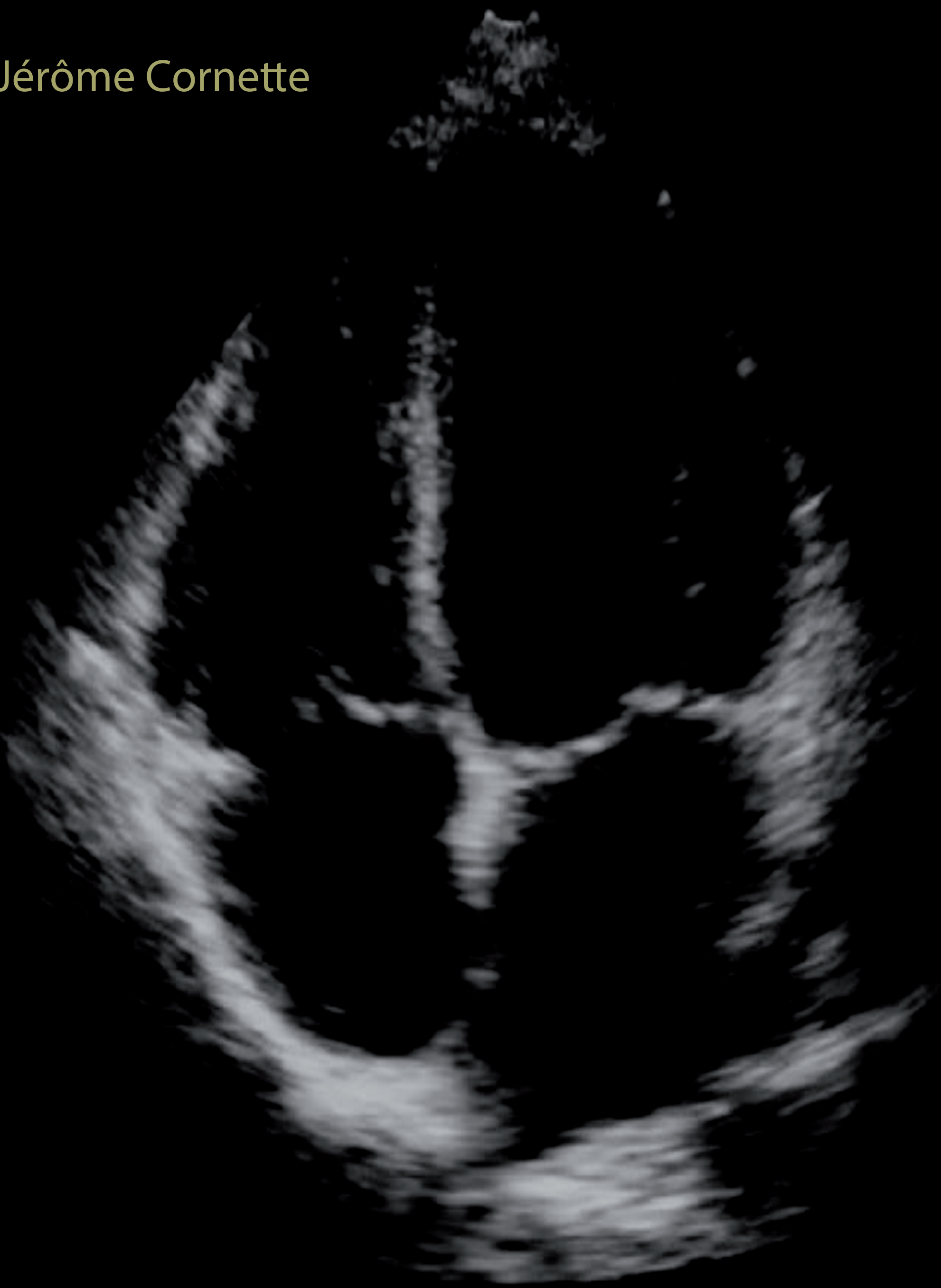
Hemodynamic Profiling in Complicated Pregnancies

Jérôme Cornette



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The studies presented in this thesis were conducted at the departments of Obstetrics and Gynaecology, Cardiology, Cardio-Thoracic Surgery, Internal Medicine, Radiology and Intensive Care and Pediatric Surgery of the Erasmus MC, Rotterdam, the Netherlands, at the department of Obstetrics and Gynaecology of the Kalafong Hospital, University of Pretoria, South Africa and at the collaborating centers of the Zahara II study.
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Chapter 1

Introduction

INTRODUCTION

Despite its natural appearance, pregnancy remains a formidable challenge to a woman's body. Most organs undergo substantial changes, in order to permit the growth of life inside her womb. These changes are particularly pronounced in the circulatory system. Vascular resistance falls early in pregnancy and triggers a rapid increase in blood volume and cardiac output up to 50% of pre-pregnancy values. The woman enters a state which is comparable to a continuous cardiovascular aerobic exercise of several months. It results in cardiac structural remodeling. This hemodynamic adaptation is essential to cope with the demands of a growing fetus.

Many complications in pregnancy either relate to or affect the cardiovascular system. The circulatory system is involved in most causes of both maternal and fetal mortality and severe morbidity. Hemodynamic maladaptation often results in hypertensive complications like pre-eclampsia and/or fetal growth restriction. In women with heart disease, a reduced cardiac reserve can compromise the ability to achieve or cope with the necessary changes. Other complications like postpartum hemorrhage and puerperal sepsis put a serious strain on the cardiovascular system. Even in preterm labor, a complication without apparent cardiovascular implications, tocolytic therapy has a substantial impact on the maternal hemodynamics.

The cardiovascular system can be considered as a closed circuit with the heart functioning as driving pump. On a macrocirculatory level, blood is distributed through elastic arteries to the organs. Exchange of nutrients and oxygen for carbon dioxide and waste products between cells and capillaries occurs at the microcirculatory level. Blood then returns to the heart trough the venous system. While blood is essentially circulating within this one continuous system, interactions between the different levels can be complex. As in many other conditions, discrepancies can be observed between changes in cardiac, macrovascular and microvascular function.

Given the importance of the circulatory system in normal and complicated pregnancies, the potential for hemodynamic monitoring seems evident. This is best achieved using non-invasive methods and by assessing several component of the cardiovascular system enabling a total overview. Initial studies using right heart catheterization and cardiac ultrasound learned us a lot about the hemodynamics in both healthy and complicated pregnancies. The invasive nature of the former limited its use in obstetrics. Furthermore, lack of validation, availability and experience in pregnancy initially prevented widespread use by obstetricians of this technique. Nowadays, evolutions in ultrasound technology permit the combined installation of obstetric, cardiac and vascular software on the same devices. It provides the opportunity to simultaneously study the maternal, uteroplacental and fetal circulation. The intense multidisciplinary collaboration with anesthesiologist and cardiologist within perinatal teams, enabling obstetric critical care, also increased the interest and knowledge in hemodynamics of obstetricians. Together it provided a new boost for hemodynamic research in pregnancy.

Recent technological developments also made non-invasive bedside analysis of the microcirculation feasible. This has led to some innovative insights in other hemodynamic conditions like sepsis and shock. Coupling microvascular to macrovascular findings potentially provides a more complete overview and offers new perspectives in understanding the pathophysiology of complex hemodynamics of pregnant women.

The focus of this thesis is to address the hemodynamics in several pregnancy complications. The specific aims of the thesis can be summarized as follows;

1. to validate transthoracic echocardiography for cardiac output measurements in pregnant women
2. to evaluate the feasibility of microvascular perfusion assessment with Sidestream Darkfield Imaging (SDF) in pregnancy
3. to evaluate the potential of non-invasive hemodynamic profiling in various important pregnancy issues like
   a. tocolysis
   b. pre-eclampsia
   c. cardiac disease

After the introduction (chapter 1), we start by providing a general overview (chapter 2) of normal hemodynamic adaptation (chapter 2.1) and the microcirculation (chapter 2.2) in pregnant women.

Subsequently several techniques of non-invasive cardiovascular monitoring are addressed (chapter 3) with the validation of transthoracic echocardiography in pregnant women (chapter 3.1) and the use of cardiovascular magnetic resonance for accurate analysis of the effects of maternal positioning during each trimester of pregnancy (chapter 3.2).

We then describe the potential of cardiovascular monitoring in several pregnancy complications (chapter 4). The hemodynamic effects on mother and fetus of nifedipine for tocolysis (chapter 4.1) and nicardipine for hypertensive crisis (chapter 4.2) are observed in respectively normotensive and severe pre-eclamptic pregnant women. Microcirculatory perfusion using SDF is assessed in women with severe pre-eclampsia with and without HELLP syndrome (chapter 4.3).

In the fifth chapter we focus on women with cardiac disease (chapter 5). With improvements in medical and surgical care, women with heart disease often reach reproductive age. We provide an overview of the management of pregnancy in women with cardiac disease (chapter 5.1) and pregnancy outcomes of women with aortic valves substitutes are presented (chapter 5.2). Maternal hemodynamic adaptation to pregnancy (chapter 5.3) and uteroplacental perfusion (chapter 5.4) are then analyzed in women with heart disease. We also address the issue of contraception in this population (chapter 5.5).

Chapter 6 contains a general discussion with reflections on further research.

Finally the results of the thesis are summarized in chapter 7.

Chapter 2.1

Normal cardiovascular adaptation to pregnancy

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ABSTRACT

Normal pregnancy is characterized by profound hemodynamic changes. These begin early in pregnancy and include a fall in vascular resistance which induces an increase in blood volume and stroke volume. Heart rate and cardiac output also rise. Arterial blood pressure is reduced. The adaptation is most prominent in the first half of pregnancy. To cope with these hemodynamic challenges, the left ventricle hypertrophies, thereby preserving systolic and diastolic function. Peripheral arterial resistance is decreased and compliance and distensibility are increased. Venous capacitance is greatly enhanced.
Uteroplacental blood flow augments with gestation to meet the increased needs of a growing fetus. Maternal cerebral blood flow is reduced. The influence of these major macrovascular changes on microvascular perfusion remains to be elucidated. During labor and delivery, cardiac output further rises. Postpartum, most hemodynamic parameters are rapidly reversed within weeks. Structural changes normalize within several months.

INTRODUCTION

Normal pregnancy is a unique physiological state. It imposes a profound challenge to the cardiovascular system in a relatively short period of time. These changes are necessary to meet the increased demands of a rapidly growing feto-placental unit. Fortunately, most young women have sufficient cardiovascular reserve. However, failure to achieve these adaptations is associated with maternal and fetal complications like hypertensive disorders and fetal growth restriction [1-6]. In women with preexisting heart disease, the work and volume load can cause deterioration in cardiac function [7-9].

The cardiovascular system can be viewed as a closed circuit. The heart is the central core organ directing flow between the venous and arterial systems. Exchange of oxygen, carbon dioxide, and nutrients, the final goal of the circulation, takes place on a microcirculatory level in the capillaries. While central hemodynamics have been mostly studied due to the prominence and accessibility of the heart and large artery systems, knowledge about the venous compartment, local organ perfusion systems, and the microcirculation are equally essential for a complete understanding of the normal physiology of pregnancy. In this chapter we will discuss normal adaptation to pregnancy of the various components of the cardiovascular system.

METHODS OF CARDIOVASCULAR MONITORING

Hemodynamic monitoring is of clinical importance in the management of women with cardiovascular disease or severe hemodynamic complications like preeclampsia [10-13].

Secondly, it can be of scientific interest in both healthy pregnant women and various other pregnancy complications [14, 15]. The ideal tool would be noninvasive, cheap, reliable, and easy to use at the bedside and offer a broad range of information. While different methods exist, experience and validation during pregnancy remain questionable for most of them [16, 17].

The pulmonary artery catheter (PAC) was often used in the 1980s and 1990s for the management of severe preeclampsia [10-13, 18-26]. As it measures both cardiac output and filling pressures, it contributed to the pathophysiological knowledge of the condition [10, 12, 23, 26]. Its invasive nature along with controversy about clinical benefit has abated the enthusiasm for this method such that it is now rarely used in pregnant women [27, 28]. However, it remains the gold standard for hemodynamic monitoring. Ideally, alternative methods should be validated in pregnancy against PAC [16]. Experience with pulse contour analysis in pregnancy (PiCCO®, LIDCO™plus, FloTrac™/Vigileo™) is limited [14, 29, 30].

Thoracic bioimpedance has mainly been used for longitudinal hemodynamic cardiac output measurements in research settings [31-35]. While the method is simple, safe, and easy to use, there are some serious concerns about its accuracy, reliability, and validation [16, 36]. Thoracic bioreactance has been developed to overcome the limitations of impedance cardiography. It is based on changes in frequency rather than amplitude and therefore less susceptible to interference. Bioreactance holds promise but has not been validated and is rarely used in pregnancy [16, 17, 37]. Esophageal Doppler output measurements in pregnancy have shown poor agreements with thermodilution, and the method is not well tolerated by all women [38].

Transthoracic echocardiography has become a preferential method for the hemodynamic assessment of both ill and healthy pregnant women [39]. Its noninvasive nature allows bedside measurements, including structural and functional information. Most advanced obstetric ultrasound devices can be equipped with supplemental cardiac modules. As such, the method is accessible and can relatively easily be learned by caregivers with prior ultrasound experience. The Doppler method for cardiac output measurements has been validated in pregnancy against both thermodilution and Fick's method [40-46]. Additionally, ultrasound permits the investigation of peripheral arterial systems by the assessment of resistance and pulsatility indexes.

Finally cardiac MRI can be used in pregnancy [47]. Although expensive, it offers accurate structural and hemodynamic information and can be of great benefit in women with structural heart disease with suboptimal ultrasound image resolution [48]. While experience in pregnancy is limited, the technique is considered safe after the first trimester. Gadolinium contrast is best avoided [49].

CENTRAL HEMODYNAMICS

Initiating Mechanisms

Cardiovascular adaptation starts very early in pregnancy. A primary fall in systemic and renal vascular tone induces an increase in the renal blood flow and glomerular filtration resulting in plasma volume expansion [50-54]. This is accompanied by a further reduction in systemic vascular resistance (SVR) and arterial pressure as well as an increase in stroke volume (SV) and cardiac output (CO) [39, 51, 55-60].

A substantial part of the adaptation occurs before the placenta becomes functional at around 8–12 weeks. In fact, similar changes as in early pregnancy have been observed in the luteal phase of the menstrual cycle [61]. It means that adaptation to pregnancy starts soon after ovulation and is probably triggered by substances produced by the corpus luteum. The exact mechanisms that initiate and sustain the primary fall in vascular resistance and subsequent hemodynamic adaptations remain to be elucidated. Reduced responsiveness to vasopressors such as angiotensin 2, thromboxane, and norepinephrine and increased sensitivity and production of vasodilators like prostacyclin and nitric oxide have been well described [62-65]. There are some indications that relaxin, a hormone structurally related to insulin, might be a key factor in initiating and sustaining the changes in pregnancy [63]. It is produced by the corpus luteum and, later, by the placenta and decidua and acts as a potent vasodilator through various nitric oxide pathways.

As mentioned before, the primary trigger is a fall in arterial and venous tone [50, 52, 66]. This leads to a rise in CO, a decrease in SVR, and reduction in mean arterial pressure [39, 50, 60, 67]. These changes are most prominent during the first trimester and reach a maximum in the second trimester when, remarkably, the nutritive requirements of the feto-placental unit still remain relatively small (Fig. 1).

Blood Volume

The expansion of blood volume is triggered by the state of vascular underfilling and the increased renal perfusion [50, 52-54, 68]. It rises gradually until 28–34 weeks and then plateaus until delivery [51]. The increase in plasma volume is more important as compared to the increase in red cell volume leading to a physiologic hemodilution [58, 69]. The total blood volume increases 50 % above nonpregnant values. Along with the drop in SVR, it allows high-flow low-resistance perfusion in order to meet the increased oxygen demands of the feto-placental unit and several maternal organs including the kidneys, skin, and heart [70]. Secondly, it forms a protective reserve for maternal blood loss around parturition.

Vascular Resistance

Vascular resistance initially drops in the first and second trimester by 30–50 %, reaching its nadir by the end of the second trimester [39, 58-60, 67]. It then remains stable until the end of the third trimester to slightly rise again towards term. Plasma renin is increased and atrial natriuretic peptide (ANP) levels are reduced, indicating that volume expansion is proportional and in reaction to the vasodilatation and increased vascular capacitance [66, 68].

Cardiac Output, Stroke Volume, and Heart Rate

The increase in CO of 30–50 % mirrors the reduction in SVR. It is initiated by a rise in heart rate (HR) and subsequently accompanied by an increase in SV as soon as plasma volume expansion occurs [39, 50-53, 67]. After a rapid climb in the first half of pregnancy, it reaches a plateau in the second trimester after which it remains constant until the end of pregnancy [35, 39, 56, 60, 67, 71-73]. Towards term there is a slight reduction in SV which is probably compensated by an elevation in HR [39, 60, 67, 71, 72]. Some studies indicate a slight reduction in CO towards term due to this fall in SV [56, 74, 75]. This discrepancy probably reflects the large interpersonal variation between subjects and the limitations of the methods used to determine CO [39, 73]. The factors contributing to an elevation in SV during pregnancy are the increasing preload due to a rising blood volume and a reduction in afterload due to the decline in SVR.

More important than the slight variations between studies is the effect of maternal position on CO. As from 20 weeks gestation, supine position directly reduces maternal CO through aortocaval compression by the gravid uterus, thereby reducing preload and increasing afterload [47, 76]. Therefore, output should be measured in a left lateral position from as soon as 20 weeks gestation. Also in case of fetal or maternal distress, left lateral tilt is critical in enhancing output in the second half of pregnancy [77].

Blood Pressure

Both systolic and diastolic pressure fall early in gestation as a result of the reduction in SVR, reaching a nadir in the second trimester of 5–10 mmHg below values prior to pregnancy [67, 78-80]. In the third trimester, blood pressure gradually returns towards non-pregnant values.

