born small for gestational age, 17 children (8.8%) had respiratory distress syndrome (59% were born premature) and 3 children (1.5%) had a cerebral (intraventricular) hemorrhage. Recurrence of CHD occurred in 10 children (5.2%). Offspring death occurred in 6 children (3.1%). Four children died in utero (>20 weeks gestation). Two children died within 28 days after birth.

Table 1. Maternal baseline characteristics (prior to pregnancy) at inclusion. N = 191 pregnancies.
AV, atrioventricular; AVA, aortic valve area; CHD, congenital heart disease; ICD, intra cardiac defibrillator; LHO, left heart obstruction; NYHA, New York Heart Association functional class; PG, peak gradient; PR, Pulmonary regurgitation.*Mean (± Standard Deviation); †With the exception of oral anti-coagulation.#Moderate/ severe.
**Corrected and uncorrected.

	n	(%)
Demographics		
Maternal age at conception (years ± SD)*	29.3	(±4.4)
Parity status		
0	124	(64.9)
1	50	(26.2)
≥ 2	17	(8.9)
Clinical situation		
NYHA class I	189	(99.0)
Past medical history		
History of arrhythmias	14	(7.3)
Left heart obstruction (PG > 30 mmHg or AVA < 1.5cm^2 or MVA < 2 cm^2)	14	(7.3)
Left heart obstruction (PG > 50 mmHg or AVA < 1.0 cm^2)	2	(1.0)
Systemic ventricular ejection fraction < 40%	2	(1.0)
Cardiac medication before pregnancy†	27	(14.1)
Systemic AV valve regurgitation#	6	(3.1)
Pulmonary AV valve regurgitation#	9	(4.7)
Mechanical valve prosthesis	11	(5.8)
Cyanotic heart disease**	50	(26.2)
Severe PR and/or depressed subpulmonary ventricular ejection fraction	22	(11.5)
Smoking history	34	(17.8)
Pacemaker / ICD	5	(2.6)
Congestive heart failure	2	(1.0)
Cerebrovascular accident	3	(1.6)
Medication use preconception		
None	164	(85.9)
Diuretics	0	(0.0)
Antiplatelet drugs	0	(0.0)
Vitamin K antagonists/Heparin	14	(7.3)
Digoxin	2	(1.0)
Beta-adrenoreceptor blocker	23	(12)
Calcium channel blocker	5	(2.6)
Angiotensin-converting enzyme inhibitor	1	(0.5)
Antiarrhythmic drugs	2	(1.0)

Table 2. Distribution of cardiovascular and offspring events by primary type of congenital heart disease in 191 completed pregnancies.

Values are number of pregnancies. AoS/BiAoV, congenital aortic valve stenosis or bicuspid aortic valve; APVR, Anomalous pulmonary venous return; PCE, primary cardiovascular events; SCE, secondary cardiovascular events; TGA, Transposition of the great arteries.

*1 Loeys Dietz, all others Marfan.

†All corrected; 2 double-outlet right ventricle (Fallot type).

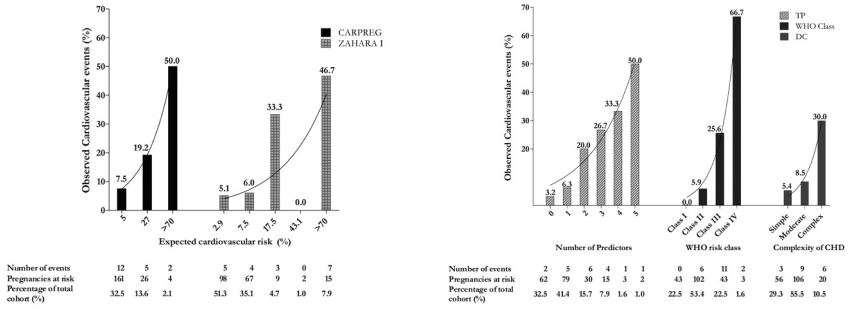
‡Pulmonary atresia with combined atrial and ventricular septal defects; truncus arteriosus.

§Isolated cleft mitral valve, corrected with mechanical valve (St Jude 25mm).

**1 twin pregnancy

††66 offspring events in 191 pregnancies; including three twin pregnancies.

			Cardiovascular events n (%)				Offspring events n (%)	
Maternal congenital lesion	N	%	PCE		SCE			
Atrial septal defects	19	9.9	2	(10.5)	5	(26.3)	8**	(42.1)
Ventricular septal defects	25	13.1	-	-	2	(8.0)	7	(28.0)
Atrioventricular septal defects	9	4.7	1	(11.1)	1	(11.1)	3	(33.3)
APVR	4	2.1	-	-	-	-	1	(25.0)
Pulmonary stenosis	19	9.9	-	-	1	(5.3)	7**	(36.8)
AoS/BiAoV	28	14.7	4	(14.3)	11	(39.3)	12	(42.9)
Aortic coarctation	22	11.5	1	(4.5)	3	(13.6)	3	(13.6)
Connective tissue disorders*	9	4.7	1	(11.1)#	2	(22.2)	3	(33.3)
Ebstein's anomaly	3	1.6	-	-	-	-	1	(33.3)
Tetralogy of Fallot†	34	17.8	3	(8.8)	6	(17.6)	13	(38.2)
TGA	13	6.8	3	(23.1)	3	(23.1)	3**	(23.1)
Fontan circulation	3	1.6	2	(66.7)	2	(66.7)	3	(100.0)
Other corrected complex cyanotic heart defects‡	2	1.0	1	(50.0)‖	2	(100.0)	1	(50.0)
Other§	1	0.5	1	(100.0)	-	-	1	(100.0)
Total	191	100	19	(9.9)	38	(19.9)	66††	(34.6)



Figures 2a and 2b show the risk of primary cardiac events during pregnancy per risk assessment technique. Overestimation of cardiovascular risk (expected events > observed events) was observed in both the ZAHARA I and CARPREG cardiovascular risk scores mainly in the mid- and/or high-risk segments, where relatively low number of patients could be included.
Figure 2a. Expected and Observed cardiovascular events for the ZAHARA I and CARPREG risk scores
Figure 2b. Observed cardiovascular event percentages for Total number of Predictors, WHO Classification and for Disease Complexity.

Validation of risk scores and comparison of different risk assessment techniques

Figure 3a shows the ROC for cardiovascular events for the different risk assessment and estimation models. All ROC curves of cardiovascular events deviate significantly from the diagonal line (no discrimination), with exception of the CARPREG risk score (AUC 0.62; 95% CI 0.47-0.77; P=0.081). The AUC for the ZAHARA I cardiovascular risk score was 0.73 (95% CI 0.59-0.87; P=0.010). Of the 5 cardiovascular risk assessment models, WHO classification had the highest AUC for prediction of maternal cardiovascular events (AUC 0.79; 95% CI 0.69-0.89; P<0.0001). A combination of WHO classification, TPc and DC had a slightly higher AUC: 0.82; 95% CI 0.72-0.92; P<0.0001).

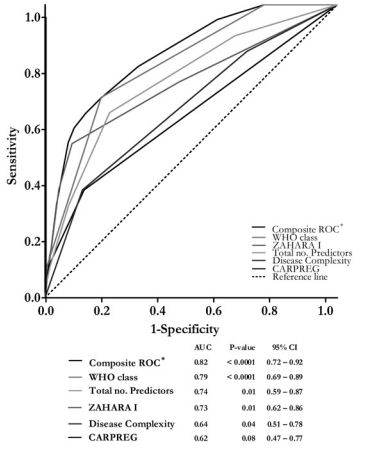


Figure 3a. Receiver Operating Characteristic Curves of cardiovascular events for the different cardiovascular risk assessment and estimation models.
*Composite ROC: optimal combination of risk assessment models (WHO class, total no. cardiac predictors and DC). The AUC differs significantly between WHO class and 1) CARPREG (p=0.0065) and 2) disease complexity (p=0.0093); as well as between CARPREG and total number of cardiovascular predictors (p=0.035).

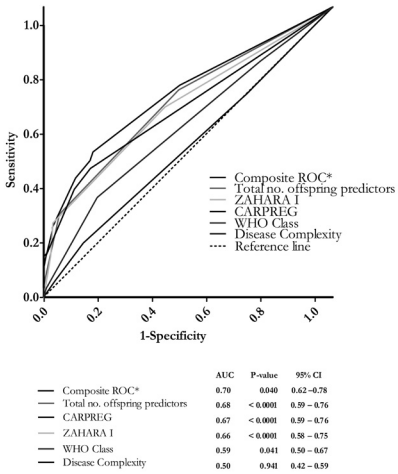
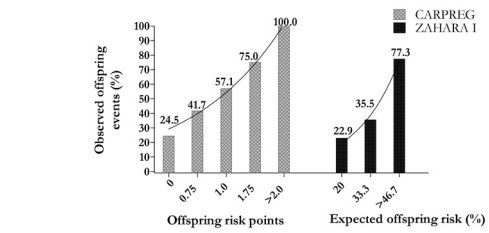


Figure 3b. Receiver Operating Characteristic Curves of offspring events for the different offspring risk assessment and estimation models.
*Composite ROC: optimal combination of risk assessment models (ZAHARA I offspring risk score and CARPREG offspring risk points). The AUC differs significantly between disease complexity and 1) total no. of offspring predictors (p=0.0008), 2) ZAHARA I (p=0.0013), and3) CARPREG (p=0.012); as well as between total no. of offspring predictors and WHO class (p=0.025).



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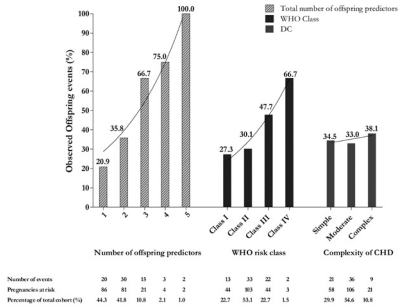

b

Figures 4a and 4b show the risk of offspring events in women with CHD per risk assessment technique. All risk assessment techniques, with the exception of disease complexity, show an increase in offspring risk with increasing risk points, number of predictors or class. Figure 3b shows the ROC for offspring events for the different risk assessment and estimation models. All models deviate significantly from the reference line, with the exception of disease complexity. A combination of the ZAHARA I offspring risk score and CARPREG offspring risk points provided the highest AUC. The addition of other risk assessment techniques did not improve the AUC significantly.
Figure 4a. Expected and Observed offspring events for the ZAHARA I risk score and Observed cardiovascular event percentage for CARPREG risk points.
Figure 4b. Observed offspring events percentages for Total number of offspring predictors, WHO Classification and for Disease Complexity.

DISCUSSION

This study is the first to validate, compare and integrate the different risk assessment models that are used to predict cardiovascular and offspring risk during pregnancy and puerperium in women with CHD. All risk assessment models are able to some extent to identify women with CHD at risk of primary cardiovascular and offspring events. When comparing the 5 individual risk assessment models, the modified WHO classification provides the most adequate individual assessment of cardiovascular risk in our cohort. For the assessment of offspring events, the difference in AUC is very small between the total number of offspring predictors, the ZAHARA risk score and the CARPREG risk points. A combination of the risk factors from ZAHARA I and CARPREG provides the highest AUC.

Maternal cardiovascular events

Our study indicates that pregnancy in women with CHD is relatively safe. The cardiac event rate in our cohort is low compared to some other studies.[5,18-20] The difference in observed cardiovascular events is mainly due to differences in study population and in definition of primary and secondary cardiovascular events. Several other studies found comparable cardiovascular event rates. [1,2,4,7,21,22] Our cohort is a relative low risk cohort, with 99% of women in

NYHA class I prepregnancy and no women with cyanosis or pulmonary arterial hypertension. Well organized prepregnancy counseling in the tertiary centers in the Netherlands prevents most high risk women from becoming pregnant, which can explain the relatively low event rate in our cohort.

Validation of cardiovascular risk assessment models

The ZAHARA I risk score discriminates the cardiovascular events in pregnancy better in this cohort of women with CHD than the more widely used CARPREG risk score. The AUC for ZAHARA I is higher and it deviates significantly from random guess (AUC =0.5), unlike the CARPREG risk score. The low prevalence of systemic ventricular dysfunction and high NYHA class as well as the absence of mitral valve stenosis in our cohort is the most likely explanation. The CARPREG risk score overestimates maternal cardiovascular risk in our cohort, in line with other studies.[4,5,21,22]

Overall, in our cohort of women with CHD, the WHO classification discriminates best for cardiovascular events. This is not surprising since the WHO classification integrates all knowledge about maternal risk, including known contraindications for pregnancy which are ignored in the CARPREG and ZAHARA I risk scores, as well as known predictors found by CARPREG and other studies, underlying heart disease and other morphological and clinical variables. A disadvantage of the WHO class may be that expert knowledge is sometimes required, especially when choosing between WHO class II and class III. Whether physicians with less expertise might make a different choice than a more experienced physician was not assessed in our study. Finally, it is important that WHO class I has a negative predictive value of 100% for maternal cardiovascular events, indicating that pregnancy is relatively safe in these women.

A combination of the risk classification systems from the WHO class with total number of cardiovascular predictors and disease complexity provides the most adequate assessment of cardiovascular risk in pregnancy. This illustrates that integration of clinical information and predictors or population-based information has additional value on top of individual risk assessment models.

Offspring events

The offspring event rate observed in our cohort is comparable to most other studies in women with CHD.[1,2,4-7,18-20,23,24] Offspring death occurred in 3.1% of pregnancies. Although offspring mortality in our cohort is in accordance with previous studies in women with CHD, it is much higher than in general Dutch population.[2,4-7,20,25] Also premature births, small for gestational age and recurrence of CHD occurred more often than would be expected in the general Dutch population.

Validation of offspring risk assessment models

The estimation of offspring risk by the ZAHARA I offspring risk score proved to be fairly accurate. The CARPREG risk score also identified pregnancies with a higher risk of offspring events, however since no risk percentage could be attributed to the CARPREG risk points a comparison with the ZAHARA I risk model could not be made.

The risk models predicting offspring events appear to be interchangeable, because the differences in AUC are very small, especially between ZAHARA I, CARPREG and TPo. This is explained by the huge overlap between the risk factors found by ZAHARA I and CARPREG. The WHO class was not designed to assess offspring events in women with CHD. Therefore it does not take into account factors such as maternal age, parity, smoking and twin pregnancy, which are known risk factors for offspring events. This is probably also the main reason why disease complexity alone is not an accurate predictor of offspring events.

Limitations and strengths

The participation rate was excellent with 98% of women providing written informed consent and only 2 women lost to follow up. Although inclusion rate is high, some limitations need to be addressed. Some inclusion bias might have been introduced, since only pregnancies of ≥20 weeks were taken into account. Additionally no patients with a high risk of maternal death, such as Eisenmenger syndrome, could be included. Nevertheless, the distribution of the CHD subtypes adequately represents a tertiary hospital pregnant CHD cohort. Additionally, the available risk prediction systems that we validated did not allow prediction of more threatening events such as heart failure separately from more innocent events such as supraventricular arrhythmias. Despite the limitations, our study is the first prospective study to validate, compare and integrate the available risk estimation models to predict the cardiovascular risks during pregnancy in women with CHD.

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Chapter 8

Outcome of pregnancy in patients with structural or ischemic heart disease: results of a registry of the European Society of Cardiology

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ABSTRACT

Objectives

To describe the outcome of pregnancy in patients with structural or ischaemic heart disease.

Methods

In 2007 the European Registry on Pregnancy and Heart disease was initiated by the ESC. Consecutive patients with valvular, congenital, ischemic heart disease or cardiomyopathy presenting with pregnancy were enrolled. Data for the normal population was derived from the literature.

Results

Sixty hospitals in 28 countries enrolled 1321 pregnant women between 2007-2011. Median maternal age was 30 years (range 16-53). Most patients were in NYHA class I (72%). Congenital heart disease (66%) was most prevalent, followed by valvular heart disease 25%, cardiomyopathy 7% and ischemic heart disease in 2%. Maternal death occurred in 1%, compared to 0.007% in the normal population. Highest maternal mortality was found in patients with cardiomyopathy. During pregnancy 338 patients (26%) were hospitalized, 133 for heart failure. Caesarean section was performed in 41%. Fetal mortality occurred in 1.7% and neonatal mortality in 0.6%, both higher than in the normal population. Median duration of pregnancy was 38 weeks (range 24-42) and median birth weight 3010 gram (range 300-4850). In centres of developing countries maternal and fetal mortality was higher than in centres of developed countries (3.9% versus 0.6%, $p < 0.001$ and 6.5% versus 0.9% $p < 0.001$)

Conclusions

The vast majority of patients can go safely through pregnancy and delivery as long as adequate pre-pregnancy evaluation and specialized high quality care during pregnancy and delivery are available. Pregnancy outcomes were markedly worse in patients with cardiomyopathy and in developing countries.

Keywords

pregnancy, congenital heart disease, valvular heart disease, cardiomyopathy, ischemic heart disease

INTRODUCTION

In women with heart disease maternal mortality is reported to be much higher than average and the risk appears to be increasing such that in western countries heart disease is the major cause of maternal death (1,2,3). However, we do not fully understand what the impact of pregnancy is on the progression of heart disease or how heart disease affects the outcome of pregnancy. The full spectrum of structural heart disease including congenital heart disease (CHD), valvular heart disease (VHD) and cardiomyopathy (CMP) and also ischemic heart disease (IHD) may be encountered in pregnant women. In developing countries that still struggle with a high prevalence of rheumatic fever, acquired valvular heart disease dominates, whereas in developed countries congenital heart disease is the main diagnostic group (2,4,5,6). In addition, over the last few years the incidence of an acute coronary event during pregnancy has increased, due to older childbaering age changes in lifestyle with more hypertension, smoking, obesity in women (9,10,11,12,13,14,15). Cardiomyopathy is uncommon during pregnancy, but it is difficult to manage a pregnancy in the context of left ventricular dysfunction or peripartum cardiomyopathy (PPCM) with a high risk of an adverse outcome for both the mother and the baby (16,17).

In developed countries optimal care and preconception counselling is available in all centres although quite often not accessed by the women concerned. In developing countries only a minority of women with heart disease are assessed and appropriately counselled prior to conception. Not surprisingly this may have a major adverse influence on pregnancy outcome.

Our understanding of the consequences of heart disease on pregnancy outcome is limited and prevents us from designing relevant randomised controled trials. To improve our understanding of this complex subject a registry has been established with the aim of determining patterns of outcome and correlating these with management strategies to determine the areas of danger for both mother and baby and to identify the best forms of treatment. To have any use such a registry has to be large to include sufficient patients with a a wide range of diagnoses. Consequently, the European registry on pregnancy and structural heart disease was initiated by the European Society of Cardiology (ESC).

METHODS

Study design

In 2007 the European Registry on Pregnancy and Heart Disease was initiated jointly by the ESC working group on grown up congenital heart disease and on valvular heart disease and embedded in the Euro Heart Survey Programme of the ESC. All national societies of the ESC were informed and invited to contact centers in their countries dealing with pregnancy and

heart disease and all members of the two ESC working groups were invited to participate. In addition other centers from around the world who were interested in the registry were invited to participate. Consecutive patients with structural heart disease or IHD presenting with pregnancy, regardless of age, any concomitant diseases and type of heart disease could be enrolled, including patients who already participated in trials or other registries. When warranted, ethical approval or Institutional Review Board (IRB approval) was obtained (e.g. Germany, USA, Canada, Belgium), however, in many countries the procedure to obtain ethical approval was waived because of the anonymised and untraceable nature of the data.

The registry started in January 2008. Pregnant patients from 2007 were included retrospectively at that time, as it was believed that the complete data of these patients were available and reliable. From January 2008 patients were included prospectively. Exclusion criteria were non-structural heart disease, for example arrhythmias occurring in the context of a normal heart.

Information included in this manuscript refer to the patients enrolled up to June 2011.

Data

Baseline data from before pregnancy were recorded including cardiac diagnosis, New York Heart Association (NYHA) functional class, prior cardiac events, surgery or interventions, rhythm status, co-morbidities , obstetric history, the use of medication and smoking. Estimation of maternal risk associated with pregnancy was done by classifying the patients to the modified World Health Organisation (WHO) categories, which integrates the available knowledge from literature on known risk factors. WHO I is low risk, II medium and III represents high risk. Importantly, WHO IV means a contraindication for pregnancy (18). Countries were divided into developed or developing according to the International Monetary Fund Classification (IMF) (19).

The following data relating directly to the pregnancy were collected: age at conception, cardiac complications, obstetric complications, perinatal complications, medication use, pregnancy duration and mode of delivery. Cardiac complications included hospitalisation, heart failure requiring treatment, symptomatic documented arrhythmia, endocarditis, cardiac intervention during pregnancy, thrombo-embolic and haemorrhagic complications, or acute coronary syndrome. Obstetric complications consisted of intra-uterine growth retardation (IUGR), pregnancy-induced hypertension (PIH i.e new onset hypertension (>140/90 at 2 occasions) after > 20 weeks of gestation), preeclampsia (PIH criteria plus >0.3 g proteinuria in 24-hour urine sample), eclampsia (preeclampsia with grand mal seizures), premature rupture of membranes (membrane rupture before onset of uterine contractions), premature labour (spontaneous onset of labour <37 weeks gestation) postpartum haemorrhage (vaginal delivery >500 ml, caesarean delivery >1000 ml or requiring transfusion) and placental abruption. Perinatal complications recorded were: fetal death (>22 weeks of gestation or >500grams);

perinatal death (<30 days postpartum) and CHD in the baby of a mother with congenital heart disease. After birth, gender, birth weight and Apgar score were recorded.

Six months after pregnancy information on additional events and complications as well as neonatal outcome was collected.

Data for the normal popupation was obtained from current publications on maternal health and pregnancy. (6, 20-22) Mean birth weight for the normal population was calculated as the mean of the reported birth weight from the countries that included patients in the registry. This figure was obtained in the countries that included most patients (together 55%: Egypt, Netherlands, Germany, United Kingdom, Italy and Spain).(6,23-27).

Data analysis

Categorical data are presented as frequencies (numbers) and percentages. One-sample Kolmogorov-Smirnov tests and histograms were used to check normality of continuous data. Normally distributed continuous data are presented as mean values ± one standard deviation (SD), whereas non-normal data are presented as medians with interquartile range (IQR). Differences in categorical data between independent patient groups were compared by binomial tests or chi-square tests. If any expected cell count was less than 5 the Fisher's exact tests or in case of more than 2 groups a Monte Carlo method of approximation was used-Mantel-Haenszel linear-by-linear chi-square tests were used to compare clinical outcomes in the WHO categories, since linear associations were expected. Differences in continuous data between independent patient groups were compared by Student's T tests, or one-way analyses of variance (ANOVA), as appropriate. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago). Unless specified otherwise, p-values <0.05 (2-sided test) were considered statistically significant.

RESULTS

The registry enrolled 1321 women with structural heart disease from 60 hospitals in 28 countries. (Figure 1)

Baseline characteristics

Median maternal age at pregnancy was 30 years (range 16-53). Fifty-six% of the women had one or more previous pregnancies. In Table 1 baseline characteristics are given, comparing patients included in the registry versus the normal population and presenting the data for the different subgroups. Most patients were in NYHA class I (70%), while only 0.3% of the patients was in NYHA class IV. Medication was used during pregnancy by 28% of the patients (Table 1).

Diagnoses

The diagnoses are shown in more detail in Figure 2. Most patients had CHD (872 patients, 66%) and only a minority had IHD (25 patients, 2%). Of the patients with CHD, 579 (66%) had at least one intervention before pregnancy. Valvular interventions were reported in 291 cases, of which 139 surgical repairs, 69 percutaneous interventions and 83 surgical valve replacement (55 mechanical valves were implanted in 52 patients). At baseline patients with IHD were older, used medication, more often suffered from hypertension and diabetes and were current smokers. More patients with CMP were in NYHA class III. (Table 1)

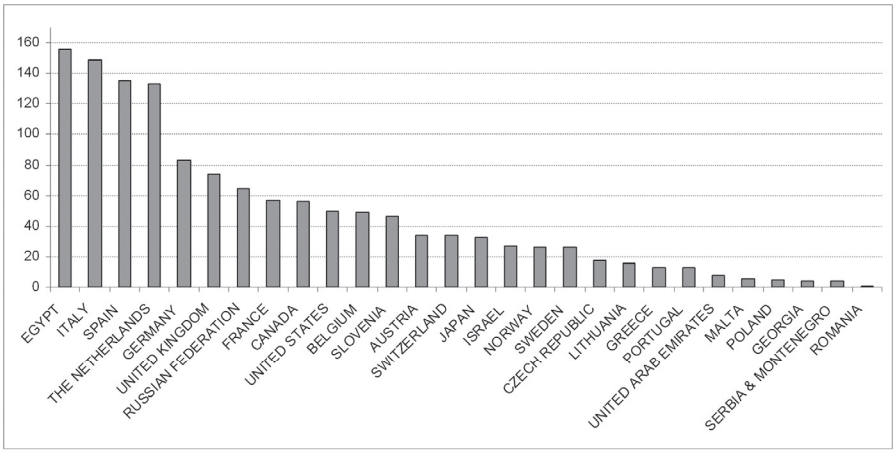

Figure 1. Inclusion per country.
Pregnant patients with structural heart disease included between 2007-2011.

Table 1

Baseline characteristics for women with structural heart disease, compared to the normal pregnant population and per subgroup.

Norm data was use from: *EURO-PERISTAT † Cutler, ‡Lawrence, §Hameed, ¶ Drenthen

CHD=congenital heart disease, VHD=valvular heart disease, CMP=cardiomyopathy, IHD=ischemic heart disease, NYHA=New York Heart Association, WHO=World Health Organisation categories.

P value comparison between CHD VHD CMP or IHD, if significant one of the groups is different compared to at least one other group.

	Normal	Reg (n=1321)	p value	CHD (n=872)	VHD (n=334)	CMP (n=88)	IHD (n=25)	p value
Mean age in years (range)*	30 (12-62)	30 (16-53)	0,93	29,6 (16-45)	30,3 (18-53)	30,7 (18-43)	37,3 (24-47)	<0,001
Prior cardiac intervention ¶ (%)	<0,5	54	<0,001	66	34	6,8	44	<0,001
Nulliparous (%) *	44	50	<0,001	55	38	46	28	<0,001
NYHA class								<0,001
NYHA class 1		70		76	58	56	64	
NYHA class 2		25		21	33	32	28	
NYHA class 3		3,1		1,3	6,8	8,0	0,0	
NYHA class 4		0,3		1,5	7,4	8,0	0,0	
WHO categories								<0,001
WHO 1		18		26	3,9	0,0	0,0	
WHO 2		39		38	47	26	0,0	
WHO 3		38		33	42	56	96	
WHO 4		4,0		2,1	7,4	10,2	4,0	
Hypertension (%)†	7	6,7	0,75	6,2	4,5	12,5	36	<0,001
Current smoker (%) *	10	3,3	<0,001	3,3	1,8	5,7	12	0,022
Diabetes (%) ‡	1,8	1,6	<0,001	1,1	2,4	2,3	8,0	0,034
Complaints of heart failure (%)	0	11	<0,001	6,7	20	15	0,0	<0,001
Any medication (%) §	2	28	<0,001	20	39	55	72	<0,001
Beta blocker ¶ (%)	<0,5	15	<0,001	10	15	44	48	<0,001
ACE inhibitor ¶ (%)	<0,5	3,7	<0,001	1,4	4,5	17	28	<0,001
Anticoagulation ¶ (%)	<0,5	10	<0,001	5,7	21	13	28	<0,001

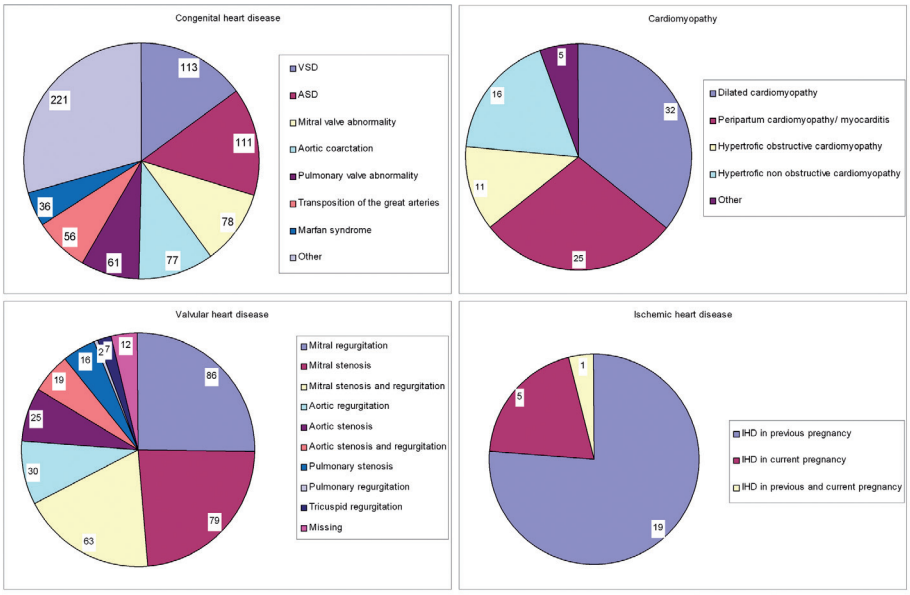

Figure 2. Cardiovascular diagnosis per sub-group

Outcome

Maternal mortality

Maternal death occurred in 13 patients (1%), of which 7 were due to cardiac reasons, 3 thromboembolic events and 3 suffered from sepsis. (Table 2)

Maternal morbidity

Outcomes are described for the total population included in the registry, compared to the normal population and for the different subgroups in Table 3.