Systemic Pressures

Central venous pressure remains within the normal nonpregnant range. The increased right ventricular preload, associated with volume expansion, is compensated for by afterload reduction through a decrease in pulmonary vascular resistance [18, 21, 52]. Left ventricular filling pressures (invasively reflected by pulmonary capillary wedge pressure) and pulmonary artery pressures, whether measured invasively or noninvasively, remain within normal nonpregnant ranges [21, 67].

CARDIAC ADAPTATION

Left Ventricular Systolic Function and Mass

Assessment of left ventricular systolic function during pregnancy is mostly performed by ultrasound. It is complicated by the inherent limitations of the ultrasound technique as well as by the major fluctuation in loading conditions during pregnancy. As such, most standard indices are relatively indirect and only partly reflect different aspects of ventricular function. A good and complete denominator of global systolic function independent of loading conditions is still lacking. Newer techniques like tissue Doppler, strain analysis and speckle tracking are promising, as they offer additional information on left ventricular function.

Ejection fraction (EF) and fractional shortening (FS) are the most classic indices of left ventricular systolic function. They primarily reflect the function of the circumferential fibers of the myocardium. Both EF and FS probably slightly increase early in pregnancy, then remain constant until 30 weeks and subsequently slightly decrease towards term

[25, 39, 56, 60, 67, 81]. The increase early in pregnancy suggests increased myocardial contractility. Still, there is discrepancy between several studies concerning the changes in EF and FS [72, 82]. It is probably due to the fact that the left ventricular volumes, used to calculate these parameters, are most often derived from the Teichholz formula, which is based on geometrical assumptions that are probably not met during pregnancy. While the Simpson methods of discs summation as well as 3D echocardiography are probably more accurate, they can be hampered by decreased echogenicity due to the cardiac axis displacement as well as engorgement of breast tissue during pregnancy.

Assessment of myocardial contractility using the less load-dependent ventricular end-systolic stress (ESS) and mean velocity of circumferential fiber thickening (Vcfc) relationship also offers conflicting results, although it seems that myocardial contractility is at least continuously preserved during pregnancy [67, 81, 83-85].

Analysis of left ventricular long axis function offers information on subendocardial longitudinally arranged fibers which are more prone to reflect subtle myocardial impairment. Apical M-mode measurements through the mitral annulus show an increase in left ventricular long axis displacement with gestation until 23 weeks with a subsequent decrease reaching values below preconceptional readings towards term [56]. Long axis shortening decreases significantly with gestation [71, 86]. Tissue Doppler of the mitral annulus, which is less load dependent, does not show any changes in S' velocity during pregnancy[71]. These findings also suggest that contractility and systolic function are preserved throughout pregnancy and might even be slightly enhanced in the first half of pregnancy.

The recent introduction of strain, strain rate analysis, as well as speckle tracking permits investigation of myocardial deformation and left ventricular twist (torsion) and untwist. A higher deformation rate in the first trimester suggests a state of increased contractility in response to the hemodynamic changes of early pregnancy [72]. In the third trimester, a small but significant reduction in longitudinal deformation and deformation rate is observed, without changes in circumferential and radial strain [72]. This reduction in longitudinal strain occurs despite an increase in global ventricular performance, reflected by left ventricular stroke work, suggesting that strain and strain rate are also influenced by loading conditions and chamber geometry. As such, they cannot be used as a surrogate for global myocardial function, but they are more sensitive than other conventional parameters in reflecting subtle changes in ventricular function.

Speckle tracking analysis shows that pregnancy is accompanied by an increase in left ventricular twist and twist velocity due to increased apical rotation without changes in untwist and untwist velocity [87, 88].

Structurally, pregnancy is characterized by a proportional increase of both chamber size and wall dimensions. This leads to an eccentric hypertrophy which is characteristic of volume loading conditions [5, 72]. Left atrial and ventricular diameters augment with increasing gestational age, reaching peaks at around 34 weeks [52, 57, 60, 67, 72, 89]. By term, left ventricular mass exceeds nonpregnant values by 50 % [57, 60, 67, 72]. This physiologic and reversible hypertrophy is similar to the one observed in endurance athletes. It is a compensatory mechanism, reducing wall stress by increasing wall thickness. As such, the necessary stroke volume can be achieved despite increases in both preload and afterload and reduced diastolic filling time [57].

In conclusion myocardial performance is increased during pregnancy. However, this is not uniformly reflected in all different markers of systolic function. This is probably related to the complex interaction between changes in left ventricular geometry, loading conditions, and limitations of the investigational methods. Globally one can conclude that myocardial function is preserved or slightly increased in normal healthy pregnancy, and the changes in left ventricular morphology and structure can be regarded as a physiological adaptation to the changes in loading conditions in order to preserve myocardial function.

Diastolic Function

As with left ventricular systolic function, the assessment of diastolic function is greatly influenced by the alterations in loading conditions during pregnancy. Pulsed wave Doppler analysis of the mitral valve shows an initial increase in E-wave (E) and A-wave (A) velocities as compared to prepregnancy values [57]. While early filling slightly diminishes with gestational age, the atrial contribution to ventricular filling increases leading to an increased A and decreased E/A ratio towards term [71, 90]. Doppler of the pulmonary venous flow shows a transient peak in systolic forward flow velocity in the second trimester, a gradual slight decrease in pulmonary venous diastolic velocity, and increase in pulmonary venous reversed flow at atrial contraction along with gestation [90]. With increasing myocardial hypertrophy, ventricular compliance and hence E-wave velocity diminishes, which partly explains this pattern of impaired relaxation. Nevertheless, the observed changes in pulsed wave Doppler of the mitral annulus mostly remain a reflection of changing loading conditions during pregnancy.

Load-independent tissue Doppler of the mitral annulus better demonstrate changes in diastolic function during pregnancy. There are no significant changes in either septal or lateral peak E′ and A′ velocities during normal gestation [71, 86]. However, E/E′ ratio reaches the upper end of normality with a broadening of the range in the late third trimester, possibly reflecting a marginal increase in left ventricular filling pressure [71]. A slight increase in A′ with subsequent decrease in E′/A′ ratio is consistent with enhanced left atrial contraction [71]. The Tei index, which is a global measure for both left ventricular systolic and diastolic function, is characterized by a broader range during pregnancy compared to nonpregnant controls [71]. The absence of changes in untwist parameters using speckle tracking echocardiography further suggests normal diastolic function during pregnancy despite the volume overload [88].

In conclusion normal pregnancy is associated with normal diastolic function. Analysis of diastolic function best includes load-independent methods like tissue Doppler or speckle tracking in order to differentiate changing loading conditions from real diastolic dysfunction.

LABOR AND DELIVERY

During labor and delivery, maternal hemodynamics are influenced by several factors like anxiety, analgesia, uterine contractions, Valsalva maneuver, blood loss, and maternal position. An increase in SV and CO is observed from the beginning of the first stage of labor which further augments as dilation progresses [91-93]. During each contraction, 300–500 ml of blood from the uterine sinusoids is forced again in the systemic circulation thereby increasing preload [94]. Maternal discomfort and exertion can further increase the HR thereby augmenting CO 50% above pre-labor values. Arterial pressure also increases during each contraction by about 15–20 mmHg (see Fig. 1). The changes can be more prominent in recumbent as compared to left lateral position due to caval compression as well as to occlusion of the distal aorta during contraction with redistribution of the stroke volume in the upper half of the body [58, 95]. It is evident that the abrupt onset and magnitude of these changes can pose a serious challenge to patients with cardiovascular disease.

Epidural analgesia also influences the hemodynamic changes during labor. Pain and anxiety are often reduced and both the fluid challenge and reactive vasodilatation can also influence loading conditions [96]. In controlled circumstances, the severe hemodynamic changes due to labor are often attenuated by epidural anesthesia.

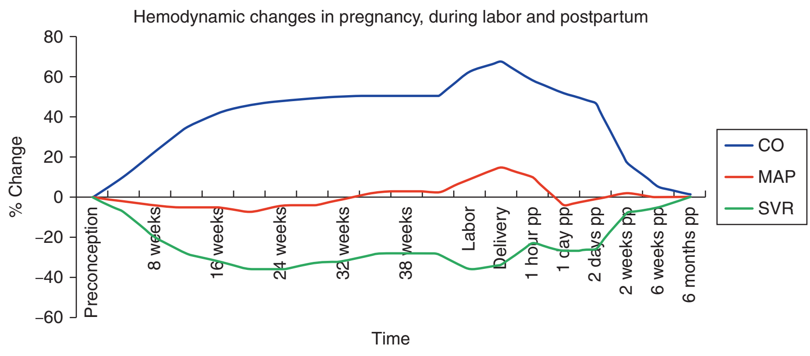

Figure 1. Hemodynamic changes in pregnancy, during labor, and postpartum. *CO* cardiac output, *SVR* systemic vascular resistance, *MAP* mean arterial pressure, *pp* postpartum

POSTPARTUM

The gradual hemodynamic adaptation to pregnancy is rapidly reversed after delivery. Immediately postpartum, CO and SV are still elevated compared to pre-labor values [58, 91-93]. The massive autotransfusion from the uterine blood volume and relief of caval obstruction compensate for postpartum blood loss [97]. Both SV and CO remain elevated for the first 24 h after which they gradually decline. The reduction is most prominent within the first 2 weeks postpartum but can continue until 6 months postpartum before reaching prepregnancy values [78, 97-99] (see Fig. 1). Heart rate falls rapidly after delivery. Mean arterial pressure initially drops immediately postpartum but returns to pre-labor levels on the second day postpartum. It then gradually declines over the following 2 weeks [97]. Left atrial dimensions normalize within the first 2 weeks, reflecting the rapid normalization of blood volume in the puerperium [100]. While most cardiac adaptations progressively return to normal values within 6 months after delivery, some minor structural changes can remain longer or even become permanent [39, 55, 67, 78, 101, 102]. In subsequent pregnancies, hemodynamic adaptation is often more prompt and pronounced. The latter suggests that pregnancy induces some form of cardiovascular imprinting which is protective in further pregnancies and possibly later life.

PERIPHERAL SYSTEMS

Arterial System

Changes in the systemic arterial circulation in normal pregnancy are characterized by a decreased peripheral resistance and increased arterial compliance and distensibility [103, 104]. The latter is mainly achieved by a reduction in smooth muscle tone, although there are some indications that some degree of structural vessel wall remodeling during pregnancy could also play a role.

Aortic valve cross-sectional area slightly increases between the first and third trimester [67, 83, 103]. Therefore, left ventricular outflow tract diameter should always be determined simultaneously with the velocity time integral, when assessing stroke volume by ultrasound at different gestational ages.

Global arterial compliance increases in the first trimester and remains elevated thereafter. The magnitude of peripheral wave reflection at the aorta is reduced [104, 105]. Noninvasive assessment of arterial stiffness by applanation tonometry, using pulse wave analysis and velocity, showed a transient decrease in augmentation index, with a nadir by the end of the second trimester. The reduction in central aortic blood pressure is more pronounced than the decline in peripheral blood pressure [105, 106].

Venous Hemodynamics

While the scientific interest in venous (patho) physiology is certainly less than their arterial and cardiac counterparts, the venous compartment nevertheless is important as it serves as a large volume reservoir storing approximately two thirds of total blood volume. In a state of extensive vascular expansion, it becomes even more prominent as it greatly contributes to the regulation of cardiac output. The splanchnic veins in particular serve as a major storage pool where much of the unstressed blood volume can remain and be mobilized when necessary [107]. In pregnancy, venous distensibility and capacitance are greatly increased. They return to prepregnancy values within 3 months postpartum [107–109]. Investigation of the venous hemodynamics can be performed noninvasively using Doppler ultrasound which also has a role in pathophysiological research of complicated hemodynamic syndromes such as preeclampsia [110].

REGIONAL BLOOD FLOWS

Uterine Blood Flow

With increasing demands of nutrition and oxygen from the rapidly growing products of conception, several adaptations take place in the uterine circulation. From early gestation, uterine artery diameter progressively increases, while pulsatility and resistance indices decrease [31, 111–117]. Uterine blood flow increases from 50 ml/min in the first trimester to 500–750 ml/min at term [114, 116, 117]. The increase in uterine blood flow is not only in absolute terms but also in proportion to the total cardiac output [118].

The trophoblast invasion with arterial remodeling of spiral arteries allows appropriate uteroplacental exchange but also contributes to the reduction of arterial resistance [116].

Renal Blood Flow

It is very clear that renal hemodynamics play a major role in normal adaptation to pregnancy [54, 115]. Renal blood flow increases during pregnancy. While the results are less conclusive, renal artery resistance index probably rises during pregnancy, reaching a peak by the end of the second trimester and then slowly returning to normal values postpartum.

Cerebral Blood Flow

The cerebral circulation can be analyzed by noninvasive transcranial Doppler and MRI. Both Doppler technique and MRI technique show a decrease in middle cerebral artery velocity as well as a 20 % reduction in total cerebral blood flow at term [119–121].

THE MICROCIRCULATION

The microcirculation is the site of exchange of oxygen and nutrients [122]. The importance of microcirculatory dysfunction, independent from macrocirculatory changes, is emerging in several pathological conditions such as sepsis and shock [123–125]. Research on microvascular parameters has mainly been hampered by technical difficulties. The gold standard, intravital microscopy, remains difficult outside the laboratory setting. Capillaroscopy, plethysmography, and laser Doppler have been used in pregnancy but are each hampered by several limitations [126–130]. More recent technical innovations like Orthogonal Polarization Spectral (OPS) imaging and Sidestream Dark Field (SDF) imaging are promising [131, 132]. They allow a combination of microvascular vessel density and flow velocity measurements at the bedside.

Thus far, microvascular research in pregnancy remains limited and mostly focused on pathological conditions like preeclampsia. Information on normal pregnancy is scarce and is mainly derived from healthy pregnant control groups. As such, it offers little information regarding the longitudinal adaptation to normal pregnancy. Anim-Nyame et al. showed a reduction in isovolumetric venous pressure as compared to nonpregnant controls [126]. Hassan et al. showed increased skin capillary density in pregnancy, reaching a peak by the end of the second trimester with subsequent gradual reduction to nonpregnant values 6 weeks postpartum [127].

KEY POINTS

- Normal pregnancy is characterized by profound hemodynamic changes.
- A marked decline in systemic vascular resistance occurs early in pregnancy.
- Cardiac output rises dramatically, especially in the first half of pregnancy.
- To cope with these hemodynamic challenges, the left ventricle hypertrophies, thereby preserving systolic and diastolic function.
- During labor and delivery, cardiac output further rises. Postpartum, most hemodynamic parameters are rapidly reversed within weeks.
- Structural changes normalize within several months.

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Chapter 2.2

The microcirculation

physiology and measurements

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ABSTRACT

The microcirculation is the largest component of the cardiovascular system. It is the site where the ultimate goal of circulation, the exchange of oxygen and nutrients for carbon dioxide and waste products with tissues takes place. The microcirculation consists of blood vessels with a diameter below 100 micrometre (μm). Arterioles regulate blood flow to the capillaries, where the exchange takes place, after which blood is drained by venules. Several non-invasive methods. have recently been developed to assess the microcirculation. Video-capillaroscopy, orthogonal polarization spectral imaging(OPS), sidestream dark field imaging (SDF), incident dark field imaging (IDF), laser Doppler imaging, O2C and retinal vessel analysis each use different techniques to investigate specific aspects in distinct microvascular beds. Which method and site are most appropriate depends on what information is required. In conditions with substantial haemodynamic disturbances, parameters of microcirculatory perfusion appear to be independently associated with outcome, prognosis and response to treatment. Inclusion of microvascular parameters in a haemodynamic profile can optimise haemodynamic management. Knowledge about microvascular function in pregnancy is very limited. Considering the haemodynamic changes that accompany both normal pregnancy and most severe pregnancy complications as well as the recent availability of non-invasive techniques, there certainly is an indication for more microcirculatory research in pregnant women.

ANATOMY AND PHYSIOLOGY

The circulatory system can be viewed as a closed circuit where the heart functions as central pump. With each beat, blood is driven through large elastic capacitance arteries and is then directed into more muscular arteries that distribute the flow to the organs according to their needs. In these tissues smaller arterioles further branch down into capillaries. Here, exchange of oxygen and nutrients for carbon dioxide and waste products takes place with tissue cells, which is in essence the primary function and ultimate goal of the circulation. Blood is then drained by venules into the venous system and returns to the heart.

The microcirculation includes vessels with a diameter (Ø) below 100 micrometre (µm) and mainly consist of the arterioles, capillaries and venules [1, 2]. It is by far the largest compartment of the circulatory system. Arterioles have a thin muscular layer and, along with precapillary sphincters, they regulate the blood flow towards the capillaries according to the tissues` needs on a microvascular level [2, 3]. Capillaries have a Ø below 20 µm allowing erythrocytes to flow through them in a single column [4]. They consist of a layer of endothelial cells with a basal membrane. Three different types of capillaries can be distinguished based on the connection between the endothelial cells [2, 5, 6]. Continuous capillaries are the most commonly found type (e.g. nervous system, muscle, lung). They are characterized by narrow intercellular clefts where one cell directly connects to the next through tight junctions. Fenestrated capillaries have pores (transcellular cytoplasmatic holes) and are found in organs where more exchange between the intra- and extravascular compartment is required (e.g. endocrine glands, gastrointestinal tract and kidneys). Discontinuous capillaries are sometimes referred to as sinusoids and can be found in e.g. the liver, spleen and bone marrow. They have more significant gaps between adjacent cells and a discontinuous basal membrane. While exchange of gasses and small molecules mainly occurs though diffusion and pinocytosis, gaps in or between the endothelial cells allow easier exchange of fluids and larger molecules. On the inside (lumen), the endothelial cells are covered with a gel-like structure called the glycocalyx [5-7]. It mainly consists of glycoproteins and soluble components and is sometimes referred to as the endothelial surface layer (ESL). It forms a film between the blood cells and the endothelium and improves rheology by preventing unnecessary interaction and adhesion of the erythrocytes, leucocytes and platelets with endothelial cells. The glycocalyx also plays an essential role in regulating the exchange of fluids and solutes (flux) between the intravascular compartment and the interstitium [8]. The classic Starling`s principle, where exchange is driven by the opposing hydrostatic and oncotic forces was revised as recent evidence suggest that the glycocalix reflects albumin into the intravascular compartments and creates a hypoalbuminamic space between the glycocalix and the endothelium [5, 6]. The inward flux created by the oncotic difference is not as large as previously assumed and most of the fluid returning from the interstitial space back into the circulatory system occurs through lymphatic drainage. Damage to the endothelial glycocalyx induces proteinuria in glomeruli and impaired permeability in systemic blood vessels [5].