During pregnancy 338 patients (26% of all pregnancies) were hospitalized, most of these patients only once (257 patients). In 203 cases this was for cardiac reasons, of which 133 (10% of all pregnancies) were for heart failure. There were 6 patients with acute coronary syndrome(ACS) during pregnancy; only one of these patients had a history of previous ACS. In 6 patients thrombo-embolic events were reported, consisting of one thromboembolic occlusion of the anterior tibial artery, 1 deep venous thrombosis, 1 ischemic cerebrovascular accident and 3 mechanical valve thromboses. So 3 of the 52 patients (6%) with at least one mechanical valve suffered from valve thrombosis. Three patients had endocarditis, two of the mitral valve (both patients had a history of endocarditis).

Table 2
Maternal mortality in women with structural heart disease.
LMWH = low molecular weight heparin, Vit K = Vitamine K antagonist, pp=postpartum, + = fetal survival, ++= twin survival, - = fetal death

Diagnosis	NYHA class	Medication used before pregnancy	Developing/ Developed	Age (years)	When	Reason	Fetal outcome
Mitral stenosis	2	None	Developing	23	35 weeks	Cardiogenic shock	-
Mitral stenosis and regurgitation	1	Antiplatelets	Developed	42	Delivery (CS)	Heart failure and sudden cardiac death	+
Mitral regurgitation	1	None	Developing	21	2 wks pp	Heart failure	-
Mechanical mitral valve	1	Antiplatelet, Vit K	Developing	29	12 weeks	Severe bronchopneumonia	-
Dilated Cardiomyopathy	1	None	Developed	32	5 wks pp	Cardiogenic shock	++
Cardiomyopathy after antracycline	2	LMWH	Developed	27	22 wks pp	Arterial thrombus of solo kidney,	+
Tricuspid regurgitation	1	UFH	Developing	19	1 wk pp	Right sided heart failure	_
Eisenmenger syndrome (ASD, VSD)	2	None	Developed	29	1 wk pp	Acute hypoxia after CS	+
Atrial septal defect	1	Vit K	Developing	30	1 wk pp	Septic shock	+
Mitral stenosis and regurgitation	1	None	Developing	25	6 wks pp	Sepsis	-
Pulmonary atresia	2	Diuretics, LMWH, antiplatelets	Developed	36	1 wk pp	Anoxic cerebral event, brain death	+
Mitral stenosis and regurgitation	2	Digoxin, Vit K	Developing	29	1 wk pp	Brain stem embolization	+
Pulmonary stenosis	1	Atenolol, antiplatelets	Developed	21	Delivery (CS)	Sudden cardiac death during CS	+

Obstetric events during pregnancy

Hospital admission for obstetric reasons was necessary in 105 patients. Pregnancy induced hypertension occurred most often (table 3). Other reasons for obstetric admission reported were vaginal bleeding (30 patients), pregnancy induced diabetes (18 patients) and abortion/ missed abortion (27 patients).

Delivery

Forty-one percent of the patients (n=533) underwent caesarean section (CS), compared to 23% in the general population. This was planned in 393 patients (of which 53 ended up with an emergency CS) and was an emergency in 141 patients who had planned vaginal delivery. Assisted vaginal delivery (forceps, vacuum) was performed in 32% of the vaginal deliveries.

Table 3. Outcome and complications per diagnosis for women with structural heart disease, compared to the normal pregnant population and per subgroup.
Normal data was use from: *EURO-PERISTAT † Hutcheon, §Hameed, ¶ Drenthen, # Oyelese, **Ferrazzani, †† Jaddoe, ‡‡Ahrari
P value comparison between CHD VHD CMP or IHD, if significant one of the groups is different compared to at least one other group.

	Normal	Reg (n=1321)	p value	CHD (n=872)	VHD (n=334)	CMP (n=88)	IHD (n=25)	p value
Maternal mortality (%) *	0,007	1,0	<0,001	0,5	2,1	2,4	0,0	0,031
Maternal hospital admission (%) §	2	26	<0,001	20	38	33	28	<0,001
Cardiac								
Heart failure(%) §	0	12	<0,001	8,0	18	24	8,0	<0,001
Supraventricular arrhythmias (%)¶	<0,5	0,9	<0,001	0,7	3,0	1,1	0,0	0,025
Ventricular arrhythmias (%)¶	<0,5	2,0	<0,001	1,6	0,6	11	0,0	<0,001
Obstetrics complications								
Pregnancy induced hypertension (%)†	2,5	2,4	0,93	2,3	2,4	3,4	4,0	0,61
Pre (Eclampsia)(%)†	4	3,3	0,23	2,2	3,9	11	4,0	0,001
Caesarean section (%) *	23	41	<0,001	38	42	58	60	0,001
Postpartum haemorrhage(%) #	5	2,9	<0,001	2,4	5,1	0,0	0,0	0,021
Fetal								
Apgar score < 7(%)*	1	10	<0,001	6,5	15	18	24	<0,001
Preterm birth <37 weeks(%)*	8	15	<0,001	13	16	30	36	<0,001
Fetal death (%)*	0,35	1,7	<0,001	0,5	3,9	4,5	4,0	<0,001
Neonatal death(%)*	0,4	0,6	0,27	0,6	0,3	1,1	4,0	0,13
Mean birth weight (grams) **, ††, ‡‡	3190	3010	<0,001	3056	2959	2878	2662	0,001
Pregnancy duration (weeks)*	40	38	<0,001	38	38	37	36	<0,001

The postpartum period

In the first week after pregnancy, 64 patients suffered a complication, consisting of heart failure in 31 and postpartum hemorrhage in 32. In the six months after pregnancy 38 additional complications occurred (25 patients had heart failure). Of the total study population 162 patients (12%) had at least one period of heart failure during or after pregnancy, while this is rarely if ever seen in the general population.

Fetal outcome

Of the 1321 pregnancies fetal outcome was unknown in 43 pregnancies; Twenty-three twins were born and therefore outcome data were available for 1301 babies. Fetal mortality (>22 weeks or 500grams) was observed in 1,7% of pregnancies, of which 62 % were intrauterine fetal death without further information, 21% were clearly due to the maternal condition and 17 % were because of structural fetal abnormalities. The cause of neonatal mortality was severe neonatal abnormalities (4), premature birth (2), bronchopneumonia (1) and one sudden death Congenital heart disease was reported in 29 of the 829 (3,5%) children born to women with CHD. Six of had the same congenital defect as their mother (2 ASD, 2 VSD, 2 Marfan) in addition two patient with coarctation had a child with a hypoplastic left heart syndrome..

Type of heart disease

Clear differences were found in maternal and fetal outcome by type of heart disease (Table 3). Maternal mortality was highest in patients with CMP(2,4%) and also heart failure and ventricular arrhythmias were seen more often in these patients. Caesarean section rate was highest in patients with IHD or CMP, while postpartum haemorrhage occurred more often in patients with VHD. Of the women who had postpartum haemorrhage 58% were receiving oral anticoagulants compared to 9% in the patients without postpartum haemorrhage. Pregnancy duration was shorter and neonatal death rate higher in patients with IHD compared to the other groups.

WHO categories

A strong correlation with cardiac, obstetric and fetal outcome was found. In particular, maternal hospital admission, heart failure, caesarean section and postpartum haemorrhage were clearly different between the different WHO categories and also birth weight and pregnancy duration showed clear differences. (Table 4)

Developed versus developing countries

Though any between group comparison is very fragile since the size of the populations were grossly unbalanced, significant differences were found: maternal mortality was 3,9% versus 0,6% ($p<0.001$) respectively and fetal death 6,5% versus 0,9% ($p<0.001$). (Table 5)

Table 4. Outcome and complications per WHO categories for severity of heart disease.
P value comparison between WHO1, WHO 2, WHO 3 or WHO 4 if significant one of the groups is different compared to at least one other group.

	WHO 1 (n = 241)	WHO 2 (n = 514)	WHO 3 (n = 504)	WHO 4 (n = 53)	p value
Maternal mortality (%)	0,4	0,6	1,5	4,0	0,035
Maternal hospital admission (%)	13	18	36	66	<0,001
Cardiac					
Heart failure (%)	1,2	5,6	19	57	<0,001
Supraventricular arrhythmias (%)	0,4	1,4	1,4	3,8	0,13
Ventricular arrhythmias (%)	1,7	0,8	3,4	1,9	0,068
Obstetrics complications					
Pregnancy induced hypertension (%)	1,7	3,1	2,4	0,0	0,91
Pre (eclampsia) (%)	2,1	2,9	3,4	3,8	0,32
Caesarean section (%)	27	37	49	60	<0,001
Post partum haemorrhage (%)	0,0	1,2	5,2	11	<0,001
Fetal					
Apgar score < 7 (%)	4,1	10	11	17	0,001
Preterm birth <37 weeks (%)	8,7	15	17	30	<0,001
Fetal death (%)	0,4	0,6	2,8	5,7	0,001
Neonatal death (%)	1,2	0,4	0,4	0,0	0,24
Birth weight (grams)	3109	3074	2925	2735	<0,001
Pregnancy duration (weeks)	39	38	38	37	<0,001

Table 5. Outcome and complications in pregnant patients with heart disease, per IMF Classification of developed versus developing countries.
P value comparison between Developed and Developing.

	Total	Developed (n = 1136)	Developing (n = 185)	p value
Baseline				
Mean age (range)	30 (12-62)	30 (16-53)	27 (18-45)	<0,001
NYHA class I (%)	70	74	47	<0,001
Type of heart disease				<0,001
Congenital (%)	66	74	18	
Valvular (%)	25	18	72	
Other (%)	9	8	10	
Prior cardiac surgery (%)	54	59	22	<0,001
Medication use before pregnancy (%)	28	26	37	0,002
Nulliparous (%)	50	52	34	<0,001
Outcome				
Maternal mortality (%)	1,0	0,6	3,9	<0,001

Table 5. Outcome and complications in pregnant patients with heart disease, per IMF Classification of developed versus developing countries. *(continued)*
P value comparison between Developed and Developing.

	Total	Developed (n = 1136)	Developing (n = 185)	p value
Baseline				
Maternal hospital admission (%)	26	23	41	<0,001
Cardiac				
Heart failure (%)	12	11	23	<0,001
Supraventricular arrhythmias (%)	0,9	1,1	2,7	0,07
Ventricular arrhythmias (%)	2,0	2,2	0,5	0,16
Obstetrics complications				
Pregnancy induced hypertension (%)	2,4	2,5	2,2	0,80
Pre (eclampsia) (%)	3,3	3,0	4,9	0,18
Caesarean section (%)	41	40	44	0,34
Post partum haemorrhage (%)	2,9	2,9	2,7	0,88
Fetal				
Apgar score < 7 (%)	10	8,7	17	0,001
Preterm birth <37 weeks (%)	15	16	11	0,12
Fetal death (%)	1,7	0,9	6,5	<0,001
Neonatal death (%)	0,6	0,6	0,5	0,90
Birth weight (grams)	3010	3027	2899	0,004
Pregnancy duration (weeks)	38	38	38	0,93

DISCUSSION

In this large contemporary international prospective registry of 1321 patients with structural or ischemic heart disease the incidence of cardiac and neonatal complications was, as expected found to be much higher than in the normal pregnant population and maternal mortality was more than 100 times higher than in the background population. However, clear disticintions could be made between the different types of heart disease and between the outcomes in developed versus developing countries. The use of caesarean delivery was higher than in the normal population (41% versus 23%) with a large variation between countries.

Congenital heart disease

This was the largest subgroup in the registry and it's outcomes were relatively good compared to other subgroups. Most of these patients were diagnosed and treated long before pregnancy and nowadays have prepregnancy counseling; as a consequence they are better prepared for pregnancy.. The high rate of successful prior cardiac corrective surgery,

favourable baseline NYHA class, and low use of medication are all factors which are likely to have contributed to the relatively favourable outcomes. However, even in this group with relatively good outcome CS rates were higher and mean birth weight was lower than in the background population. The recent ESC guidelines advocate spontaneous onset of labour with vaginal delivery for most CHD patients. However, this is not based on hard data and clearly needs further investigations. It is possible that doctor's decision was the main reason for the high number of CS. Premature birth was reported in 13% of our CHD patients, which is slightly lower than the 16% reported in the a previous literature review, but higher than the 8% found in the normal population. (6) The prematurity in this group is likely to have been influenced in part by the decision to perform elective CS but nevertheless prematurity in any context must taken seriously as it has the potential to influence neonatal outcome adversely.

Valvular heart disease

Patients with VHD were often not known to have heart disease before pregnancy and many patients were in NYHA class II and III before pregnancy. As expected mitral stenosis and/or regurgitation were the commonest lesions (63%), while aortic valve disease occurred in 23%. Patients with VHD had a higher maternal mortality rate than patients with CHD. Heart failure was the most frequently observed maternal complication as was also found earlier by Hameed et al and was recorded in 18% of cases (7). In 38% hospital admission was necessary and supraventricular arrhythmias were more common than in other patient subgroups. Furthermore postpartum haemorrhage was encountered more often, probably associated with the higher use of anticoagulation. The way that this high incidence of complications relates to the diagnosis of valvular heart disease, the country of residence, and the time they present for the first time (before or during pregnancy) will be investigated in more depth when more patients have been included in the registry.

Cardiomyopathy

In the 88 patients with CMP the pre-pregnancy NYHA class was even worse than in the patients with VHD. Furthermore, maternal mortality, heart failure and ventricular arrhythmias occurred more often than in any other group. Currently, the numbers are limited making it impossible to correct for ejection fraction and type of CMP. As the registry is still ongoing we expect this analysis will be possible.in the future Until now, no European studies have reported on the prognosis for women with PPCM. In South Africa, case series have demonstrated that mortality rates have slowly improved over time but rates of mortality within 6 months of delivery remain as high as 10%. Our study shows that more attention needs to be paid to this group. A dedicated registry for patients with PPCM will start within the ESC-EURObservational Research Programme.

Ischemic heart disease

Ischemic heart disease is seldomly encountered during pregnancy, although the incidence is increasing and it was found to be an important contributor to maternal mortality in the British Enquiry "Saving Mothers Lives" (9,11,12). In this registry to date only 25 patients with IHD have been included. Not surprisingly, this patient group was older at baseline with more risk factors for coronary artery disease. Of the 20 patients who suffered from myocardial infarction prior to pregnancy, only one experienced a new ACS during the current pregnancy. Although these numbers are small they are encouraging and may positively influence the current practice of cardiologists in counselling these patients. Until now, only case reports on patients becoming pregnant after ACS have been described in literature In the 5 other patients a "new" ACS occurred during the current pregnancy, all mothers survived. However, fetal outcome was poor with babies from this group having the greatest proportion of low Apgar scores, preterm deliveries, the lowest birth weight and the highest mortality. Whether medication use, smoking, older age or other factors were the contributors to this unfavourable outcome has to be determined in larger series. Indeed in some women the high incidence of preterm deliveries and low birth weight may be the expression of a diffuse vasculopathy causing chronisc placental insufficiency.

Developed versus developing countries

Cultural and social pressures may have a greater influence on the decision to become pregnant in developing countries, meaning that pregnancies occur in a higher-risk population than in developed countries. In this study, we found higher maternal mortality and morbidity in developing countries. This is a very complex issue but if achievable, pre-conception counselling focusing on the severity of the heart disease with a clear statement of the consequences of pregnancy may save lives.

Future directions

The pregnancy registry will continue to enrol patients over the next few years. This should allow a very large database to accumulate so that with more detailed analysis in larger disease specific groups firmer conclusons can be raised on the available data. These conclusions can then be used as the evidence base for improved management plans. Hopefully these will make pregnancy safer for both mother and baby in this challenging situation.

Study limitations

Although this study describes a large population of patients, subgroup analysis was not performed in detail due to small numbers per group. Differences by diagnosis will exist, therefore, pooling patients is an over-simplification. In addition the input and quality of data was checked in only 5-10% of cases. In 5% of patients, the data was incomplete. In addition some centers had much higher volumes than others. Therefore, there may be bias of data.

Although most data were collected prospectively (2008-2011), pregnancies of 2007 (14% of patients) retrospectively. As participation to the registry was voluntary and there may be differences between sites that agreed to participate and those that did not, the registry may not be representative and therefore all conclusions must drawn with caution. Finally, it was difficult to find a good control population. By including large prospective series from the countries that included most patients we hope to have provided the best possible information for comparison.

CONCLUSIONS

Pregnancy in patients with heart disease results in a maternal mortality of 1% which is a hundred times higher than in normal pregnant patients. However, clear differences were found in pregnancy outcomes with respect to the underlying diagnosis and between patients in developed and developing countries. Most patients with adequate counseling and optimal care should not be discouraged and can go safely through pregnancy. The caesarean section rate is high and more research should focus on the optimal mode of delivery for these patients.

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The investigators participating in the Registry On Pregnancy And Cardiac disease (ROPAC) are listed in the Supplementary Appendix.

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Chapter 9

Mode of delivery for patients with heart disease. Observations from the Registry On Pregnancy And Cardiac disease (ROPAC).

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ABSTRACT

Objectives

Only limited data exist on the optimal mode of delivery in women with heart disease. The reported use of caesarean section (CS) varies widely. A large study assessing the use and impact of CS is mandatory.

Purpose

To examine the use and impact of the mode of delivery on pregnancy outcome in women with heart disease.

Methods

The Registry on Pregnancy and Cardiac Disease is a prospective observational registry, which enrolled 1321 (information about mode of delivery was available in 1262) pregnant women with structural heart disease between January 2007 and June 2011 from 60 hospitals in 28 countries.

Results

Vaginal delivery (VD) was planned in 869 women (69%), of whom 728 (84%) actually delivered vaginally and 143 (16%) had an emergency CS. CS was planned in 393 women: 172 (44%) for cardiac and 221 (56%) for obstetric reasons. Post partum heart failure was highest in the patients who had a planned CS for cardiac reasons (9.9%). There was no difference in pregnancy outcome (post partum heart failure or haemorrhage) in those delivered by elective or emergency CS for obstetric reasons.

Conclusion

The high rate of post partum heart failure in women delivered by CS for cardiac reasons was most probably due to the severity of the underlying heart disease. Complications were similar in elective and emergency CS and therefore attempting VD may have neonatal benefits in terms of later delivery and greater birth weight and are not necessarily associated with a greater risk of adverse maternal outcome.

Keywords

Heart disease, pregnancy, delivery, maternal outcome, foetal outcome

ABBREVIATIONS

CS = Caesarean Section
OAC = Oral Anticoagulation
PET = Pre-eclamptic toxaemia
VD = Vaginal delivery
WHO = World Health Organization

INTRODUCTION

Only limited data exist on the optimal mode of delivery in women with heart disease. The reported use of caesarean section (CS) in patients with heart disease varies from 21% to 52% in different registries and studies.(1-7) Clinical (practice) guidelines in this field are largely based on expert opinion(8). Evidence from large-scale prospective series is scarce if not absent. Generally, vaginal delivery (VD) is preferred in women with an adequate cardiac output, but CS may be the best option in selected high-risk patients.(8) European guidelines on pregnancy and heart disease recommend CS in women on oral anticoagulants (OAC) in preterm labour, patients with Marfan syndrome and an aortic diameter >45 mm, patients with acute or chronic aortic dissection and in those with acute intractable heart failure. Caesarean delivery may also be considered in Marfan patients with an aortic diameter larger than 40 mm.(8) For all other patients VD is the preferred method, since VD, if necessary with an effective epidural is held to cause fewer and less dramatic changes in hemodynamic parameters. Furthermore, VD is known to be associated with lower risks of maternal complications such as haemorrhage, infection and thrombosis.(9) Set against this, clinicians have to consider the risk of an emergency CS, which probably carries a greater risk of an adverse outcome for both mother and child.

The CS rate in pregnancies uncomplicated by heart disease varies widely between different countries. For example the CS rate in the Netherlands is 14%, while it is as high as 40% in Italy.(10) Although the populations are not exactly the same, the marked differences in CS rates between countries suggest that the attitude towards mode of delivery varies widely.

Our aim is to describe the current mode of delivery in a large population of women with congenital or acquired heart disease from various parts of the world. The relationship between pregnancy outcome and the mode of delivery is studied and determinants of the wide variations in the mode of delivery observed between countries are explored.

METHODS

Study design

In 2007 the European Registry on Pregnancy and Heart Disease was established as a part of the Euro Heart Survey Program of the ESC. All patients with structural (valvular, congenital, or cardiomyopathy) or ischemic heart disease were eligible for enrolment. The prospective registry started in January 2008. However, patients who where pregnant in 2007 could be included retrospectively, when the complete data of these patients were available. A total of 60 hospitals in 28 countries enrolled 1321 pregnant women with structural heart disease. Data on the mode of delivery were available in 1262 (96%) patients.

When warranted, ethical approval or Institutional Review Board (IRB approval) was obtained (e.g. Germany, USA, Canada, Belgium), however, in many countries the procedure to obtain ethical approval was waived because of the anonymised and untraceable nature of the data.

Data

On June 1st 2011 the analysis performed from this on-going registry, served as the basis for this manuscript. The study protocol and first results of this registry were published previously. (11) Information on delivery included place of delivery, intended mode of delivery (planned mode of delivery), performed mode of delivery, reason for CS, start of labour, rupture of membranes and complications during delivery.

We stratified the patients into 4 risk groups using a modified World Health Organization (WHO) risk classification for pregnancy in women in cardiac disease. In this risk stratification model the patients are allocated to a score according to diagnosis and severity of disease. A WHO category 1 indicates low risk, WHO 2 indicates intermediate risk, WHO category 3 indicates high risk and WHO category 4 indicates a contraindication for pregnancy.(8, 12) Endpoints for this study were maternal and fetal mortality, heart failure (requiring treatment), postpartum haemorrhage (VD>500 ml, CS >1000 ml or requiring transfusion), gestation length, the occurrence of premature labour (spontaneous onset of labour <37 weeks gestation) and birth weight.

Statistical methods

Categorical data are presented as frequencies (numbers) and percentages. One-sample Kolmogorov-Smirnov tests and histograms were used to check normality of continuous data. Normally distributed continuous data are presented as mean values ± one standard deviation (SD), whereas data which were not normally distributed were presented as medians with interquartile range (IQR). Differences in categorical data between independent patient groups were compared by chi-square tests. Fisher's exact tests were applied if any expected cell count was less than 5 (a Monte Carlo approximation was used in case more than 2 independent

groups were involved). Differences in continuous data between independent patient groups were compared by Student's T tests. Odds ratios were calculated using logistic regression. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago). Unless specified otherwise, p-values <0.05 (2-sided test) were considered statistically significant.

RESULTS

Baseline characteristics

Median maternal age was 30 years (SD 5.6 range 16-53). Half of the women had had one or more previous pregnancies. The baseline characteristics are shown in table 1.

Table 1. Baseline characteristics and outcome in patients with planned CS versus patient who where planned to have VD.

	Total group	Planned VD	Planned CS	p value
Age (range, SD)	30 (5,6)	30 (6,0)	30 (5,5)	0.105
Prior cardiac intervention (%)	54	48	56	0.029
Nulliparous (%)	50	44	52	0.012
Type of heart disease				0.028
Congenital heart disease (%)	67	58	69	
Valvular heart disease (%)	24	30	25	
Cardiomyopathy (%)	6	10	4.4	
Ischemic heart disease (%)	2	3.1	1.2	
NYHA class 1 (%)				<0,001
NYHA class 1 (%)	70	61	76	
NYHA class 2 (%)	25	31	21	
NYHA class 3 (%)	3	6.1	1.4	
NYHA class 4 (%)	0	0.5	0.5	
Pre eclampsia	3.3	2.3	5.9	0.001
Anticoagulation	10.4	9.1	14.5	0.004
Outcome				
Maternal mortality (%)	1	0.6	2	0.018
Postpartum HF (%)	3.6	2.4	6.9	<0,001
Postpartum haemorrhagic event (%)	2.9	2.5	4.1	0.138
Late fetal death (%)	1.7	1.6	1.5	0.912
Neonatal death (%)	0.6	0.5	0.8	0.684
Pregnancy duration (weeks)	38	38	37	<0,001
Birth weight (grams)	3010	3106	2809	<0,001
APGAR score at 1 min < 7 (%)	9.8	9.4	12	0.133

Location of delivery

Two third (864) of the patients delivered in a tertiary centre, 27% (361 patients) delivered in regional centres and 0.5% (7 patients) delivered at home. We had no information on the place of delivery in 7.5% (99 patients).

Mode of delivery

Information on the mode of delivery was available in 1262 women. Vaginal delivery was planned in 69% (869) and CS was planned in 31% (393) as shown in Figure 1. Of patients planned for CS 14 % (53) delivered by emergency CS of which 47% (25) were for cardiac reasons (heart failure n=13, acute coronary syndrome n=1, arrhythmia n=5 and ischemic cerebral event n=1, specific indication not stated n=5) and 53% (28) were for obstetric reasons.

WHO risk categories

The distribution of WHO categories varied widely between the modes of delivery as is shown in Figure 2. A larger number of high-risk patients had a CS for cardiac reasons (p<0.001, Fig. 2b). Other groups (VD, elective CS for obstetrics reasons and emergency CS for obstetrics reasons) had a comparable WHO category distribution (Fig. 2c).

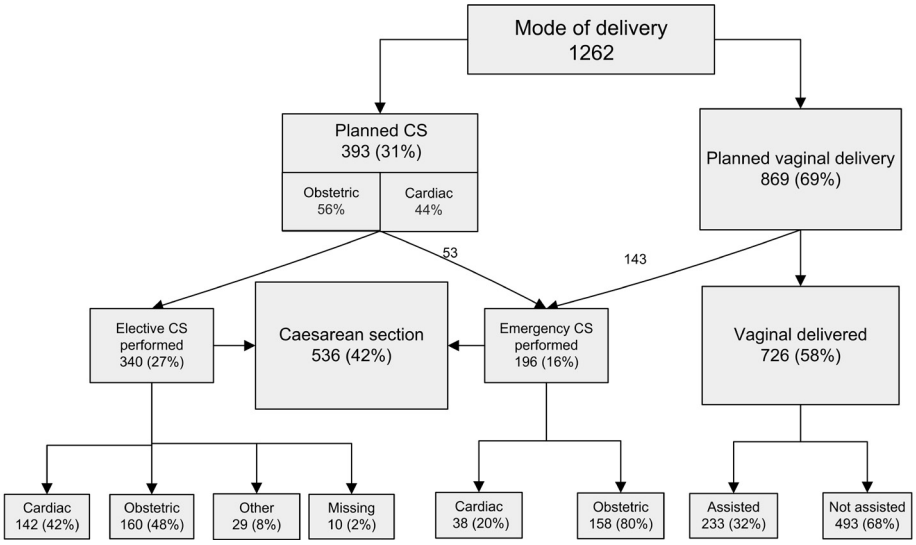

Figure 1. Flowchart: Mode of delivery

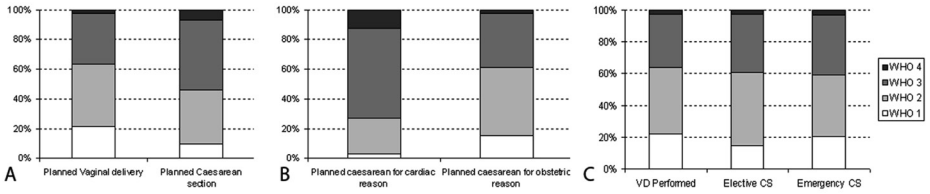

Figure 2. Distribution of WHO category
Planned CS for obstetric reasons, planned CS for cardiac reasons and planned VD
Performed VD, elective CS for obstetric reason and emergency CS for obstetric reason

Table 2. Baseline characteristics and outcome in patients planned CS for obstetric reasons versus for cardiac reason.

	Planned obstetric CS (n=221)	Cardiac reason for CS (n=172)	p value Cardiac CS versus obstetric CS
Baseline			
Age (SD)	31 (6.1)	30 (5.8)	0.17
Prior cardiac intervention (%)	52	44	0.11
Nulliparous (%)	43	45	0.61
Type of heart disease			0.028
Congenital heart disease (%)	64	49	
Valvular heart disease (%)	25	35	
Cardiomyopathy (%)	8.6	13	
Ischemic heart disease (%)	2.7	3.5	
NYHA class			<0.001
NYHA class 1 (%)	73	45	
NYHA class 2 (%)	22	43	
NYHA class 3 (%)	2.3	11	
NYHA class 4 (%)	0	1.2	
Pre-eclampsia (%)	7.7	4.1	0.14
Anticoagulantia use	6.5	25	<0.001
Outcome			
Maternal mortality (%)	0	4.7	0.001
Postpartum HF (%)	7.2	9.9	0.35
Postpartum haemorrhagic event (%)	4.5	7.6	0.200
Fetal death (%)	0.9	2.3	0.25
Neonatal death (%)	1.4	0	0.26
Pregnancy duration (weeks)	38	37	<0.001
Birth weight (grams)	2890	2827	<0.001
APGAR score at 1 min < 7 (%)	10	15	0.12

Outcome related to planned mode of delivery

The outcome in relation to planned mode of delivery is shown in table 1 and 2. Maternal death was higher in patients with planned CS 2% versus planned VD 0.6% (p=0.018). Post partum heart failure was higher in patients planned for CS (p<0.001). Women with planned CS had higher rates of pre-eclamptic toxaemia (PET). Postpartum heart failure was higher (6.9% versus 2.4%) in patients with a planned versus planned VD (p=0.035). The odds ratio of PET for post-partum heart failure was 10 (CI 95% 5-20) in the total registry. Fetal outcome was better in the patients planned for VD with longer pregnancy duration (p<0.001) and higher birth weight (p<0.001) as shown in table 1. Compared to VD, fetal mortality and birth weight were similar within the planned CS groups. When looking further in to detail in the patients planned for CS, patients with CS for cardiac reasons had a high rate of maternal mortality 4.7% versus 0% in patients with CS for obstetric reasons 0% (p<0.001). Post partum heart failure and haemorrhage was comparable between the two reasons for CS.

Outcome related to performed mode of delivery

In this analysis patients with cardiac reasons for CS were excluded so that we could examine the impact of mode of delivery in a group of women deemed suitable for VD. Maternal mortality and postpartum haemorrhage did not differ between patients delivered by emergency CS, elective CS or VD (table 3). Postpartum heart failure was highest in patients with an elective CS 7.6% versus 5.2% after emergency CS (p=0.37). Heart failure was different between elective CS 7.6% and after VD 2,9% (p=0.002). This may be influenced by the co-existence of PET. Pre-eclampsia had an odds ratio for heart failure of 13 (CI 95% 6-29) in the patients in this analysis.

Table 3. Outcome in patients delivered vaginally, elective CS or emergency CS.

	Performed VD (n=726)	Elective CS (n=197)	Emergency CS (n=154)	p value VD vs elective	p value elective vs emergency
Pre-eclampsia (%)	1.9	8.1	5.2	<0.001	0.29
Anticoagulantia use	8.9	7.1	5.9	0.42	0.64
Postpartum HF (%)	2.9	7.6	5.2	0.002	0.37
Postpartum haemorrhagic event (%)	4.7	5.1	4.5	0.82	0.83
Fetal death (%)	1.8	1.0	0.6	0.52	0.72
Neonatal death (%)	0.4	1.5	0.6	0.12	0.45
Pregnancy duration (weeks)	38	37	38	<0.001	0.09
Birth weight (grams)	3145	2835	2920	<0.001	0.25
Apgar score at 1 min < 7 (%)	7.9	10	17	0.30	0.06

Variation in mode of delivery in different populations

There were large differences in mode of delivery for patients with heart disease between countries. For example the rate for CS was 56% for patients in Italy, whereas this was 20% in the Netherlands. The results are displayed in figure 3. Overall the CS rate was 160% of the expected CS rate. In a univariable analysis the CS rate in the women with heart disease appeared to be independent of the normal population CS rate (R^2 = 0.13 p =0.12, figure 4a) but depended of the proportion of patients with WHO category > 2 (figure 4 b). Using a multivariate analysis, we found that both the normal CS rate for the general population (p= 0.015) and the proportion of patients with high WHO category (p=0.003) were predictors for CS rate (with a combined R^2 = 0.501 with p = 0.004).

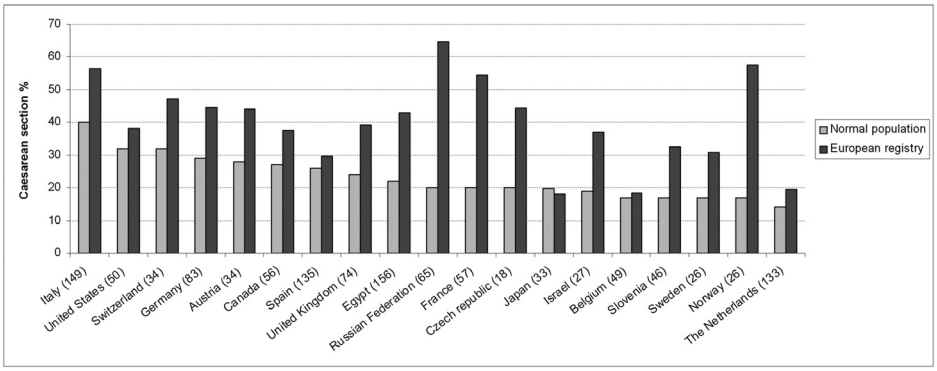

Figure 3. Percentage caesarean section per country in the normal population and the ROPAC.

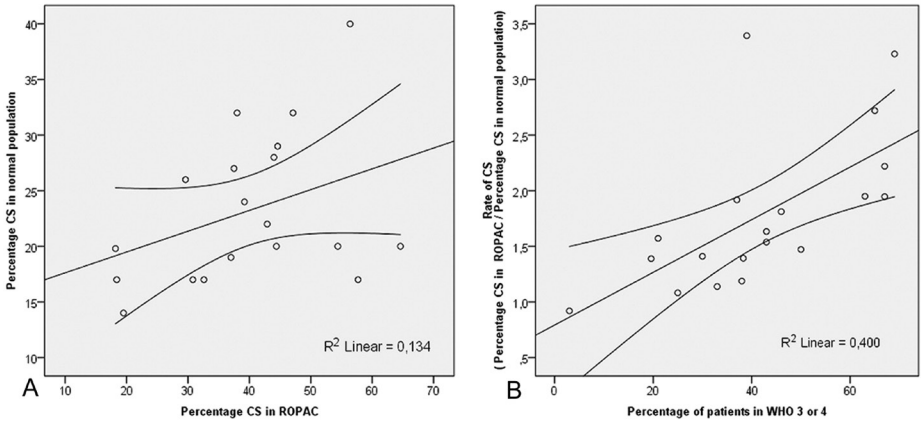

Figure 4. CS rate per country
Distribution of expected (normal) CS rate against CS rate in the registry
Distribution of CS rate (CS rate in registry divided by the CS rate in the background population) compared with percentage of patient with WHO category 3 or WHO category 4.

DISCUSSION

In this large cohort of patients with heart disease almost half of the patients were delivered by CS, which is more than one and a half times higher than the rate in normal pregnant women. Large differences between countries were found.

Study design

This study is primarily hypothesis generating, but equally, performing a randomised trial in this heterogeneous population seems very difficult and ethically challenging. Performing a prospective observational registries with matched patients is the only practical way to draw conclusions about which mode of delivery is preferable. To date, the published observational studies have been relatively small and retrospective. Stangl et al. showed a higher rate of CS in high-risk patients in a single-centre study of 93 pregnancies. Other studies, published by Khairy (90 pregnancies), Siu (599 pregnancies), Jastrow (312 pregnancies) and Drenthen (1301 pregnancies but mode of delivery was not reported), focused on risk stratification mainly.(2-4,13) Jastrow and Khairy reported a CS rate of around 23%. In the study of Siu et al, the CS rate was higher in women with heart disease compared with normal patients (29% versus 23%).(2) In a study by Robinson et al. including 559 patients, rates of caesarean section was comparable with controls. In this study caesarean section was related with adverse neonatal outcome.(21) Certainly, these studies did not focus on the association between mode of delivery and fetal or maternal morbidity and mortality.(1-4,13-15) In the current study, we gathered information on both the planned and performed mode of delivery, the underlying reason for the decision (obstetric or cardiac) and outcome related to the mode of delivery. However, since CS is chosen as the mode of delivery in selected severely ill patients, major bias is present with respect to baseline characteristics of the patients.

Maternal complications

The greater proportion of women with poor NYHA status having a cardiac CS may explain the higher maternal mortality rate and occurrence of post-partum heart failure. However, the rate of post-partum heart failure was higher in the CS for obstetric reasons too, suggesting that delivery by CS may increase the risk of heart failure. This group had higher rates of pre-eclampsia, which would increase the risk of developing pulmonary oedema. Therefore the risk for heart failure seems to have been mediated primarily through the occurrence of PET and not through the occurrence of CS itself. Further, a greater proportion of women with planned CS were delivered preterm, consequently the mothers would have been given antenatal steroids to help to mature the fetal lungs and this too may have increased the tendency for fluid retention and consequently for developing pulmonary oedema. Further investigation of the occurrence of maternal death and heart failure, by excluding women with a cardiac indication for CS showed that the high rates of maternal mortality were no

longer apparent.(Table 2) This confirmed our suspicion that this risk was predominantly in women with severe heart disease (with cardiac CS). Post partum haemorrhage was similar across all 3 groups in our initial analysis. This was counter to our expectations as CS is associated with an increased risk of post partum haemorrhage (22-23). First we thought that the data may have been skewed by OAC use, but usage was similar across all groups, suggesting that this is not the case. In addition the definition of significant blood loss differs between CS (>1000ml) and VD (>500 ml) and haemorrhage is assessed visually, which can be inaccurate. Therefore it is still hard to draw firm conclusions.

Fetal complications

In terms of fetal complications, fetal and neonatal death rates were not different, but pregnancy duration was shorter and birth weight lower in CS deliveries (Table 1). This difference persisted after cardiac CS cases were excluded (Table 2). It was particularly marked in the elective CS group, even when corrected for the presence of pre-eclampsia, which is associated with reduced fetal growth. These data suggest that those women who were delivered by CS actually had impaired fetal growth, which may have resulted in fetal distress in labour and the need for delivery by emergency CS. Indication for delivery by CS may have been fetal growth restriction and this may be another reason for the co-existence of early delivery and low birth weight. Apgar scores tended to be lower in the CS group (Table 1), but these differences did not reach significance even after exclusion of cardiac cases (Table 3). Pregnancy duration was consistently shorter in the planned CS groups (Tables 1 and 2).

Elective vs. Emergency

CS is associated with an increased risk of complications, such as venous thrombo-embolism, infection, peripartum haemorrhage and the risk of general anaesthesia.(16-19) and these risks are held to be greater in emergency as compared to elective CS.(25) Indeed, the greater risk with emergency CS is often the stated rationale for choosing an elective CS over attempting a VD in women at high-risk of an emergency CS. However, we found that maternal complications were similar in both CS groups. This is important as it means that we can reassure women who are advised to have VD that if they need an emergency CS during labour that the risks are no greater than with an elective CS. Clearly, this is not a randomised controlled trial, consequently, conclusions should be drawn with caution. The only consistent finding was the shorter pregnancy duration, which, can be associated with increased neonatal morbidity.(24)

Distribution around the world

We observed marked differences between different countries in this cohort of women with heart disease. Large differences between countries exist in CS rates in healthy women.(10) We thought that the variation in the CS rates between countries could explain the differences we observed, but in our initial analysis there was no relationship between the background

CS rate of each country and the observed rate in our study. However, when we corrected for the background CS rate, we found a relationship between the CS rate and the proportion of women with more severe heart disease, supporting the idea that the severity of the heart disease also influenced the CS rate. A further variation is likely to be introduced by the experience of the attending specialist (either cardiologist or gynaecologist).

Limitations

Given the heterogeneity of the population studied with a multitude of different underlying cardiac diagnoses, collected from 60 different hospitals, conclusions should be drawn with caution. As in every registry, some data (in 5% of patients) are missing, especially on obstetric complications. For instance the type of anaesthesia used during CS was not collected in the case report form of this registry and this could have influenced our results. As participation to the registry was voluntary, there may be differences between sites that agreed to participate and those that did not.

CONCLUSION

Higher rates of maternal mortality were found in women having a CS for cardiac indications, probably due to the severity of their underlying heart disease. The greater rates of postpartum heart failure in both CS groups seemed to be related primarily to the higher rates of pre-eclampsia. Complications were similar in elective and emergency CS and therefore attempting VD may have neonatal benefits in terms of later delivery and greater birth weight and are not necessarily associated with a greater risk of an adverse maternal outcome.

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The investigators participating in the ROPAC at 1 June 2011 are listed in the Supplementary Appendix.

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If you are interested to join this registry, please go to the following website:

http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx

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Chapter 10

The impact of maternal cardiac medication on fetal outcome: data from the ROPAC.

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ABSTRACT

Aim

Data on pharmacological management of pregnant women with heart disease is scarce. The aim was to describe type and frequency of cardiac medication used in pregnancy in patients with cardiovascular disease and to monitor impact on fetal outcome.

Methods and results

Between 2007 and 2011 sixty hospitals in 28 countries enrolled 1321 pregnant women. All had structural heart disease (congenital 66%, valvular 25% or cardiomyopathy 7%) or ischemic heart disease (2%). Medication was used by 424 patients (32%) at some time during pregnancy, some patients had more then one type of medicine, 22% used beta blockers, 12% antiplatelets, 7.1% diuretics, 2.8% ACE inhibitors and 0.5% statins. Compared to those who did not take medication patients taking medication were older, multiparous, had valvular heart disease and were less often in sinus rhythm. The odds ratio of a fetal adverse event in users versus non-users of medication was 2.6 (95% CI 2.0-3.5) and after adjustment for cardiac and obstetric parameter 2.4 (95% CI 1.8-3.2). The babies of patients treated with beta blockers had a significantly lower adjusted birth weight of 3140 gram versus 3240 gram, p=0.002. The highest rate of fetal abnormalities was found in patients treated with ACE-inhibitors (7.9%).

Conclusion

One third of pregnant women with heart disease used cardiac medication during their pregnancies. During their pregnancies, these women had more cardiac and obstetric complications than those women who had heart disease, but were not taking any medication. Birth weight was significantly lower in children of patients taking beta blockers.

Keyword

Medication, pregnancy, heart disease, fetal outcome, birth weight

ABBREVIATIONS

ACE = angiotensin-converting-enzyme
NYHA= New York Heart Association
ROPAC = Registry on pregnancy and cardiac disease
SGA = small for gestational age
WHO = World Health Organisation

INTRODUCTION

The number of women with heart disease becoming pregnant is growing and some of these women will need cardiac medication for the management of their heart condition.(1) Heart failure, arrhythmias and/or hypertensive disorders may complicate pregnancy in patients with heart disease.(2) These complications compromise not only the mother but also the baby and adequate treatment is of vital importance for both. With the increasing use of cardiac medication,(3) it is crucial to have information on the adverse fetal effects of cardiac medication so that the advantages of treating the mother can be weighted against the possible negative effects on the baby.

Most experience is present with cardiac medication used in the treatment of hypertension and pre-eclampsia,(4) where some mediations have been shown to be fetotoxic and others to be teratogenic.(5) Some drugs are considered safe and are commonly used in pregnancy, for other drugs there is a lack of clear information.(6)

One of the main reasons for starting the Registry On Pregnancy And Cardiac disease (ROPAC), which is supported by the European Society of Cardiology, was to study the use of cardiac medication in pregnant women with cardiac disease. The first aim of the current study was to assess the percentage of patients with heart disease actually using cardiac medication during pregnancy and to define which cardiac medication was being used most often. The second aim was to investigate the effect of cardiac medication on pregnancy and fetal outcome. Our overall aim is to optimise the care of women with heart disease during pregnancy.(7)

METHODS

Patients

ROPAC started in January 2008, pregnant patients from 2007 could be included retrospectively and from January 2008 all patients with structural heart disease (valvular, congenital, or cardiomyopathy) or ischemic heart disease were enrolled prospectively. The full protocol has been described previously.(7)

Data and definitions

This registry is on-going and an interim analysis, which was performed on June 1st 2011, served as the basis of this manuscript. Recorded data included cardiac medications used before pregnancy and continued during pregnancy and also cardiac medication started during the index pregnancy. Outcome parameters included: birth weight, all fetal abnormalities (either cardiovascular or any other) and fetal adverse events. A fetal adverse event was defined as: fetal death (defined as fetal death after 22 weeks of pregnancy or birth weight 500

gram), neonatal death, low birth weight (< 2500 grams) or premature birth (< 37 weeks of gestation). In this manuscript we did not focus on anticoagulation in detail, since more data is necessary to draw conclusions in this topic. However, anticoagulation was included in the calculations of "any cardiac medication".

We used the modified World Health Organisation (WHO) categories to stratify patients into different risk categories. The categories are: WHO category 1: low risk, WHO category 2: intermediate risk, WHO category 3: high risk and WHO category 4: contraindication for pregnancy.(8)

Statistical methods

Continuous data are presented as mean with standard deviation and were compared using the Student-T or Mann-Whitney test as appropriate. Discrete variables are presented in absolute numbers and percentages and were analysed using the chi-square or Fischer's exact test and Mann-Whitney test for ranked discrete data. Odds ratios for fetal adverse events (both univariable as multivariable) were calculated using binomial logistic regression. Odds ratio was first adjusted for parameters described to have influence on fetal outcome, such as maternal diabetes, smoking, age, hypertension and preeclampsia and secondly also for the occurrence of heart failure during pregnancy, WHO class and main diagnosis. To calculate corrected birth weight and the association with the use of beta-blockers a linear regression was used. This analysis was adjusted for gestational age, smoking, fetal sex, maternal age, diabetes and pre-eclampsia. The level of significance was $p < 0.05$ (2-sided). The data were analysed with the SPSS version 20.0 software (SPSS Inc, Somers, NY).

RESULTS

Cardiac medication was used by 32% of the 1321 female patients at some time during their pregnancy. In table 1 the baseline characteristics of these women are compared to the patients without cardiac medication. Patients taking cardiac medication were older, multiparous and typically had an underlying diagnosis of valvular heart disease. Their pregnancies were more often complicated by heart failure.

Beta blockers were used by 291 patients. As shown in figure1, in women taking beta-blockers the birth weight was on average 100 grams lower (p=0.002) than those not taking beta blockers. When considering the women in the different WHO categories, this difference was most significant in WHO category 2 (p=0.04). The indication for the use of beta blockers (before and/or during pregnancy) is shown in table 2. The group of patients with "other" indications for the use of beta blockers included diagnosis such as transposition of the great arteries with atrial switch (n=7), Tetralogy of Fallot (n=5) and double outlet right ventricle (n=2).

Table 1. Baseline characteristics.
SD= standard deviation. NYHA = New York Heart Association

	Total	No cardiac medication	Any cardiac medication	P value
		897	424	
Mean age (SD)	30 (5.6)	29.7 (5.4)	30.6 (6.1)	0.005
Sinus rhythm (%)	93	94	87	<0.001
Type of heart disease				<0.001
Congenital (%)	66	75.8	45.3	
Valvular (%)	25	20.7	35.4	
Cardiomyopathy (%)	7	3	14.4	
Ischemic (%)	2	0.4	5	
Current smoking (%)	3	3.1	3.5	0.69
Diabetes (%)	1.6	1.1	2.8	0.023
NYHA class 1 (%)	70	77.9	54.1	<0.001
Nullipara (%)	50	53	42.7	<0.001
Heart failure during pregnancy (%)	10	4.7	21.5	<0.001

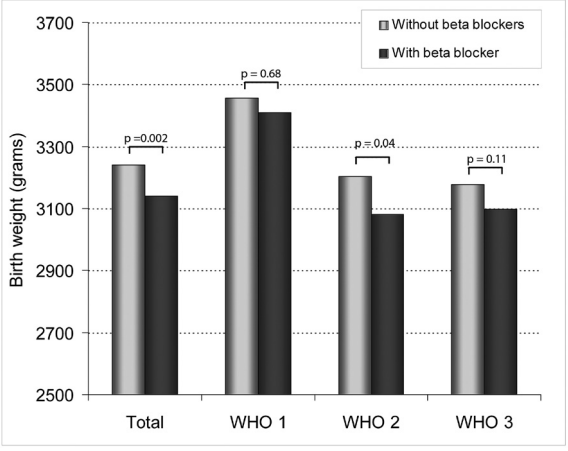

Figure 1. Birth weight in patient with and without beta blockers per WHO class adjusted for gestational age, smoking, fetal sex, maternal age, diabetes and pre-eclampsia.

The crude odds ratio of a fetal adverse event (fetal death, neonatal death, low birth weight, premature birth) was 2.6 (95%CI: 2.0-3.5) in patients who used any cardiac medication during pregnancy versus patients without medication. The odds ratio was 2.5 (95%CI: 1.9-3.3). After correction for obstetric confounders: maternal age, smoking, diabetes, hypertension and preeclampsia). The odds ratio was 2.4 (95%CI: 1.8-3.2) after correction for cardiologic confounders: heart failure during pregnancy, WHO class and main diagnosis.

Table 2. Indications for use of beta blockers.
* Adjusted for gestational age, smoking, fetal sex, maternal age, diabetes and pre-eclampsia.

	Beta blockers continued during pregnancy (n=164)	Beta blockers started during pregnancy (n=127)	Total (n=291)	Reduction in birth weight (grams)	p value
Valvular disease	42	19	61	-169	0.007
Arrhythmias	14	40	54	-119	0.07
LV dysfunction	38	10	48	-72	0.30
Hypertension	34	11	45	1	0.99
Aortic disease	29	6	35	-21	0.81
Other	7	25	32	-268	0.002
Heart failure	0	16	16	-9	0.94

Table 3. Outcome per cardiac medication group.
AT II = Angiotensin II receptor antagonist
ACEi = angiotensin-converting-enzyme (ACE)-inhibitors

	Total group	No medication	Any med	p value	Beta blocker	Anti platelet	Diuretic	Anti arrhythmic	ACEi	Statin	AT II
Number	1321	897	424		291	155	94	55	38	6	7
Fetal mortality (%)	1.7	1.1	2.8	0.023	2.1	3.2	4.3	7.3	2.6	16.7	0
Fetal abnormalities (%)	4.7	5	4	0.42	4.1	5.2	2.1	1.8	7.9	0	0
Pregnancy duration (weeks)	38	38	37	0.004	37	36.7	37	36.3	38	38	37.5
Mean birth weigth (grams)	3010	3100	2835	0.019	2830	2789	2720	2774	2921	2770	2652
Small birth weight (<2500 gram) %	14	9.7	23.3	<0.0001	23	27.1	23.4	23.6	13.2	16.7	42.9
Pregnancy duration (< 37 weeks) %	15	11	23.6	<0.0001	23	33.5	31	36.4	15.8	16.7	14.3
Apgar (< 7) %	10	8.1	13.6	0.003	13	13.5	12.8	20	15.8	16.7	0

The effects of different drugs on fetal mortality and rates of abnormality are shown in table 3. The highest rate of fetal abnormalities was found in patients treated with angiotensin-converting-enzyme (ACE)-inhibitors (n=3; 7.9%) of which 1 dandy walker 1 delay in arterial duct restriction and 1 non-cardiac abnormality. Fetal abnormalities included a wide spectrum of different cardiac (e.g. univentricular hearts and persistent arterial ducts) and non-cardiac abnormalities (e.g. syndactyly, trisomy 18 and encephalocele).

DISCUSSION

This study shows for the first time very clearly that cardiac patients receiving cardiac medication during pregnancy had more fetal adverse events than patients without cardiac medication. Up until now it has been generally thought that although cardiac medication taken during pregnancy may have disadvantages, not treating the mother hampered fetal outcome even more. In our analysis we corrected for potential obstetric and cardiological confounders and still the odds ratio of having a fetal adverse event was 2.38 for mothers taking cardiac medication. Khairy et al. showed that both anti-platelet therapy and anti-arrhythmic cardiac medication were univariable predictors for spontaneous abortion.(9) Drenthen et al. showed that cardiac medication was a predictor for neonatal complications in multivariable analysis. (10) We showed that mothers taking cardiac medication had more adverse fetal events, despite correcting for many obstetric and cardiovascular parameters. The question remains whether the patients needing cardiac medication during pregnancy had worse cardiac function, or had other parameters for which we did not correct or that the effect found is indeed valid. Although we corrected for WHO categories and diagnosis, the patients needing cardiac medication probably are the more symptomatic patients within their patient group. On the other hand, medication was also prescribed as prophylactic therapy, for instance in patients with Marfan syndrome, as advised by the guidelines, and no clear impact of more severe disease can be expected here. We have not studied the effect of intentional omission of treatment. Therefore we cannot give the advice that all cardiac medication is contraindicated during pregnancy. However, a high degree of reluctance to medicate, which is a sentiment often expressed by pregnant women, seems to be an appropriate position.

The rate of fetal abnormalities was comparable in patients with and without cardiac medication. Although rates of 4-5% for fetal abnormalities seem quite high, this should not be compared with the rate of fetal abnormalities in normal healthy women as women with CHD are more likely to have children with a cardiac anomaly. Indeed the recurrence risk of fetal cardiac disease was been reported to be 3-5% in most studies focussing on congenital patients (forming two thirds of our study population), therefore these figures were expected. (11,12) Fetal abnormalities were especially high in patients taking ACE-inhibitors. In most patients taking ACE inhibitors, the drugs were stopped during the first trimester and cardiac medication was only taken for a short period of time, this may explain why the 8% rate of fetal abnormalities was lower than previously described.(13-15) In the 6 patients taking statins there was one fetal death and no fetal abnormalities. No conclusions can be drawn from such a small patient group, more data is clearly needed. Statins have been reported to cause fetal abnormalities in animal studies when given in excessively high dosages, but consistent with our observation of no malformations, a recent meta-analysis showed only isolated congenital anomalies without a consistent pattern in human studies.(16)

The birth weight of the whole group was lower than expected (partly because of premature birth and partly probably due to maternal cardiac dysfunction).(7,17) In this study beta blockers showed an additional significant overall reduction in birth weight of 100 grams. In our study we also found differences in the effect on birth weight when considering the indication for beta blockade; this reduction was most marked in the patients with valvular heart disease (of whom most had mitral valve disease) and in the arrhythmia group. In patients with aortic disease the effect on birth weight was intriguingly small. Also in patients taking beta blockade for hypertension this weight reduction was not found, which confirms the results of a randomised study by Movi et al. In this study mildly pre-eclamptic patients were treated with labetolol, methyldopa or standard care and they showed no influence of cardiac medication on birth weight.(18) On the other hand Meidahl et al and Nakhai-Pour et al showed an increase in the number of babies who were small for gestational age (SGA) after use of beta blockers, in these studies most patients received beta blockers for hypertension or pre-eclampsia.(19,20) This study can be seen as hypothesis-generating. Hereby urging either a case-control study or randomised trial to confirm the impact of beta blockers on fetal outcome, though designing such a trial will present ethical obstacles, which might be difficult to overcome.

An important question is whether these children show catch-up growth as has been described in most SGA children and preterm children of healthy mothers.(21,22) A low birth weight could lead to long term effects such as short stature and intellectual impairment. (21,23,24) The effects of beta blockers must be studied in further detail in the future.

Clinical implications

During pre-pregnancy counselling the use of cardiac medication should be discussed with both parents commenting on the available findings and explaining the persistent uncertainties. Patients needing cardiac medication should be considered as having a higher risk for adverse fetal outcome. Doctors and pregnant women should maintain the current state of caution to medicate unless absolutely necessary, and especially beta blockers should be titrated to keep the dose as low as possible. Depending on the indication, stopping the drug should be contemplated with restarting them after pregnancy as appropriate. This especially holds for cardiac medication only given to improve long-term prognosis. Equally, although this study supports the idea of using the minimum dose of a given drug, it clearly does not lend any support to the notion that all drugs should be stopped with the diagnosis of pregnancy. Such an approach could be catastrophic for both mother and child in some condition, such as peripartum cardiomyopathy with a subsequent pregnancy in women remaining with poor left ventricular systolic function.(25)

Limitations

Although this is a large registry, some subgroups are small. As in most registries some data (5%) were missing. We did not collect the exact dosage of cardiac medication, therefore we could not correct for this. In addition the use of hard and soft drugs of addiction and caffeine have been described to have influence on birth weight and these data were not collected. As participation to the registry was voluntary and there may be differences between sites that agreed to participate and those that did not, the registry may not be completely representative. Finally the observational methodology is not appropriate to test efficiency of cardiac medication therefore all data and comments on this matter must be seen in this light.

CONCLUSION

Pregnant women with heart disease receiving cardiac medication had more fetal adverse events than comparable patients who did not receive medication. Fetal abnormalities were found most often in patients taking ACE inhibitors. The birth weight in women taking beta blockers was 100 grams lower compared to women without beta blockers.

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If you are interested to join this registry, please go to the following website:
http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx

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Chapter 11

Heart failure in pregnant patients with cardiac disease: data from the ROPAC.

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ABSTRACT

Aim

Heart failure is one of the most important complications in pregnancy, causing maternal mortality and morbidity. The aim of this study is to describe the incidence, onset, outcome and predictors of heart failure (HF) in patients with structural or ischemic heart disease during pregnancy.

Methods and results

Sixty hospitals in 28 countries enrolled 1321 pregnant women with valvular heart disease, congenital heart disease, ischaemic heart disease, or cardiomyopathy presenting with pregnancy between 2007-2011. In total 173 (13.1%) of the 1321 patients developed HF, making HF the most common major cardiovascular complication during pregnancy. Baseline parameters associated with HF in multivariable analysis were NYHA class>2, signs of HF, WHO category>2, cardiomyopathy or pulmonary hypertension. HF occurred at a median time of 31 weeks gestation (IQR 23-40) with the highest incidence in the second trimester (34%) or peripartum (31%). Maternal mortality was higher in patients with HF (4.8% in patients with HF and 0.5% in those without HF p<0.001). Pre-eclampsia was strongly related to HF (odds ratio 7.1, 95% CI 3.9-13.2, p<0.001). Fetal death and the incidence of preterm birth rate were higher in women with HF compared to women without HF (4.6% versus 1.2%, p=0.001; and 30% versus 13%, p=0.001).

Conclusion

HF was the most common complication during pregnancy and occurred typically in the second and third trimester or after birth. It was most common in women with cardiomyopathy or pulmonary hypertension and was strongly associated with pre-eclampsia and an adverse perinatal outcome.

Keywords

pregnancy, heart failure, maternal outcome, neonatal outcome

ABBREVIATIONS

CHD = Congenital Heart Disease
HF = Heart failure
IHD = Ischemic Heart Disease
IQR = Inter Quartile Range
NYHA class = New York Heart Association
ROPAC = Registry on Pregnancy and Cardiac disease
SD = Standard Deviation
VHD = Valvular Heart Disease
WHO = World Health Organization

INTRODUCTION

Pregnancy may be considered as a physiological stress test, revealing latent medical conditions such as hypertension and diabetes.(1) This is particularly true for women with underlying heart disease, where pregnancy may cause a deterioration of a known heart condition or precipitate the presentation of an undiagnosed heart problem.(1) During pregnancy cardiac output increases by 30%–50%.(2) The increase in cardiac workload may precipitate heart failure (HF)(3-5), which is associated with significant maternal and fetal morbidity and mortality.(6)

Despite the poor prognosis associated with the diagnosis of HF, there is very little information in the literature on the subject. With a first manifestation of peripartum cardiomyopathy HF by definition occurs towards the end of pregnancy or in the months following delivery. (7) In women with Valvular Heart Disease (VHD), Elkayam et al observed that HF occurs most commonly on the day after delivery.(8) Data are lacking on the onset of HF in patients with underlying Congenital Heart Disease (CHD). Labour and delivery are considered a particularly high-risk period due to the rapid fluid shifts occurring at this time. (9)

In pregnant women with underlying heart disease, the risk of developing complications depends on the type and severity of cardiac disease.(2,5,10-14) Large cohort studies have focused on prediction of a composite endpoint of cardiac events (arrhythmia, HF and other cardiovascular complications).(2-4) This approach fails to distinguish between the relatively easily managed complications, such as most supraventricular arrhythmias, and the more severe complications, such as HF. Therefore, in this study, we have investigated the timing of the diagnosis of HF, its associations and the factors which predict its occurrence in a large cohort of pregnant women with structural or Ischemic Heart Disease (IHD).