Delivery of oxygen and nutrients to the tissues is essential to maintain cellular homeostasis and function but the required amounts are not constant. The circulatory system has several mechanisms to regulate the supply according to the specific needs and situations. Cardiac output can be adapted by modifying stroke volume and heart rate. Blood flow can be redirected to central organs or specific tissue areas and bypass others, by regulating the muscular tone of arteries and arterioles. In severe haemodynamic conditions like septic shock, this redistribution might result in increased core organ perfusion on a macrovascular level but heterogeneous perfusion on microvascular level which can be detrimental for the tissues [1, 9, 10].

Delivering oxygen from the microvascular level to the cells occurs trough two main mechanisms. The first is convective oxygen transports which is dependent on the red blood cell velocity and the capacity of the red blood cell to carry oxygen. The second is diffusion which is dependent of the pressure gradients between the red blood cell and the tissues and is inversely related to the distance between the capillary and the cell [11, 12]. With homogeneous capillary flow, tissues are steadily perfused in a continuous and equally distributed manner allowing optimal exchange between the capillaries and the cells. During heterogeneous tissue perfusion the total amount of flow may be similar, but some parts closer to the capillaries are hyper perfused, while others cells further away receive less resulting in suboptimal exchange and tissue dysfunction [1].

METHODS OF ASSESSING THE MICROCIRCULATION

The study of the microcirculation has mainly been limited by technical difficulties. Major advances in the last 2 decades have permitted more rapid, easier and non-invasive assessment of microvascular beds of various organs with several different techniques. The microcirculation can either be assessed morphologically by looking at the diameter or at the number of capillaries (capillary density (CD)), the appearance of capillaries or integrity of the glycocalyx layer. Alternatively one can assess microcirculatory perfusion by looking at red blood cell velocity in the microcirculation (Microvascular flow index (MFI)) and/or heterogeneity of microvascular perfusion (heterogeneity index (HI)). Finally, the endothelial function in the microcirculation can be assessed by assessing the response to specific challenges like drugs, flickering light, post ischemic (occlusive) vasodilatation or thermal stimuli.

Which technique, site or parameter of microvascular assessment is most appropriate in a specific circumstance can be answered by addressing the four W questions.

Who: who is going to assess the microcirculation (e.g. a highly dedicated and skilled investigator for research purpose or a medical worker as part of routine clinical observations) and who is going to be assessed (e.g a neonate or an adult, a patient with chronic rheumatologic disease or patient with septic shock).

Why: does one intents to assess morphology, perfusion or endothelial function (e.g. in order to understand pathophysiology or to monitor treatment).

Where: refers to which microvascular bed is best assessed (e.g., sublingual, skin, nail-fold, retina, gut, brain, vaginal mucosa) and in which setting (e.g. in a laboratory setting, outpatient clinic, at the bed side or during surgery)

When: is one interested in single measurements, repeated intermitted or continuous measurements.

Video capillaroscopy

Video capillaroscopy uses an intravital microscope coupled to a video camera to study the microcirculation in vivo [13-17]. The initial devices were quite bulky and cumbersome, limiting their use to research setting. Current video capillaroscopes are small hand held devices that couple a microscope to a digital video camera [14, 16, 17]. They allow direct visualization of moving erythrocytes in the capillaries. The vessel wall is not visualized and as such only perfused capillaries can be investigated. In the nail fold, capillaries run parallel to the skin and the technique can be used to assess the morphology of capillaries and estimate red cell velocities. It is used in rheumatic and skin conditions like systemic sclerosis and Raynaud disease [15]. In the skin, the capillaries run perpendicular to the to surface. They are observed as small red dots and the technique can merely be used to assess capillary density (basal capillary density (BCD)) and capillary recruitment (maximal capillary density (MCD)) after certain stimuli like venous congestion, post-occlusive reactive hyperaemia and thermal challenges [17, 18]. Still one has to bare it mind that skin perfusion is very heterogeneous and several sampling sites must be assessed and averaged in order to have reproducible measurements.

Orthogonal Polarization Spectral imaging (OPS), Sidestream Dark Field Imaging (SDF) and Incident Dark Field Imaging (IDF).

These three types of handheld videomicroscopes use green light (wave length of +- 530 nm), which penetrates the surfaces of organs to a depth of approximately 3 mm, to allow direct visualization of the superficial microcirculation. Green light of this wave length allows optimal absorption by hemoglobin in red blood cells. The surrounding tissues mostly reflect the light which creates contrast. This is captured by a video camera, which allows visualization in high contrast images of flowing red blood cells as little black moving targets in the superficial microcirculation. Here again the vessel walls are not visualized [19-22]. Depending of the size of the moving red blood cell column and direction of flow one can discern arterioles from capillaries and venules. Tissues with a thin epithelial layer are most easily studied. The sublingual mucosa is often used as it is easily accessible, located in close proximity of the brain and from the same embryologic origin as the gastrointestinal system, which is often substantially involved in the pathophysiology of conditions like shock and sepsis [1, 10]. Nevertheless other sites like the vaginal mucosa, cervix, skin, or the microcirculation of internal organs like bowel and brain during surgery can be examined [23-27]. As such these techniques allow immediate non-invasive visualization of the microcirculation at the bedside. They can be used in adults, children and even preterm neonates [28-30].

The recorded images need to be analyzed with specific software. These allow semiautomatic analysis and still require a substantial human input. Analysis is therefore often performed off line and can be time consuming [31, 32]. Several aspects of the microcirculatory perfusion can be examined [4]. Vessels are divided according to their size into small (capillaries, Ø < 20µm) and non-small vessels (arterioles and venules, Ø 20-100 µm). For both groups vessel density (VD) and perfused vessel density (PVD) can be assessed. The MFI describes the predominant flow pattern in a semiquantiative score of 0-4 (0 =absent, 1 = intermittent, 2 = sluggish, 3 = normal or 4 = hyperdynamic flow) of both vessel types. The HI is an important parameter of microvascular tissue perfusion and is calculated from the MFI scores by subtracting the lowest score from the highest score divided by the mean score. The integrity of the glycocalyx can also be assessed with specific software by analysing the dimensions of the red blood cell perfused boundary regions (PBR) [8, 33].

Usually 3-5 video clips are recorded and analyzed for the measurements. These are performed according to consensus recommendations of an international round table conference for standardization purpose and the validation and reliability has been demonstrated in non-pregnant adults, pregnant women and neonates [29, 30, 34-37].

Orthogonal polarization spectral (OPS) (cytoscan cytometrics, Philadelphia, USA) was developed in the late 1990`s and can be considered as the first generation of these handheld video microscopes which opened the field of bedside study of the superficial microcirculation [21, 22]. Further developments resulted in the second generation side-stream dark field imaging technique (SDF) (MicroScan Video Microscope, MicroVision Medical, Amsterdam, the Netherlands) with improved image contrast and quality (Figure 1 a,c) [20]. The mobility and ease of use at the bedside was improved by allowing battery depend operation. This device of approximatively 320 grams still contains an analogue video camera necessitating conversion to digital images for time consuming off line analysis [29, 31, 32, 38].

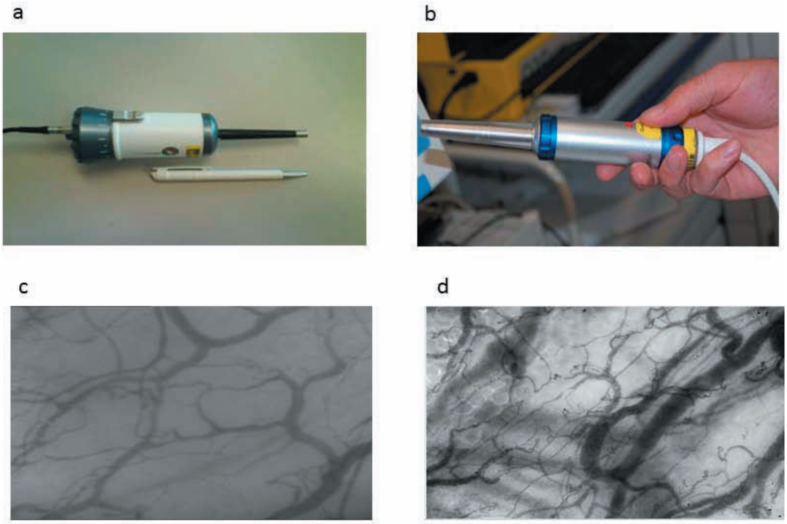

Figure 1 Sidestream dark field (SDF) (a-c) and incident dark field (IDF) (b-d) probes with respective snapshot images of movies obtained from the sublingual microcirculation.

Recently a third generation camera was developed using incident dark field (IDF) illumination technique (cytocam Braedius medical, Huizen, The Netherlands) (Figure 1 b,d) [19, 36]. It weighs around 120 gram. Image quality was again substantially improved by the use of high-resolution optics, computer controlled illumination units and a digital camera with computer controlled high resolution sensors. Image collection is further facilitated by a quantitative focus mechanism which determines and remembers an individual's characteristic focus depth for serial measurements.

The device also includes an improved automatic analysis software which substantially quickens and facilitates analysis of several parameters and promises complete instant bed side analysis in a nearby future [19, 39]. This will permit the incorporation of microvascular measurements as independent parameters in a haemodynamic profile for immediate clinical decision making at the bedside.

Laser Doppler imaging

With Laser Doppler imaging, a beam of laser light is directed on the skin with a wavelength that penetrates to a depth of approximatively 1mm and reflected light is measured. The principle is based on the wavelength change (Doppler shift) the light undergoes when hitting moving red blood cells in the superficial microcirculation of the dermis. This Doppler shift is related to the number and velocities of the blood cells. It provides an index of skin perfusion called flux, expressed in arbitrary units (AU), which is the product of average red blood cell velocity and concentration [13, 17, 40-43].

Initially the technique was developed as laser Doppler flowmetry (LDF) or Laser Doppler perfusion monitoring (LDPM) assessing blood flow in a single area of less than 1 mm^3. High sampling frequencies allowed good temporal variability making LDF interesting for the assessment of rapid changes in blood flow as a response to a stimulus [42]. Nevertheless, spatial variability and therefore reproducibility are limited due to the important heterogeneity in skin perfusion [44].

With Laser Doppler Imaging (LDI) or laser Doppler perfusion imaging (LDPI), all individual single measurement points are combined and a large area of interest is scanned by the laser beam (up to 50 x 50 cm^2) [13, 17, 44-47]. The backscattered light is analyzed and a 2-D color coded image is created with each pixel representing a perfusion value.

This overcomes the problem of spatial resolution and reproducibility encountered with LDF but at the cost of reduced temporal resolution. As such it cannot be used to assess rapid changes in microcirculatory perfusion. Nevertheless, recent developments in high speed cameras, multichannel lasers and mapping algorithms permit much faster scanning [46, 47].

A latest technique is called laser speckle contrast imaging (LSCI)[48-50]. The laser light penetrates tissue to a depth of 300 µm and induces a phenomenon called laser speckle. This is the irregular backscattering pattern of the light created by irregularities in the tissue structure. This pattern is influenced by movements in the tissue, such as by blood flow, creating a blurring of this pattern. Speckle contrast is a quantification of this blurring [45]. It allows instant scanning of lager areas combining the advantages of LDF with LDPI but measures in a more superficial layer of the skin [51-53].

All these techniques are mostly used to assess microvascular skin reactivity to certain challenges like iontophoresis of vasoactive drugs, post occlusive reactive hyperaemia and thermal challenges [17, 42-44, 54].

With iontophoresis a low intensity current is used to deliver charged molecules in the dermis. Acetylcholine (Ach) and nitroprusside (SNP) are the most commonly used drugs, respectively eliciting an endothelial dependent and endothelial independent vasodilatation. In post occlusive reactive hyperaemia, the increase in skin blood flow is analyzed after the relieve of a temporary arterial occlusion. Alternatively, the effect on skin perfusion of local heat or cold stimuli can also be analyzed. Nevertheless the exact underlying biological mechanisms of all these reactions remain complex. As such rather than specifically assessing distinct pathways, these tests merely reflect microvascular reactivity and function [17, 42-44]. Standardization remains essential in order to allow comparison between studies as many variables may influence the response and reproducibility of these tests.

O2C

The O2C device (Lea Medizintechnik, Gieβen, Germany) combines laser Doppler flowmetry with tissue spectrophotometry. It consist of a small glass fiber probe that can be attached to the skin, tongue or internal organs during surgery (Figure 2). The spectrophotometer transmits continuous wave laser light and white light into the tissue and the reflected light is split into its spectral components by charge-coupled device array and converted into an electrical signal. It allows simultaneous, continuous (beat to beat) and operator independent measurements of relative blood flow (in Arbitrary Units (AU), blood flow velocity (in AU), capillary-venous oxygen saturation (in %, which reflects the oxygen reserve after extraction of oxygen by tissues) and relative amount of haemoglobin (in AU) in the microcirculation[55-60].

Retinal vessel analysis

With a non-mydriatic or mydriatic fundus camera retinal arterioles and venules can be non-invasively and directly visualized. Static imaging analysis of retinal vessels is the automatic measurement of the mean arteriolar and venular diameter, expressed as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)[61].

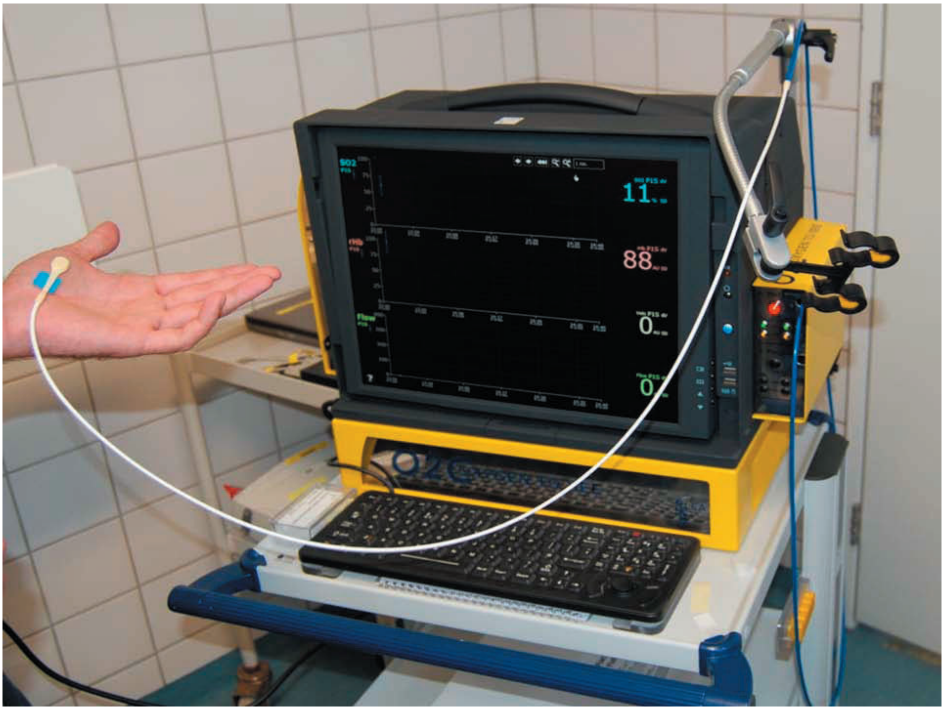

Figure 2 O2C monitoring device with glass fibre probe measuring microvascular perfusion on a hand palm.

Therefor the largest arterioles and venules within the superior temporal region are simply marked, using a Retinal Vessel Analyzer (eg. RVA, Imedos, Jena, Germany) (Figure 3). The superior temporal region represents a circular area of 0.5-2 disk diameters from the optic disc margin. Whereas arteriolar constriction is often accompanied by venular dilatation, the arteriolar to venular ratio (AVR) is commonly used instead. Hence a reduced AVR indicates arteriolar narrowing as a sign of hypertensive retinopathy, which is frequently seen in hypertension and even associated with 5-year incident severe hypertension[62].

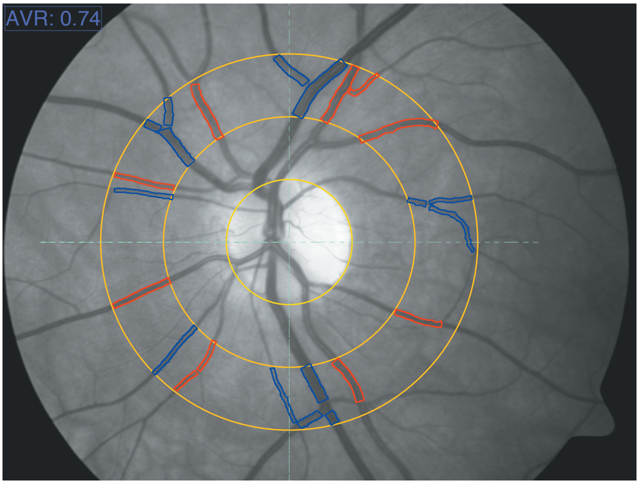

Figure 3 This retinal vessel imaging, recorded with a fundus camera (Retinal Vessel Analyzer, Imedos, Jena, Germany), demonstrates the direct measurement of retinal arterioles (red marks) and venules (blue marks) .