METHODS

Study design

The Registry On Pregnancy And Cardiac disease (ROPAC) was established in 2007. Sixty hospitals in 28 countries enrolled 1321 pregnant women with structural or IHD. Enrolled patients were pregnant between 2007 and June 2011.

Data

The study protocol with definitions and the first results of this registry were published previously.(14) Heart failure was defined as signs or symptoms of HF requiring new treatment or change of treatment or hospital admission. Pulmonary hypertension was judged as such by the including cardiologist. Onset of HF in terms of gestational age was calculated using the expected term date. When a patient developed HF after delivery, we described the timing as the number of weeks after delivery. In patients with both HF during and post pregnancy, only the first manifestation of HF was used to compute the time of HF. For the calculation of median time of HF per diagnosis, we added the number of weeks after delivery to 40 weeks when HF occurred after delivery. For example, HF occurring 6 weeks after delivery in a woman delivered at 38 weeks is calculated as HF at 46 weeks.

We stratified the patients into 4 risk groups using a modified World Health Organization (WHO) risk classification for pregnant women with cardiac disease. Dependent on diagnosis and severity of disease, risk classification ranges from class I (low risk), to class IV (contraindication for pregnancy).(5,15) CHD patients were further classified by complexity of heart disease, according to a generally accepted classification.(16) Diseases that were not accounted for in this classification were scored by 2 authors (TR and PP). In addition the type of heart lesion was classified into left-sided lesions (such as aortic valve disease, mitral valve disease and most cardiomyopathies), right-sided lesions (such as Ebstein's anomaly, tetralogy of Fallot, pulmonary stenosis) and shunt lesions (such as atrial or ventricular septal defects).

Statistical methods

Categorical data are presented as frequencies (numbers) and percentages. One-sample Kolmogorov-Smirnov tests and histograms were used to check normality of continuous data. Normally distributed continuous data are presented as mean values ± one standard deviation (SD), whereas data which were not normally distributed were presented as medians with interquartile range (IQR). Differences in categorical data between independent patient groups were compared by chi-square tests. Fisher's exact tests were applied if any expected cell count was less than 5. Differences in continuous data between independent patient groups were compared by Student's T tests. Adjusted birth weight was calculated using a linear regression, and was adjusted for gestational age, smoking, fetal sex, maternal

age, diabetes and pre-eclampsia. Univariable logistic regression analysis was performed to identify baseline patient characteristics (before pregnancy) associated with HF. The following baseline variables were assessed: CHD, VHD, cardiomyopathy, IHD, right-sided lesion, left-sided lesion, shunt lesion, NYHA (New York Heart Association) class > 2, modified WHO class > 2, atrial fibrillation, nulliparity, hypertension, smoking, developing versus developed countries (according to international monetary fund classification), signs of HF, pulmonary hypertension, mechanical valves and the use of any medication before pregnancy. Echocardiographic data (fractional shortening<30 or ventricular function (qualitatively scored) moderate/severely impaired: systemic or pulmonary) were used only in the univariable regression, since adequate data were only available in 259 patients. We excluded patients with first manifestation of peripartum cardiomyopathy in current pregnancy for the univariable and multivariable analysis only. Variables that were associated with an increased incidence of the studied endpoints ($p<0.15$) entered the multivariable analysis. Unless specified otherwise, p-values <0.05 (2-sided test) were considered statistically significant. All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago).

RESULTS

Baseline characteristics

Of the 1321 enrolled patients 173 (13.1%) developed HF during pregnancy or after delivery. Baseline characteristics of patients with and without HF are shown in Table 1. There was a significant difference in type of lesion ($p<0.001$), with fewer women with HF having a right-sided lesion (12% vs. 27%) or a shunt lesion (20% vs. 27%). In contrast, more women with HF had left-sided lesions (68% vs. 45%).

Predictors of HF

The results of the univariable and multivariable logistic regression are shown in Table 2. Independent baseline parameters associated with HF were NYHA class>2 and signs of HF prior to pregnancy in agreement with previous studies. New independent baseline factors associated with HF were WHO category>2, cardiomyopathy or pulmonary hypertension. During pregnancy, a diagnosis of pre-eclampsia was related to the occurrence of HF with an odds ratio of 7.1 (95% CI 3.9-13.2 $p<0.001$). Of all patients in the registry who developed pre-eclampsia, 30% developed heart failure as well. Of patients with both pre-eclampsia and HF 29% had peripartum cardiomyopathy. In the univariable analysis CHD was associated with a lower risk of HF than other diagnoses with an odds ratio of 0.3 (95% CI 0.2-0.4). When corrected for other univariable predictors of HF in a multivariable model, this was still significant with an odds ratio of 0.40 (95% CI 0.23-0.62 $p<0.001$).

Table 1. Baseline characteristics of patient with and without heart failure.

	Total group n=1321	Patient with HF n=173	Patient without HF n=1148	p value
Mean age in years (SD)*	30 (5.6)	29 (6,2)	30 (5,6)	0,18
Nulliparity (%)	50	42	51	0,021
Atrial fibrillation (%)	2	6,4	1,3	<0,001
Hypertension	6,7	8,1	6,5	0,45
Smoking (%)	3,3	4	3,1	0,53
Any medication before pregnancy (%)	28	36	27	0,01
NYHA class				<0,001
NYHA class 1 (%)	70	36	76	
NYHA class 2 (%)	25	48	21	
NYHA class 3 (%)	3,1	15	1,3	
NYHA class 4 (%)	0,3	1,2	0,2	
WHO category				<0,001
WHO 1 (%)	18	1,8	21	
WHO 2 (%)	39	19	42	
WHO 3 (%)	38	60	35	
WHO 4 (%)	4	19	1,9	
Type of heart disease				<0,001
Valvular heart disease (%)	25	37	24	
Cardiomyopathy (%)	6,7	21	4,5	
Ischemic heart disease (%)	1,9	1,2	2	
Congenital heart disease (%)	66	41	70	
Complexity of CHD				0,24
Simple heart disease	35	35	26	
Moderate complex disease	52	52	57	
Complex heart disease	13	13	17	

Table 2. Predictors for heart failure.

Univariable	**Odds ratio**	**95% CI**	**p value**
Congenital heart disease	0,3	(0,2-0,4)	<0,001
Valvular heart disease	1,9	(1,4-2,7)	<0,001
Cardiomyopathy	4,8	(3,0-7,88)	<0,001
Ischemic heart disease	0,6	(0,1-2,4)	0,45
Right sided lesion	0,4	(0,2-0,6)	<0,001
Left sided lesion	2,7	(1,9-3,8)	<0,001
Shunt lesion	0,7	(0,5-1,0)	0,08
NYHA class > 2	6,2	(3,7-10,5)	<0,001
WHO > 2	5,3	(3,7-7,6)	<0,001
Nulliparity	0,7	(0,5-0,9)	0,02
Hypertension	1,3	(0,7-2,3)	0,45
Smoking	1,3	(0,6-3,0)	0,53
Developing countries	3,2	(2,2-4,6)	<0,001
Signs of HF prior to pregnancy	17,3	(11,6-25,7)	<0,001
Rhythm: Atrial fibrillation before pregnancy	5,1	(2,3-11,4)	<0,001
Pulmonary hypertension	4,5	(3,1-6,6)	<0,001
Mechanical valves	0,5	(0,2-1,5)	0,25
Any medication before pregnancy	1,6	(1,1-2,2)	0,011
Echo prior to pregnancy:			
Systemic ventricular function moderate/ severely impaired	4,2	(1,7-10,3)	0,002
FS < 30	3,4	(1,3-8,9)	0,02
Pulmonary ventricular function moderate/ severely impaired	3,1	(0,9-10,5)	0,07
Multivariable			
Valvular heart disease	1,0	(0,5-1,7)	0,88
Cardiomyopathy	4,6	(2,3-9,1)	<0,001
Developing countries	0,9	(0,5-1,6)	0,77
NYHA class > 2	2,3	(1,2-4,4)	0,01
WHO > 2	2,3	(1,5-3,6)	<0,001
Any medication before pregnancy	0,8	(0,4-1,0)	0,08
Rhythm: Atrial fibrillation before pregnancy	2,4	(0,8-6,9)	0,11
Signs of HF prior to pregnancy	9,6	(5,9-15,5)	<0,001
Pulmonary hypertension	1,8	(1,0-3,0)	0,04
Left sided lesion	1,6	(1,0-2,7)	0,07

Onset of HF

Median onset of HF was at 31 weeks of gestation (IQR 23-40). Of all patients with HF, 106 (61%) had HF only during pregnancy, 40 (23%) only after delivery and 27 (16%) patients both during pregnancy and after delivery. HF occurred in 7% in the first trimester, 34% occurred in the second trimester, 28% in the third trimester, 10% at delivery and 21% postpartum. More detailed timing of HF is displayed in Figure 1. There is a peak in week 23-30 of gestation and in the first weeks after delivery. Heart failure after delivery mainly occurred in the first week (20 patients, 61%). In 11 of these patients (55%) HF occurred in the first 24 hours after delivery. There were large differences in frequency and timing of HF in different patient groups (Figure 2). HF was common in patients with a cardiomyopathy and occurred mainly in the weeks around delivery. In VHD patients HF occurred throughout pregnancy. In patients with shunt lesions HF typically occurred around 25 weeks of gestation and was more common in patients with uncorrected shunts and/or pulmonary arterial hypertension.

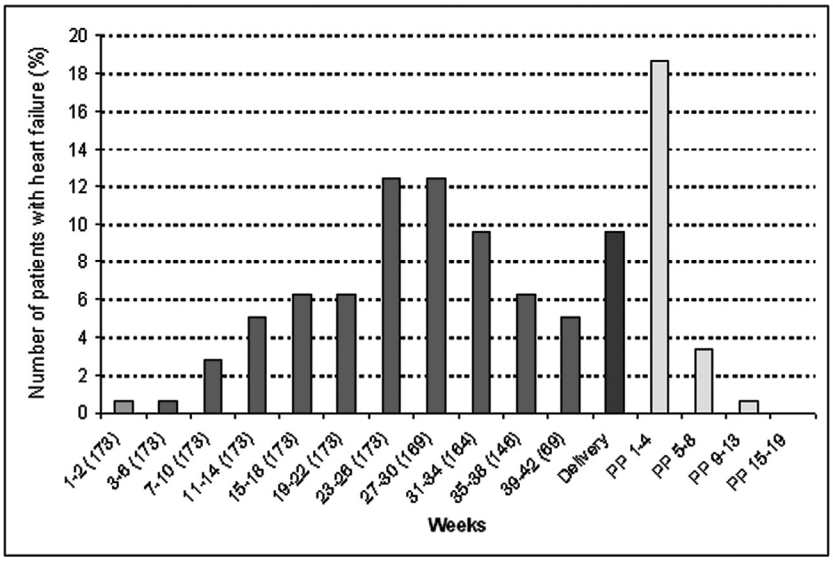

Figure 1. Occurrence of heart failure in patients with structural heart or ischemic heart disease during and after pregnancy

Percentage of patients with heart failure and distribution over time. In between brackets numbers of patients still pregnant at the beginning of the period. In dark blue heart failure at the first day after delivery. In light blue heart failure in the weeks post partum (PP).

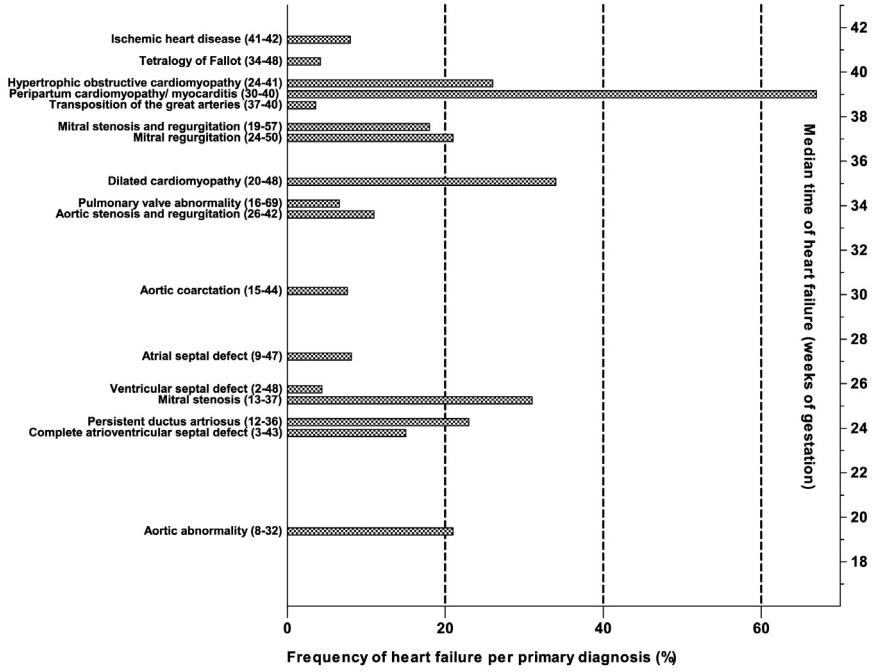

Figure 2. Onset of heart failure in patients per different diagnostic group.
On the left Y-axis the timing of HF in weeks of gestation in different diagnosis is showed (IQR), with a reference of time at the right Y-axis. The X-axis displays the frequency of heart failure for each diagnosis.

Maternal and fetal outcome

The diagnosis of HF was associated with a significantly higher maternal mortality ($p<0.001$). Obstetric complications were also more common in these patients, as shown in Table 3. Mode of delivery in patients with HF, was by emergency caesarean section in 22%, by elective caesarean section in 36% and vaginally in 40%; in 3% mode of delivery was not recorded. Overall, 58% of patients with HF were delivered by caesarean section compared to 38% in patients without HF ($p<0.001$). Caesarean section was for cardiac reasons in 57% of all HF patients with a caesarean section, versus 29% in patients without HF ($p<0.001$).

Fetal death occurred more often in patients with HF ($p=0.001$). Birth weight was lower than 2500 grams in 13% in patients without HF and in 24% of patients with HF ($p<0.001$). Of these children 33(80%) were born prematurely. Median time of delivery was 38 weeks (IQR 36-39) for patients with HF and 39 weeks (IQR 37-40) in patients without HF ($p<0.001$). There was no correlation between onset of HF and timing of delivery ($R^2=0.003$) nor was there a correlation ($R^2=0.023$) between onset of HF and birth weight (corrected for time of delivery).

Table 3. Pregnancy outcome in patients with and without heart failure.
*Birthweight corrected for: Gestational age, smoking, preeclampsia, fetal sex and nulliparity.

	Total Group n = 1321	Patients with HF (n=173)	Patients without HF (n=1148)	p value
Maternal mortality (%)	1	4,8	0,5	<0,001
Cardiac				
Atrial fibrillation (%)	0,9	1,2	0,9	0,71
Ventricular arrhythmias (%)	2	2,9	1,8	0,35
Thrombo-embolic events (%)	0,5	1,2	0,3	0,14
Endocarditis (%)	0,2	1,2	0,1	0,006
Bleeding complications during pregnancy (%)	1,6	2,9	1,4	0,14
Bleeding complications post partum (%)	4,9	4,6	5	0,85
Obstetric				
Intra uterine growth retardation (%)	5,8	13	4,6	<0,001
Pregnancy induced hypertension (%)	2,4	2,9	2,4	0,67
(Pre-)eclampsia (%)	3,3	12	1,9	<0,001
Fetal outcome				
Fetal death (%)	1,7	4,6	1,2	0,001
Neonatal death (%)	0,6	0,7	0,6	0,92
Premature birth < 37 weeks (%)	15	30-	13	<0,001
Birth weight < 2500 gram (%)	14	24	13	<0,001
Apgar score < 7 (%)	10	13	9,3	0,10
Adjusted mean birth weight (grams) *		3328	3358	0,46

DISCUSSION

In this large worldwide registry of patients with underlying cardiac disease, HF was the most common complication, occurring in 13% of the patients. We showed that the onset of HF depended on the underlying cardiac diagnosis, with HF most frequently diagnosed in the second or third trimester or shortly after delivery. Heart failure was found most often in women with poor pre-pregnancy cardiac function with a diagnosis of cardiomyopathy or pulmonary hypertension. Patient with HF had a higher rate of adverse maternal and fetal outcomes. Furthermore this is the first study to identify specific predictors for the occurrence of heart failure.

Rate of HF in relation to different underlying cardiac diagnoses

In this registry the rates of HF in various diagnoses slightly differ from reported rates in the literature. For simple diagnosis such as mitral regurgitation, aortic coarctation, aortic abnormalities and shunt lesions rates of HF are high in this registry when compared to the literature. (17,18) This may be partially explained by the high percentage of unrepaired shunt defects,

mainly in developing countries, leading to a relatively high rate of pulmonary hypertension associated with these lesions. Yap et al. described a higher rate of complications in patients with uncorrected shunts, in patients with atrial septal defects and ventricular septal defect, but none of the women developed HF.(19,20) We reported a HF rate of 3.8% in patients with atrial correction for transposition of the great arteries which is relatively low compared to previously reported rates of 2,7%, 4.1% and 7.1%.(21-23)

Predictors

In our univariable analysis several factors were associated with an increased or low risk of HF. (Table 2) The factors cardiomyopathy, NYHA class>2, WHO>2, pre-pregnancy HF and pulmonary hypertension remained significantly associated in the multivariate analysis (Table 3). The presence of a left sided lesion and medication use prior to pregnancy showed a weak association. The loss of several of the factors of the univariate analysis suggests that their risk was indirectly mediated through a second factor. For example the relationship of HF with developing countries was probably due to the severity of heart disease. Of those factors that remained significant the strongest were pre-pregnancy HF and poor functional class and in addition high risk of pregnancy as represented by high WHO class. These are useful parameters in counselling of women with heart disease considering pregnancy. In the prospective study of Siu et al., EF<40% predicted complications. We found that EF and fractional shortening were univariable predictors of heart failure in the subgroup of patients in which these data were available, however, these variables could not be tested in the multivariable model due to missing data. Pulmonary hypertension has also been identified as a high risk condition in previous studies,(24). However, because of low prevalence pulmonary hypertension did not predict complications in the studies of Drenthen et al. and Siu et al.(2,3) We could identify pulmonary hypertension as a predictor of HF because we included patients from developing countries where the prevalence is relatively high.

In our series, the presence of a mechanical valve was not a predictor of HF, but these patients are mainly at risk for other complications such as haemorrhage and valve thrombosis. Similarly, IHD was not a predictor of HF, possibly because left ventricular function was almost normal in most of these patients. Patients with CHD had a lower risk than patients with VHD, IHD or cardiomyopathy, but compared to the rate of HF in the normal healthy population this risk is still increased.

Timing

To date, data on the timing of HF in pregnant women with heart disease are scarce. The peripartum period has been regarded as high risk period because of the rapid fluid shifts. (9) While peripartum cardiomyopathy by definition occurs in the months around delivery, also patients with VHD are reported to present with HF mainly in the peripartum period (7,8) In our study, there appeared to be two peaks, one at the end of the second and beginning

of the third trimester and the other around delivery. Within this pattern, there were distinct clusters of diagnostic groups. Women with pulmonary hypertension typically went into HF before 30 weeks gestation, for those with VHD HF tended to occur in mid to late pregnancy. In those with cardiomyopathy HF was diagnosed peripartum. The first peak, corresponding to 23-30 weeks occurred when most of the important haemodynamic changes had taken place. Stroke volume then has reached its maximum (up to 130% of normal) for a number of weeks, but heart rate is just starting to increase. Firm conclusions for all diagnostic groups can't be made, some of the diagnostic groups were small.

Pregnancy outcome in patients with HF

Pre-eclampsia during pregnancy was associated with HF with an odds ratio of 7.1. In previously healthy women who develop pre-eclampsia, diastolic and systolic left ventricular function abnormalities have been demonstrated, but these rarely develop into HF.(25) However, in women with pre-existing heart disease, the added strain of pre-eclampsia precipitates HF resulting in a rate as high as 30% of the patients. This is an important novel finding of our study, which indicates that patients with heart disease who develop pre-eclampsia should be monitored carefully for the development of HF. One third of the heart failure associated with pre-eclampsia was in patients with peripartum cardiomyopathy, which is a known association (26). However, two-third of the heart failure occurring in patients with pre-clampsia occurred in patients with other underlying diseases. .(26) Caesarean section rates were high in patients with HF, with the majority having a CS for cardiac reasons. Women with HF were often delivered preterm probably to shorten the period of volume load and to be able to institute more aggressive therapy for the treatment of HF, however the decision for early delivery may have a negative impact on the offspring in the longer term.(27) On the other hand, fetal death and intra-uterine growth retardation were higher in patients with HF, which may keenly illustrate the difficult balance between early delivery and prolonging pregnancy in this high risk situation. Reassuringly, neonatal death rates were not different.

Limitations

Some of the parameters previously described in the literature were not collected in this database, such as the severity of left ventricular outflow tract obstruction (peak aortic gradient >50 mmHg or aortic valve area <1.0 cm^2). Therefore we could not confirm nor contradict the value of these previously identified predictors. Important measures of ventricular function and HF, such as LV EF and natriuretic peptides, were not known in most patients and could not be involved in the multivariable analysis. Although we showed that timing of HF was dependent of underlying heart disease, some of the subgroups were small. Consequently, our findings need to be confirmed in future large studies. As with all registries there was some missing information, this was about 4%.

CONCLUSION

HF was the most common complication in this pregnancy registry. Timing of HF was dependant on the underlying cardiac diagnosis, with HF in the second trimester occurring mainly in patients with shunt lesions or VHD. In contrast, patients with cardiomyopathy and IHD developed HF shortly after delivery. In addition to the previously recognised risk factors such as pre-pregnancy signs of HF, high NYHA class or WHO category>2, we discovered new predictors for HF: cardiomyopathy or pulmonary hypertension. Furthermore pre-eclampsia during pregnancy was associated with HF and patients with HF were delivered preterm more frequently.

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The investigators participating in the ROPAC at 1 June 2011 are listed in the Supplementary Appendix.

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If you are interested to join this registry, please go to the following website:

http://www.escardio.org/guidelines-surveys/eorp/surveys/pregnancy/Pages/welcome.aspx

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Chapter 12

Coronary Artery Disease and Pregnancy.

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JW Roos-Hesselink

ABSTRACT

The occurrence of an acute coronary syndrome in women of childbearing age is rare, but when it happens it can have devastating effects on the mother and the child. Pregnancy has shown to increase the risk of ACS 3- to 4-fold. With an overall reported incidence of pregnancy related acute coronary syndrome of 6 per 100,000 deliveries. One of the most important risk factor for ACS during pregnancy is maternal age.

Pregnancy is a hypercoagulable state and has a major impact on hemodynamics. The increase in blood volume, stroke volume and heart rate and the decrease of vascular resistance results in 30-50% increase of cardiac output. The presence of reduced left ventricular function increases the chance of an adverse maternal and fetal outcome.

Evaluating chest pain in pregnant women can be challenging, since chest pain in pregnancy is common and may be caused by benign as well as life threatening diseases. In addition physical examination and diagnostic tests can be misleading during pregnancy. The underlying cause of an acute coronary syndrome may be different from outside pregnancy and especially dissection and coronary spasm are more often encountered then in the non-pregnant population. With the introduction of PCI as the preferred treatment modality, mortality due to ACS during pregnancy has decreased.

The mode of delivery should be planned in a multidisciplinary team consisting of at least an obstetrician, anaesthesiologist and cardiologist. In women with adequate cardiac output vaginal delivery is preferred but caesarean section may be the best option in high risk patients.

Keywords

Pregnancy, acute coronary syndrome, outcome.

INTRODUCTION

Although an acute coronary syndrome (ACS) in women of childbearing age is rare, consequences are considerable, especially in pregnant women. In this chapter we will give an overview of the current literature regarding pregnancy and ACS. Acute coronary syndrome prior to pregnancy, acute coronary syndrome in the antepartum, peripartum and post partum period and heart failure during pregnancy will be described using patient cases, followed by an overview of literature and recommendations. Epidemiology, pathophysiology, counselling, use of medication, treatment possibilities, delivery, maternal and fetal outcome will be discussed.

EPIDEMIOLOGY

Acute coronary syndrome (ACS) is rare in women of childbearing age (16 to 45 years of age). During these years pregnancy has shown to increase the risk of ACS three- to fourfold. (James et al., 2006) Between 1991-2000 the overall incidence of pregnancy related acute coronary syndrome was reported 2,7 per 100.000 deliveries (Ladner et al., 2005). A decade later James published on risk factors of ACS during pregnancy in a population based study in the United States. He reported an incidence of 6,2 per 100.000 deliveries between 2000-2002. (James et al., 2006) The higher incidence can be explained by three causes: First of all with the improved diagnostic tests, especially troponine assessment, more women with acute chest pain have been diagnosed with ACS; secondly, an increase of known cardiovascular risk factors is seen in the pregnant population; and finally, maternal age increased in the western world (Ventura et al., 2004).

Cardiovascular risk factors specific for ACS during pregnancy are very similar to the risk factors of non-pregnant patients. The main risk factors for ACS in women are smoking, lipid metabolism disorders, hypertension and diabetes. But in pregnant patients also thrombophilia and anaemia are risk factors for ACS. In the last decades lifestyle has changed in the western world. (Ogden et al., 2006) As a consequence of high calorie intake and little exercise the incidence of obesity and diabetes has increased drastically. (Cecchine et al., 2010)

In addition to cardiovascular risk factors, a few obstetric risk factors have been discovered. The most important being multiparity, but also a history of preeclampsia, post-partum haemorrhage, transfusions and post-partum infections are risk factors for ACS during pregnancy. (Ladner et al., 2005). In addition, obstetric complications may elevate the risk of delevoloping ACS later in life. Still birth, preeclampsia and recurrent miscarriage are a risk factor for ACS

later in life in the general population. Endothelial dysfunction is hypothesised to be the link between hypertension in the pregnancy and cardiovascular disease later in life. (Pina, 2011).

Maternal age is one of the most important risk factor for ACS during pregnancy. Over the age of 30 women have an odds ratio of 9.5. This is even higher in women over 40, with an odds ratio of 31.6. (James et al., 2006) There is a continuing trend of childbearing at older ages, caused by carrier choices of highly educated women. The advances in reproductive technology enable many older women to conceive, leading to more women with a high risk for ACS during pregnancy. Therefore it may be expected that the incidence of ACS during pregnancy will increase further in the coming years.

CHANGES DURING PREGNANCY

Knowledge of the normal physiological changes during pregnancy, labour and the postpartum period is essential for doctors looking after pregnant women with heart disease. In the following section we will give an overview of the most important physiological changes in pregnancy.

The majority of the cardiovascular changes occur in the first twenty weeks of gestation. The first hemodynamic change is a decline in total peripheral vascular resistance (TPVR) of 40-70%. The decline in TPVR is a response to circulating gestational hormones. The drop in TPVR results in a relatively underfilled vascular state reflected by a fall in blood pressure. The blood volume increases with 1-1,5 litre (30-50%) as a response to the low blood pressure. The increase in plasma volume is relatively higher than the increase in red blood cells resulting in a physiological haemodilution. The combined changes result in a fifty percent increase in circulating blood volume during pregnancy. (Robson et al., 1989)

Cardiac afterload decreases with the fall in TPVR and cardiac preload increases with the rise of blood volume. These changes result in an increase in cardiac output of 30-50% from the 20th week of gestation as shown in figure 1. During pregnancy heart rate increases by 10-20 beats per minute, this mainly happens in the third trimester. Pregnancy is associated with changes in cardiac structure secondary to the increase in cardiac output, with left ventricular dimensions increasing from between 10-30%, ejection fraction and fractional shortening also increase. (Hunter & Robson, 1992)

The vascular system changes with the increase in stroke volume. Arterial stiffness decreases during the first trimester, but slightly rises from the second trimester and vascular distensibility is increased (Ulusoy et al., 2006). These changes are partially mediated by gestational hormones, for example estrogen has favourable effects on the endothelium and vascular

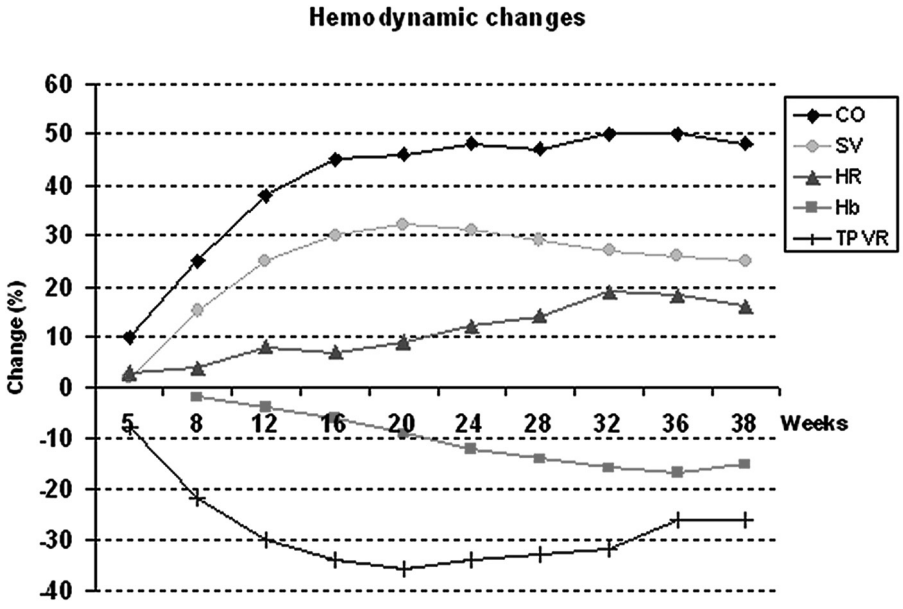

Figure 1. Hemodynamic changes in the normal pregnancy: CO cadiac output, SV stroke volume, HR heart rate, Hb haemoglobin concentration and TPVR total peripheral vascular resistance. Reproduced from: "Karamermer Y, Roos-Hesselink JW. Pregnancy and adult congenital heart disease. Expert Rev Cardiovasc Ther 2007; 5: 859-869" with permission of Expert Reviews Ltd .

smooth muscle cells and increases vasodilatation (Mendelsohn & Karas, 1999), but progestins reduce estradiol-induced endothelium-mediated vascular relaxation. (Skafar et al., 1997).