The dynamic behavior of retinal vessels can be solely assessed with a mydriatic fundus camera, which is part of the Dynamic Vessel Analyzer (eg. DVA, Imedos, Jena, Germany)[63]. After 1% tropicamide administration to reach mydriasis, this device measures the arteriolar and venular diameter continuously, under the influence of flickering light stimulation. Retinal flicker response is a function of neurovascular coupling, caused by enhanced retinal ganglioneuronal activity, which primarily dilates capillaries. The secondary increase in blood flow thereby induces an NO-mediated dilatation of larger arterioles and venules, independently of perfusion pressure, with a physiological subsequent arteriolar constriction[64]. Therefore the resulting sum curve of flicker analysis consists of a baseline diameter, flicker-induced dilatation (FID) and maximum arteriolar constriction component (MAC). The arteriolar amplitude is the percentage change from peak FID to MAC (Figure 4) [65]. Endothelium-dependent retinal flicker response, which includes FID and MAC, is impaired in chronic hypertension and aging, indicating pre-aged and stiffened retinal vessels with dysfunctional endothelium[66, 67].

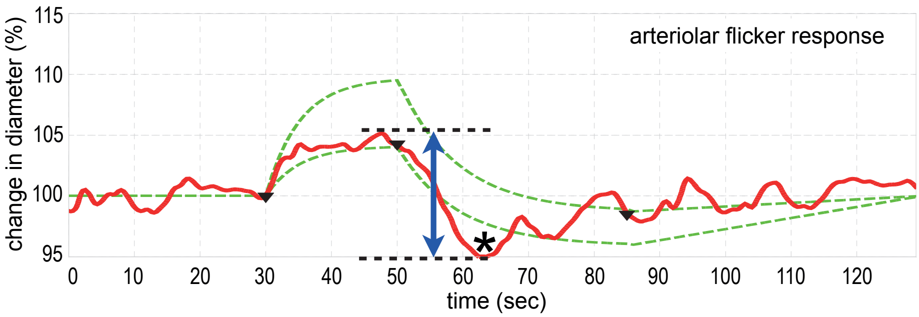

Figure 4. This sum curve of a dynamic retinal flicker analysis of a women with normal pregnancy outcome at 34 weeks gestation demonstrates the arteriolar flicker-induced dilatation (second black arrowhead), the physiologic maximum arteriolar constriction (asterisk) and the resulting arteriolar amplitude (blue double-headed arrow) along a normal distribution curve (dashed green lines).

POTENTIAL AND IMPORTANCE OF MICROVASCULAR MEASUREMENTS

With the recent developments of new techniques allowing direct visualization, the importance and potential of microvascular assessment for understanding the pathophysiology, predicting prognosis and directing therapy in conditions with haemodynamic imbalance is emerging. It is well known that macrocirculatory parameters like cardiac output, blood pressure and filling pressures are poorly performing as predictors of outcome or end-points for guiding therapy in conditions like sepsis and cardiac shock [68-71]. In pregnancy, discordance between macrovascular and microvascular parameters was demonstrated in women with severe pre-eclampsia and changes in capillary perfusion were observed in women with HELLP syndrome [29, 72-74]. Parameters of microcirculatory perfusion are independently associated with outcome and can be better predictors of prognosis and response to treatment [10, 75-83]. Several experiments have shown that improving microcirculatory perfusion results in better outcome. If available at the bedside, microvascular assessment can become an important extension of conventional macrovascular haemodynamic monitoring in managing complex conditions with cardiovascular imbalance [11].

Even in normal pregnancy the cardiovascular system is severely challenged [84-86]. Most complications in pregnancy and causes of adverse maternal or fetal outcome like pre-eclampsia, growth restriction, cardiac disease, sepsis, diabetes, post-partum haemorrhage and thrombotic disease result in or from substantial haemodynamic dysregulation and endothelial dysfunction which suggest an involvement of the microcirculatory compartment [87-90]. Many of these complications are still poorly understood and major improvements are still to be achieved in their management. The advent of improved bedside techniques holds promise for research and clinical implications as it did in other conditions like sepsis and shock. Along with new non-invasive techniques assessing the macrocirculation and uteroplacental Dopplers, a concept of global foetomateral haemodynamic monitoring or cardiovascular profiling can be developed to unravel many issues of these complex disease states[72].

As an example for the potential of microcirculatory assessment we will discuss fluid management, which is one of the most common therapeutic interventions performed in medicine for a variety of indications and disciplines including obstetrics. In the literature large scientific debates have been held on which type of fluid, either colloids or crystalloids, to use in case of shock [91-93]. However, on even more fundamental issues like when to start , how much to give and when to stop this common therapeutic act that is performed countless times on a daily base, one can hardly find any evidence or guidance. Clinical signs (eg. hypotension, capillary refill test, decreased urinary production or consciousness), laboratory finding (lactate levels) and dynamic indices (CO, CVP, PCWP) are often arbitrary and do not offer information on how much to give and when to stop. The main goal of fluid managements is to enhance oxygen delivery to the cells. As discussed previously there are 2 main determinants of oxygen transport to the cells. Convective transport and passive diffusion. The former is dependent of the RBC velocity and oxygen carrying capacity. Diffusion is dependent of the pressure gradient and inversely related to the distance between the RBC and tissue. While colloids and crystalloids in themselves contain little components that might actually improve cellular function , they do so by increasing red cell velocity (thereby enhancing convective transport) and opening previously closed capillaries (thereby reducing diffusion distance between RBC and tissue). However, too much fluid will result in oedema which will increase diffusion distance. Despite increased perfusion this would lead to a reduction in cellular function. Finding the balance between knowing when to start and how much to give in order to improve tissue perfusion, but knowing when to stop before side effects prevail, can be helped by direct assessment of the microcirculation using OPS, SDF or IDF where convective transport is reflected by the MFI and the diffusion distance by functional capillary density (FCD). Fluid administration can be monitored and directed according to specific predefined MFI and FCD values. This concept is called functional microcirculatory haemodynamics [11, 12, 94].

NORMAL PREGNANCY

Pregnancy is characterized by a major cardiovascular adaptation to meet the needs of growing a foetus. Early in pregnancy vascular resistance starts to fall and cardiac output rises. RBC mass is increased but not as much as plasma volume resulting in a physiologic haemodilution [84, 85]. In fact perfusion of nearly all organs undergo major changes.

It is therefore likely that the microcirculatory compartment, which is the largest of the cardiovascular tree, is equally involved. Still, mainly hampered by technical limitations, very little is known about the microcirculation in normal pregnancy.

Using nailfold capillaroscopy 2 different groups showed a substantial increase in erythrocyte velocity during pregnancy and reduced vasodilatatory response after ischemia, which was attributed to the normal physiologic vasodilatation occurring in pregnancy [95, 96]. Recently, George et al. compared the sublingual microcirculatory perfusion between third trimester healthy pregnant women and non-pregnant controls using SDF [97]. They found significant increase in MFI reflecting increased RBC velocity. There were no changes in PVD. These values were similar to those of third trimester healthy pregnant controls from another study assessing sublingual capillary perfusion in severe pre-eclamptic women, equally showing a PVD within normal non pregnant reference ranges and a hyperdynamic capillary flow (MFI) [29]. Hasan et al. used intravital microscopy on the finger skin in 22 healthy pregnant women [98]. They initially showed an increase in BCD and MCD after venous congestion reaching a peak at mid gestation and mirroring a decrease in blood pressure. In a later study in 225 healthy primigravid caucasian women, the same group using the same technique found opposite results with a reduction in BCD and MCD but these changes also mirrored the rise in blood pressure with advancing gestation that was now observed in the population [99]. While these findings suggest that, as in other disease states, the microcirculation partly contributes to the regulation of blood pressure, it does not offer an explanation for the discrepancy in both microvascular and macrovascular findings between these 2 studies. Moreover, these findings of capillary rarefaction were not observed in the sublingual or nailfold microcirculation in other studies.

Knowledge about the effects of Ach and SNP challenges on microvascular forearm flow measured with laser Doppler during normal pregnancy is very limited and mainly derived from small control groups and the results are not equivocal. Ramsay et al. found an increased dose dependent vascular responsiveness to Ach and SNP during the third trimester as compared to several months postpartum [100]. Khan et al. observed a similar response for Ach but no difference for SNP [101]. In the same study there were no differences in vascular reactivity to Ach or SNP between 22-26 or 34 weeks of gestation, suggesting a steady increase in endothelium-dependent dilatation during normal pregnancy with return to normal values postpartum. The same group also showed an association between birth weight, augmentation index and endothelial function during pregnancy, suggesting microvascular involvement in the adaptation of cardiovascular system to normal pregnancy [102]. Eneroth-Grimfors et al. could not find difference between pregnant and non-pregnant woman but they only used one charge stimulus and may not have reached a plateau level [103].

Physiological changes in the microcirculation can be visualized using static image analysis of retinal vessels, which provides insights into vascular tone and peripheral resistance. Similar to capillary density of the finger skin, the retinal arteriolar and venular diameter mirrored the fall and rise in blood pressure throughout pregnancy. The maximum retinal vascular diameter was reached at 19 weeks gestation, the nadir at delivery and baseline values 6 months postpartum, which reflects a decreased vascular resistance at mid-gestation as one of the cardiovascular adaptions that occur during healthy pregnancy[104].

From this overview is clear that knowledge about microvascular function in normal pregnancy is very limited. There certainly is a necessity for further assessment, in order increase insights and to determine normal values as it is definitely different from the non-pregnant state. This would best be achieved longitudinally in a large population, preferably using the latest techniques and in conjunction with macrovascular haemodynamic parameters. We would suggest that this would be done using different techniques but in a standardized manner as to allow comparison with other studies and/or with other health and disease states. We would also suggest to assess the microcirculation of several organ systems as to discover which are most affected and which would best represent global microvascular function in pregnancy in future studies. Only when including the microcirculation into the concept of global foetomaternal haemodynamic profiling, will we be able to better understand the complex cardiovascular adaptation to pregnancy and its disturbances that occur in many complications.

KEY POINTS

- The microcirculation includes vessels with a diameter below 100 micrometer (µm) and mainly consist of the arterioles, capillaries and venules.
- Exchange of oxygen and nutrients for carbon dioxide and waste products occurs at a capillary level.
- Several techniques allow non-invasive assessment of the microcirculation at the bedside.
- Microcirculatory perfusion can predict outcome and response to treatment independent from macrovascular haemodynamic parameters.
- Inclusion of microvascular parameters completes the haemodynamic profile.
- Knowledge about microvascular function in pregnancy is limited and more research in this area is required.

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Chapter 3.1

Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheters in severely ill pregnant women

A prospective comparative study and systematic review

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ABSTRACT

Introduction

Most severe pregnancy complications are characterized by profound hemodynamic disturbances. There is a need for validated hemodynamic monitoring systems in pregnant women. Pulmonary artery catheterization (PAC) using thermodilution is the clinical gold standard for CO measurements. However this reference methods is nowadays rarely performed due to its invasive nature. Transthoracic echocardiography (TTE) allows non-invasive determination of the cardiac output (CO). We aimed to validate TTE against PAC for CO determination in pregnant women.

Methods

This study consist of a meta-analysis combining data from a prospective study and a systematic review. Simultaneous CO measurements by TTE and PAC were compared. The prospective arm was conducted in Pretoria (South Africa) in 2003. Women with severe pregnancy complications requiring invasive monitoring with PAC according to contemporary guidelines were included. Comparative measurements were extracted from similar studies retrieved from a systematic review of literature and added to a database. Agreement between both methods was assessed with Bland-Altman statistics and intraclass correlation.

Results

Thirty-four comparative measurements were obtained in the meta-analysis.
Mean CO obtained by PAC and TTE were 7.39 l/min and 7.18 l/min respectively. The bias was 0.21 l/min with lower and upper limits of agreement of -1.18l/min and 1.60 l/min and percentage error of 19.1% . Intraclass correlation coefficient was 0.94.

Conclusion

CO measurements by TTE show excellent agreement with PAC measurements in pregnant women. Given its non-invasive nature and availability it could be considered as a reference for the validation of other CO techniques in pregnant women.

INTRODUCTION

Pregnancy induces a substantial challenge on the maternal cardiovascular system[1, 2]. Complications like pre-eclampsia, cardiac disease, sepsis, hemorrhage and pulmonary embolism that account for the majority of severe maternal morbidity and mortality are characterized by profound hemodynamic disturbances[3-6]. Maternal pulse and blood pressure are easily obtained and are often solely used as indirect surrogates of maternal cardiovascular function. Nevertheless, knowledge about the cardiac output (CO) can be important when managing hemodynamic compromised pregnant women or studying (patho)physiological conditions in pregnancy[3, 4, 7-12]. Thermodilution by pulmonary artery catheter (PAC), often referred to as Swan-Ganz catheter, is considered to be the clinical gold standard for CO measurements[13]. Until the beginning of the previous decade, it was commonly used for hemodynamic monitoring and guiding therapy in intensive care settings[14, 15]. In pregnancy, critically ill and severe pre-eclamptic pregnant women were also managed with PAC[16-25]. Still, this invasive technique requires right heart catheterization with inherent procedure related risks[26-29]. Controversy started after several reports failed to show the benefits or even suggested increased mortality with the use PAC's in various critical conditions [13, 30-36]. The initial enthusiasm for this technique faded in the intensive care and subsequently in the obstetric community, leaving a gap for hemodynamic monitoring which has not yet been replaced by newly emerged minimal or non-invasive alternatives as validation of these methods remains of concern.

Transthoracic echocardiography (TTE) using 2-D and pulsed wave (PW) Doppler of the left ventricular outflow tract (LVOT) is commonly used to determine CO both in and outside pregnancy. The technique is non-invasive, safe and accessible to pregnant women as many obstetric ultrasound devices allow upgrading with cardiac software and probes. Nevertheless, validation in pregnancy against the clinical gold standard, being PAC has not been adequately performed. As indications for PAC in pregnancy were limited to severely ill women, comparative studies included limited number of subjects and were often performed using statistical methods that are nowadays considered suboptimal or inappropriate. By combining data from a single center comparative study and systematic review, our aim was to validate CO determination using TTE against PAC in pregnant women.

METHODS

A meta-analysis combining data from a prospective study and from a systematic review of literature was performed using appropriate statistical methods according to current standards in order to compare CO measurements obtained by TTE with PAC.

Prospective study

The prospective comparative trial was conducted at the Kalafong Hospital, which is a tertiary care referral center for the University of Pretoria in South-Africa, from May 2003 until October 2003. Severe pre-eclamptic women, admitted to the obstetric high care unit and requiring PAC for their clinical management, were included in the study after informed consent. The study was approved by the medical ethical board of the University of Pretoria (40-2003). Indications for PAC were according to the contemporary guidelines[16, 18, 21, 25]. These recommended to consider PAC in severe pre-eclampsia complicated by either oliguria (not responding to fluid challenge), severe hypertension (not controlled by a combination of 3 different antihypertensive drugs), pulmonary edema or by clinical or echocardiographic signs of cardiac dysfunction. A triple lumen continuous CO PAC catheter (7.5F) (Edwards Life Sciences) was inserted via internal jugular vein approach. Correct position was confirmed by waveform analysis and chest X-ray. This type of catheter allows both intermittent and continuous CO determination using a vigilant CO computer (Edwards Life Sciences).

Intermittent CO determination obtained by bolus thermodilution is considered the clinical gold standard and was used for comparison. Measurements were performed after inclusion and insertion of the pulmonary artery catheter. CO was calculated from the mean of three consecutive thermodilution curves using 10 ml physiological saline room temperature injectates at different phases of the respiratory cycle. Subsequent CO measurements were performed with the CCO module. For the latter a 10 cm thermal filament is incorporated into the pulmonary artery catheter 15-25 cm proximal of the catheter tip which emits pulses of energy and thereby heats blood in a repetitive intermittent sequence. Differences in temperature measured by thermistor at the catheter tip are correlated with the emitted signal. CO is determined by a similar equation as for thermal dilution without the need of repetitive fluid injections. A continuous output is deduced which is an average of the CO measured over the previous 5 to 15 minutes[13, 37]. Clinical management was based on continuous CO measurements and cardiac and pulmonary pressure readings.

Subsequently transthoracic echocardiography was performed by the principal investigator using an obstetrics ultrasound system with appropriate cardiac transducer and software package (Siemens sonoline ominia). The left ventricular outflow tract diameter (LVOTd) was measured at the base of the aortic leaflets from a parasternal long window from which the left ventricular outflow tract cross sectional area (LVOTcsa) was calculated (0.7854 x $LVOTd^2$). The left ventricular outflow tract velocity time integral (LVOTvti) was obtained by pulsed wave Doppler from an apical 5 chamber view and stroke volume (SV) computed as LVOTcsa x LVOTvti. CO was calculated by multiplying SV with the corresponding heart rate (HR) derived from the simultaneous electrocardiography recordings. The mean of three measurements were taken into account. Measurements were recorded and calculations of the LVOTcsa, SV and CO were performed off-line after completion of the TTE exam.

Both pulmonary artery thermodilution and echo Doppler measurements were performed in a 15° left lateral tilt to limit the possible interference of aortocaval compression. PAC and TTE measurements were performed within 15 minutes from one another without the occurrence of new therapeutic interventions or major clinical changes between the 2 measurements.

The investigator performing the ultrasound measurements was blinded for the thermodilution measurements.

Systematic review

A systematic review of the literature was performed. We searched Embase, Medline, Web-of-Science, Scopus, Cochrane, Cinahl, Pubmed publisher and Google Scolar with search headings such as pulmonary artery catheter, echocardiography, Doppler and pregnancy. A list of the search strategy for each database is included in appendix 1. Reference lists of relevant articles were screened for potential additional hits not discovered by the search strategy.

Articles in English language describing direct comparison during or immediately after pregnancy of CO determined by TTE using 2-D and PW at the LVOT with PAC using bolus thermodilution were included. Studies using a different reference method (e.g. Fick method) or different ultrasound method (e.g., CW Doppler in the aortic, mitral or pulmonary position) were excluded. The methodology employed was in accordance with the PRISMA statements. The titles and abstracts obtained from the search and full text reports were obtained and analyzed from the studies that seemed to be relevant. Individual comparisons between both methods were extracted from the manuscripts that met the predefined criteria.

Meta-analysis

A database was created containing direct comparisons between TTE and PAC obtained during the prospective arm of the study combined with data obtained from the systemic review. Agreement between both methods of CO measurement was evaluated with Bland-Altman plots and statistics as appropriate for both the prospective arm of the study and the combined database. Mean CO, bias, standard deviation around the bias, limits of agreement (mean CO +-1.96 standard deviation around the bias) and percentage error ((1.96 standard deviation around the bias / mean CO) x 100%) were determined. Agreement was considered to be good if bias would be low and percentage error below 30% as proposed by Chritchley et al[38]. Absolute agreement in ratings was evaluated using intraclass correlation.

RESULTS

Prospective study

Seven severe pre-eclamptic women were included in the prospective arm of this study. Demographics, indications for right heart catheterisation and time of measurement (antepartum or postpartum) are represented in table 1 for the three studies. No maternal mortality occurred. One neonate born at 25 weeks died immediately postpartum after comfort care was offered, as this gestational age was considered non-viable in the South African context. No clinically relevant complication related to the pulmonary artery catheterisation occurred, with exception of a balloon rupture in one woman. The problem was suspected rapidly after insufflation of the balloon with air failed to produce a typical wedged waveform. Replacement of the catheter over a guidewire confirmed the suspicion. Close observation could not reveal any clinical sign of air embolism. Mean CO obtained by thermodilution and Doppler echocardiography was 6,89 l/min (+-2.17) and 6.46 l/min (+-1.84) respectively. Mean CO was 6.67 l/min (+-1.99) with a bias of 0.43 l/min and standard deviation around the bias of 0.63 l/min. The limits of agreement were 0.43 +- 1.23 l/min (-0.8 – 1.66). Percentage error was 18.4% .Intraclass correlation coefficient was 0.97 (95% CI .0.79 - 0.99).

Table 1. Gestational and maternal age, indications for right heart catheterisation and time of measurement are represented for each of the three individual included studies as well as for the combined population.

	Cornette (n = 7)	**Lee (n = 16)**	**Belfort (n = 11)**	**Meta-analysis (n = 34)**
Gestational age	29* (25-31)	34,9+ +-1.2	33* (17 - 39)	na
Maternal age	24* (18 - 37)	21+ +- 1	23* (17 - 36)	na
Indication				
Preeclampsia	7	14	2	23
Oliguria	3			
Pulmonary edema	1			
Cardiac dysfunction	3			
Hypertension	0			
Sepsis	0		4	4
Hemorrhage	0	1	0	1
Cardiac	0	0	3	3
Pulmonary embolus	0	0	1	1
Renal	0	1	1	1
Time				
Antepartum	6	8	10	24
Postpartum	1	8	1	10

***Expressed as** median with rage, + Expressed as mean with SD

Systematic review

The search revealed a total of 366 hits; one additional record was identified through reference list reviews. 220 records remained after duplicates removed, which were screened on title and abstract. Twenty five full text articles were assessed for eligibility. Of these 10 included a direct comparison between pulmonary artery catheter measurements and echocardiographic measurements in general during pregnancy[39-48]. Seven described comparative measurements of CO in specific of which four were excluded as methods of CO determination were different from our predefined methods. Finally three articles, including an abstract of the current study, were retained for direct comparison and meta-analysis (figure 1)[39, 40, 43]. One study by Lee et al. included 16 subjects[43]. One woman had been excluded from the study due to a technical difficulty resulting from a faulty pulmonary artery catheter. The manuscript included a table with comparative measurements in each subject from which the data was extracted. The other study by Belfort et al included eleven women[39]. No complications related to the right heart catheterisation were reported. Data points were derived from the regression lines presented in the manuscript.

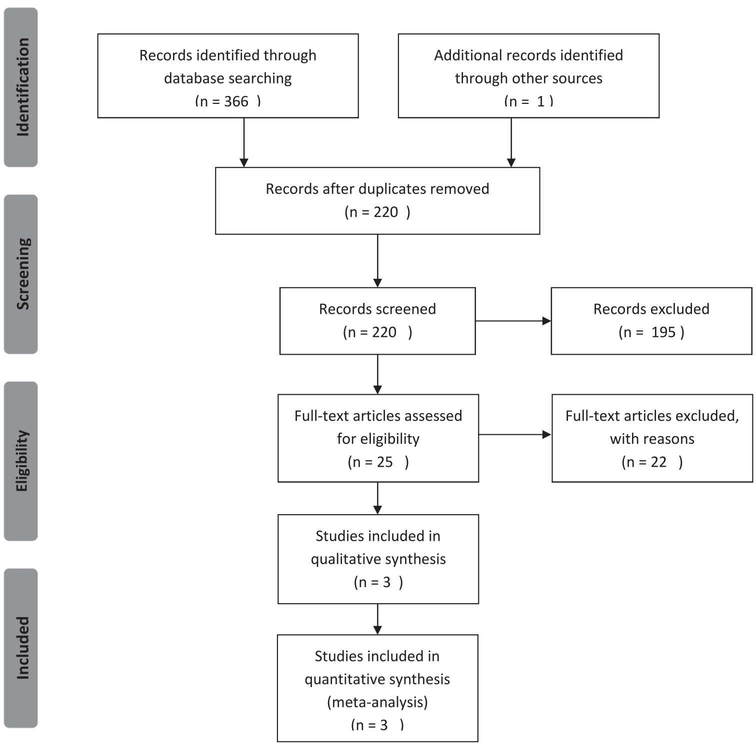

Figure 1 PRISMA flow diagram representing the results of the systematic review

Meta-analysis

Measurements comparing TTE with TD from our study were added to data retrieved from the systematic review. All three studies contained one single paired measurement per subject.

In total 34 subjects are included in the meta-analysis of which 24 were measured antepartum and 10 postpartum. The Bland-Altman plot represented in figure 2 suggests good agreement between both methods over a wide range of CO measurements (3.95 – 11.40 l/min). Mean CO obtained by thermodilution and Doppler echocardiography was 7.39 l/min (+-2.09) and 7.18 l/min (+-2.10) respectively. Mean CO was 7.28 l/min (+-2.07) with a bias of 0.21 l/min and standard deviation around the bias of 0.71 l/min. The limits of agreement were 0.21 +- 1.39 l/min (-1.18 – 1.60). Percentage error was 19.1%. Intraclass correlation coefficient was 0.94 (95% CI 0.88 - 0.97).

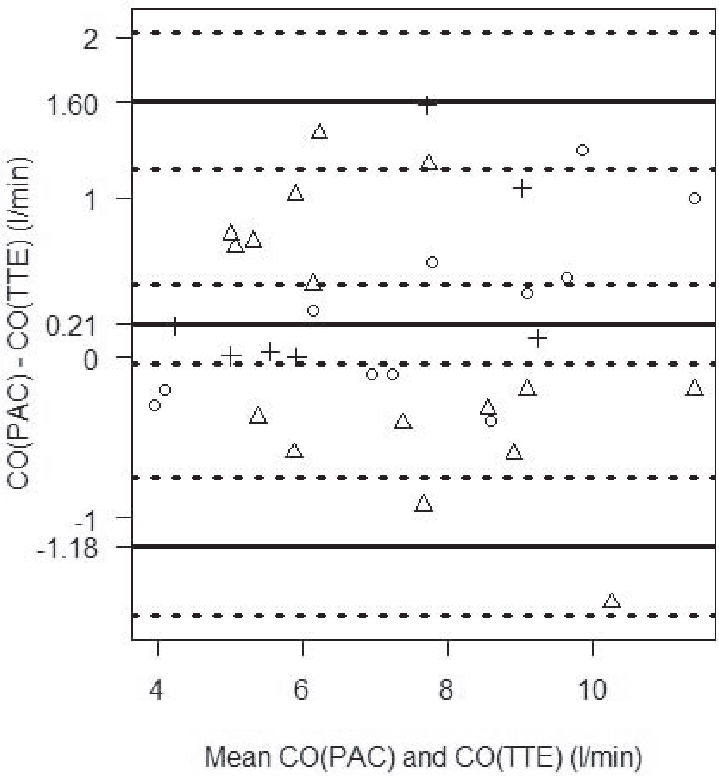

Figure 2 Bland & Altman Plot showing agreement between CO measurements obtained by PAC and TTE. The differences between both methods of CO measurements are plotted against the respective means. The circles correspond with the measurements reported by Belfort et al., the triangles with the measurements reported by Lee et al, and the crosses with the measurements obtained by Cornette et al.. The continuous lines represent the bias and limits of agreement, each with their respective upper and lower 95% CI (dotted lines).

DISCUSSION

Maternal CO is an important hemodynamic parameter which is subjective to substantial changes in pregnant women[1, 49]. TTE using PW Doppler ultrasound from the LVOT position is commonly used for CO measurements[2, 3, 8, 12, 50]. Still, our systematic review revealed only three validation studies of limited size against the clinical gold standard, including our own prospective study[39, 40, 43]. By combining them we were able to analyse 34 paired measurements using the appropriate statistics. These data covered a wide range of CO, gestational and maternal ages, both during pregnancy and immediately postpartum, in different pathological conditions and in three independent research groups. Our results show excellent agreement with a small bias, limits of agreements and percentage error well within our predefined margins and an excellent intraclass correlation coefficient. When a new method to assess a clinical variable is introduced it is usually compared against an established reference technique. Adoption of this new method usually depends on the degree of agreement with the reference technique and other potential benefits[51].

PAC remains an invasive technique with inherent risks that have been well described both in and outside pregnancy[26-29, 52, 53]. In our systematic review, we encountered 2 complications related to the procedure. TTE is non-invasive and increasingly accessible as many obstetrics ultrasound devices allow upgrading with cardiac software and probes. It can be used in all pregnant women ranging from healthy to critically ill at the bedside. As fetal and adult echocardiography are in essence very similar, it would take most feto-maternal medicine specialist little effort to learn the appropriate planes. In analogy with its homonyms in other critical circumstances (FAST, BLEEP, FATE or HART) a ROSE (rapid obstetric screening echocardiography) scan can be developed along with obstetric anaesthesiologist and congenital cardiologist for rapid, accessible and now reliable bedside hemodynamic monitoring in pregnant women[9].

Agreement between two different techniques depends on the accuracy and precision of the new method. Accuracy describes how close the measurement is to the reference value and precision how close the values of repeated measurements are. Cecconi et al. nicely visualised it by comparing it to target shooting, where accuracy is the characteristic of being able to shoot close to the bullseye and precision is how close repeated shots are close to each other[54]. Most studies outside pregnancy and the 2 studies included in our meta-analysis compared both techniques by correlation and regression. However these merely reflect the strength of a relation and not the agreement. If for example each CO determined by TTE would be exactly 5 l/min higher than the one determined by TD, the standard Pearson coefficient would still show perfect correlation despite substantial differences between the 2 techniques. By centering and scaling data using a pooled mean and standard deviation, the intraclass correlation coefficients is more appropriate to reflect the variance and agreement between 2 methods of measurement.

In their reference paper Bland and Altman proposed bias and precision statistics to analyse agreement between 2 methods where the differences (bias) are plotted against the means of each pair of measurements[55, 56]. This is now considered the gold standard for comparison between 2 techniques of CO measurements. The bias, reflecting accuracy, and the standard deviation around the bias as well as limits of agreement (limits in which 95% of points fall on each side of the bias), estimating precision, can be calculated. In order to conclude that agreement between 2 methods is acceptable, it should be defined beforehand wherein the limits of agreement should fall. It is often difficult to determine which limits are clinically acceptable. The reference method of thermodilution is merely the clinical standard and does not reflect the true CO. It carries some inherent errors in accuracy and precision (10-20%) due to fluctuations in CO with respiration and technical limitations[13, 37]. Also it is evident that a bias of 1 l/min is more significant at a low CO (e.g. 3 l/min) than in a high output state (e.g.10l/min). To overcome these problems Chitchley et all. proposed that a new method should be accepted if the level of accuracy and precision is at least equal to that of the reference. They proposed the percentage error of the limits of agreement as compared to the mean to be used to assess agreement between 2 methods of CO determination with a cut-off of 30%[38, 51, 57]. Studies comparing both methods of CO determination in non-pregnant adults using the appropriate Bland-Altman statistics are equally rare. They are approximatively of similar size and suggest a similar degree of agreement[58-60].

The importance of CO measurements in obstetrics is highlighted by the emergence of multitude of new techniques assessing CO in a minimally or non-invasive way. Several devices calculate CO using pulse contour analysis (LidCO®, Nexfin®,…), impedance cardiography (Niccomo®, Physioflow®, NICOM®,…) or continuous wave ultrasound (Uscom®)[7, 61-64]. Some of these allow continuous measurements, some require only a limited amount of training and skill making them more operator independent. Nevertheless validation of these devices, especially in pregnancy, remains an major issue, mainly by the lack of a gold standard[65].

PAC is still considered the clinical gold standard but indications for its use in obstetrics became extremely rare. Our study nicely showed that TTE is equivalent to PAC in pregnant women and besides for clinical use it can be considered as a surrogate gold standard to validate other techniques.

The strength of this study lies in the fact that by the systematic review approach we were able gather a maximal amount of cases for analysis using the appropriate statistics. The main limitations are that 34 comparisons remain modest and, while obvious given the invasiveness, our study does not include healthy pregnant women.

In conclusion our data indicated that CO measurements by TTE agree with PAC measurements in severely ill pregnant women. Given its non-invasive nature and availability it could be considered as a reference for the validation of other techniques in pregnant women.

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APPENDIX 1: SEARCH STRATEGY WITH SPECIFIC SEARCH HEADINGS FOR EACH DATABASE.

Literature search

Embase.com	117	116
Medline (OvidSP)	50	8
Web-of-science	29	10
Scopus	119	44
Cochrane	0	0
Cinahl	0	0
PubMed publisher	1	1
Google scholar	50	40
Total	**366**	**219**

Embase.com 117

('pulmonary artery catheter'/exp OR 'pulmonary artery catheterization'/exp OR (('heart catheterization'/exp OR 'artery catheterization'/exp) AND ('pulmonary artery'/exp OR 'lung artery'/exp)) OR ((Swan NEAR/3 Ganz) OR ((pulmon* OR lung) NEAR/3 arter* NEAR/3 catheter*) OR (right NEAR/3 (heart OR cardi*) NEAR/3 catheter*) OR fick):ab,ti) AND (echocardiography/exp OR echography/exp OR 'Doppler flowmetry'/exp OR (echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) NEAR/3 (cardi* OR heart)) OR doppler):ab,ti) AND (pregnancy/exp OR 'pregnant woman'/exp OR mother/de OR 'pregnancy disorder'/exp OR (pregnan* OR mother OR maternal* OR preeclamp* OR (pre NEXT/1 eclamp*)):ab,ti)

Medline (OvidSP) 50

(Catheterization, Swan-Ganz/ OR ((Cardiac Catheterization/) AND (Pulmonary Artery/)) OR ((Swan ADJ3 Ganz) OR ((pulmon* OR lung) ADJ3 arter* ADJ3 catheter*) OR (right ADJ3 (heart OR cardi*) ADJ3 catheter*) OR fick).ab,ti.) AND (exp Ultrasonography/ OR (echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) ADJ3 (cardi* OR heart)) OR doppler).ab,ti.) AND (exp pregnancy/ OR pregnant women/ OR mothers/ OR exp Pregnancy Complications/ OR (pregnan* OR mother OR maternal* OR preeclamp* OR (pre ADJ eclamp*)).ab,ti.)

Cochrane 0

(((Swan NEAR/3 Ganz) OR ((pulmon* OR lung) NEAR/3 arter* NEAR/3 catheter*) OR (right NEAR/3 (heart OR cardi*) NEAR/3 catheter*) OR fick):ab,ti) AND ((echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) NEAR/3 (cardi* OR heart)) OR doppler):ab,ti) AND ((pregnan* OR mother OR maternal* OR preeclamp* OR (pre NEXT/1 eclamp*)):ab,ti)

Web-of-science 29

TS=((((Swan NEAR/3 Ganz) OR ((pulmon* OR lung) NEAR/3 arter* NEAR/3 catheter*) OR (right NEAR/3 (heart OR cardi*) NEAR/3 catheter*) OR fick)) AND ((echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) NEAR/3 (cardi* OR heart)) OR doppler)) AND ((pregnan* OR mother OR maternal* OR preeclamp* OR (pre NEAR/1 eclamp*))))

Scopus 119

TITLE-ABS-KEY((((Swan W/3 Ganz) OR ((pulmon* OR lung) W/3 arter* W/3 catheter*) OR (right W/3 (heart OR cardi*) W/3 catheter*) OR fick)) AND ((echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) W/3 (cardi* OR heart)) OR doppler)) AND ((pregnan* OR mother OR maternal* OR preeclamp* OR (pre W/1 eclamp*))))

Cinahl 0

(MH "Swan-Ganz Catheterization+" OR ((MH "Heart Catheterization+") AND (MH "Pulmonary Artery+")) OR ((Swan N3 Ganz) OR (("pulmonary artery" OR "right heart") N1 catheter*) OR fick)) AND (MH Ultrasonography+ OR (echocardiogra* OR echogra* OR cardioechogra* OR ((echo* OR ultraso*) N3 (cardi* OR heart)) OR doppler)) AND (MH pregnancy+ OR MH "Expectant Mothers+" OR MH mothers+ OR MH "Pregnancy Complications+" OR (pregnan* OR mother OR maternal* OR preeclamp* OR (pre N1 eclamp*)))

PubMed publisher 1

(Catheterization, Swan-Ganz[mh] OR ((Cardiac Catheterization[mh]) AND (Pulmonary Artery[mh])) OR ((Swan AND Ganz) OR ((pulmon*[tiab] OR lung) AND (arter*[tiab] OR artery[tiab] OR arteri*[tiab]) AND catheter*[tiab]) OR (right AND (heart OR cardi*[tiab]) AND catheter*[tiab]) OR fick)) AND (Ultrasonography[mh] OR (echocardiogra*[tiab] OR echogra*[tiab] OR cardioechogra*[tiab] OR ((echo*[tiab] OR ultraso*[tiab]) AND (cardi*[tiab] OR heart)) OR doppler)) AND (pregnancy[mh] OR pregnant women[mh] OR mothers[mh] OR Pregnancy Complications[mh] OR (pregnan*[tiab] OR mother OR maternal*[tiab] OR preeclamp*[tiab] OR pre eclamp*[tiab])) AND publisher[sb]

Google scholar

"Swan Ganz"|"pulmonary|lung artery|arteries catheter|catheterization"|"right heart|cardiac catheter|catheterization"|fick echocardiogram|echocardiography|echography|echogram|echo|ultrasound pregnancy|pregnant|mother|maternal|preeclampsia|"pre eclampsia"

Chapter 3.2

Quantitative cardiovascular magnetic resonance in pregnant women

cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position

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J Cardiovasc Magn Reson. 2011 Jun 27;13:31.