Delivery increases the stroke volume by 20%, which contributes to the 25% increase in cardiac output. This is initiated by the greater maternal oxygen consumption caused by the increase in uterine contractions in combination with maternal stress and pain, which in turn stimulates higher epinephrine levels.

Major hemodynamic changes also occur during the puerperium, (from birth until 6 to 8 weeks after delivery). Decompression of the inferior cava and the return of uterine blood to the circulation (auto-transfusion) cause a period of overfilling. In women with impaired cardiac function this may result in cardiac decompensation. All gestational hemodynamic changes return to prepregnancy levels 3-12 months after pregnancy.

Pregnancy is a hypercoagulable state, probably an evolutionary adaptation to reduce the risk of severe haemorrhage after labour. There is a decrease in releasable tissue plasminogen activator (tPA), an increase in fast-acting tPA inhibitor and an increase in factors V, VII, VIII, IX, X, XII and von Willebrand factor (Fletcher et al, 1979). Protein S is increased through out pregnancy, while increased resistance to activated protein C is only seen during the second

and third trimesters (Coolman et al., 2006). The hypercoagulable state is partially reversed by haemodilution and the activation of the fibrinolytic system. During delivery the placenta and myometrium release tPA inhibitors further increasing the hypercoagulable state (Yoshima et al., 1992); but by around 6 weeks after pregnancy the coagulation and fibrinolytic systems return to normal.

In summary pregnancy is a hypercoagulable state and an increase of 30-50% in cardiac output is seen as a result of decrease of vascular resistance and increased blood volume, stroke volume and heart rate.

MEDICATION DURING PREGNANCY

The food and drug administration (FDA) made a classification system for the use of drugs in pregnant women:

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Table 1. Medication during pregnancy
ACE: Angiotensin-converting enzyme inhibitors. ARB: Angiotentin receptor antagonists.

Medication	Indication	FDA	Safe during pregnancy	Extra information	Safe during breast feeding	Extra information
Atenolol	Hypertension, Arrhythmias,	D	Yes	IUGR and premature birth	No	A case report of adverse effects
Other beta blockers	Hypertension, Arrhythmias, Marfan disease ACS	C	Yes	Low birth weight, hypoglycemia and bradycardia in the fetus	Yes	Careful monitoring of the neonatal heart rate.
ACE inhibitors	Hypertension, Heart failure	D	No	High incidence fetal death and fetotoxic effect: renal failure, renal dysplasia	Yes	Traces are detected in breast milk, fetal monitoring is advisable
ARB	Hypertension, Heart failure	D	No	High incidence fetal death and fetal anuria	No data	
Spironolactone	Hypertension, Heart failure	D	No	Potential anti-androgenic effects on the developing male fetus	Yes	
Thiazide diuretics	Hypertension, Heart failure	C	No	Hypovolemia can lead to reduced uterine perfusion	Yes	May suppress lactation.
Loop diuretics	Hypertension, Heart failure	C	Yes	Hypovolemia can lead to reduced uterine perfusion	Yes	
Digoxin	Arrhythmias	C	Yes	No reports of congenital defects	Yes	Neonatal heart rate should be monitored after delivery.
Nitrates	Hypertension, Angina	B	Yes	Careful titration is advised to avoid maternal hypotension.	No data	
Calcium channel antagonists	Hypertension, Preeclampsia	C	Yes	Diltiazem: an increase in major birth defects have been reported	Yes	Excreted in breast milk.
Statins	Lipid disorders	X	No	Animal studies demonstrated increased skeletal abnormalities, fetal and neonatal mortality.	No	Probably appears in breast milk, there are some concerns with disruption of infant lipid metabolism
Aspirin	ACS, Arrhythmias	C	Yes	Low dose aspirin is safe	Yes	No adverse effects have been reported in low dose.

PRE-EXISTING CORONARY DISEASE

A 39 year old woman was seen at the out patient clinic of a referral hospital for counselling. Three month earlier she had suffered a non ST elevation myocardial infarction (NSTEMI). On coronary angiogram (CAG) a thrombotic occlusion of an atherosclerotic lesion of the left coronary artery was seen and treated with a drug eluting stent. She had never been pregnant, had recently stopped smoking, was a non diabetic and normotensiv. Her family history did not reveal any cardiovascular disease. Her left ventricular function was assessed with echocardiography and the estimated ejection fraction was 48%. She was prescribed aspirin, clopidogrel, simvastatine, perindopril and nifedipine.

Counselling prior to pregnancy

Ideally all women of reproductive age with cardiac disease should undergo thorough evaluation before becoming pregnant. This evaluation should focus on identifying and quantifying risk to the mother and the unborn child. During pre pregnancy counselling life expectancy and ethical aspects of parenthood should also be discussed. An exercise test, and echocardiogram should be performed. Risk stratification is made to inform the patient of possible complications during pregnancy. The influence of pregnancy on the cardiac condition has to be considered, but also the cardiac condition may influence pregnancy outcome, especially the incidence of hypertension, preeclampsia, arrhythmias and thrombotic complications may be higher.

Low dose aspirin, beta blockade and nitrates should be continued during pregnancy. The safety of clopidogrel is unknown. In individual cases with recent drug eluting stent placement, continuation should be considered. ACE inhibitors and ARBs should be stopped in all patients or in the pre-conception clinic or immediately when pregnancy is diagnosed. Generally, statins should be stopped, however, in an individual patient with very high cholesterol, continuation may be considered.

Recurrence rate

Only limited data on recurrence risks have been published. Badui et al described 18 women in the literature with previous ACS, the mothers were 1 or 2 years after ACS and none of these patients had a recurrent ACS. (Badui & Enciso, 1996) One of the reasons for this lack of data is the fact that many women are advised against pregnancy after ACS. Doctors advise against pregnancy for a number of reasons, first it is suggested that the hypercoagulable state of pregnancy raises the chance of recurrence of thrombotic obstruction of the coronary arteries. Second the increase in left ventricular mass and heart rate lead to a high cardiac oxygen demand. The increased cardiac oxygen demand can lead to relative coronary flow mismatch

in patients with pre-existing coronary artery disease. Finally, fear of complications may make them conservative.

The first patient was advised to wait for at least 3 more months before trying to become pregnant to make sure that she was cardiovascularly stable. Before conception perindopril, statin and clopidogrel are advised to be discontinued until after delivery. If pregnancy occurred, then the plan was made for outpatient review at 6, 12, 20 and 32 weeks of gestation.

Impaired left ventricular function

A 41 year old patient presented to the out patient department of a referral hospital with a desire for pregnancy. She had not been pregnant before. One year earlier she had suffered from a STEMI, CAG at that time revealed atherosclerosis and thrombosis of the LAD and she was treated with thrombosuction and a drug-eluting stent. Six month after the ACS her left ventricular function was measured with echocardiography, ejection fraction was 35 %.

In 2000 Siu published predictors of cardiac events, mainly heart failure and arrhythmias. Prior cardiac events, left ventricular outflow obstruction, NYHA class > II, cyanosis and systemic ventricular dysfunction (ejection fraction >40%) were predictor for adverse maternal outcome. If one predictor was present, cardiac event rate was 27%. (Siu et al., 2001) However, the patient population consisted of patients with congenital or valvular disease and a diminished systemic ventricular function was mainly found in patients with transposition of the great arteries after atrial repair. To use these results to predict cardiac events in ischemic cardiomyopathy patients is at least questionable.

Generally women are advised against pregnancy if they have a left ventricular dysfunction with an ejection fraction under 40% and have a dilated left ventricle (Prebitero et al., 2009). In a study on pregnancy in patients with dilated cardiomyopathy, an OR of 43 was found for moderate or severe left ventricular dysfunction and 39% of the pregnancies where complicated (Grewal et al., 2009). Risk factors for adverse events were moderate (EF 30%-44%) or severe (EF<30%) ventricular dysfunction and NYHA class III or IV at baseline or prior cardiac event. Compared with non-pregnant patients with dilated cardiomyopathy, pregnant patients needed more medication and adverse cardiac events were more common. Pregnancy seemed to have a negative impact on the short-term clinical course for women with dilated cardiomyopathy (Grewal et al., 2010). We need similar data for women with ischemic left ventricular dysfunction.

In case of heart failure during pregnancy diuretics are considered to be first choice, but diuretics could result in hypovolemia, leading to reduced uterine perfusion and so should be used with caution. Nitrates can be used safely and digoxin can be considered, especially

if the patients has atrial fibrillation. Such patients should be treated in hospital and bed rest is advisable.

In the study of Grewal et al, the neonatal complication rate was high, especially in women with severe dilated cardiomyopathy, suggesting that in the context of severe left ventricular dysfunction, the heart may not be able perfuse the utero-placental circulation sufficiently. Therefore, regular growth scans to indentify fetal growth restriction and frequent review in a combined clinic with an obstetrician and cardiologist is advised. (Signore et al., 2010)

The second patient was informed about the high maternal and fetal risks associated with pregnancy in women with impaired left ventricular function as well as the lack of information on the recurrence rates of ACS during pregnancy. She decided not to take the risk.

Delivery

Planning delivery should be done in a multidisciplinary team consisting of an obstetrician, anaesthesiologist and cardiologist. The patient should be informed about the considerations prior to delivery, since patients preference has to be taken into account. Timing of delivery is individualized, according to the cardiac and obstetric status of the mother and fetal well being. In patients with heart failure delivery at 34 weeks can be considered to allow early optimisation of treatment modalities for the mother.

The mode of delivery depends on the maternal hemodynamic situation and obstetric factors. Women with adequate cardiac output may tolerate induction of labour and vaginal delivery. Vaginal delivery can lead to fluctuations in blood pressure, especially in prolonged labour. Assisted vaginal delivery (by vacuum or forceps extraction) is recommended in some women to avoid excessive maternal efforts and prolonged labour (Roth & Elkayam, 2008). Adequate pain relief is very important, but epidural anaesthesia is contraindicated when the patient is on antithrombotic or anticoagulant treatment.

During caesarean section blood pressure can be controlled, stress and pain can be relieved and a stable environment can be created. However, caesarean section has been associated with a higher risk of venous thrombo-embolism, infection and peripartum haemorrhage. In some cases general anaesthesia will be necessary with some risk of complication (Deneux-Tharax et al., 2006). In addition, blood loss during caesarean section has been shown to be greater than during vaginal delivery.

Post partum period

The volume shifts caused by auto-transfusion can be dangerous in patients with diminished left ventricular function. Close monitoring on a medium care unit may be advisable for the

first 3 days after delivery. Early recognition of heart failure and immediate treatment with diuretics can be achieved by close monitoring of the patients and measurement of the central venous pressure. Some cardiologists advise prophylaxic diuretics in patients with severe systemic ventricular dysfunction. Ideally monitoring should be done in a unit with neonatal care, since early bonding of mother and child is very important. In patients with normal ventricular function after ACS prior to pregnancy close monitoring in-hospital for at least three days after delivery is advisable. The main risk during this period consists of thrombo-embolic events cause by the hypercoagulable state of pregnancy exacerbated by even higher tPA inhibitor levels immediately after delivery.

Breast feeding

The effects of breast feeding on maternal cardiovascular function are caused by circulating hormones. High levels of oxytocin circulate through the body. In the study of Mezzacappa cardiac output during breastfeeding was found to be higher than in bottle feeding mothers. They describe a decrease in heart rate and a slight increase in systolic blood pressure during the first minutes of breast feeding (Mezzacappa et al., 2001). Light et al described a lower blood pressure in breast feeding mothers one hour after breast feeding (Light et al., 2000). In the first weeks of breast feeding, women produce around 800 millilitres of milk daily. With the production of breast milk large volume shifts take place, these may cause a problem in patients with reduced left ventricular function.
The fluctuations in blood pressure may be harmful in severely symptomatic patients and bottle feeding should be considered. Lactation is also associated with a risk of bacteraemia secondary to mastitis. (Guideline pregnancy and heart disease

ANGINA IN THE PREGNANT PATIENT.

A 41 year old patient presented to the emergency department with acute chest pain. There was a myocardial infarction at young age in her family history. She was 18 weeks pregnant with her first child. She did not, take any alcohol or medication during pregnancy. But she was continuing smoking during pregnancy. She had a blood pressure of 135/85mmHg, a pulse of 95 beats per minute and auscultation of the chest revealed normal breath sounds without rales. The ECG was normal. Transthoracic echocardiography revealed no wall abnormalities. Troponine levels were normal. During exercise testing she performed 92% of expected and during testing a down sloping ST depression of 2-3 mm was found in lead II, III and aVf.

Signs and symptoms

Evaluating chest pain in pregnant women can be challenging, since chest pain in pregnancy is common and can be caused by various conditions. Most often chest pain is caused by

gastro-oesophageal reflux which is benign in most cases. Chest pain should never be ignored as it may also represent possible life threatening disease such as pericarditis, myocarditis, aortic dissection, hypertensive crisis, pulmonary thrombo-embolism or acute coronary syndrome. Urgent complete cardiac review is always appropriate if a pregnant woman who presents with chest pain.

Physical examination can be misleading, hypotension and tachycardia are physiological responses to normal pregnancy (as describe in sub-chapter 3). In this case normal lung examination and oxygen saturation made pneumonic disease less likely, but pulmonary thrombo-embolism remained a possibility. Measuring blood pressure in both arms is important since aortic dissection is a part of the differential diagnosis.

Diagnostic testing

Criteria for ACS in pregnancy are the same as in non pregnant women, consisting of a combination of symptoms, ECG changes and positive cardiac markers. Normal diagnostic tests can be used in pregnancy, but outcome has to be evaluated against normal pregnancy values, since abnormal values can be normal in pregnancy. Table (2) gives a brief summary of the changes most often seen in diagnostic tests.

The electrocardiogram (ECG) changes as a result of the upward shift of the diaphragm with the growing uterus. A left axis deviation with Q waves in lead III and aVF is seen in the third trimester. T waves can be inverted in lead III, V1 and V2. In case of a caesarean section with general anaesthesia ST depression is seen often (Prebitero et al., 2009).

The use of echocardiography is safe in pregnancy because echocardiography does not involve radiation. Detection of wall motion abnormalities can be used as a sign of possible acute coronary syndrome. In normal patients exercise tests are used to confirm the diagnosis of coronary artery disease or after ACS to establish exercise capacity and exclude residual ischemia. In pregnancy it is advisable to use submaximal exercise (<70% of the maximum predicted heart rate) testing, since fetal bradycardia and absence of body movement have been described after heavy maternal exercise (Elkayam et al., 1998). There is no evidence of increased risk of spontaneous abortion after exercise testing.

Biomarkers are used in the cardiological practice to confirm the diagnosis of acute coronary syndrome. During labour elevated creatinine kinase (CK) and CK MB are found due to uterine contractions. These levels normalize during the second day after labour. (Poh & Lee, 2010) Troponine I is not elevated in normal pregnancy, as a result troponin I is the recommended biomarker in pregnancy. However, troponin I serum levels can be elevated in patients with

pre-eclampsia and hypertensive crisis. It is not totally clear whether this is a sign of cardiac ischemia in these partients.

Table 2. Changes in diagnostic tests in normal pregnancy.

Diagnostic test	Effect of normal pregnancy
Electrocardiogram	Left axis deviation and Q waves in lead III and aVF, inverted T waves in lead III
Exercise test	Decreased exercise tolerance
Echocardiogram	Increase in left ventricular mass, mild mitral regurgitation
Serum creatinin kinase	Elevated during labour
Troponin	Not affected during normal pregnancy

Chest radiography is only used in pregnancy during emergency medical conditions. If proper shielding of the abdomen is used radiation of chest radiography is considered relatively safe (especially in the third trimester). (Hirshfeld et al., 2005)

Treatment choices in patients with chest pain

The choice of treatment is dependent on the diagnosis and the presence of ECG changes. In patients without any ECG changes, other causes of chest pain should be considered; troponin should be measured in all patients. In women with ACS, conservative treatment (bed)rest, nitrates and beta blockers is advised. In NONSTEMI patients a careful assessment should be made. Troponin levels, hemodynamic state and relief of pain determine whether the patient should have a coronary angiogram. A coronary angiogram will reveal the origin of the problem, eg dissection, thrombus. But a conservative treatment may be best in the majority of patients. STEMI patients need immediate treatment and PCI as first choice treatment should be performed as soon as possible.

In patients with angina catherization should be considered. If proper shielding of the abdomen is used, radiation dose is low. An interventional procedure may result in a fetal exposure of <1 rad. Termination of pregnancy is generally not recommended, although it may be considered when the fetal radiation dose exceeds 10 rad. (Roth & Elkayam, 2008)

The patient became pain free after the use of nitroglycerine and was treated with beta blockade. Further pregnancy was uneventful and she delivered a healthy baby boy at 39 weeks after spontaneous vaginal delivery.

Acute coronary syndrome during the first or second trimester of pregnancy.

A 38 year old patient came to the emergency department with acute chest pain. She was 25 weeks pregnant with her second child. The first pregnancy was complicated by preeclampsia.

She has no dyspnoea, syncope, cough or fever. She did not smoke nor use any alcohol or medication during pregnancy. She had a blood pressure of 100/60mmHg, a pulse of 105 beats per minute and was tachypnoeic at 24 breath per minute. Oxygen saturation by pulse oximetry was 99%. Auscultation of the chest revealed normal breath sounds without rales. The heart sounds were normal, no murmur or gallop was heard. Abdominal examination did not reveal any abnormalities and there was no oedema. The results of the ECG were consistent with STEMI of the anterior wall with ST elevation in V1-V3 and ST depression in lead II, III and aVF. Transthoracic echocardiography revealed a dyskenetic left anterior wall. The patient underwent coronary angiography three hours after onset of complaints and revealed a thrombotic obstruction of the left main artery with TIMI flow grade 1.

Cause of ACS

ACS in pregnancy has other causes than in the non-pregnant state. In the review of Roth and Elkayam only 40% (41 of the 103 patients) was caused by coronary artery stenosis. (Roth & Elkayam, 2008) Other causes were thrombus in 8%, coronary artery dissection in 27%, vascular spasm in 2% and normal coronary arteries were found in 13% of the patients. (Roth & Elkayam, 2008) ACS has been noted to occur more often in the anterior wall (Iadanzo et al., 2007).

Coronary dissection is very rare in the non-pregnant population, but more frequently seen in pregnancy (27%) especially in patients with ACS in the peripartum period (50%). Excess of progesterone is thought to be one of the causes of coronary dissection, since it causes biochemical changes of collagen in the coronary vessel wall and weakens the media. The impact of increased blood volume and cardiac output may cause extra wall stress which is hypothesised to be an additional factor (Roth & Elkayam, 2008) also autoimmune conditions, such as systemic lupus erythromatosis and anti-phospolipid-antibody syndrome, have also been linked to coronary artery dissection. (Nallamonthu et al., 2005)

Normal coronary artery morphology is found in 13% of patients, perhaps caused by transient coronary spasm or thrombus. Vascular spasm was found in 2 % of the case reports described by Roth. (Roth & Elkayam, 2008) Spasm might be caused by enhanced vascular reactivity to angiotensin II, norepinephrine and endothelial dysfunction (Nisell et al., 1985). Vascular spasm in combination with the hypercoagulable state of pregnancy may cause coronary thrombus leading to acute coronary syndrome. Patients who continue to smoke during pregnancy have an increased risk of coronary artery thrombosis due to enhanced platelet aggregability in smokers.

Treatment

When tests have confirmed the diagnosis of acute coronary syndrome, it is important to make a treatment plan and inform the patient about maternal and fetal risks of all possible treatment options.

There is only limited information available on PCI during pregnancy. Nowadays pregnancy is not a contraindication for PCI and since PCI is the primary treatment for non-pregnant STEMI patients, more and more cases of stenting during pregnancy are published. With PCI as a treatment modality during pregnancy mortality of ACS has dropped. James described PCI in 135 patients (of which 127 were with stenting), but no information on outcome was published. In the first review of Roth and Elkayam in 1996 only 3 of the 125 patients had PCI (Roth & Elkayam, 1996). Whereas in their second review 38 patients had a PCI, all with bare metal stenting. In this review 92 patients had a coronary angiogram (of which 43 were postpartum). After PCI one patient needed CABG because of extensive coronary dissection (Roth & Elkayam, 2008).

The preference for bare metal stenting is caused by the requirement of dual anti-platelet treatment around the delivery and the lack of experience. The use of drug eluting stents has been described in 2 case reports. One patient with STEMI at 27 weeks of gestation received a drug eluting stent, she delivered a healthy child by elective caesarean section at 35 weeks. Antiplatelet therapy was continued during delivery. However, post partum she had a haemoglobin drop of 5 g/dL and needed a blood transfusion (Al-Aqeedi & Al-Nabti, 2008).

Since pregnant women are excluded from most clinical trials no randomised controlled trials have been preformed on thrombolytic therapy, PCI or CABG in the pregnancy. However, thrombotic therapy is considered to be relatively contraindicated in patient with acute coronary syndrome because of bleeding complications. In stroke, pulmonary embolism and mechanical heart valve thrombosis there is some clinical experience with several strategies such as tPA, urokinase and streptokinase. This medication does not cross the utero-placental barrier (Leonhardt et al,. 2006). Maternal and fetal outcomes were favourable, but complications, as maternal haemorrhage, fetal loss, abruption placenta, preterm delivery and post partum haemorrhage have been reported in up to 10% and maternal mortality was 1.2 % (Turrentine et al,. 1995). The risk of haemorrhage is highest in the peripartum period (Murugappan et al,. 2006) and given the high incidence of coronary dissection in pregnancy, the use of thrombolytic therapy could lead to haemorrhage and further progression of the dissection. Thrombolytic therapy should be considered in case of thrombosis and possibly when primary PCI is not available. (Roth & Elkayam, 2008)

Very limited data is available on coronary artery bypass grafting (CABG) during pregnancy, no conclusion on safety for the mother or the unborn child can be made. In normal non-pregnant patients with ACS CABG is used when multiple vessels or the left main coronary artery are involved (Nallamonthu et al., 2005). In the data by James 61 women underwent CABG, but there was no specific data on outcome in these patients. In the case study of Roth and Elkayam 10 patients were described who underwent CABG, of which were 7 due to coronary artery dissection (Roth & Elkayam, 2008), in these cases one fetal death and one late maternal death were reported (Garvey, 1998). Large differences in maternal mortality rates were found for ACS in pregnant women in the last decades, ranging from 5,1%(James et al., 2006) to 38%(Koul et al., 2001). The decline in mortality rate could be explained by the detection of ACS in less severely ill patients as well as improvement in treatment options in the last decades (Roth & Elkayam, 2008).

Delivery

Delivery should be postponed if possible for at least 2 or 3 weeks after the ACS to allow adequate healing. (Prebitero et al., 2009) Anti-platelet therapy should be continued in case of recent stent implantation, low dose aspirin is also advisable in patient with other forms of coronary artery disease, but doctors should be aware of a higher risk of post partum haemorrhage. Vaginal delivery with shortened second stage of labour and adequate pain relief can be safe. Caesarean section is the preferred mode of delivery in patients with cardiac instability.

Post partum period

Close monitoring on a medium care unit may be advisable for the first 3 days after delivery. With anticoagulant and anti-platelet therapy given during pregnancy, special attention should be paid to major haemorrhage. Ideally monitoring should be done in a unit with neonatal monitoring.

In our patient thrombosuction was performed and a bare metal stent was inserted. She was treated with heparin for 24 hours and received aspirin beta blockade and nitrates during the remainder of the pregnancy. Clopidogrel was not given during pregnancy. She delivered 12 weeks later at 37 weeks by the assisted vaginal route. Epidural pain medication was given to limit pain and stress. A healthy girl (3045 gram) was born. After delivery she was treated with a statin and an ACE inhibitor.

ACUTE CORONARY SYNDROME IN THE THIRD TRIMESTER

A 34 year old patient presented to the emergency department with acute chest pain. She was 36 weeks pregnant. The results of the ECG were consistent with acute myocardial infarction of the anterior wall. The patient underwent cardiac catheterisation two hours after onset of symptoms, coronary angiogram revealed a coronary artery dissection of the left anterior descending artery.

ACS in the third trimester

Coronary artery disease in the peripartum period differs from ACS in the antepartum period in terms of coronary abnormality, cause, treatment options and mortality rate. Coronary dissection was the primary cause of coronary artery disease in the peripartum period (50%) and more commonly in post-partum period (34%) compared to antepartum period (11%). This is probably the result of hormonal changes and the stress on the walls of the coronary arteries during labour. In some cases an association with the administration of the medicine terbutaline (a medicine used to stop early uterine contractions) was found.

The mortality rate in patients with ACS in the peripartum period is 18% versus 9% in the antepartum and postpartum period (Roth & Elkayam, 2008). This was also shown in the study of Ladner, who reprted a mortality rate of 19% in the peripartum period. No specific cause for the high maternal mortality in the peripartum period was given. Different causes for high mortality rates could be hypothesized. The symptoms could be misinterpreted during delivery and both patient delay as well as doctor delay could lead to late recognition of ACS. A second reason could be the complication and mortality rate is relatively higher in patients with coronary artery dissection compared to coronary arthrosclerosis (Basso et al., 1996). A third reason is that major haemorrhage may result from anti-thrombotic therapy. And finally, cardiac failure after delivery caused by autotransfusion with stressing the injured myocytes could lead to maternal death. Moran et al described myocardial ischemia in normal patients during elective caesarean section. By using Holter monitoring and analysis of troponin I he showed ischemic changes in 8% of the patients and 81% had ST segment changes. None of these patients needed any form of treatment. This study showed that even normal healthy women experience ECG changes which may reflect some myocardial ischemia during caesarean section. (Moran et al., 2001)

Treatment in peripartum period

Treatment options are limited in the peripartum period, since anticoagulation and anti-thrombotic therapy should be discontinued 24 hours prior to delivery to avoid major bleeding complications. PCI is the treatment of choice in patients with STEMI. As pregnant patients

have a substantial higher chance of coronary dissection and a high maternal mortality, PCI should be preformed in a larger referral centre with cardiothoracic surgery standby.

Delivery and postpartum period

Caesarean section prior to CAG is a possible strategy in patients with ACS diagnosed after 32 to 34 weeks of gestation (Hameed & Sklansky, 2007). At this point fetal outcome is generally good and maternal benefit is high because of reduced stress during the last weeks of pregnancy and the use of antithrombotic therapy after PCI. Close monitoring on a medium care unit may be advisable for the first 3 days after delivery.

It is very important to consider ACS in peripartum patients with acute chest pain. Early recognition and diagnosis can save lives. A healthy baby girl was born at 39 weeks. The patient stayed in the hospital until 3 days after delivery.

ACUTE CORONARY SYNDROME IN THE POSTPARTUM PERIOD

After delivery of a healthy girl, a 31 year old patient was treated with bromocriptine to suppress lactation. Four days after delivery she presented to the emergency department with acute severe chest pain. The ECG showed an acute anterior myocardial infarction with ST elevation in V1-V3. Coronary angiography revealed a dissection of the left anterior descending artery and she was treated with bare metal stenting. She remained in the hospital for 3 more days and was treated with betacblockade, aspirin and clopidogrel.

Post partum ACS

Coronary dissection was found in 34% of the coronary angiograms and this was the most frequent cause of ACS in the postpartum period as it was in the peripartum period. Postpartum, some cases of ACS are associated with the administration of medicine. There are nineteen cases reported of ACS after the administration of bromocriptine, which is used to suppress lactation. Bromocriptine has dopaminergic agonist properties and may have vasopastic effects which can lead to thrombus formation (Hopp et al., 1996). This medication has been taken off the market as a lactation suppressant because of these reports. The second medicine associated with ACS is ergotamine, which is commonly used to prevent post partum haemorrhage by stimulating uterine contractions. Ergot derivatives are known to reduce the capacity of the intravascular lumen by 15-20% in normal coronary arteries. Eight cases of postpartum myocardial infarction have been described. (Eom, 2005) It is important to consider ACS as a possible complication before administration of this medicine in high risk patients (high age and cardiovascular risk factors).

Treatment post partum ACS

After delivery the treatment options are greater. Only maternal health determines the treatment, as is usual in "normal" cardiac patients PCI is the treatment of choice. Drug eluting stents can be used now. However, the uterine vascular bed has to be considered a large wound until one week after delivery.

Bromocriptin, ergotamine and terbutaline have been associated with post partum ACS.

NEONATAL OUTCOME

Neonatal outcome is strongly correlated with maternal outcome. In the first report of Roth and Elkayam 16 fetal deaths in 125 pregnancies (13%) were reported, of which 10 (62%) associated with maternal death (Roth & Elkayam, 1996). In the second report only a 9% fetal death rate was reported, of which two were elective terminations because of potential drug teratogenicity (Roth & Elkayam, 2008). Ladner et al described low birth weight and prematurity in patients with antenatal ACS and a 10% fetal death rate was reported in patients with intrapartum ACS (Ladner et al, 2005).

Fetal mortality is high in cardiac surgery during pregnancy with rates as high as 30% reported (Parry & Westaby, 1996). Factors which predicted an adverse fetal outcome were severity of maternal illness, total operative time, emergency surgery, reoperation, advanced maternal age and gestational age. (Barth, 2009)

During cardiopulmonary bypass, continuous fetal monitoring should be performed. The fetal heart rate can be used as an indicator of placental perfusion to guide bypass pump flow (Chandrasekhar et al., 2009). Uterine monitoring is essential to allow early control of these contractions as they are associated with significant fetal loss. (Parry & Westaby, 1996). Deleterious effects on the fetus are thought to be related to hypotension, hypothermia, embolic complications and inadequate placental flow. Caesarean delivery prior to CABG or PCI can be considered from 28 weeks of gestation. (Barth, 2009)

Fetal mortality in PCI compared to CABG is low. Proper shielding of the abdomen is essential in fetal protection. (Roth & Elkayam, 2008) Where chest radiography is considered relatively safe (especially in the third trimester). Cardiac catherization and intervention procedures may result higher fetal exposure with some chance of fetal abnormalities especially when used in the first trimester.

CONCLUSION

Acute coronary syndrome in women of childbearing age is rare, but pregnancy has shown to increase the risk of ACS 3- to 4-fold. (James et al., 2006) The overall incidence of pregnancy related acute coronary syndrome was reported between 2.7 and 6.2 per 100,000 deliveries and seems to have been increased in the last decadetime. Maternal age is one of the most important risk factor for ACS during pregnancy. Mortality rate has declined over the last decades from 19% in 1922-1994 to 5,1% in 2001-2002, probably as a result of improvement in treatment modalities.

Evaluating chest pain in pregnant woman can be challenging, since chest pain in pregnancy is common and may be caused by benign as well as life threatening diseases. Physical examination and diagnostic tests can be misleading, since normal pregnancy changes the results of these tests. Coronary artery disease in pregnancy has different causes than seen in non-pregnant women, artherosclerosis is less frequently found, whereas thrombus, dissection, spasm and normal coronary arteries are more often reported.

Table 3. Oversight of different patient groups in ACS in pregnancy.

Patient group	Counselling	First treatment choice	Maternal outcome	Fetal outcome
Previous ACS	Check medication	Medication	No data	No data
ACS and impaired LV function	Risk stratification	Medication	No data, high risk	No data
ACS antepartum	Not applicable	PCI	9 % mortality	11 % mortality
ACS peripartum	Not applicable	PCI	18 % mortality	5 % mortality
ACS postpartum	Not applicable	PCI	9 % mortality	No fetal mortality

Not all medication is safe during pregnancy, fetal and maternal risks have to be taken into account when medication is given. Pregnancy is not a contraindication for PCI anymore and this is probably the main reason maternal mortality has fallen recently. Very limited data is available on CABG during pregnancy, and it should only be considered when all other therapeutic options have failed.

The delivery should be planned by a multidisciplinary team consisting of an obstetrician, anaesthesiologist and cardiologist. Women with adequate cardiac output may tolerate induction of labour and vaginal delivery, but it is possible to create a potentially more stable environment during a caesarean section in high risk patients. Close monitoring in-hospital for at least one week after delivery is advised for patients with ACS in pregnancy.

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Chapter 13

A pregnant patient with native aortic coarctation and aneurysm, a case report.

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KEYWORDS

Aortic coarctation; pregnancy; thoracic aortic aneurysm

CASEREPORT

Aortic coarctation accounts for 6-9% of all congenital heart disease. In most cases aortic coarctation is discovered and treated during childhood. Uncorrected coarctation in adult patients is rare. In adult life uncorrected coarctation may lead to therapy resistant hypertension.[1] Retrospective observational studies showed hypertension and occasionally aortic dissection to be the principal risks during pregnancy after correction of aortic coarctation.[2] The risks of pregnancy in patients with uncorrected coarctation are largely unknown.

A 28-year-old pregnant lady presented at our outpatient clinic with severe hypertension at 32 weeks of gestation. Two previous pregnancies had also been complicated by hypertension, but no diagnosis was made at that time. On physical examination we saw a healthy woman with blood pressure of 186/80 mmHg at the right and 126/65 mmHg at the left arm. The ECG showed left ventricular hypertrophy. Echocardiography showed an increased systolic velocity of up to 4 meters per second over the distal aortic arch and continuous antrograde flow throughout diastole. Furthermore, severe dilatation of the descending aorta, distal to the left subclavian artery was discovered. (Panel A and B). The X-ray showed rib notching and signs of an aortic aneurysm (Panel C). On MRI the diagnosis of native coarctation (minimal diameter of 0,8 cm) and a huge saccular aortic aneurysm of 4,5 x 8,8 cm was confirmed. An elective caesarean section under regional anesthesia was performed at 35 weeks of gestation and a healthy girl (2625 gram) was born. After delivery a CT-angiography was performed showing a stable situation (Panel D). Two months later successful resection of the aneurysm and aortic coarctation, with graft interposition was performed (Panel E and F).

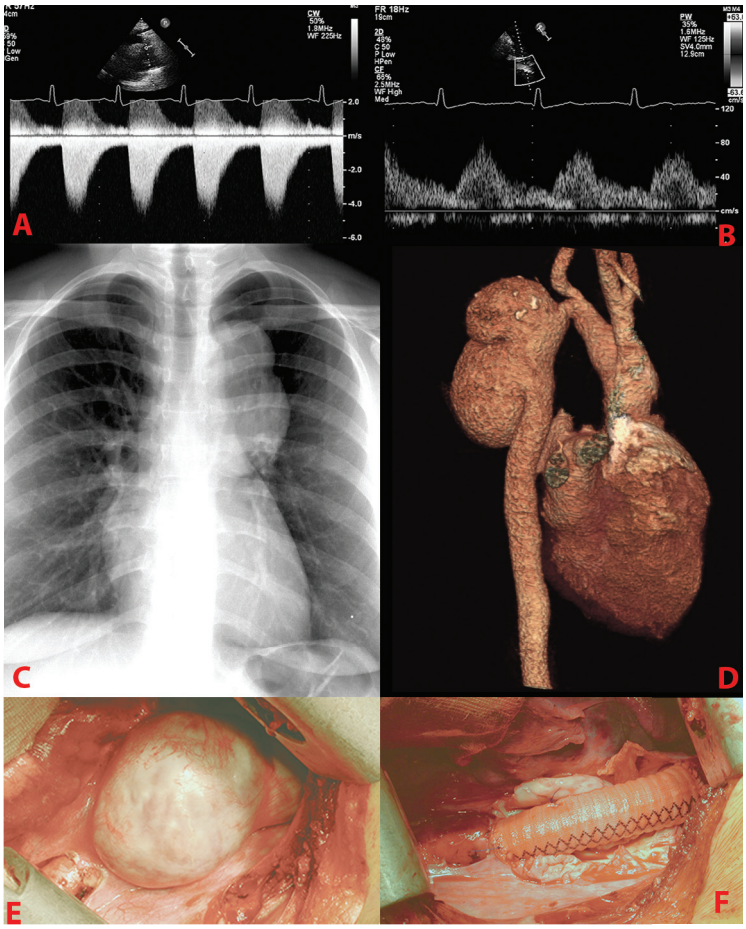

Figure 1
Panel A Echocardiography: Descending aorta with diastolic runoff
Panel B Echocardiography: Abdominal aorta with diastolic runoff
Panel C Chest radiography showing rib notching and aortic aneurysm
Panel D 3D reconstruction of CT angiogram showing an aortic aneurysm of 4,5 x 8,8 cm
Panel E Photograph: The aneurysm during operation
Panel F Photograph: Graft interposition after operation

DISCUSSION

No other pregnant patient with native coarctation and aortic aneurysm was described so far. Beauchesne described a series of 44 pregnancies in 16 patients with native coarctation. (3) Seven additional cases were published since 1990. [4-10]

Our patient was known with hypertension and the diagnosis was missed in an earlier stage. Diagnosis requires a high index of suspicion in young patients with hypertension. The arm-leg blood pressure difference and a diastolic run off Doppler pattern in the abdominal aorta can easily unmask the diagnosis. Our case stresses the importance of thorough physical examination and echocardiography in young patients with hypertension. The latter should always include Doppler registration of the abdominal aorta. Timely diagnosis of coarctation, as the cause of hypertension, may prevent the occurrence of difficult late complications.

During pregnancy, due to hormonal changes, the aortic wall may become more vulnerable to dissection. [11] Choosing the optimal time and mode of delivery in this patient with native coarctation complicated by hugh aneurysm formation was difficult. We decided to plan caesarean section at 35 weeks, since this patient already had 2 successful pregnancies and an elective caesarean section was thought optimal with all specialists available. Although arguments for immediate aneurysm resection after delivery were present, we choose to wait 2 months to let the placenta bed recover, before performing surgery under full heparinisation.

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C

Part III Children of women with heart disease

Chapter 14

Growth in children of mothers with congenital heart disease.

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ABSTRACT

Aim

To describe the growth of children born from mothers with congenital heart disease and to study if the children born small for gestational age remained small or showed catch-up growth.

Methods

Mothers participating in the ZAHARA I-study (focussing on cardiac and obstetric and neonatal outcome in patients with congenital heart disease) were asked to participate in this neonatal study. Growth data (height, weight and head circumference) of their children measured at standard intervals at the counselling centres were collected. These data were converted into a standard deviation by using Growth Analyser.

Results

The growth of 450 children was studied from birth to 2.5 years of age. At birth the children had a height and weight of 0.3 standard deviations smaller than of the normal population. Height, weight and head circumference showed some catch-up growth, mainly in the first 6 month. Premature children showed slower and less catch-up growth. Of the small for gestational age children 87% reached normal values after 1 year. Children of mothers with complex heart disease had a smaller height and weight at birth. Children of mothers with complex heart diseas showed a similar growth pattern to premature children, their growth was slower and they remained smaller during follow-up.

Conclusion

Although children were born smaller than normal, most showed catch-up growth in the first 6 months of life, although premature children grew slower and remained smaller. Head circumference reached nearly normal values. Children of mothers with complex heart disease showed slower catch-up growth and remained smaller.

Key Words

Pregnancy, heart disease, small for gestational age, premature, neonatal growth

ABBREVIATIONS

GGD = Dutch: Gemeenschappelijke GezondheidsDienst (Municipal Health service),
SDS = Standard Deviation Score,
SGA = Small for Gestational Age,
ZAHARA = Dutch: Zwangerschap bij Aangeboren HARtAfwijkingen (Pregnancy and congenital heart abnormalities)

INTRODUCTION

With the progress made in open heart surgery more and more women with congenital heart disease are reaching childbearing age and become pregnant. Although still rare in the obstetric practice, these women now constitute the majority (>70%) of pregnant women with heart disease in the developed world.(1,2) These patients need careful attention as they are at risk of maternal mortality and morbidity.(3, 4)

Studies on pregnancy in women with congenital heart disease have shown a high rate of preterm delivery and fetal mortality.(1,5,6) Fetal outcome was associated with maternal disease and problems during pregnancy.(6,7) More children were small for gestational age or had lower birth weight in babies from mothers with heart disease, especially when the mother had cyanotic heart disease.(5,8) How these outcomes influence the development of these children during their further life is important but until now not investigated.

There have been studies investigating growth patterns in preterm and small children from mothers with no heart disease. These studies show that most children show catch-up growth within the first year.(9,10) Children who do not show catch-up growth are at risk for short stature and neurodevelopmental disorders.(11)

The goal of this study was to describe the growth in children of mothers with congenital heart disease. We aimed to study if children born small for gestational age showed catch-up growth after birth. Furthermore, we were interested if there were predictors for neonatal growth, such as complexity of maternal disease and premature birth.

METHODS

Patients

Previously we studied the outcome of women with congenital heart disease in the ZAHARA I study (NL26121.078.08). This is a multicenter retrospective clinical study in the Netherlands, collecting the data of women with congenital heart disease who became pregnant between 1980 and 2007. The results of maternal and fetal outcome of this study have been published

previously.(6) In the current study we focus on the neonatal outcome of the babies born alive from the mothers with mild, moderate or complex congenital heart disease. In the Netherlands every child is prospectively followed in a nationwide standard program with check-ups every 4 weeks in the first four months, than every 8 weeks until the first year and every 3/6 months thereafter until the age of 3 at special counselling centres everywhere in the country.

Data

Height and weight data and head circumference values have been collected by contacting the mother, GGD (Dutch local authority of health care) and the counselling centres. In addition to growth parameters, we collected data on disorders and medication use of the child and the medical condition and medication use of the mother. All data have been collected with written informed consent of the parents.

Birth weight was corrected for gestational age. Height, weight and head circumference were compared to the general Dutch population using the programme Growth Analyzer (version 35). For a precise interpretation of height, weight and head circumference standard deviation scores (SDS) were calculated and used for analysis. The average of the normal population lies on 0.0 SDS and the values for the normal limits lie between 2.0 and –2.0 SDS. Growth Analyser was not corrected for gestational age and starts to collect data from week 1. Birth weight was corrected for gestational age. This creates a fictive difference between birth and week 1. Therefore in premature children birth weight was not used in the analysis.

Definitions

Small for gestational age: Height or weight or both height and weight at birth smaller than 2,0 SDS of normal.(11) Catch up growth: Growth velocity (cm/y) greater than the median for chronologic age and gender.(12,13) Premature birth was defined as birth before 37 weeks of gestation.

Statistical analysis

Categorical data were presented as frequencies (numbers) and percentages. Normally distributed continuous data were presented as mean values ± one standard deviation (SD), whereas data which were not normally distributed were presented as medians with interquartile range (IQR). Unless specified otherwise, p-values <0.05 (2-sided test) were considered statistically significant.

To account for the correlation in the measurements take from the same child we performed a repeated measurements analysis for each parameter using linear mixed effects models.(14) Due to the fact that the evolution of each parameter during pregnancy may be nonlinear, we used in our model specifation regressions splines (in particular natural cubic splines) for both the fixed- and random effects parts, allowing thus for nonlinear patient-specific trajectories. The models assumptions were validated using residuals plots.

To assess the strength of the association between the maternal and fetal risk factor and growth we fitted for each parameter linear mixed models that allowed for different, possibly nonlinear, average longitudinal evolutions per risk factor. All these analyses have been controlled for baseline differences in maternal and paternal weight and height. To account for the fact that each risk factor is tested three times (i.e., for each parameter) we adjusted p-values using Holm's method. All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago) or in R version 2.15.1 (2012-06-22) using package nlme (version 3.1-105).

RESULTS

In this study 246 women agreed to participate with a total of 450 pregnancies. The growth of these 450 children was studied. Mean number of measurements was 13.3 (±3.4) per child. Mean follow up time was 3.3 years (± 1.29).

Table 1. Type of heart disease of the mother

	Number of patients	Percentage of total patients
Atrial septal defect	66	15%
Pulmonary valve stenosis	62	14%
Aortic coarctation	50	11%
Tetralogy of Fallot	42	9.3%
Ventricular septal defect	42	9.3%
Aortic stenosis*	38	8.4%
Complete transposition of the great arteries (atrial switch)	32	7.1%
Marfan syndrome	16	3.5%
Pulmonary atresia	10	2.2%
Right ventricular outflow tract obstruction	9	2%
Mitral regurgitation	8	1.8%
Congenital corrected transposition of the great arteries	6	1.3%
Morbus Ebstein	6	1.3%
Persistant ductus arteriosus	5	1.1%
Pulmonary hypertension	3	0.7%
Double outlet right ventricle	3	0.7%
Atrioventricular septal defect	2	0.4%
Congenital complete heart block	2	0.4%
Other	8	1.8%

Baseline characteristics of the parents

Type of heart disease of the mother is described in table 1. Simple congenital heart disease was present in 28%, moderately complex in 59% and complex heart disease in 13%. Mean maternal height was 170 cm (±6.9) and weight 70 kg (±12.5). Mean paternal height was 182 cm (±7.9) and weight 86 kg (±15). This was comparable to the normal Dutch population.(15)

Baseline characteristics of the children

Mean pregnancy duration was 38 weeks (±7.7) and 8.7% of the children (54% male) was born premature. In total 13.3% of the children had a disease or abnormality: 4% a cardiac abnormality (e.g. Marfan syndrome, atrial septal defects or aortic coarctation), 2% some kind of psychiatric disorder (mainly autism spectrum) and 1% had asthma. Medication was used by 12.4% of the children, mostly inhalation (e.g. ventolin, flixotide) or ADHD medication.

Overall growth

At birth children of mothers with heart disease had a height and weight of 0.4 standard deviation smaller than expected. As can be seen in figure 1, height-, weight- and head circumference growth showed catch–up growth, mainly in the first 6 months. Both weight and height stabilised after the first year. After this period children showed a growth pattern similar to the normal population.

Growth was comparable in male and female (p=0.75) children. No significant difference was found between children with or without a disease (weight growth p=0.24 and height growth p=0.25) and between children with or without medication (p=1.0).

Growth in premature children

At the first measurement. 2 weeks after birth. weight. height and head circumference were 2.0 SDS smaller in premature children compared to children in the normal population. As shown in Figure 2 premature children showed fast catch-up weight growth in the first month. Height growth of these children took a bit longer, up to 1 year. Head circumference showed some catch-up growth until 1 year. The growth was different from that in children not born premature ($p<0.001$). After 2.5 years they remained 1.0 SDS smaller than expected.

Small for gestational age

In total 23 children were born small for gestational age (SGA), of which 8 had a small height, 12 a low weight and 3 had both small height and weight. Five of the 23 children were both small for gestational age and born premature. Of these 23 children 87% showed catch up growth to > -2 SDS, of which 89% within the first 6 month and the other 11% within 2 years. In total 18 children (4%) had a small head circumference and of these, 16 showed catch-up growth, while in the two others only one measurement was available.

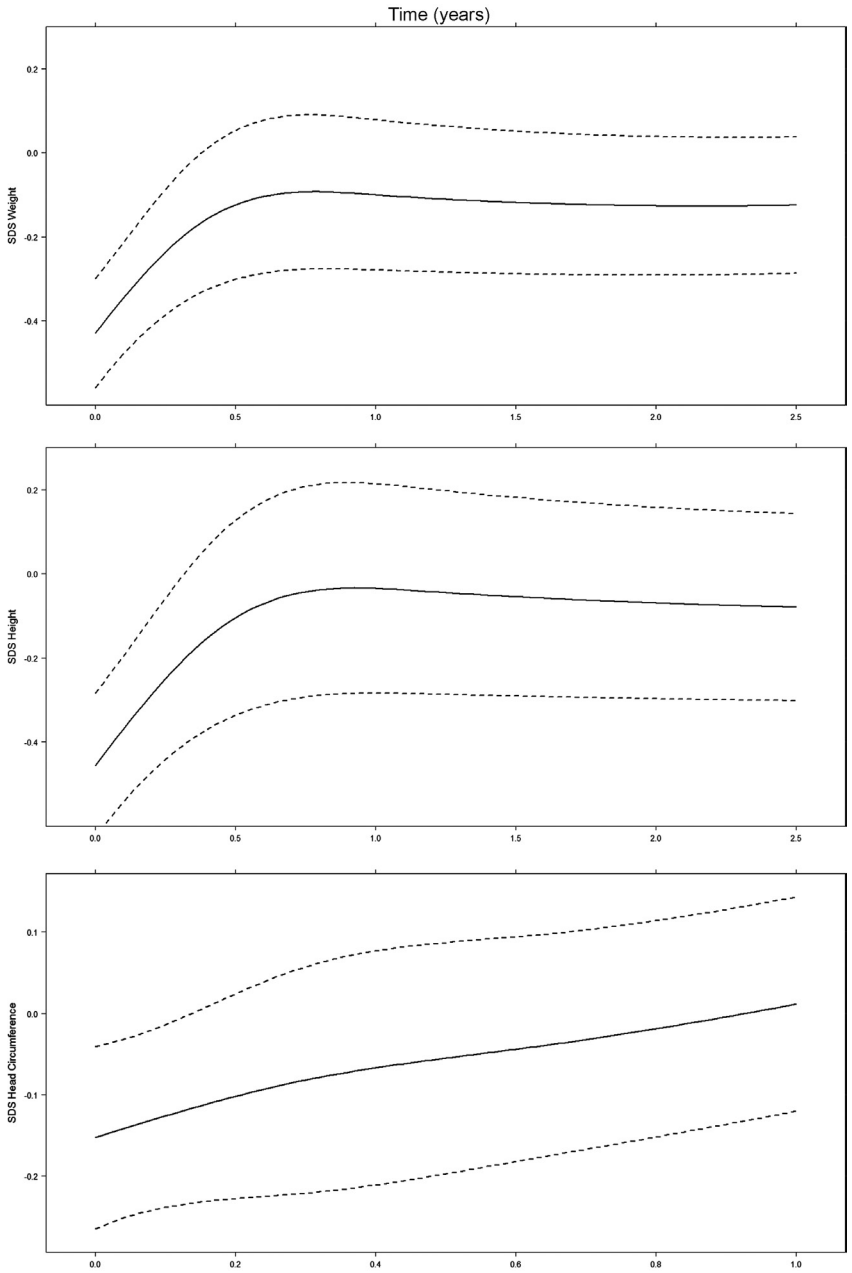

Figure 1. Overall height, weight and head circumference growth in children of mothers with congenital heart disease.

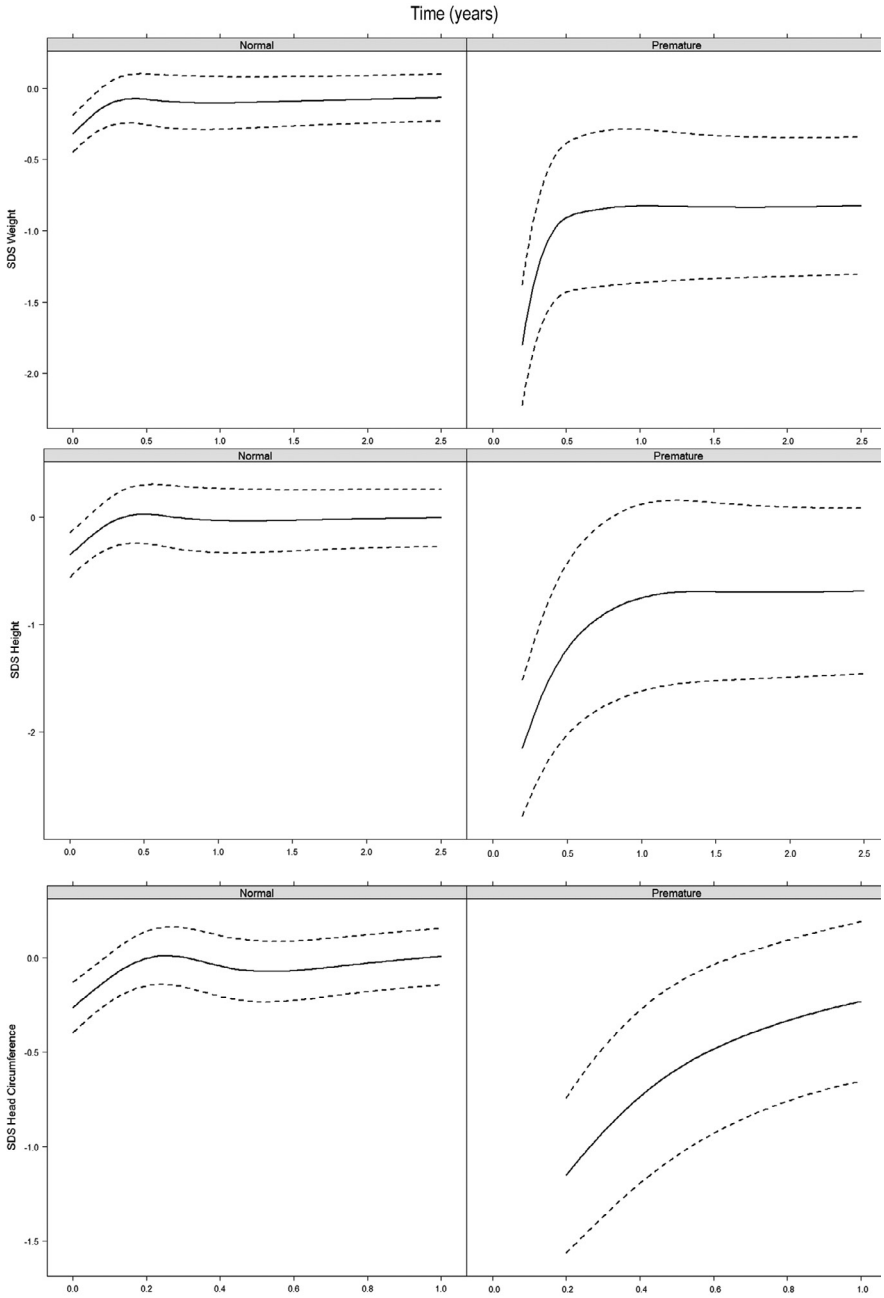

Figure 2. Height, weight and head circumference growth of premature children and non premature children.

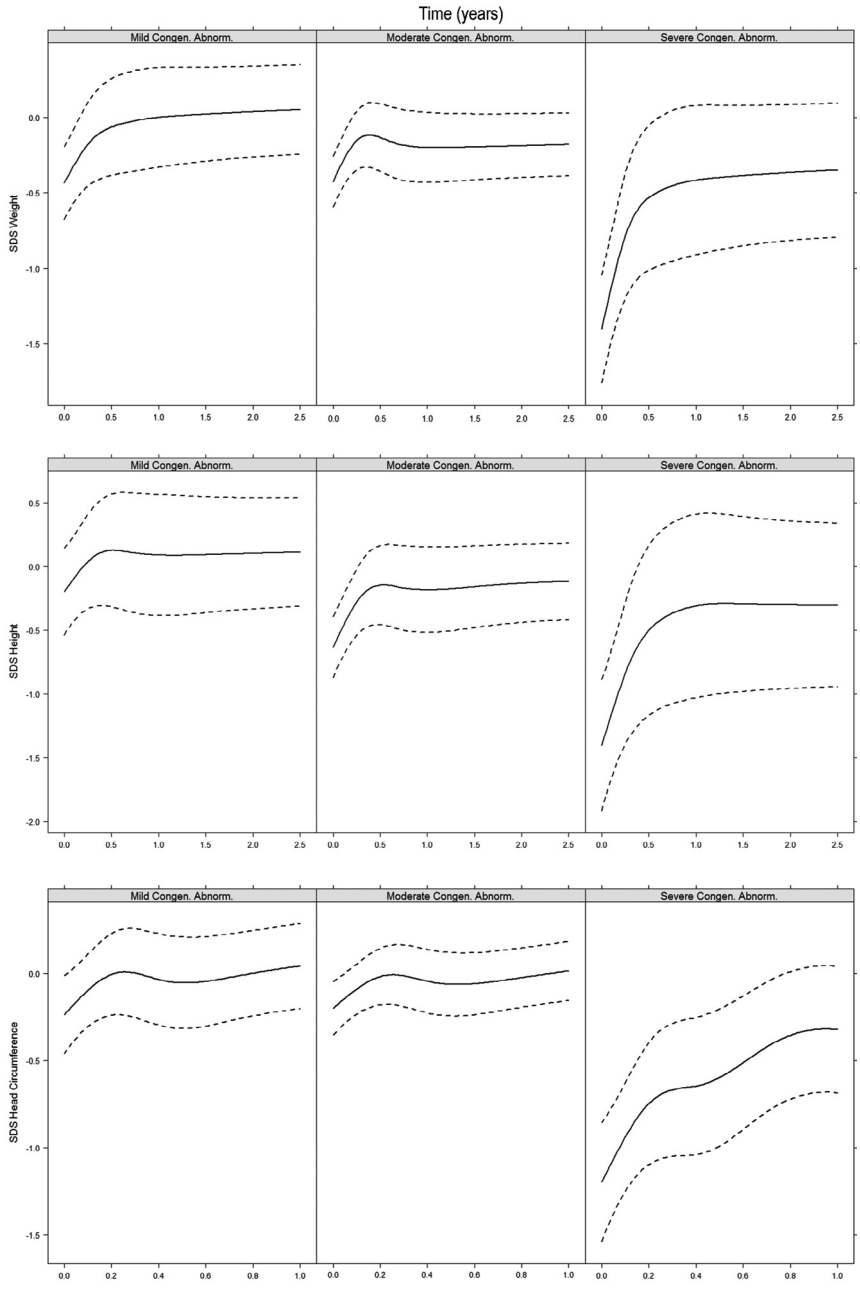

Figure 3. Height, weight and head circumference growth of the children divided per maternal complexity of congenital heart disease.

Table 2. Baseline characteristics of children divided per complexity of congenital heart disease of the mother

	Simple	Moderately complex	Complex	p value
Number of children (n)	126	226	58	
Male (%)	49.2	54.5	65.5	0.119
Child with disease (%)	3.2	8.3	10.3	0.058
Child with medication (%)	7.9	13.2	19	0.094
Premature (%)	6.1	9.4	25	0.002
Median gestational age (IQR)	40 (38-40)	40 (38-40)	39 (36-40)	0.085

Growth in different complexity of maternal heart disease

Baseline characteristics of children per complexity of maternal heart disease are shown in table 2. Figure 3 shows birth weight in relation to severity of maternal heart disease. All growth parameters (weight, height and head circumference) were statistically different between the groups of disease complexity in the mother ($p<0.002$). Children of mothers with simple heart disease started almost at a normal weight and height and these children grew within the first 6 month towards the expected values. Children of mothers with moderate complex heart disease started at 0.5 SDS smaller than normal. These children showed catch-up growth within the first 6 month, but remained slightly smaller than normal after 2.5 years. Children of mothers with complex heart disease had a 1.5 SDS smaller weight, height and head circumference at birth. After birth these children showed catch-up weight growth in the first month of life. But height growth took longer and looked similar to the pattern of premature children with slower catch-up growth until 1 year. In these children there was a strong catch-up growth of head circumference. After the first year these children remained growing at 0.5 SDS under the normal growth curve.