ABSTRACT

Background

There are physiological reasons for the effects of positioning on hemodynamic variables and cardiac dimensions related to altered intra-abdominal and intra-thoracic pressures. This problem is especially evident in pregnant women due to the additional aorto-caval compression by the enlarged uterus. The purpose of this study was to investigate the effect of postural changes on cardiac dimensions and function during mid and late pregnancy using cardiovascular magnetic resonance (CMR).

Methods

Healthy non-pregnant women, pregnant women at 20th week of gestation and at 32nd week of gestation without history of cardiac disease were recruited to the study and underwent CMR in supine and left lateral positions. Cardiac hemodynamic parameters and dimensions were measured and compared between both positions.

Results

Five non-pregnant women, 6 healthy pregnant women at mid pregnancy and 8 healthy pregnant women at late pregnancy were enrolled in the study. In the group of non-pregnant women left ventricular (LV) cardiac output (CO) significantly decreased by 9% ($p=0.043$) and right ventricular (RV) end-diastolic volume (EDV) significantly increased by 5% ($p=0.043$) from the supine to the left lateral position. During mid pregnancy LV ejection fraction (EF), stroke volume (SV), left atrium lateral diameter and left atrial supero-inferior diameter increased significantly from the supine position to the left lateral position: 8%, 27%, 5% and 11%, respectively ($p<0.05$). RV EDV, SV and right atrium supero-inferior diameter significantly increased from the supine to the left lateral position: 25%, 31% and 13% ($p<0.05$), respectively. During late pregnancy a significant increment of LV EF, EDV, SV and CO was observed in the left lateral position: 11%, 21%, 35% and 24% ($p<0.05$), respectively. Left atrial diameters were significantly larger in the left lateral position compared to the supine position ($p<0.05$). RV CO was significantly increased in the left lateral position compared to the supine position ($p<0.05$).

Conclusions

During pregnancy positional changes affect significantly cardiac hemodynamic parameters and dimensions. Pregnant women who need serial studies by CMR should be imaged in a consistent position. From as early as 20 weeks the left lateral position should be preferred on the supine position because it positively affects venous return, SV and CO.

BACKGROUND

Increasing numbers of women with pre-existing heart disease are reaching childbearing age and are deciding to become pregnant [1]. Pregnancy induces marked physiological changes in cardiac parameters, with a 30-50% increase in cardiac output, through an increase both in stroke volume and heart rate [2]. While usually well tolerated in healthy pregnant women, these changes can induce adverse effect in women with pre-existing heart disease on both right and left-sided lesions [3, 4]. Therefore, heart function should be closely monitored during pregnancy in these patients. Echocardiography has been used for many years but cardiovascular magnetic resonance (CMR) is more reliable in the context of congenital heart disease [5]. To date, most data have been derived using echocardiography with the patients in lateral position [6], while CMR is usually performed in supine position. As aortocaval compression is important in advanced pregnancy [7, 8] data of both techniques can not be compared. Many women with complex cardiac conditions will require CMR during pregnancy, however there is relatively little data regarding both the use of CMR during pregnancy and of the impact of supine and lateral positions on cardiac parameters. The purpose of this study was to investigate the impact of maternal position on cardiac parameters derived from CMR during 2nd and 3rd trimesters of pregnancy in normal women.

METHODS

Patient selection

Healthy non-pregnant women, pregnant women at 20th week of gestation and at 32nd week of gestation with no history of cardiac disease were recruited to the study between June 2009 and January 2010. Study participants underwent CMR in supine and left lateral positions. Exclusion criteria were the common contraindications for CMR studies (pacemaker, cochlea implants and claustrophobia). The study was approved by the institutional review board and each subject gave informed consent.

CMR protocol

CMR was performed using a 1.5T scanner (Signa CV/*I*, GE Medical System, Milwaukee, WI). Firstly the patient was placed in the supine position and entered feet first into the magnet. A dedicated cardiac 8 channels coil was placed on the thorax of the subject and used for the acquisition of the images. CMR cines were obtained using a breath-holding ECG triggered balanced steady state free precession sequence. Imaging parameters were as follows: FOV 36-40 x 28-32 cm; matrix 224 x 196; TR: 3.4 milliseconds; TE: 1.5 milliseconds; flip angle 45 degrees; 12 views per segment. Slice thickness was 8 mm with a gap of 2 mm. These parameters resulted in a temporal resolution per image of 41 milliseconds. At first, three rapid surveys were obtained for the determination of the cardiac position and orientation; two- and four-chamber cine MR images were then obtained. The series of short axis (SA) images were obtained from the reference images provided by the two- and four- chamber end-diastolic images at the end of expiration. Approximately 10 to 12 slices were acquired to cover the entire length of the heart. Directly after the first CMR study, the subject was repositioned on the left lateral side position for the second examination. The acquisition of images was performed by the same operator.

Image analysis

All the studies were analysed on a remote workstation using the CAAS-MRV (version 3.2; Pie Medical Imaging, Maastricht, The Netherlands).

Left end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using a combination of classic SA and long-axis images. The long-axis view was used to limit the extend of volumes at the base and at the apex of the heart. The Simpson rule was used to calculate volumes based on the SA images where the first basal and the last apical were only partially included relating to the area outlined on two- and four- chamber images. More details about this approach have been previously reported [9]. The papillary muscles were considered as being part of the blood pool shortening the analysis time without compromising the accuracy of LV volumes compared to standard short-axis technique [10]. Ejection fraction (EF) was calculated as (EDV – ESV)/EDV. Cardiac output (CO) was calculated from stroke volume (SV) and heart rate (HR). Left atrium volume (LAvol) was measured using a combination of the two- and four chamber views in the diastolic phase of the atria. Lateral (LAlat) and supero-inferior (LAsi) left atrial diameters were measured on a four-chamber view during the phase of cardiac cycle with the largest left atrium (Figure 1). The lateral diameter was taken from the perpendicular constructed from the midpoint of the LAsi diameter extending to the atrial borders. The LAsi dimension corresponds to a line bisecting the left atrium and extending from the midpoint of the mitral annulus to the midpoint of the superior left atrium.

Right EF, EDV, ESV, SV and CO were calculated using cine images acquired in SA view, parallel to the tricuspid valve annulus and applying the same methods of the left ventricular hemodynamic measurements without long-axis corrections. In addition, lateral (RAlat) and supero-inferior (RAsi) right atrium diameters were taken during the phase of the cardiac cycle with the largest right atrium, on a four-chamber view (Figure 1). The RAlat diameter corresponds to the line extending from the atrial borders and perpendicular to the RAsi diameter. The RAsi diameter is the line from the midpoint of the tricuspid valve to the midpoint of the superior right atrium.

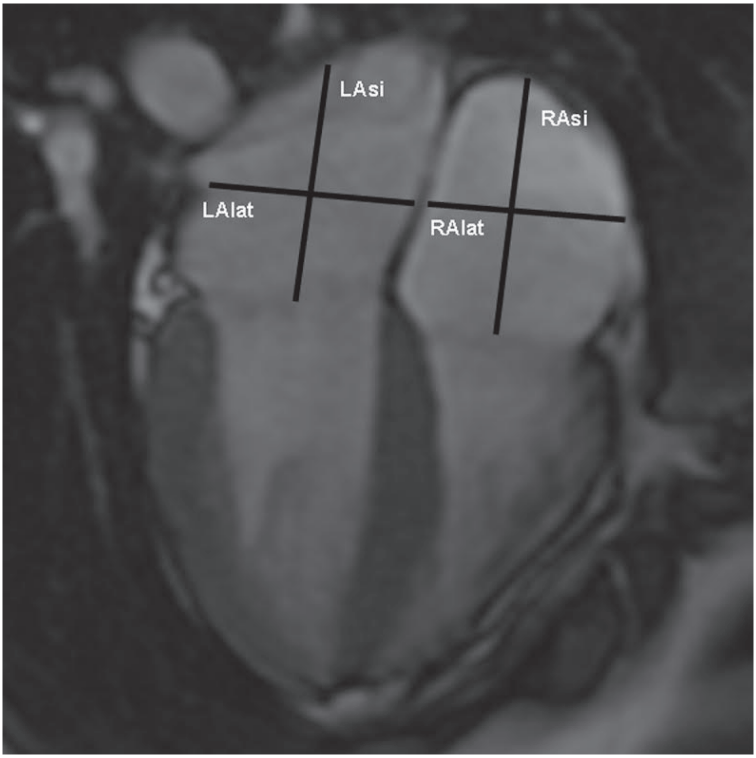

Figure 1 Cardiac dimensions: four-chamber end-systolic view:
LAlat: left atrium lateral diameter; LAsi: left atrium supero-inferior diameter; RAlat: right atrium lateral diameter: RAsi: right atrium supero-inferior diameter.

Due to the low inter-observer variability reported in a previous study [11] image analysis was performed by one operator with 3 years-experience in CMR. The operator was blinded to the same patient at the other position. CMR analyses were performed in a random order at different days.

Analysis by gestational week

The patients were categorized into 3 groups according to gestational age. The first group consists of non-pregnant controls, the second group of women in the 20th gestational week and the third group of women in the 32nd gestational week.

Statistical analysis

All analyses were done using SPSS 15 (SPSS Inc.) software. Parametric data were reported as mean ± standard deviation. For each gestational group mean values of HR, EDV, ESV, EF, SV, CO, left and right atrium diameters of supine and left lateral positions were tested for significance, using Wilcoxon's two sample test. A p-value <0.05 was considered significant. The percentage of change in the measure of left ventricle (LV) and right ventricle (RV) parameters (X) and left atrium (LA) and right atrium (RA) parameters (X) between supine and left lateral position was calculated using the following formula:

$$\text{percentage change in } X = [(X_{lateral} - X_{supine})/X_{supine}] \times 100.$$

RESULTS

A total of 14 healthy women with singleton pregnancies (30.3±5.2 years) were included in the study. Five non-pregnant women (29.4±5.7 years) were recruited as controls. The time interval between the examinations in supine and left lateral position ranged between 8 and 12 minutes. Table 1 gives the data regarding hemodynamic parameters and cardiac dimensions as related to gestational week and maternal posture. Percentage differences of cardiac volumes between supine and left lateral position are graphically reported in Figure 2 and 3 and will be reported in more detail below.

Table 1. Influence of position related to gestational weeks

	Pre pregnancy (N = 5)					T20 (N = 6)					T32 (N = 8)				
	Supine position Mean (SD)		Left lateral position Mean (SD)		p-value	Supine position Mean (SD)		Left lateral position Mean (SD)		p-value	Supine position Mean (SD)		Left lateral position Mean (SD)		p-value
							LEFT ATRIUM AND LEFT VENTRICLE								
HR	78.2	(12.7)	73.0	(12.1)	0.180	80.5	(11.3)	72.3	(5.3)	0.104	80.8	(15.7)	75.2	(10.6)	0.237
EF (%)	56.2	(3.5)	55.9	(4.3)	0.686	53.8	(4.4)	57.8	(4.6)	0.046	51.8	(7.2)	57.7	(8.0)	0.012
EDV (ml)	156.5	(23.3)	153.5	(24.7)	0.686	140.8	(37.1)	157.4	(20.7)	0.115	138.4	(22.1)	166.1	(25.6)	0.012
ESV (ml)	68.6	(12.7)	67.8	(14.1)	0.893	64.6	(17.9)	66.5	(11.8)	0.917	67.1	(16.4)	71.4	(22.3)	0.484
SV (ml)	87.8	(12.9)	85.7	(13.4)	0.223	76.0	(21.1)	90.9	(13.4)	0.028	71.2	(12.2)	94.8	(13.1)	0.012
CO (L/min)	6.8	(0.8)	6.2	(1.2)	0.043	6.5	(1.1)	6.5	(1.6)	0.917	5.6	(0.7)	6.9	(0.9)	0.012
LA vol (ml)	65.5	(13.3)	57.1	(15.8)	0.068	51.8	(12.7)	60.8	(10.3)	0.028	49.0	(20.9)	68.6	(15.7)	0.012
LA lat (mm)	39.7	(2.8)	37.8	(3.3)	0.080	35.0	(3.9)	36.7	(3.7)	0.028	35.4	(2.4)	40.7	(3.7)	0.012
LA si (mm)	45.1	(6.7)	43.7	(3.4)	0.500	40.3	(3.9)	44.9	(3.2)	0.027	39.7	(6.3)	44.7	(8.2)	0.025
							RIGHT ATRIUM AND RIGHT VENTRICLE								
EF (%)	51.5	(5.5)	46.4	(4.0)	0.225	50.5	(3.4)	52.9	(4.7)	0.249	53.2	(6.8)	54.6	(6.6)	0.575
EDV (ml)	161.0	(24.8)	168.6	(29.2)	0.043	132.0	(34.6)	156.1	(22.3)	0.028	138.8	(37.3)	155.9	(22.6)	0.161
ESV (ml)	78.7	(18.8)	90.5	(17.6)	0.080	65.1	(16.5)	73.1	(8.9)	0.463	65.7	(22.6)	71.8	(18.7)	0.484
SV (ml)	82.3	(10.7)	78.1	(14.1)	0.345	66.9	(19.3)	84.1	(16.9)	0.028	73.1	(17.2)	84.1	(7.9)	0.050
CO (L/min)	6.4	(1.0)	5.6	(1.1)	0.138	5.3	(1.5)	5.9	(1.8)	0.075	5.6	(0.6)	6.3	(0.7)	0.025
RA lat (mm)	34.4	(5.0)	33.5	(5.2)	0.345	32.4	(4.0)	33.2	(5.2)	0.500	33.9	(6.2)	36.2	(7.1)	0.484
RA si (mm)	47.5	(2.8)	45.9	(4.4)	0.345	40.4	(4.4)	45.1	(5.6)	0.042	44.5	(6.0)	45.2	(7.8)	0.889

T20: 20th gestational week; T32: 32nd gestational week.

EF (ejection fraction), EDV (end-diastolic volume), ESV (end-systolic volume), SV (stroke volume), CO (cardiac output), LAvol (left atrium volume), LAlat (left atrium lateral diameter), LAsi (left atrium supero-inferior diameter), RAlat (right atrium lateral diameter), RAsi (right atrium supero-inferior diameter)

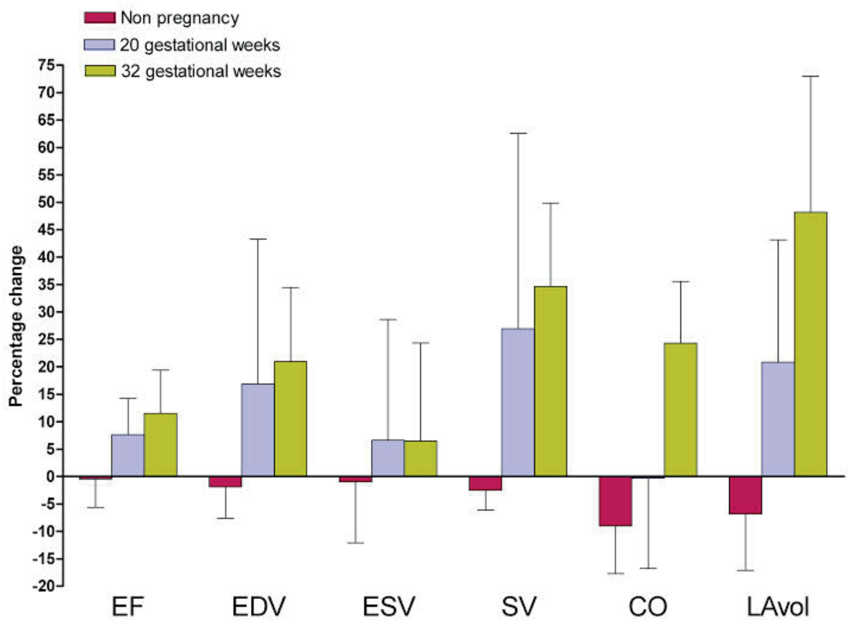

Figure 2 *Percentage differences of hemodynamic parameters of left side of the heart.*
EF (ejection fraction: %), EDV (end-diastolic volume: ml), ESV (end-systolic volume: ml), SV (stroke volume: ml), CO (cardiac output: L/min), LAvol (left atrium volume: ml)
Percentage difference from supine to left lateral position is calculated with the following formula:
X (%) = $[(X_{lateral} - X_{supine})/(X_{supine})]$ x100 where X is a cardiac parameter.

Pre pregnancy

HR did show a slight although not significantly decrease between supine and left lateral position: 78±12 versus 73±12. Left CO significantly decreased by 9% (p=0.043) and right EDV significantly increased by 5% (p=0.043). There were no other significant changes of hemodynamic parameters and cardiac dimensions between the two recumbent positions.

20 gestational weeks

Six pregnant women were in the 20th gestational week. HR was 80±11 bpm in the supine position and 72±5 in the left lateral position (p=0.15). A significant increment of EF and SV of the left ventricle was observed between the supine and the left lateral position: 8% (p=0.046) and 27% (p=0.028), respectively. Left atrial dimensions increased significantly between the supine and the left lateral position by 5% for LAlat (p=0.028) and by 11% for LAsi (p=0.027). Regarding the right side of the heart, EDV increased by 25% (0.028) and SV increased by 31% (0.028) between the supine and the left lateral position. RAsi significantly increased by 13% (p=0.042) between the supine and the left lateral position.

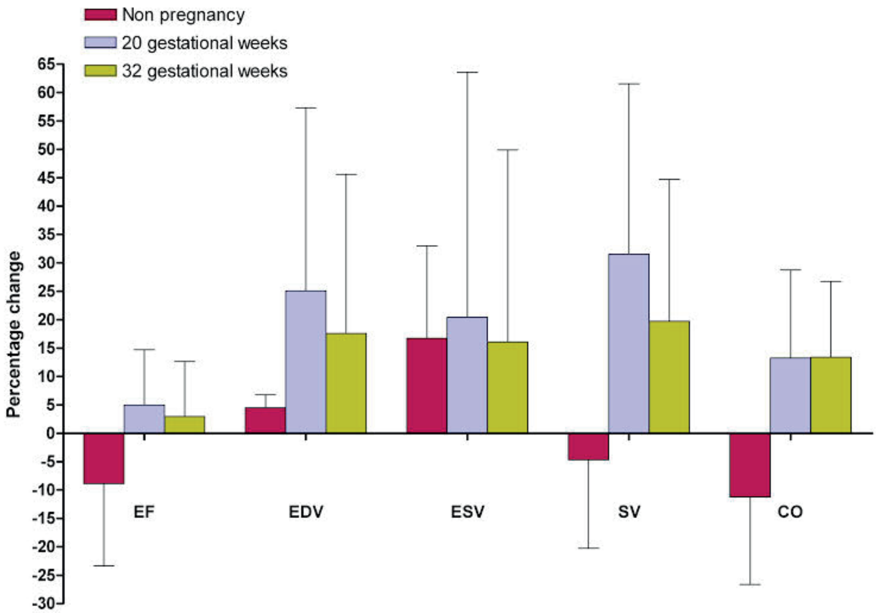

Figure 3 *Percentage differences of hemodynamic parameters of right side of the heart.*
EF (ejection fraction: %), EDV (end-diastolic volume: ml), ESV (end-systolic volume: ml), SV (stroke volume: ml), CO (cardiac output: L/min), LAvol (left atrium volume: ml)
Percentage difference from supine to left lateral position is calculated with the following formula:
X (%) = $[(X_{lateral} - X_{supine})/(X_{supine})]$ x100 where X is a cardiac parameter.

32 gestational weeks

Eight pregnant women were in the 32nd gestational week. HR did not significantly change between the supine and the left lateral position: 81±16 versus 75±8 bpm (p=0.237). A significant increment of EF, EDV, SV and CO was observed between the supine and the left lateral position: 11% (p=0.012), 21% (p=0.012), 35% (p=0.012) and 24% (p=0.012), respectively. Left atrial dimensions increased significantly between the supine and the left lateral position by 15% for LAlat (p=0.012) and by 13% for LAsi (p=0.025). No significant changes of right hemodynamic parameters and dimensions were observed between the two recumbent positions with the only exception of CO (p=0.025).

Impact of gestational age

A progressive increase of percentage changes of hemodynamic parameters and cardiac dimensions of the left side of the heart was found throughout gestation. The only exception was the percentage change of ESV which substantially did not change between 20 and 32 weeks of gestation. During late pregnancy left ventricle CO significantly increased between supine and left lateral position; the percentage of increment at 32 weeks was 24%. This was associated to an increase of 21% of left ventricle EDV. A significant increase in LA dimensions was also found. The difference between the two recumbent positions was less clear at 20th gestational week with an increase of left ventricle EDV and LA dimensions but with no clear impact on CO. For the right side of the heart we observed a similar trend of increment of ventricular and atrial dimensions at 20 weeks but no further increase during late pregnancy.

DISCUSSION

This study investigated how the supine and the left lateral positions during CMR affects heart rate, cardiac volumes and dimensions at different gestational ages. To our knowledge this is the first study investigating the effect of two recumbent positions on cardiovascular hemodynamic measurements and changes in cardiac dimensions during pregnancy using CMR. The data show a clear difference between the two positions, which become more marked as pregnancy advances but are significant from as early as 20 weeks. There were minimal changes in the non-pregnant subjects. The existing data from non-pregnant humans with regards to the effect of different positions on hemodynamic parameters are limited and sometimes conflicting. Some report that cardiac output is higher in the supine position compared to the right or left lateral position [12, 13], while others have shown that cardiac output is higher in the left lateral position than in the supine position [14] and still others that there is no difference in either position [15, 16]. In our series, we found that there was no significant effect on hemodynamic parameters and cardiac dimensions of moving from the supine to the left lateral position in non-pregnant women. However, we did observe a non significant decline in both heart rate and stroke volume leading to a borderline significant reduction in cardiac output.

Pregnancy itself is a circulatory burden with a significant impact on the cardiovascular system. Cardiac output increases 30-50% above pre-pregnancy levels. In addition, when a pregnant woman lies flat on her back, the gravid uterus partially compresses the inferior vena cava with the consequent reduction of venous filling load and cardiac output [2, 17]. From our data it appears that the increase of left atrial volume accounts for the majority in increase in stroke volume. As such it seems that the relief of caval obstruction (preload) is far more important that the relief of aortic compression (afterload) for the increase in cardiac output. In our series the significant increase in LA dimensions and the trend to increase EDV in the left lateral position suggest an increased venous return in this position which is already present at 20 gestational weeks. The effect of the gravid uterus compressing the abdominal vessels might be enforced by the increase in plasma volume even as early as 20 weeks of pregnancy [2]. An increase of right atrial pressure [18] and left and right ventricular peak systolic and end-diastolic pressures [19] in the left lateral position can also help to explain the increased venous return. It is of interest to observe that the heart rate was higher in the supine position compensating for the fall in stroke volume in this position [16] in an attempt to recover cardiac output. This could be partly explained by the fact that during mid-late pregnancy the suppression of cardiac vagal activity and the enhancement of cardiac sympathetic activity are greater in the supine position [20] than in the lateral position. In this series left ventricle EDV, EF, CO and SV increase significantly from the supine to left lateral position. These findings are easily explained: the change from the supine to the lateral position relieves the compression on the vena cava from the gravid uterus. The increasing venous return leads to an increased SV and so CO. Ueland et al [16] demonstrated that a change in position from the supine to the left lateral side produced a rise in CO by 8% at 20 to 24 weeks gestation, 13.6% at 28 to 32 weeks gestation and 28.5% at term in a group of eleven healthy pregnant women. We observed that the SV increased by approximately 27% at 20 weeks gestation. At 32 weeks gestation SV increased significantly by 35%. In our series turning to the left lateral position we observed an increment of the SV of the right ventricle which is more evident in the mid than in the late pregnancy. More studies are needed to better explain the consistency of this finding.

Some concerns may develop regarding the use of CMR in pregnant patients. Most studies evaluating MR safety during pregnancy do not show ill effects on the fetus [21-23]. It is anyway good practice to avoid MR studies during the first trimester of pregnancy although it can be used if clinical indicated. All our patients were studied during the second or third trimester of pregnancy.

Several limitations of this study should be highlighted. First, our results should be tested in a larger sample of women including women with cardiac disease. Indeed the normal physiological respond to pregnancy could be different in patients with congenital or acquired cardiovascular diseases. In addition, the small sample size may justify the large standard deviation in our series. Second, because the interval between each MR acquisition was between 8 and 12 minutes it is possible that cardiac parameters had not returned to baseline. Additional studies using more time points and also investigating the reverse change from lateral to supine could clarify this interesting subject. Third, this study is a cross-sectional study. The effects of the position on cardiac hemodynamic should preferably be studied in a prospective-longitudinal study investigating the same population at different gestational times.

CONCLUSION

In the non-pregnant state, turning from supine to left lateral position have minimal effect on cardiac parameters. During pregnancy, from as early as 20 weeks, turning to the left lateral position has positive effects on cardiac hemodynamics inducing a significant increase of venous return, SV and CO. Pregnant women requiring CMR should be studied in a consistent position for serial studies and the left lateral position is preferred from early pregnancy onwards, also to limit uteroplacental hypoperfusion.

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Chapter 4.1

Maternal and fetal haemodynamic effects of nifedipine in normotensive pregnant women

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ABSTRACT

While nifedipine is commonly used for tocolysis, the controversy on its safety remains. So far, the haemodynamic effects on maternal and fetal circulations have not been well documented. Fifteen normotensive women who received 20 mg nifedipine were included in this prospective observational study. The maternal and fetal haemodynamic effects were analysed using maternal echocardiography and fetal Doppler ultrasonography. Nifedipine induced a significant afterload reduction in all women. It triggered a compensatory increase in cardiac output, which maintained blood pressure. These maternal changes had no influence on the uteroplacental and fetal circulations.

INTRODUCTION

Nifedipine is a potent cardiovascular drug, registered for the treatment of ischaemic heart disease and hypertension. This calcium channel blocker is also commonly used for tocolysis in preterm labour. It was found to be superior to β-agonists with a better cardiovascular safety profile.[1] Nifedipine does not seem to affect blood pressure significantly in normotensive pregnant women, despite high-dose regimens.[1–4] Nevertheless, there are some concerns on its safety.[5,6] Rare but serious maternal cardiopulmonary and fetal complications have been reported in both humans and animals after tocolysis with calcium channel blockers. Nifedipine is not licensed for tocolysis and has not been subjected to specific safety assessments for this indication. With the availability of atosiban, a registered alternative in Europe, the controversy on the use of nifedipine tocolysis has increased.[6]

Most adverse events can be explained by the cardiovascular profile of the drug, which is more extensive than a mere antihypertensive effect.[4] By blocking calcium influx, nifedipine diminishes smooth muscle and myocardial contractility. In vascular tissue it results in an arterial relaxation with afterload reduction and increased coronary perfusion. On cardiac function, nifedipine has a negative inotropic potential, which may result in an undesirable myocardial depression and pump failure. However, the peripheral vasodilatation can induce a baroreceptor-mediated increase in sympathetic tonus, leading to a compensatory cardiostimulation by increasing the heart rate.[4]

Despite the large-scale and off-label use of nifedipine in pregnancy, data on maternal haemodynamic effects of nifedipine in women are limited to maternal heart rate and blood pressure recordings. The effects on uteroplacental and fetal circulation are also largely unknown.

In this prospective observational study, we investigated the effects of nifedipine tocolysis on maternal, fetal and uteroplacental haemodynamics in normotensive pregnant women.

METHODS

The study was conducted from September 2007 to October 2008 at the Department of Obstetrics of the Erasmus Medical Centre of the University of Rotterdam. To selectively assess the influence of nifedipine and avoid interference from labour-induced changes, we investigated women who received tocolysis for external cephalic version.

Informed consent was obtained from 15 healthy normotensive pregnant women with an uncomplicated singleton pregnancy between 35 and 37 weeks. Women with a complicated cardiovascular history or signs of uteroplacental insufficiency were excluded. The study protocol was approved by the local medical ethical committee. After confirmation of the breech presentation and 15 minutes of bed rest, baseline measurements for blood pressure as well as maternal haemodynamics (trans-thoracic echocardiography) and fetal and uteroplacental haemodynamics (Doppler ultrasound) were obtained. Then, one 10 mg capsule of nifedipine was administered twice with a 20-minute interval. Women were instructed to swallow the whole capsule with a little water. Sixty minutes after the administration of the first capsule, all measurements were repeated. Finally, external cephalic version was attempted. The fetal condition was monitored by cardiotocography, in between ultrasound measurements and for 45 minutes after the external cephalic version.

Systolic and diastolic blood pressure were measured by sphygmomanometry and mean arterial pressure was calculated. All ultrasound measurements were performed using a commercially available ultrasound device (iU22; Philips Ultrasound, Bothell, WA, USA), with cardiac and obstetric software packages. A 1–3-MHz sector probe transducer was employed for trans-thoracic echocardiography and a 2–5- MHz curved array transducer was used for the obstetric Dopplers. All measurements were obtained in a 15° left lateral tilt by one investigator (JC). Two-dimensional, M-mode and Doppler waveform images were digitally stored. Tracing and analysis were performed off site. For each variable the mean of three measurements was taken. The examination was usually completed within 30–45 minutes.

During maternal echocardiography, determinants of systolic and diastolic function were assessed. Left atrial diameter, aortic diameter and left ventricular end-diastolic and end-systolic diameters were obtained by M-mode. Left ventricular end-diastolic and end-systolic volumes were derived according to Teichholz formula and ejection fraction and fractional shortening were calculated.

The left ventricular outflow tract diameter was measured at the base of the aortic leaflets. The ventricular outflow tract velocity time integral (LVOTvti) was obtained by pulsed wave Doppler from an apical window and the corresponding heart rate (HR) was derived from the simultaneous electrocardiography (ECG) recording.

Stroke volume (SV), cardiac output (CO) and total vascular resistance (TVR) in dynes x s/cm^5 were calculated accordingly.

Diastolic function was assessed by pulsed wave Doppler analysis of mitral and right superior pulmonary vein inflow signals. Mitral valve peak velocities in early diastole (E-wave), during atrial contraction (A-wave) and the E/A ratio, as well as the deceleration time and isovolumetric relaxation time, were measured. Pulmonary vein peak systolic, diastolic and atrial reversal flow velocities were recorded. The maximum and minimum left atrial area were traced and the left atrial fractional area change was calculated. Peak regurgitation velocities over the pulmonary and tricuspid valves were determined by continuous wave Doppler.

All uteroplacental and fetal Doppler measurements were obtained using colour-directed pulsed wave Doppler. Pulsatility indices and time-averaged maximum velocities of the uterine arteries, umbilical artery, middle cerebral artery and ductus venosus were calculated.

Statistics were performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Variables were tested for normality and measurements before and after nifedipine were compared with a student's t test for paired samples or the nonparametric Wilcoxon signed ranks test as appropriate. In view of the number of parameters evaluated, we set $P \leq 0.01$ (two-sided) as the limit of significance.

RESULTS

Mean maternal age was 33 years. The external cephalic version was performed at a mean gestational age of $36^{4/7}$ weeks and was successful in a third of the women (5 of 15). All women received a total of 20 mg nifedipine and no major maternal or fetal complications occurred. One woman reported minimal nausea, one a sensation of lightheadedness and another reported minor flushes after nifedipine administration. All these adverse effects were transient. None of them was accompanied by a significant change in blood pressure, or required additional treatment. Paired measurements of all major parameters of systolic and diastolic function as well as uteroplacental and fetal Dopplers were obtained in most women. The results for all parameters are depicted in Table 1.

Nifedipine did not cause a change in arterial blood pressure but induced a significant increase in maternal CO (15.5%) and a decrease in TVR (13.8%). Moreover, this pattern of reduced afterload and raised output was consistent in all women (except in one woman where the CO remained unchanged). Both significant increases in maternal HR (7.4%) as well as in LVOTvti (7.7%) and SV (6.7%) contributed equally to the increased output.

There were no significant changes in cardiac dimensions, other determinants of systolic or diastolic function or in uteroplacental and fetal Dopplers.