DISCUSSION

Children of mothers with congenital heart disease are born smaller and more often born small for gestational age and/or prematurely.(1,6) In this large cohort most children did show catch-up growth in the first 6 months of life. However. especially premature babies and babies from mothers with more complex heart disease showed slower growth and they remained smaller than expected.

Overall growth

In the first 6 months height, weight and head circumference clearly showed catch–up growth as shown in figure 1. After one year both height growth and weight growth stabilised and reaches nearly normal values. This catch-up growth is probably an indication for beneficial

long-term outcomes. In different populations it has been shown that low birth weight or being small for gestational age is associated with a wide range of metabolic disorders including hypertension, obesity and cardiovascular disease later in life.(15,16,17) It will therefore be of interest to study this population further. As surgical repair is only available since the 1960's, most mothers and therefore especially their children are just reaching middle age.

Growth in premature children

Premature children showed catch-up height growth around half a year later than non-premature children in this cohort and premature children remained smaller than the normal population. Gibson et al described impairment in growth in premature children of normal mothers, with children remaining having a short length after 60 months. He hypothesised that this impaired catch up growth was long lasting, thereby causing children to remain smaller than others.(9)

Small for gestational age

Various factors are associated with SGA children such as fetal syndromes, fetal cardiac abnormalities, maternal hypertension or maternal cyanosis.(13) In our study almost all children born small for gestational age showed catch-up growth to normal limits for weight and height mainly in the first 6 months. Similar catch-up growth has been described in studies of children from "healthy" mothers.(10,11,13) A study by Casey et al showed that the absence of catch-up growth within the first 2 years was associated with short stature and a lower Intelligence Quotient at 8 years of age. In their study no difference was found in behavioural status or general health status between children with and without failure to thrive.(19) In a 26 years follow-up study by Strauss no differences were found in employment, marital status, or satisfaction with life between SGA children and healthy controls.(20) To confirm his findings we would need a prospective follow-up study in the children of our patient with congenital heart disease.

Growth in different complexity of maternal heart disease

Previous studies have shown that fetal growth and birth weight are associated with the type of maternal cardiac disease.(7,8,9) In one study the presence of maternal cyanosis and a reduced cardiac output were the most significant predictors for reduction in fetal growth rate.(9) We showed that this influence remains visible after birth, with large differences in growth between different complexities of heart disease. Children of mothers with mild and moderate complexity showed comparable growth patterns. Although they were born slightly smaller than normal, both groups showed catch-up growth in the first half year until nearly normal values. A quarter of the children of mothers with complex heart disease were born premature. Children of mothers with complex heart disease showed slower catch-up height growth and remained smaller than the normal population. This strengthens the hypothesis

that maternal heart disease has a long-lasting effect on the child. Head circumference was also smaller, but showed remarkable catch-up growth until nearly normal values. Whether this results in normal intelligence development is unclear. To study this further and confirm our current results a prospective case-control study with longer follow-up is indicated.

Study limitations

Since this study was done only in the Netherlands data may not be representative for other countries. The analyses have not been corrected for some factors which have been described to have influence on birth weight, such as smoking, caffeine intake, pre-eclampsia and diabetes since information concerning these factors were not collected. Some data were missing (9%). By using a linear mixed model, which takes missings into account in the analysis, this will probably have had no major effect on the growth curves.

CONCLUSION

This large retrospective cohort study assessed child growth of mothers with congenital heart disease. Although children were born slightly smaller than normal, most showed catch-up in the first 6 months of life. Catch-up growth was slower in premature children and these children remained smaller after 2.5 years with consequently worse long term prospective. Almost all children small for gestational age showed catch-up growth in the first 6 months. Complexity of maternal heart disease had a long lasting influence on growth, as children of mothers with complex heart disease showed slower catch-up growth and remained smaller. Whether the lower birth weight and catch-up growth are predictors of metabolic disorders or lower intelligence later in life in this population remains to be studied.

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E

Discussion

Chapter 15

Summary/ Samenvatting

SAMENVATTING

In dit proefschrift richt ik mij op de groeiende groep van volwassenen met een aangeboren hartafwijking. Vaak wordt de diagnose "aangeboren hartafwijking" al op jonge leeftijd gesteld en zijn op de kinderleeftijd al één of meerdere operaties uitgevoerd. Sommige kinderen zijn na één ingreep volledig genezen, maar de meesten hebben nog restafwijkingen, variërend van een lekkende hartklep tot hartfalen of ritmestoornissen. Velen hebben een nieuwe ingreep nodig op volwassen leeftijd. Weinig is nog bekend over de uitkomsten in de verschillende periodes van operatie en weinig is nog bekend over het verloop van een zwangerschap bij mensen die zelf een hartafwijking hebben. Zwangerschap met een hartafwijking heeft impact op zowel de moeder als op het kind. Deze twee thema's vormen het onderwerp van mijn onderzoek waarvan ik de resultaten in dit proefschrift heb beschreven. Hieronder vat ik de verschillende hoofdstukken kort samen.

DEEL I VOLWASSENEN MET EEN AANGEBOREN HARTAFWIJKING

Studie naar lange termijn uitkomsten

In 1968 vond in Rotterdam de eerste open hart operatie plaats met behulp van de hartlongmachine. Het eerste cohort patiënten, geopereerd in Rotterdam tussen 1968 en 1980, werd uitgebreid cardiologisch en psychologisch onderzocht in 1990 en 2001. De resultaten van dit onderzoek werden eerder gepubliceerd en het leidde tot vier proefschriften[1,2,3,4]. De patiënten werden bestudeerd met een elektrocardiogram (ECG), een 24-uur ECG (Holter monitoring), een fietstest en een echocardiogram. Tevens ondergingen de patiënten een 2.5 uur durend psychologisch onderzoek waarbij verschillende gestandaardiseerde vragenlijsten werden afgenomen.

In 2009 hebben wij eenzelfde onderzoek uitgevoerd maar nu bij de patiënten die geopereerd zijn tussen 1980 en 1990: het tweede cohort. Daarbij gebruikten wij dezelfde onderzoekmethode, zodat we de uitkomsten van de patiënten geopereerd tussen 1968 en 1980 konden vergelijken met patiënten geopereerd tussen 1980 en 1990. Het idee achter de vergelijking van deze twee cohorten was dat de overleving, de cardiale functie en het psychologisch welbevinden zouden zijn verbeterd, aangezien de chirurgische techniek, de postoperatieve zorg en de begeleiding van de ouders zijn verbeterd in de loop van de tijd. In dit proefschrift bespreken we de resultaten van twee groepen patiënten, namelijk die met een transpositie van de grote vaten en patiënten met een tetralogie van Fallot, en we vergelijken de uitkomsten van het eerste cohort met die van het tweede cohort. Bij beide cohorten vond het na-onderzoek 25 jaar na de correctieve operatie plaats.

Transpositie van de grote vaten

Bij patiënten met een transpositie van de grote vaten zijn bij de geboorte de lichaamsslagader (aorta) en de longslagader (arteria pulmonalis) verwisseld. In de eerste twee dagen na de geboorte worden deze kinderen cyanotisch (blauw). Zonder ingrijpen van de chirurg sterven ze meestal in het eerste levensjaar, dus vóór 1968 waren er weinig kansen voor deze kinderen.

In de eerste chirurgische periode (1968-1980) kregen patiënten eerst een shunt van de aorta naar de arteria pulmonalis. Later in het leven kregen deze kinderen een hartoperatie, de Mustard of Senning procedure. Tijdens deze operatie wordt chirurgisch een verbinding aangelegd om het zuurstofrijke bloed naar het lichaam te laten stromen. Dit gebeurt door een verbinding op boezemniveau te maken. De rechterhartkamer is hierbij de systemische kamer, dat wil zeggen dat hij hoge druk moet opbouwen om het bloed naar de hoge druk in de lichaamscirculatie te pompen. De rechter hartkamer bleek hier op lange termijn niet goed aan te kunnen voldoen en ging uiteindelijk falen.

In de loop van de 80-er jaren worden de meeste kinderen op nog jongere leeftijd, vrijwel direct na de geboorte, geopereerd. Vanaf deze periode worden de arteria pulmonalis (longslagader) en aorta (grote lichaamsslagader) teruggedraaid in plaats van de omleiding op boezemniveau. Bij deze zogenaamde "Arteriële Switch Operatie" (ASO) moeten wel de kransslagaderen (coronairen) opnieuw geïmplanteerd worden. In onze studie (hoofdstuk 2) tonen we aan dat de patiënten geopereerd met een ASO een betere lange termijn overleving hebben. De re-operatie/re-interventie vrije overleving na 25 jaar is 77% na ASO ten opzichte van 44% na een Mustard operatie ($p=0.04$). Wel zien we dat de patiënten met een ASO soms een her-operatie nodig hebben voor vernauwing van de arteria pulmonalis. Ook heeft 21% van de ASO patiënten een licht tot matig lekkende aortaklep, terwijl dit slechts bij 16% van de Mustard patiënten wordt gevonden ($p=0.31$). Na vijfentwintig jaar blijkt de pompfunctie van de systeem linker kamer goed te functioneren in 93% van de ASO patiënten, terwijl na de Mustard operatie de functie van de systeem rechter kamer maar in 6% van de patiënten goed blijft ($p<0.01$). Dit is dus een enorme verbetering. Aangezien een aantal patiënten met een ASO toch restafwijkingen hebben en de toekomst nog grotendeels onbekend is, is het belangrijk ook deze patiënten levenslang te blijven volgen.

Tetralogie van Fallot

Patiënten met een Tetralogie van Fallot (ToF) worden geboren met een aanlegstoornis die leidt tot een viertal hartafwijkingen: 1) de aorta (lichaamsslagader) staat zowel boven de rechterkamer als boven de linkerkamer, 2) er is een gat in het tussenschot van de kamers, 3) er is een vernauwing van de arteria pulmonalis (longslagader) en 4) de rechterkamerwand is verdikt. In de zeventiger jaren werd vaak eerst een shunt geplaatst tussen de aorta en de arteria pulmonalis. Bij de correctieve operatie werd vervolgens het eerste deel van de arteria

pulmonalis verwijd, het obstruerend myocard (spier) weefsel uit de rechterkamer uitstroombaan verwijderd en het gat tussen de twee kamers gesloten.

In de jaren tachtig opereerde men de patiënten op jongere leeftijd, waardoor een shunt niet nodig was. Relatief werd er vaker een transannulaire patch geplaatst ter hoogte van de pulmonalis klep. Onze studie, waarin we opnieuw een vergelijking maken tussen het eerste cohort patiënten, geopereerd in de 70-er jaren (ToF70), en het tweede cohort, geopereerd in de 80-er jaren (ToF80), lijkt een trend te laten zien dat de sterfte in de eerste dertig dagen na de operatie is verminderd in het tweede chirurgische cohort (p=0.098) (hoofdstuk 3). De vijfentwintig jaars overleving na succesvolle operatie is 93% voor ToF70 en 98% voor ToF80 (p=0.22). ToF80 patiënten hebben minder vaak een verwijde aortawortel en een verwijde linkerkamer. Verder blijkt aorta insufficiëntie aanwezig in 21.1% van de ToF70 patiënten en in 7.5% van de ToF80 patiënten (p<0.001). Dit zijn allemaal gunstige ontwikkelingen. Wel blijkt dat patiënten uit ToF80 die een transannulaire patch hebben, vaker een pulmonalis klep vervanging nodig hebben. Ook lijkt de rechterkamer van patiënten geopereerd in de jaren tachtig vaker een verminderde functie te hebben. Samenvattend kunnen we vaststellen dat er verbeteringen en verslechteringen zijn in het tweede cohort vergeleken met het eerste cohort. Dit geeft aanleiding om de chirurgische techniek verder onder de loep te nemen en waar mogelijk aan te passen. Vooral het gebruik van de transannulaire patch lijkt nadelen te hebben en mogelijk geeft een kleinere patch betere lange termijn uitkomsten. Dit zal in een nieuwe studie moeten worden onderzocht.

Psychologische functie

In hoofdstuk 4 laten we zien dat patiënten met een transpositie van de grote vaten geopereerd met de nieuwere techniek (ASO) beter scoren op psychologische functie, gemeten met de zogenaamde SF36, een gestandaardiseerde vragenlijst, in vergelijking met dezelfde meting na de Mustard operatie en zelfs beter dan gezonde "controle" proefpersonen. Arteriële switch (ASO) patiënten hebben een significant betere score vergeleken met Mustard patiënten in de subdomeinen fysiek functioneren (p<0.01), algemeen welbevinden (p=0.04) en vitaliteit (p=0.04). Arteriële switch patiënten hebben een significant hogere score vergeleken met gezonde proefpersonen in de subdomeinen fysiek functioneren, vitaliteit en beperkingen door emotionele problemen (p<0.01). Een mogelijke oorzaak hiervan zou overcompensatie kunnen zijn, dit is een beschreven coping strategie bij patiënten met een aangeboren hartafwijking. Daarbij is beschreven dat patiënten die lang leven met een ziekte zich gelukkiger voelen, omdat ze al zoveel problemen hebben doorstaan.

Bij patiënten met Tetralogie van Fallot blijkt geen duidelijk verschil in psychologisch functioneren tussen patiënten in het eerste en het tweede cohort. Vergeleken met gezonde patiënten scoren Fallot patiënten minder goed op fysiek functioneren. Dit zou het gevolg kunnen zijn van ziektebesef in het dagelijks leven. Ze scoren echter beter op sociaal functi-

oneren. Daarnaast hebben ze minder gedragsproblemen zoals angst en agressie. Ze voelen zich niet beperkt in sociaal en mentaal functioneren.

DEEL II ZWANGERSCHAP BIJ VROUWEN MET EEN HARTAFWIJKING.

Veranderingen in het hart tijdens de zwangerschap

In hoofdstuk 6 beschrijven we de veranderingen van het hart tijdens een zwangerschap bij vrouwen met een hartafwijking, gemeten door middel van echocardiografie. In eerdere echocardiografische studies worden gezonde vrouwen bestudeerd. Deze studies tonen aan dat er een toename optreedt van hartspierweefsel en van het volume bloed dat per minuut door het hart wordt uitgepompt: het hart minuut volume. Tevens wordt in deze studies aangetoond dat alle veranderingen ongeveer drie tot twaalf maanden na de zwangerschap normaliseren, afhankelijk van het wel of niet geven van borstvoeding.

In onze studie beschrijven wij de cardiale verandering van 35 vrouwen met een hartafwijking. Daarbij tonen wij aan dat in sommige gevallen linker ventrikel dilatatie optreedt. Dit negatieve effect blijft bestaan na de zwangerschap. Verder tonen we een toename van hart minuut volume aan zoals ook bij gezonde zwangere vrouwen wordt gezien. Bij de hartpatiënten wordt deze toename echter in mindere mate veroorzaakt door een stijging in hartfrequentie en meer door het slagvolume. Tevens tonen we een toename aan van diastolische dysfunctie met een toename van E/E' ratio.

Hieruit kunnen we concluderen dat de veranderingen van het hart tijdens de zwangerschap bij vrouwen met een hartafwijking anders verlopen dan bij gezonde vrouwen. Dit is een kleine studie. Het is van belang deze resultaten te bevestigen met een grotere studie en dit inzicht vervolgens te gebruiken om beter te bepalen welke vrouwen het grootste risico lopen tijdens de zwangerschap.

Risico inschatting van vrouwen die zwanger willen worden

Het is van belang voor een cardioloog om tijdig te weten of een patiënt zwanger wil worden, zodat er tijdig verdere onderzoeken kunnen worden gedaan. Daarna kan goede informatie worden gegeven over de eventuele risico's van een zwangerschap voor de individuele patiënt. Het is van belang een inschatting te kunnen maken welke patiënten een hoog risico hebben op complicaties tijdens de zwangerschap. Als dit risico voor moeder of kind sterk is verhoogd, kunnen eventueel extra maatregelen worden genomen. Ook kan doorverwezen worden naar een centrum met speciale expertise of kan het zelfs nodig zijn een zwangerschap af te raden.

In hoofdstuk 7 vergelijken we verschillende risicomodellen die verschillende predictoren hebben onderzocht om te kunnen voorspellen welke patiënten een verhoogd risico hebben. De volgende 5 modellen zijn vergeleken: Khairy, Siu (CARPREG), de Zahara onderzoekers,

ziektecomplexiteit score en de WHO risico categorieën. Daarbij maken we gebruik van de oppervlakte onder de curve van de "receiver-operating characteristic curve", waarbij 1 de optimale waarde aangeeft. Voor ZAHARA I was de waarde 0.73, voor CARPREG 0.62, voor WHO 0.79 en voor ziekte complexiteit score 0.64. Van al deze modellen blijkt de WHO risico categorie het best te voorspellen welke patiënten een complicatie zouden kunnen krijgen. Een combinatie van de WHO en ziekte complexiteit score, geeft de hoogste waarde van 0.82.

Uitkomst van zwangerschap bij vrouwen met een hartafwijking (resultaten van de ROPAC)

Professor Roos-Hesselink en Professor Hall hebben in 2007 met hulp van de Europese vereniging voor Cardiology (ESC) een grote internationale zwangerschap registratie geïnitieerd. In deze digitale registratie, de Registry Of Pregnancy And Cardiac disease (ROPAC), worden vanuit de hele wereld patiënten ingevoerd. In hoofdstuk 8 beschrijven we de analyses uitgevoerd op 1321 patiënten die in deze registratie zijn opgenomen in 2011. De meeste patiënten hebben een aangeboren hartafwijking (66% van de patiënten), anderen hebben een klepafwijking (25% van de patiënten), cardiomyopathie (ziekte van de hartspier, 8% van de patiënten) of een ischemische hartziekte (hartinfarct, 1.9% patiënten).

In totaal overleed 1 op de 100 hartpatiënten tijdens of vlak na de zwangerschap, dit is 100 keer zo veel als in de gezonde bevolking. Ook blijkt de sterfte van het ongeboren kind 4 keer hoger dan verwacht. Deze studie toont daarnaast aan dat de kans op complicaties bij patiënten die in ontwikkelingslanden wonen nog eens extra is verhoogd. Dit kan worden verklaard uit het feit dat in deze landen ziekere vrouwen (vaak tegen advies van de dokter in) zwanger worden. Dit is mede cultureel bepaald, de maatschappelijke status is afhankelijk van het krijgen van een kind. Uit deze studie blijkt dat patiënten met een aangeboren hartafwijking relatief minder complicaties hebben dan patiënten met andere typen hartafwijkingen zoals kleplijden of cardiomyopathie. Patiënten met cardiomyopathie ontwikkelen het meest hartfalen tijdens de zwangerschap.

Bevalling bij vrouwen met een hartafwijking (ROPAC)

Relatief vaak (42%) bevallen vrouwen met een hartafwijking door middel van een keizersnede. In hoofdstuk 9 laten wij zien dat dit zowel om obstetrische als om cardiale redenen wordt gedaan. Vrouwen met een cardiale reden voor een keizersnede hebben een relatief hoog cardiaal risico profiel (volgens de WHO categorieën). Deze patiënten hebben tevens vaker hartfalen na de bevalling. Er is geen verschil in uitkomst gevonden tussen patiënten die een geplande en zij die een spoed keizersnede ondergaan. De kinderen geboren met een keizersnede worden relatief vaak vroeg geboren (vóór 37 weken) en hebben vaker een laag geboorte gewicht (onder 2500 gram).

Er is een groot verschil tussen de diverse landen in het toepassen van de keizersnede. Dit verschil zien we ook bij gezonde vrouwen. Daarnaast kan dit gebruik van de keizersnede

verklaard worden door het aantal vrouwen met een ernstige vorm van hartziekte. Conclusie is dat het aantal complicaties in de eerste dagen na de bevalling niet afhankelijk is van de manier van bevallen maar eerder van de ernst van de hartafwijking bij de moeder. Problemen bij het kind, zoals vroeggeboorte en laag geboorte gewicht, komen wel vaker voor na een bevalling door middel van een keizersnede.

Medicijngebruik bij vrouwen met een hartafwijking (ROPAC)

In deze sub-studie van de ROPAC tonen we aan dat ongeveer 33% van de vrouwen met een hartafwijking op enig moment tijdens de zwangerschap medicijnen gebruikt. Dit is hoger dan verwacht. In hoofdstuk 10 vergelijken we de uitkomsten van vrouwen met en zonder medicijngebruik tijdens de zwangerschap.

We tonen aan dat medicijngebruik bij vrouwen met een hartafwijking tijdens de zwangerschap vaak ongunstige gevolgen heeft voor het kind (zoals vroeggeboorte, laag geboortegewicht, foetale sterfte of kindersterfte in de eerste 30 dagen). Na correctie voor bekende risicofactoren (zoals roken, suikerziekte en preeclampsie) en cardiale risicofactoren (ernst van de hartafwijking en hartfalen tijdens de zwangerschap) concluderen we dat de kans op een ongunstige uitkomst voor de baby 2,4 keer zo hoog is bij vrouwen die medicijnen gebruiken tijdens de zwangerschap. Zo tonen we ook aan dat het gebruik van zogenaamde "betablokkers" (medicijnen die de hartslag en bloeddruk verlagen) gepaard gaat met een geboortegewicht van gemiddeld 100 gram lager. Dit is vergelijkbaar met het effect van roken tijdens de zwangerschap.

De vraag blijft of het de medicatie is die deze ongunstige effecten veroorzaakt, of dat patiënten die medicatie gebruiken tot de ziekere groep van patiënten behoort. De toekomst moet uitwijzen in hoeverre een laag geboorte gewicht en vroeggeboorte daadwerkelijk nadelige gevolgen hebben voor het kind op de lange termijn.

Hartfalen tijdens de zwangerschap (ROPAC)

In hoofdstuk 11 beschrijven we in een substudie van de ROPAC, hoe vaak hartfalen optreedt tijdens de zwangerschap bij vrouwen met een hartafwijking. Hartfalen tijdens de zwangerschap uit zich in kortademigheid en het vasthouden van vocht. In de ROPAC is hartfalen de meest voorkomende complicatie, namelijk in 13% van de gevallen. In de literatuur wordt niet eerder beschreven op welke momenten tijdens de zwangerschap de kans op hartfalen het hoogst is. Meestal wordt aangenomen dat dit vooral is rond de bevalling. In onze studie laten we zien dat er twee pieken zijn, één rond de 25 weken (vooral bij klep- en shuntafwijkingen) en één rondom de bevalling (vooral bij vrouwen met cardiomyopathie en ischemische hartziekte).

Specifieke voorspellers voor hartfalen zijn: klachten van hartfalen voor de zwangerschap, pulmonale hypertensie, cardiomyopathie en score >2 bij WHO risico inschatting of NYHA klasse. Patiënten met zwangerschapsvergiftiging (pre-eclampsie) hebben een sterk verhoog-

de kans om ook hartfalen te ontwikkelen en dienen dan ook extra in de gaten gehouden te worden en zo nodig opgenomen te worden in het ziekenhuis. Patiënten met hartfalen hebben relatief vaak kinderen die ofwel te vroeg worden geboren of een laag geboortegewicht hebben.

Acuut coronair syndroom (ACS) en zwangerschap

In hoofdstuk 12 geven wij een samenvatting van de literatuur over patiënten met een hartinfarct voor of tijdens de zwangerschap. Allereerst beschrijven wij de literatuur over patiënten die voor de zwangerschap een hartinfarct hebben gehad en die zwanger willen worden. Als de linker ventrikel goed werkt, is het niet nodig een zwangerschap af te raden. Wel moet de bestaande medicatie tevoren goed in kaart worden gebracht om te beoordelen of de medicijnen schadelijk zijn voor het ongeboren kind. Deze medicijnen kunnen dan, wanneer mogelijk, gestopt worden en vervangen worden door andere medicijnen die veilig zijn. Of de dosis kan worden aangepast. Er is in de literatuur weinig bekend over de kans op herhaling van een hartinfarct tijdens een zwangerschap. Meer onderzoek is zeker nodig op dit gebied.

Daarnaast beschrijven wij de klachten, de risicofactoren en de diagnose van een hartinfarct tijdens de zwangerschap. Hartinfarcten tijdens de zwangerschap komen steeds vaker voor. Enerzijds door toename van cardiale risicofactoren zoals roken en overgewicht. Anderzijds doordat de gemiddelde leeftijd waarop vrouwen zwanger worden de laatste jaren is toegenomen. Tenslotte is de diagnostiek van het hartinfarct verder aangescherpt mede door de introductie van gevoelige markers zoals troponine. Als een hartinfarct optreedt tijdens de zwangerschap, is dat vooral in het laatste trimester van de zwangerschap. Aangezien klachten van kortademigheid en pijn op de borst (bij maagzuur) ook kunnen voorkomen bij een gezonde zwangerschap, worden hartklachten niet altijd onderkend. Er is een verhoogde kans op moedersterfte bij de vrouwen die tijdens de zwangerschap een hartinfarct doormaken. Deze sterfte bij vrouwen is de laatste jaren sterk gedaald door tijdige interventie, vooral tijdens de bevalling. Bij tekenen van een acuut hartinfarct op het ECG bij een zwangere patiënt dient men in principe hetzelfde te handelen als bij niet zwangere patiënten: een catheterisatie met zo nodig stenting. Bij deze patiënten heeft echter een bare metal stent de voorkeur boven een drug eluting stent. Een drug eluting stent wordt vaak geplaatst bij andere patiënten met een hartinfarct, maar daarbij moet de patient 6 tot 12 maanden speciale bloedverdunnende medicijnen (clopidogrel of prasugrel) nemen. Van clopidogrel en prasugrel is geen informatie bekend over de mogelijke nadelige effecten op de baby, zoals teratogeniteit. Daarom worden deze medicijnen bij voorkeur niet gegeven.

Patiënt casus

In hoofdstuk 13 presenteren we een casus van een zwangere patiënt die in het Erasmus Medisch Centrum werd behandeld. Ze was 32 weken zwanger van haar 3^{e} kind en presenteerde zich met hoge bloeddruk en kortademigheid bij inspanning. Ze had een bloeddrukverschil

tussen haar rechter en linker arm en er werd een geruis gehoord. Dit is het beste te horen op de rug. Met echo en MRI werd een ongecorrigeerde coarctatio aorta (vernauwing van de grote lichaamsslagader) in beeld gebracht. Daarnaast bleek ze een groot aneurysma (verwijding van 8 bij 4 cm) van de aorta descendens te hebben. Dit is een levensbedreigende situatie.

Zij zou, als zij niet zwanger was geweest, meteen worden geopereerd. Echter gezien haar gevorderde zwangerschap, werd na uitgebreid overleg met de aanstaande ouders besloten te wachten tot na de geboorte. Ze werd met regelmaat gecontroleerd en er werd bij 35 weken zwangerschap een keizersnede gedaan. Direct postpartum is een operatie een te groot risico vanwege bloedingsgevaar. Daarom werd zij pas 2 maanden later geopereerd. Deze casus presenteren we omdat niet eerder in de literatuur een patient is beschreven die zich presenteert met een natieve coarctatio en aneurysma van de aorta. Gelukkig maken moeder en kind het goed.

DEEL III KINDEREN VAN MOEDERS MET EEN HARTAFWIJKING.

In eerder onderzoek is aangetoond dat moeders met een hartafwijking vaker kinderen met een laag geboortegewicht krijgen of vaker vóór 37 weken zwangerschap bevallen. De onderzoeksvraag van de studie, beschreven in hoofdstuk 14, is of kinderen inhaalgroei laten zien. Een tweede vraag is of er verschil is in de uitkomst van de gezondheid van de kinderen als de moeders een meer of minder ernstige en meer complexe hartafwijking hebben.

Aangezien we in een eerdere studie de uitkomsten van moeders met een hartafwijking hebben onderzocht, konden we deze moeders vragen of we de groeigegevens van hun kinderen mochten gebruiken. De meetgegevens van het consultatiebureau werden via de ouders verkregen. Met een speciaal groeiprogramma, de “Growth analyser”, worden de gegevens vergeleken met de groei van kinderen van moeders zonder hartafwijking.

We hebben laten zien dat kinderen van moeders met een hartafwijking in het eerste half jaar duidelijk inhaalgroei laten zien. Daarna zijn de kinderen bijna net zo groot als kinderen van gezonde moeders. Na een jaar stabiliseert de groei en groeien ze net zoals andere kinderen. Kinderen van moeders met een complexe hartafwijking zijn bij de geboorte een stuk kleiner dan kinderen van moeders met een simpele afwijking. Deze kinderen laten meer inhaalgroei zien, ze blijven echter na een half jaar kleiner dan de andere kinderen.

Of de inhaalgroei van de kinderen van moeders met een hartafwijking enkel een positief teken is, blijft de vraag. In studies naar inhaalgroei is aangetoond dat op lange termijn snelle inhaalgroei hormonale veranderingen met zich mee brengt. Als gevolg daarvan hebben deze kinderen op volwassen leeftijd mogelijk meer kans op hart- en vaatziekte. Hart- en vaatziekten presenteren zich vaak pas later, vanaf het vijftigste levensjaar. Of kinderen van moeders met een hartafwijking ook vaker hart en vaatziekten krijgen blijft dan ook vooralsnog een vraag.

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PART I ADULT CONGENITAL HEART DISEASE

Study of long-term outcome

Since the introduction of cardiothoracic surgery in Rotterdam, the long-term outcome of surgical procedures in children with congenital heart disease is studied in a structured manner. In 1990/91 and 2000/01 cardiac and psychological outcome, and survival have been studied in the first cohort of patients operated on between 1968 and 1980 in Rotterdam. The study protocol consisted of an electrocardiogram (ECG), 24 hours ECG (Holter monitoring), exercise test and an echocardiogram. In addition patients were assessed with various psychological questionnaires.

In 2009 we performed a similar study, but now focusing on the second cohort of patients, operated in Rotterdam between 1980 and 1990. We used the same study protocol to enable a comparison of these two surgical cohorts. We expected to find an improvement in cardiac and psychological outcome, as surgical techniques, postoperative care and psychological guidance have improved over time.

Transposition of the great arteries

In the first surgical cohort the surgical procedure for transposition of the great arteries consisted of an atrial correction (the Mustard or Senning procedure). Studies on long-term outcome in this group showed that right ventricular (systemic) dysfunction and sinus node disease were common late complications. In the second surgical period the arterial switch operation was introduced and became the method of choice. In chapter 2 we showed that patients with an arterial switch operation (ASO) had a better (event-free) survival after 25 years of follow-up. The event-free survival was 77% after ASO versus 44% after Mustard operation ($p=0.04$). The main indication for re-intervention in ASO patients was pulmonary artery stenosis. In our study nearly half of the arterial switch patients had a residual gradient across the pulmonary artery or pulmonary valve. Some of these may need additional re-interventions in the future, warranting further close monitoring.

With the left ventricle as the systemic ventricle in arterial switch patients, symptomatic heart failure was not encountered and most patients remained in good health. Good systemic ventricular function was present in 93% after ASO versus 6% after Mustard operation ($p<0.01$). Aortic regurgitation was found in 21% of the arterial switch patients versus 16% of the Mustard patients ($p=0.31$). However, aortic regurgitation was mild in most. An other study suggested that neo-aortic dilatation may stabilize in adulthood, but follow-up in that study is too short to be certain.(1)

Tetralogy of Fallot (ToF)

In chapter 3 we compare patients operated upon in the first surgical period (1968-1980: ToF70) with patients operated upon in the second surgical period (1980-1990: ToF80). In the

ToF70 patients more shunts were used prior to corrective surgery and the age of correction was relatively higher. With the shift towards earlier corrective surgery, more transannular patches were implanted in the second surgical cohort. We demonstrated that early mortality showed a trend to diminish when compared to the first surgical period (p=0.098). Survival at 25 years after successful surgery was 93% for ToF70 and 98% for ToF80 (p=0.22).

The left side of the heart seemed to benefit most from earlier surgery, with positive effects on left venticular- and aortic dimensions. In addition aortic regurgitation was present in 21% for ToF70 versus only 8% for ToF80 (p<0.001). However, patients operated in the 70's showed a trend towards less right ventricular dysfunction and needed less often a pulmonary valve replacement for pulmonary regurgitation at long-term follow-up. The use of a transannular patch was the only factor associated with an increase in re-operation for pulmonary valve dysfunction. By avoiding the extensive use of a transannular patch, which was done in the 90's, the need for reoperations may hopefully decrease further in future cohorts. In conclusion the left side of the heart seemed to benefit at the costs of more right side problems.

Psychological findings

In chapter 4 we showed that patients with an ASO for transposition of the great arteries performed better on physical scales than patients after the Mustard procedure and also performed better than healthy controls. A significant higher score was seen in arterial switch patients compared to Mustard patients in the sub domains physical functioning (p<0.01), general health perceptions (p=0.04) and vitality (p=0.04). Arterial switch patients and the normal Dutch population had comparable quality of life scores and arterial switch patients scored even better on the scales physical functioning, vitality and role limitations due to emotional problems (p <0.01). A possible reason for this may be overcompensation, which has been described as a coping strategy in patients with Congenital Heart Disease (CHD).

Psychological or emotional functioning did not differ in patients with a tetralogy of Fallot operated on in the 70's and 80's. ToF patients of both cohorts scored lower compared to healthy controls with respect to general health. This could be the result of an awareness of disease in daily life. But patients with ToF scored higher on social functioning and experienced less behavioural problems such as anxiety and aggression. Thereby indicating they did not feel to be hindered in social and mental functioning.

PART II PREGNANCY IN WOMEN WITH HEART DISEASE

Hemodynamic adaptation to pregnancy in women with structural heart disease.

In chapter 6 we describe the changes of the heart in pregnant women with heart disease measured with echocardiography. Other echocardiographic studies have described these

changes in healthy women and showed an increase of cardiac output, stroke volume and left ventricular mass. In healthy women haemodynamic changes normalised 3-12 months after pregnancy.(2)

In our study we showed that patients with structural heart disease show some similar changes as in healthy women. But in addition to the normal changes, we showed a dilatation of the left ventricle, which did not return to normal after pregnancy. Heart rate did not increase as much as it did in healthy women during pregnancy. With an increase in E/E' ratio, our findings suggest a progressive diastolic dysfunction in women with structural heart disease with advancing gestational age.

We concluded that the cardiac changes during pregnancy have a different pattern in patients with heart disease compared to healthy women. A large prospective trial is warranted to confirm our findings, considering the small number of patients in this study.

Risk predictor models in pregnant patient with cardiac disease

When patients with a CHD want to become pregnant, doctors use risk predictor models to stratify patients in different risk groups. These models have been used for a number of years to counsel patients. Over the years there have been a number of trials that created a predictor model for cardiovascular events during pregnancy and the first months after delivery.

In a large cohort of congenital heart disease patients we studied the validity of the known risk scores: CARPREG, ZAHARA, World Health Organisation (WHO) category and the disease complexity score (chapter 7). A combination of WHO classification and disease complexity provided the highest area under the curve. The WHO classification was the most accurate individual risk assessment model for estimating cardiovascular risk in pregnant women with CHD.

Outcome in pregnant patients with structural heart disease (results of the ROPAC)

Professor Roos-Hesselink and Professor Hall founded a registry on pregnancy and heart disease in 2007. The European Society of Cardiology endorsed this registry and provided ICT support. The registry became part of the European Observations Research Program (EORP). This on-going online database was named the Registry On Pregnancy And Cardiac disease (ROPAC).

In chapter 8 we describe the first analysis performed in 2011 on 1321 patients. Most patients had congenital heart disease (66%) others had valvular heart disease (25%), cardiomyopathy (8%) or ischemic heart disease (2%).

The total maternal mortality was 1%. This is 100 times higher than expected in the normal population. Fetal mortality was 4 times higher than expected. In addition we showed that patients living in developing countries are more at risk of having complications, probably related to the impact of the culture in some countries where having children is of utmost

importance. First results showed that congenital patients did better than other types of heart disease. Heart failure was encountered in 13% of patients, most frequently in patients with cardiomyopathy.

Mode of delivery in patients with cardiac disease (ROPAC)

Patients with cardiac disease underwent caesarean section in 42% of cases. In chapter 9 we describe that caesarean section (CS) was planned for cardiac reasons in 44% and obstetrical reasons in 56%. Women with a cardiac reason for CS often experienced heart failure after delivery. Patients delivering with CS had more often adverse fetal events. However, there was no difference in maternal outcome after an elective or an emergency CS. Children born with CS were more often premature and more often had a low birth weight.

There was a large variation in CS rate between countries. This variance was dependend on the use of CS in the normal population and the inclusion of women with more complex heart disease.

Medication in pregnant women with cardiac disease (ROPAC)

One third of women with cardiac disease becoming pregnant use cardiac medication at some point during their pregnancy.

We showed that women using medication during pregnancy had more adverse fetal events (defined as premature birth, low birth weight, fetal death and neonatal death). The corrected odds ratio was 2.4 (after correction for smoking, diabetes, pre-eclampsia and severity of cardiac disease). The question remains whether patients needing medication have a worse cardiac function (and therefore more fetal events) or that the medication itself has negative impact on fetal outcome. In addition we showed that patients needing beta-blockers had children with a corrected birth weight of 100 grams lower than in other patients with heart disease. This may be an important difference with implications for later life in these children.

Based on our results, we cannot give the advice that all cardiac medication is contraindicated during pregnancy, since we have not studied the effect of intentional omission of treatment. However, a high degree of reluctance to medicate, which is a sentiment often expressed by pregnant women, seems to be an appropriate position.

Heart failure in pregnant patients (ROPAC)

In chapter 11 we describe risk factors, onset and outcome of heart failure during pregnancy. In pregnant women heart failure is difficult to diagnose. Signs and symptoms, such as shortness of breath and oedema can also be found in normal healthy women.

In the ROPAC heart failure was found in 13% of patients. Heart failure occurred most often around 31 weeks of pregnancy (inter quartile range 23-40) with two peaks in incidence: in the second trimester (34%) and directly after birth (31%). Onset of heart failure was associated with the underlying diagnosis. Patients with valvular disease or shunt lesions had heart

failure earlier in pregnancy (around 25 weeks). Patients with cardiomyopathy and ischemic heart disease had heart failure most often in the first days post partum.

Baseline parameters associated with heart failure in multivariable analysis were worse functional class, signs of heart failure before pregnancy, severity of heart disease, a diagnosis of cardiomyopathy or pulmonary hypertension. Pre-eclampsia was strongly related to heart failure with an odds ratio of 7.1. One third of all patients who developed pre-eclampsia also developed heart failure. Therefore all patients with pre-eclampsia should be carefully monitored. Fetal death and preterm birth rate were higher in women with heart failure.

Acute coronary syndrome (ACS) and pregnancy

In chapter 12 we reviewed the current literature on pregnancy and ACS.

In the first part we described the literature on patients with a history of ACS. Only limited data on recurrence risk of ACS during pregnancy has been published. Badui et al described 18 women in the literature with previous ACS. None of these patients had a recurrent ACS.(2) Generally women are advised not to become pregnant if they have left ventricular dysfunction with an ejection fraction under 40% or have a dilated left ventricle. ACE inhibitors and spironolacton should be stopped, since these medications may have fetotoxic properties.

In the second part of this chapter we described symptoms, risk factors, diagnosis and treatment of ACS during pregnancy. Acute coronary syndrome is rare in women of childbearing age. But the incidence has increased over the years, probably due to improved diagnostic tests, an older age during pregnancy and an increase of cardiovascular risk factors in young women, such as obesity. Evaluating chest pain in pregnant women can be challenging, since chest pain in pregnancy is common and can be caused by various conditions. Most often chest pain is caused by gastro-oesophageal reflux, which is mostly benign. Physical examination can be misleading; hypotension and tachycardia are physiological responses to normal pregnancy. ECG is very important in diagnosing infarction. ST elevation myocardial infarction patients need immediate treatment and PCI is the first choice treatment and should be performed as soon as possible. Coronary dissection was the primary cause of myocardial infarction in the peripartum period (50%) and more commonly in post-partum period (34%) compared to antepartum period (11%). The mortality rate in patients with ACS in the peripartum period is 18% versus 9% in the antepartum and postpartum period.

Patient case

Chapter 13 includes images of echocardiography, X-ray, CT and the surgical procedure of a patient presenting with native coarctation and a huge aortic aneurysm during pregnancy. No other patient with native coarctation and aortic aneurysm has been described in literature.

A 28-year-old pregnant lady presented at our outpatient clinic with severe hypertension at 32 weeks of gestation. On MRI the diagnosis of native coarctation (minimal diameter of 0,8 cm) and a huge saccular aortic aneurysm of 4.5 x 8.8 cm was confirmed. An elective caesarean

section under regional anesthesia was performed at 35 weeks of gestation and a healthy girl (2625 gram) was born.

Our patient was known with hypertension and the diagnosis was missed in an earlier stage. Diagnosis requires a high index of suspicion in young patients with hypertension. Our case stresses the importance of thorough physical examination and echocardiography in young patients with hypertension.

PART III CHILDREN OF MOTHERS WITH CARDIAC DISEASE

Some of our studies on pregnancy in women with CHD have shown an increased rate of preterm delivery, low birth weight and fetal mortality. Fetal outcome was associated with maternal disease and problems during pregnancy. How adverse fetal outcomes will influence the development of these children later in life is important. Until now growth in these children has never been investigated.

In chapter 14 post natal growth of children of mothers with congenital heart disease was assessed in a large retrospective cohort of 450 children. We showed that although children were born slightly smaller than normal, most showed catch-up growth in the first 6 months of life. Catch-up growth was slower in premature children and these children remained smaller after 2,5 years. Almost all children small for gestational age showed catch-up growth in the first 6 months.

Complexity of maternal heart disease had a long lasting influence on growth, as children of mothers with complex heart disease showed slower catch-up growth and remained smaller. Low birth weight and catch-up growth have been described to cause metabolic disorders (such as hypertension, diabetes mellitus and cardiovascular disease).(3) Whether this is also an issue in this special population remains to be studied.

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Chapter 16

Future directions

FUTURE DIRECTIONS

In this thesis I focussed on the importance of long-term follow up in congenital heart disease. For instance patients with an arterial switch operation showed an excellent survival, but there was an ongoing risk of neo-aortic regurgitation and pulmonary artery stenosis. In tetralogy of Fallot, the patients operated in the 80's showed a better left ventricular function with less aortic root dilatation, aortic regurgitation and a smaller end diastolic left ventricle diameter when compared with patients operated in the 70's. However, patients operated in the 80's needed more often a pulmonary valve replacement. So some advantaged but also some disadvantages occurred with changes in surgical technique and timing.

By studying pregnancy and heart disease in further detail we showed that heart failure was the most observed complications and was found in 13% of patients with structural heart disease. Heart failure most often occurred at the end of the second trimester and near delivery. We showed that pregnant patients with structural heart disease often needed a caesarean section, the patients with caesarean section had shorter pregnancy duration and their children had a lower birth weight. Patients with structural heart disease using medication during pregnancy had more fetal complications, such as preterm birth, low birth weight and fetal death. In children of patients with congenital heart disease neonatal growth showed some compensation after birth, which was correlated to complexity of maternal disease.

In this section I will try to place our most important findings in the general context and will try to illustrate the implications for future research. In addition I will describe some of the areas of interest.

PART I CONGENITAL HEART DISEASE

Cohort studies on long-term prognosis of patients with congenital heart disease have been published since the start in the 1950s. In most of these studies, patients were selected from the out-patient clinic and not as a surgical cohort. Studies from the out-patient clinic and from surgical cohorts are equally important. In out-patient clinic cohorts the focus is on most encountered complaints and complications. However, these studies present often a biased population, since patients will go to the outpatient-clinic when they become symptomatic. Surgical cohort studies focus on changes in outcome with the changes made in surgical techniques and these studies provide unbiased information.

In the LUCCA (Lange termijn Uitkomsten in congenitale cardiale aandoeningen) study we compared the outcome in two surgical periods: 1968-1980 and 1980-1990. We aimed to evaluate whether both short term and long term survival have been improved with experience gained by surgeons over time.

Transposition of the great arteries

We showed that patients with an arterial switch operation (ASO) had better (event-free) survival after 25 years follow-up compared with the Mustard correction. In the future we will study the cohort of 1990-1995, when these patients will have reached adult age. We hypothesized that this second cohort of arterial switch patients will have a better survival and cardiac function when compared to the first cohort of arterial switch patients. De Koning et al. showed that patients operated between 1990-2000 showed excellent survival rate and low re-intervention rate (6%) 10 years after ASO. We will be interested to see if these favorable results remain after 25 years.(1)

As we have shown that most patients have residual lesions, they should be followed for the rest of their life. With the transition from pediatric care to adult clinic, some patients may be lost to follow up. As it is important to intervene before permanent damage will occur in most residual lesions, it is of great importance to find all patients who are lost to follow-up. By studying a specific cohort we found some of these "lost" patients. In the future extra attention will be paid to the transition from the pediatric to the adult clinic.

Tetralogy of Fallot

In our cohort study comparing patient operated on in 1968-1980 and 1980-1990, we showed more pulmonary valve interventions after the use of a transannular patch in the right ventricular outflow tract during corrective surgery for ToF. Surgery was done at an earlier age in the 80s, in this 80s cohort aortic regurgitation was reduced and left ventricular function appeared to be better.

In patients operated on between 1990 and 2000 surgeons tried to avoid the use of a transannular patch and operated at an even earlier age. It would be interesting to study this cohort of patients and compare the results to the results from our study. Possibly both left and right ventricular function will be better in this cohort. Apitz et al. described in a review that patients were sometimes operated upon in the first days of life. Nowadays, most centres prefer to operate on children aged 3–6 months, reserving earlier open-heart surgery for those presenting with severe cyanosis or hypercyanotic spells.(2) With operations immediately after birth there is a frequent need for aggressive outflow tract procedures. In addition there are adverse effects of early bypass surgery on the neonatal brain, the often complicated and lengthy postoperative recovery in small infants, and implications of all these factors for late adverse outcomes. (3)

Elderly patients with congenital heart disease

The first corrective surgeries were performed on children and teenagers with congenital heart disease in the 1960s. The first results on survival in these patients were very promising. Therefore it was thought that most patients would be able to reach a normal lifespan.

As congenital heart disease patients grow older, they become more likely to develop coronary artery disease (CAD).(4) In the normal "healthy" population CAD becomes manifest in the fifth or sixth decade of life. Endothelial dysfunction is one of the main causes of CAD. Injury to the endothelium precipitates atherosclerosis by leading to smooth-muscle-cell migration and proliferation, induction of expression of growth factors and impairment in the plasmatic coagulation and endogenous fibrinolysis system.(5)

It has been proven by Oechslin et al that cyanotic congenital heart disease patient have systemic endothelial dysfunction. They showed strikingly reduced endothelial vasodilation to acetylcholine. They hypothesized that secondary erythrocytosis results in increased shear stress in cyanotic congenital heart disease, which modified the balance between vasodilators and vasoconstrictors and affect systemic endothelial function.(6) Also patients with an aortic coartation do not have normal endothelial function. Barton et al showed in an animal model that coarctation induced hypertension is associated with increased nitrotyrosine abundance in all tissues exposed to high arterial pressure, denoting enhanced reactive oxygen species -mediated inactivation and sequestration of nitric oxide in these sites.(7) Whether the described endothelial dysfunction in these patients leads to coronary abnormalities and atherosclerosis needs to be investigated.

A study by giannakoula et al. with 250 asymptomatic CHD patients studied the prevalence of CAD, in patients who had a coronary angiogram in a pre-operative screening. They showed that the prevalence of significant CAD in a hospital adult CHD cohort was similar to that in the general population. In their study predictors for coronary abnormalities were hypertension, hyperlipidemia and chest pain. However they did not study prevalence of myocardial infarction.(3)

With these studies showing endothelial dysfunction it will be very interesting to see if these patients develop coronary artery disease and myocardial infarction at an earlier age. I hope to see additional studies on prevalence of coronary disease in elderly congenital heart disease patients in the near future.

PART II PREGNANCY AND HEART DISEASE

Research in pregnancy and heart disease

Researching pregnancy and heart disease is challenging for a number of reasons. Firstly, cohorts are frequently heterogeneous in diagnosis. Secondly, patient numbers are rather small per centre. Finally, randomized controlled trials are difficult to perform in pregnancy and should preferably be done using an international collaboration. With the Registry On Pregnancy And Cardiac disease (ROPAC) a large international collaboration was established. At the moment this is an observational registry, but hopefully this collaboration opens the door to more studies.

The future of the Registry On Pregnancy And Cardiac disease (ROPAC)

In the current analysis of the ROPAC on June 1st 2011, 1321 patients were studied. However, the inclusion is ongoing and by April 2013 more than 2300 patients have been included already.(figure 1) By advertising the registry at national society congresses efforts are made to involve more centres from more countries to include patients. The goal is to include over 4000 patients in this registry, especially with a good representation of patients from all over the world. This will allow us to perform specific subgroup analysis, focussed on mechanical valve patients, patients with pulmonary hypertension patients or Marfan patients. Furthermore, with this growing number of patients in the registry the existing risk models can be validated. In 2011 we changed the case report form (CRF), adding information on different subjects, such as baseline characteristics and additional information on mode of delivery and medication.

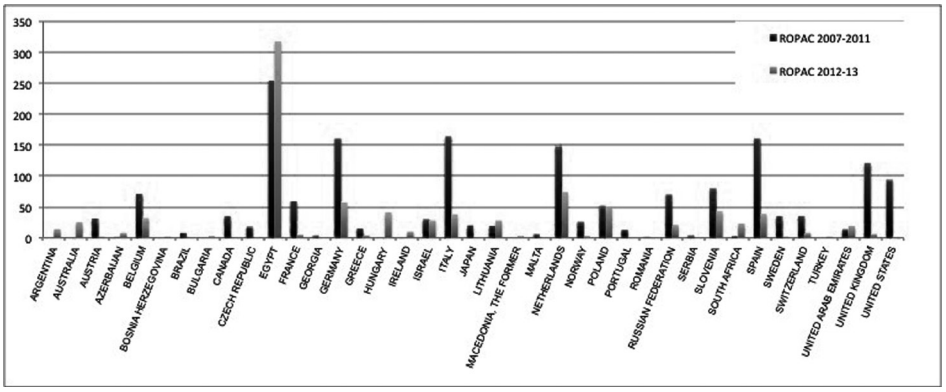

Figure 1. Inclusion in ROPAC per country.

Mode of delivery

Determining the best mode of delivery in patients with cardiac disease can be challenging. In most patients vaginal delivery is the option of choice, because of reduction of blood loss, infections and thrombo-embolic events. Still in some individual patients the choice remains difficult. Some cardiologists and obstetricians may choose a planned caesarean section to avoid an emergency caesarean section. With the ROPAC study on mode of delivery we showed that emergency caesarean section did not cause more cardiac complications than a planned caesarean section. The ideal way to study mode of delivery would be a randomised controlled trial. But some ethical issues remain. With the new CRF we are now collecting additional information on reasons for planned and emergency caesarean section. With this information we hope to do some more analysis when patient numbers are large enough.

Medication

The ROPAC showed that one third of pregnant women with heart disease used medication during their pregnancies and these women had more cardiac and obstetric complications than the women who had heart disease, but were not taking any medication. Birth weight was significantly lower in children of patients taking beta blockers.

With these results, there is a demand for randomised controlled trials on cardiac medication in pregnancy. Studying stopping prophylactic medication would be a good start. Prophylactic medication is given to improve long-term outcome, not to reduce symptoms. Important for such a trial would be to match patients, since differences in outcome should not be caused by differences in baseline characteristics. The results of such a trial would be very important for future guidelines, to give a solid advice whether or not to stop medication before pregnancy.

Another randomised trial could focus on starting medication in high-risk patient, such as diuretics, statins and betablockers prior to pregnancy. By starting medication before pregnancy maybe events such as atrial fibrillation, pre-eclampsia or heart failure may be avoided. By doing such randomised controlled trials, answers could be given whether medication is actually causing the fetal adverse events, or that the mothers needing medication have a worse cardiac function, which causes the adverse events.

New diagnostics tools in pregnancy in heart disease

Biomarkers have been developed in general cardiologic practice to predict cardiac events.(8,9) Some of these markers, such as pro-BNP, are already used in research in the congenital heart disease patients.(10) More biomarkers are being analysed, and evaluated to predict both anti-arrhythmic events and heart failure.(9) We are excited to see the influence of these new laboratory measurements in both research and every day practice. But so far there has been little information on pregnancy and biomarkers. We know that the normal values of biomarkers are not valid in pregnancy, since hormones and hemodynamic status alter the clearance and distribution of these markers. Increased B-type natriuretic peptide levels are found during pregnancy in many pregnant women with heart disease. In the study by Tanous et al. B-type natriuretic peptide levels lower than 100 picograms per milliliter had a negative predictive value of 100% for identifying events during pregnancy.(11) Additional studies are clearly warranted.

PART III CHILDREN OF MOTHERS WITH HEART DISEASE

Intelligence in children of mothers with heart disease

In the ROPAC we showed that premature birth and low birth weight were more common in mothers with heart disease than in the normal “healthy” population. In the Kinderen In

Moeders met Aangeboren Hart Afwijkingen (KIMAHA) study we showed that most children showed catch-up growth in the first 6 months of life. Casey et al showed that in children of healthy mothers the absence of catch-up growth within the first 2 years was associated with a lower *Intelligence Quotient* at 8 years of age. In this study no differences were found in behavioural status or general health status between children with and without failure to thrive.(12) Therefore it would be very interesting to investigate intelligence and school performance of children of mothers with cardiac disease.

Cardiovascular disease in children of mothers with heart disease

A wide range of metabolic disorders including hypertension, obesity and cardiovascular disease have been associated with children born small for gestational age or with low birth weight in different populations. It is believed that poor nutrition in early life or even before birth results in permanent changes in glucose-insulin metabolism, leading to a decreased capacity for insulin secretion and insulin resistance.(13) This may cause a higher risk on developing a metabolic syndrome later in life, including diabetes, hypertension and cardiovascular disease.(14,15) Therefore it would be interesting to study the children of mothers with cardiac disease when they have reached adult or even better elderly age. The question is whether they have an increased rate of metabolic syndromes. But considering the fact that the children of the eldest congenital patients are just reaching 30 years of age, this question will not be answered for the next couple of decades.

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Additional information

ABOUT THE AUTHOR

Pauline Titia Elisabeth Ruys was born on 6th of May 1985 in Den Haag, the Netherlands. After graduation from secondary school in 2003 (Onze Lieve Vrouwe Lyceum Breda), she started medical school at the University Medical Centre in Groningen. During medical school she worked with Dr. W van Son and Dr. W Bakker on a research project on cytomegalovirus in patients with kidney transplantation, for which she received a studentship of the Junior Scientific Master class.

From 2007 till 2008 she did an internship in the Deventer Ziekenhuisen, where she developed a special interest in cardiology. During this period she worked with Dr. Vierhout in Mutolere, Kisoro, Uganda. She started her master thesis at the Erasmus Medical school in Rotterdam on October 2008 "Long-term outcome and quality of life after arterial switch operation for Transposition of the Great Arteries: Follow-up of 25 years." In between she travelled to Florence where she followed a semester of Art History and Photography at the Florence University of Arts.

After finishing medical school, with a last studentship at the Cardiology department of the Havenziekenhuis, she started with this thesis in January 2011. Under the supervision of Professor J.W. Roos-Hesselink, she has been working for the ROPAC (Registry On Pregnancy And Cardiac disease) from the EuroObservational Research Programme of the European Society of Cardiology. The subject of her thesis is long-term outcome of congenital heart disease with special interest in pregnancy and heart disease. From January 2013 she is working as an intern at the cardiology department of the Erasmus Medical Centre.

Course title	Attendance	ECTS
Specific courses offered by COEUR		
Congenital cardiology 2010	3 days	1.5
Heart failure Research 2010	3 days	1.5
Arrhythmia's 2011	3 days	1.5
Intensive care 2011	3 days	1.5
Courses and workshops of third parties		
Nihes, CC02, Classical methods for Data-analysis 2011	21 days	5.7
BROK course 3th November 2009	3 days	1.5
Erthacan (NIHES) 2012	1 day	0.3
COEUR Research seminar		
Aortic pathology 2010	1 day and oral presentation	1.0
Congenital heart disease 2011	1 day and oral presentation	1.0
Symposia - Congresses		
European Congenital Echocardiography course, Oktober 2009, Rotterdam	3 days	0.9
Cardiac problems in pregnancy, February 2010, Valencia	3 days plus poster presentation	1.5
NVVC voorjaars congress, April 2010, Papendal	2 days and poster presentation	1.2
Karel V symposium, March 2010, Utrecht	1 day	0.3
Society of Improvement of Quality in Cardiology congress, March 2011, Davos	3 days and 1 oral presentation	1.8
Aorta pathology congress, March 2011, Rotterdam	1 day	0.3
Karel V symposium, March 2011, Utrecht	1 day	0.3
ESC update, March 2011, Rotterdam	2 days	0.6
ESC congress, August 2011, Paris	5 days and oral presentation	2.1
Society of Improvement of Quality in Cardiology congress, March 2012, Davos	3 days and 1 oral presentation	1.8
Karel V symposium, March 2012, Utrecht	1 day	0.3
ACC congress, March 2012, Chicago	3 days and 2 moderated posters	1.5
NVVC voorjaars congress, April 2012, Noordwijkerhout	1 days and poster presentation	0.8
Cardiac problems in pregnancy, May 2012, Berlin	3 days plus 2 oral presentations	2.0
ESC update, June 2012, Rotterdam	2 days	0.6
ESC congress, August 2012, Munich	5 days and 2 poster presentation	2.0
NVVC najaars congress, Oktober 2012, Papendal	1 days and oral presentation	0.9
Other		
Erasmus PhD Day, May 2010	1 day	0.3
COEUR PhD Day, June 2010	1 day	0.3
COEUR PhD Day, April 2011	1 day and oral presentation	0.9
Teaching		
Teaching writing review articles, January 2012	3 weeks (8 hours)	0.3
Aneasthesia in gynaecology, April 2012, Utrecht	Oral presentation	0.6
Presentation (staflunch), April 2012	Oral presentation	0.6
Presentation pregnancy and heart disease Minor students 3th year, Oktober 2012	Oral presentation	0.6
Presentation (staflunch) November 2012	Oral presentation	0.6
Guide 4th years student with research thesis, March-July 2013	20 weeks (12 hours)	0.6
Guide 6th years student with research thesis, November 2012-April 2013	20 weeks (12 hours)	0.6
CVOI heart failure in pregnancy, January 2013, Utrecht	Oral presentation	0.6
Aneasthesia in gynaecology, March 2013, Leuven	Oral presentation	0.6
Heart failure in pregnancy, Gyneacology congress, April 2013, Rotterdam	Oral presentation	0.3
Total		**41.3**

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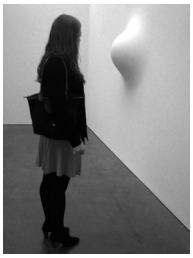

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Foto: Ea de Gaay Fortman, De Pont, Tilburg, Anish Kapoor "When I am Pregnant" (1992)

De vreugde van het schrijven.
Het vermogen te bewaren.
De wraak van een sterfelijke hand.

Wislawa Szymborska