DISCUSSION

This is the first study investigating the effects of nifedipine tocolysis on central maternal haemodynamics in combination with fetal and uteroplacental haemodynamics. Our results clearly indicate that nifedipine systematically induces a vascular relaxation with a significant reduction in TVR in normotensive pregnant women. It is masked by a constant blood pressure, as the fall in peripheral resistance is balanced by a compensatory rise in CO. Our observations are in accordance with the findings of invasive stud-

Table 1. Parameters of maternal, fetal and uteroplacental haemodynamics divided into determinants of maternal systolic function, maternal diastolic function and uteroplacental and fetal Doppler results

Parameter*	No. of pairs	Mean before nifedipine	Mean after nifedipine	Mean difference (95% CI)	*P*-value
Maternal systolic function					
SBP (mmHg)	15	110	111	1 (−2 to 4)	0.364
DBP (mmHg)	15	71	70	−1 (−4 to 1)	0.253
MAP (mmHg)	15	84	84	0 (−2 to 1)	0.657
LVEDd (cm)	15	4.75	4.85	0.10 (−0.02 to 0.22)	0.087
LVESd (cm)	15	2.89	2.73	−0.16 (−0.48 to 0.16)	0.296
EDV (ml)	15	106	111	5 (−1 to 12)	0.085
ESV (ml)	15	33	33	0 (−3 to 3)	0.883
EF (%)	15	69	71	2 (−1 to 5)	0.234
FS (%)	15	39	41	2 (−1 to 4)	0.144
Ao (cm)	15	2.39	2.42	0.03 (−0.13 to 0.20)	0.670
LVOTd (cm)	15	2.02	2.01	−0.01 (−0.03 to 0.02)	0.582
LVOTcsa (cm^2)	15	3.23	3.21	−0.02 (−0.10 to 0.06)	0.565
LVOTvti (cm)	15	22.4	24.1	1.7 (0.7 to 2.8)	0.003
HR (bpm)	15	80	86	6 (2 to 10)	0.005
SV (ml)	15	72	77	5 (1 to 9)	0.015
CO (l/min)	15	5.7	6.6	0.9 (0.5 to 1.2)	< 0.001
TVR (dyne s/cm^{-5})	15	1247	1075	−172 (−239 to −105)	< 0.001
Maternal diastolic function					
E (cm/s)	15	87	90	3 (−4 to 10)	0.420
A (cm/s)	15	59	64	5 (−1 to 11)	0.112
E/A	15	1.5	1.4	−0.1 (−0.2 to 0)	0.155
Adur (ms)	15	125	122	−3 (−11 to 4)	0.324
DT (ms)	15	178	170	−8 (−22 to 7)	0.262
IVRT (ms)	15	74	72	−2 (−7 to 3)	0.375
Pvs (cm/s)	12	50	49	−1 (−8 to 5)	0.610
Pvd (cm/s)	12	45	42	−3 (−7 to 2)	0.221
Pva (cm/s)	12	31	32	1 (−3 to 4)	0.746
Pvadur (ms)	12	111	116	5 (−7 to 17)	0.352
LA (cm)	15	3.59	3.69	0.10 (−0.11 to 0.31)	0.325
LA_{max} (cm^2)	15	15.25	15.56	0.31 (−1.14 to 1.77)	0.646
LA_{min} (cm^2)	15	6.62	6.54	0.08 (−1.06 to 0.88)	0.848
LAFAC (%)	15	57	58	1 (−3 to 6)	0.561
TR (cm/s)	11	132	140	8 (−18 to 35)	0.500
PR (cm/s)	12	139	149	10 (−5 to 25)	0.178
Uteroplacental and fetal Doppler					
PIruter	14	0.68	0.69	0.01 (−0.06 to 0.07)	0.862
TAMVruter (cm/s)	14	102	101	1 (−15 to 16)	0.924
PIluter	15	0.73	0.77	0.04 (−0.05 to 0.13)	0.379
TAMVluter (cm/s)	15	114	96	18 (−1 to 37)	0.061
PIuter	14	0.71	0.74	0.03 (−0.04 to 0.09)	0.387
TAMVuter (cm/s)	14	109	97	12 (−3 to 28)	0.119
PIumb	15	0.91	0.98	0.07 (−0.01 to 0.15)	0.069
TAMVumb (cm/s)	15	32	34	−2 (−7 to 3)	0.337
PImca	15	1.80	1.76	−0.04 (−0.22 to 0.14)	0.635
TAMVmca (cm/s)	15	26	28	−2 (−6 to 2)	0.311
PIVdv	12	0.57	0.57	0.00 (−0.10 to 0.1)	0.985
TAMVdv (cm/s)	12	64	54	10 (−5.8 to 25.8)	0.191

***A, mitral** valve peak velocity during atrial contraction; Adur, duration of the A wave; Ao, aortic diameter; CO, cardiac output; DBP, diastolic blood pressure; DT, deceleration time; E, mitral valve peak velocity during early diastole; E/A, E/A ratio; EDV, left ventricular end-diastolic volume; EF%, ejection fraction; ESV, left ventricular end-systolic volume; FS%, fractional shortening; HR, heart rate; IVRT, isovolumetric relaxation time; LA, left atrial diameter; LAFAC, left atrial fractional area change; LA_{max}, maximal left atrial area; LA_{min}, minimal left atrial area; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; LVOTcsa, left ventricular outflow tract cross sectional area; LVOTd, left ventricular outflow tract diameter; LVOTvti, left ventricular outflow tract velocity time integral; MAP, mean arterial pressure; PIluter, left uterine artery pulsatility index; PImca, middle cerebral artery pulsatility index; PIruter, right uterine artery pulsatility index; PIumb, umbilical artery pulsatility index; PIuter, mean uterine artery pulsatility index; PIVdv, ductus venosus pulsatility index for veins; PR, pulmonary valve regurgitation; Pva, pulmonary vein peak atrial reversal velocity; Pvadur, pulmonary vein atrial reversal duration; Pvd, pulmonary vein peak diastolic velocity; Pvs, pulmonary vein peak systolic velocity; SBP, systolic blood pressure; SV, stroke volume; TAMVdv, ductus venosus time-averaged maximum velocity; TAMVluter, left uterine artery time-averaged maximum velocity; TAMVmca, middle cerebral artery time-averaged maximum velocity; TAMVruter, right uterine artery time-averaged maximum velocity; TAMVumb, umbilical artery time-averaged maximum velocity; TAMVuter, mean uterine artery time-averaged maximum velocity; TR, tricuspidal regurgitation; TVR, total vascular resistance.
***P*-values were** calculated using student's t test.

ies on nifedipine using right heart catheterisation, although most were performed in nonpregnant individuals suffering from cardiac disease or hypertension.[4] These studies showed a decrease in vascular resistance and BP, which led to both a compensatory rise in HR as well as to an improved ventricular emptying with increased SV and CO and decreased ventricular filling pressure. As the magnitude of the changes, especially in BP, was dependent on the pre-treatment degree of cardiac dysfunction and hypertension, it is often stated that vascular relaxation does not occur in normotensive people. However, invasive measurements in normotensive volunteers and in pregnant ewes given equivalent doses of nifedipine showed a similar pattern of significant decrease in systemic vascular resistance which triggered an increase in HR and CO but without changes in blood pressure.[7,8]

The capacity to further reduce TVR is remarkable as peripheral resistance is already largely decreased during pregnancy as an adaptive mechanism initiating plasma volume expansion. Despite this, there still seems to be a reserve for further reduction in the healthy pregnant woman. One could argue that our study was performed near term when peripheral resistance has already slightly risen from its nadir, but the magnitude of the changes indicates that this could only offer a partial explanation.

Both a rise in HR as well as in SV equally contributed to the elevation in CO in the women in this study. Although the increased HR reflects sympathetic stimulation, the increase in SV is interesting. Apparently, a further afterload reduction, on top of the already lowered TVR can still induce a more efficient myocardial contraction with improved ventricular emptying, which is superior to the negative inotropic effect of nifedipine, and results in an increased SV. It reflects myocardial reserve in a normal healthy pregnant woman.

The absence of effects on diastolic function resembles the findings in invasive studies, where changes in filling pressures were limited to people with impaired systolic function.[4] This study objectifies the pharmacodynamic profile of nifedipine in normotensive pregnant women. Our results show that two 10 mg capsules of nifedipine induce significant but hidden changes in maternal central haemodynamics 1 hour after administration. The balance between these opposite effects on TVR and CO is probably the reason why high doses of this potent drug can be used for tocolysis without complications in most people.

However, these findings cannot automatically be extrapolated to the longer treatment schedules or higher doses that are common for tocolysis.

Our results may also explain the observation that major maternal cardiovascular complications with nifedipine use are more likely to occur in women with reduced cardiac reserve.[6] In women with pre-existing cardiac disease, multiple pregnancy, (sub)clinical sepsis in preterm prelabour rupture of membranes, or use of multiple medications, further reduction of the TVR beyond a critical point or the incapacity to adequately compensate with the CO may induce haemodynamic compromise.

Nifedipine readily crosses the placenta with a maternal/fetal plasma ratio of 0.93.[3] Despite significant changes in maternal haemodynamics we could not demonstrate any changes in the uterine, umbilical or middle cerebral pulsatility indices or time-averaged maximum velocities. This suggests that nifedipine has no effect on the uteroplacental or fetal circulation but the limitations of both measurements in reflecting total blood flow should be noted.

Our results are consistent with two studies on the short- term influence of a loading dose of nifedipine for tocolysis on placental, fetal cerebral and fetal atrioventricular Doppler results in normotensive women with preterm labour, where both maternal blood pressure and uteroplacental and fetal Doppler results were unaffected.[2,9] Another study observed a significant decrease in uterine artery resistance but without changes in the arcuate or umbilical artery Doppler flows.[3] The absence of changes in the uterine circulation is remarkable considering the substantial maternal afterload reduction. It indicates that in healthy normotensive pregnancy without signs of placental insufficiency, trophoblast invasion has lowered downstream resistance to such an extent that nifedipine is unable to further reduce uterine resistance, despite its potency to reduce the systemic resistance. Consequently, uterine hypoperfusion will only occur with hypotension, when the fall in TVR is not compensated by a rise in CO. This hypothesis is further supported by a study on prolonged nifedipine tocolysis, that only observed a decrease in uterine and middle cerebral pulsatility index when maternal blood pressure decreased significantly.[10]

Fetal acidaemia and hypoxaemia without changes in placental perfusion have been observed in animal studies.[11] Despite widespread use of the drug in human pregnancy, there are no reports of fetal or neonatal acidosis related to nifedipine. Pirhonen et al.[3] observed cord blood pH and oxygen contents within normal ranges in postnatal samples. The reported fetal death could be attributed to maternal hypotension.[12] An explanation for the discrepancy between animal and human findings is that while changes in pH and oxygen content are statistically significant in animal studies, it is questionable whether they are clinically relevant.

Precordial venous Dopplers may reflect changes in fetal acid–base status. This is the first report investigating the effect on paired ductus venosus measurements. We could not observe any changes after nifedipine administration. However, it is likely that minor changes in pH are too subtle to be reflected by this method.

The originality and strength of this study lie in the use of a non-invasive measurement tool as well as in the selection of its population. The former allowed a thorough evaluation of maternal central haemodynamics, the latter permitted the examination of pregnant women in nearly physiological, controlled conditions without interference from labour-induced changes.

Our study is limited by its observational design, the small number of women and large number of investigated parameters. Still we believe that its set-up, along with the magnitude and remarkable consistency in the observed changes, allows us to draw conclusions on the haemodynamic effects of nifedipine tocolysis despite the small population size. It is further supported by the observation that our results are in accordance with the effects one could expect based on the pharmacological profile of nifedipine.

CONCLUSION

Our results indicate that tocolysis with 20 mg oral nifedipine influences maternal haemodynamics 1 hour after intake in normotensive healthy pregnant women near term. Nifedipine induces an afterload reduction which triggers a rise in cardiac output. As a result, blood pressure often remains unchanged. Nifedipine has no negative effect on ventricular function. Neither the profound changes in maternal haemodynamics nor nifedipine itself seem to affect uteroplacental or fetal haemodynamics.

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Chapter 4.2

Hemodynamic effects of intravenous nicardipine in severely pre-eclamptic women with a hypertensive crisis

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ABSTRACT

Objective

Nicardipine permits rapid control of blood pressure in women with severe pre-eclampsia (PE) and hypertensive crisis. Our objective was to investigate its maternal and fetal hemodynamic effects.

Methods

Ten severely pre-eclamptic pregnant women who required intravenous nicardipine for severe hypertension were included in this prospective observational trial. Maternal macrocirculation was assessed by transthoracic echocardiography. Maternal microcirculatory perfusion was examined sublingually with the sidestream dark field imaging technique. Fetal hemodynamics were assessed by Doppler examinations of the uteroplacental and fetal circulations. Maternal cardiac output, total vascular resistance, mitral E/A ratio and capillary heterogeneity index, uterine artery pulsatility index and fetal cerebroplacental ratio were considered primary outcomes. Paired measurements, obtained before administration of nicardipine infusion and after stabilization of blood pressure, were compared.

Results

Administration of nicardipine significantly reduced the mean arterial blood pressure (median difference, 26 mmHg; $P = 0.002$) and total vascular resistance (median difference, 791 dynes $\times$ s/cm^5; $P = 0.002$) in all included women. This induced a reflex tachycardia with consequent increase in cardiac output of 1.55 L/min ($P = 0.004$). There were no significant changes in the other determinants of maternal or fetal hemodynamic parameters.

Conclusions

Nicardipine effectively reduces blood pressure through selective afterload reduction that triggers an increase in cardiac output, without affecting maternal diastolic function, or microcirculatory, uteroplacental or fetal perfusion. This hemodynamic response is uniform and predictable. Fetomaternal cardiovascular profiling can be achieved by combining transthoracic echocardiography with obstetric Doppler.

INTRODUCTION

A hypertensive crisis, defined as the occurrence of a systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg in women with pre-eclampsia (PE), is a hypertensive emergency[1,2]. These women are at risk of developing complications such as cerebrovascular accidents and pulmonary edema[3-6]. Their blood pressure must be lowered rapidly without compromising the maternal or uteroplacental circulations. Nicardipine is a calcium channel blocker structurally related to nifedipine but with a distinctive pharmacological and hemodynamic profile that makes it attractive for the treatment of hypertensive emergencies in women with PE[7-10]. Its administration in intravenous form, rapid onset of action and short half-life allow easy titration against blood pressure while transplacental passage is limited (15%)[11-13]. Nicardipine induces general arterial relaxation that is more pronounced in cerebrovascular and coronary arteries[8,14,15]. The depressant action on myocardial muscle cells is less than with nifedipine and its cerebrovascular selectivity renders it more effective in preventing ischemic stroke and hypertensive brain damage than other antihypertensive drugs[16]. Results from observational and comparative trials in women with severe PE are encouraging[12,17-21]. Nicardipine seems equivalent or superior in reducing blood pressure to other intravenous drugs that are used commonly (labetalol, ketanserin, hydralazine), with excellent maternal and fetal outcomes[22,23]. However, acute cardiac failure was described recently in two women with severe PE who were administered nicardipine combined with magnesium sulphate[24]. In addition, there are several reports of acute pulmonary edema associated with nicardipine when used for tocolysis, and animal studies have repeatedly shown uteroplacental hypoperfusion, acidosis and fetal death[25–30]. In fact, little is known on the effect of nicardipine on hemodynamic parameters other than blood pressure in cases of severe PE. The latter is important as PE is characterized by a profound hemodynamic instability due to generalized endothelial dysfunction. We therefore aimed to investigate the hemodynamic effects of rapid blood pressure reduction with nicardipine in women with severe PE by analyzing the maternal macrocirculation, maternal microcirculatory perfusion, and uteroplacental and fetal circulations in a prospective observational study.

METHODS

The study was conducted at the Department of Obstetrics and Prenatal Medicine, Erasmus Medical Centre, University of Rotterdam, Rotterdam, The Netherlands. Ten women with severe PE requiring intravenous nicardipine for a hypertensive crisis (SBP of ≥160mmHg and/or DBP of ≥110 mmHg) were included in the study. Severe PE was defined according to the NICE guideline on hypertension in pregnancy[31]. Informed consent was obtained from all women and the study protocol was approved by the local medical ethics committee.

To minimize treatment delay, the presence and immediate availability of the main investigator at the time of inclusion was required. Inclusion was irrespective of previous or concomitant use of other oral antihypertensive medication. Women with known cardiac dysfunction, signs of imminent eclampsia or severe neurological symptoms, or those with signs of fetal distress or the need for respiratory support were excluded.

Patients were admitted to the obstetric high care unit and received a radial arterial line. All women were managed according to our standard protocol for severe PE. Fetal lung maturation was induced with steroids before 34 weeks and all women received magnesium sulphate for seizure prophylaxis. Restricted amounts of intravenous fluids were administered with medication. Nicardipine was initiated at 1 mg/h by continuous infusion through a peripheral venous line. The dosage was subsequently titrated against blood pressure. Dose adaptations of 0.5mg/h occurred at 15-min intervals with a maximum infusion rate of 10mg/h. Treatment was targeted to a SBP ≤155mmHg and a DBP ≤100 mmHg.

Baseline hemodynamic measurements were obtained before treatment with nicardipine. Measurements were repeated once blood pressure had been stabilized around the target values. Paired measurements, before and after nicardipine, were taken and compared in all women. Intra-arterial blood pressure recordings were obtained from the radial arterial line after appropriate cardiac levelling of the pressure transducer. Maternal central hemodynamics were assessed non-invasively by transthoracic echocardiography, investigating the determinants of systolic function (cardiac dimensions, ejection fraction (EF), fractional shortening (FS), stroke volume (SV), cardiac output (CO) and total vascular resistance (TVR)) and diastolic function (mitral and pulmonary venous inflow patterns). Left ventricular end-diastolic and end-systolic diameters were obtained by M-mode ultrasound from which end-diastolic and end-systolic volumes were derived according to the Teichholz formula, and EF and FS were calculated. The left ventricular outflow tract diameter was measured at the base of the aortic leaflets. The ventricular outflow tract velocity time integral was obtained by pulsed-wave Doppler from an apical window and the corresponding heart rate was derived from the simultaneous electrocardiography recording. SV, CO and TVR were calculated accordingly. Diastolic function was assessed by pulsed-wave Doppler analysis of mitral and right superior pulmonary vein inflow signals. Mitral valve peak velocities were measured in early diastole (E) and during atrial contraction (A) to give the E/A ratio, and the deceleration time and isovolumetric relaxation time were also measured. Pulmonary vein peak systolic, diastolic and atrial reversal flow velocities were recorded. The maximum and minimum left atrial areas were traced and the change in left atrial fractional area was calculated.

Peak regurgitation velocities over the pulmonary and tricuspid valves were determined by continuous-wave Doppler.

Uteroplacental and fetal hemodynamics were investigated by color-directed pulsed-wave Doppler. Pulsatility index (PI) and time-averaged maximum velocity (TAMV) of the uterine arteries, umbilical artery, middle cerebral artery and ductus venosus were obtained, from which the cerebroplacental ratio (CPR; the middle cerebral artery PI/ umbilical artery PI) and gestational age-adjusted percentiles were calculated.

All ultrasound measurements were obtained at a 15° left lateral tilt by one investigator (J.C.) using a commercially available ultrasound device (iU22, Philips Ultrasound, Bothell, WA, USA), with cardiac and obstetric transducers and software packages as described in detail previously[32]. Two-dimensional, M-mode and Doppler waveform images were stored digitally. Tracing and analysis were performed off site. For each variable the mean of three measurements was used for analysis.

Changes in maternal cardiac function were also assessed by determination of the maternal serum brain natriuretic peptide (BNP). Contrary to the N-terminal prohormone BNP (NT-proBNP), BNP has a short half-life and can thus be used to monitor rapid changes in filling pressures[33,34]. From the arterial line, 4mL of blood was drawn and centrifuged and the plasma was stored at −80°C. After collection of all samples, plasma was extracted on Sepac columns and the level of BNP was assessed using a commercially available radioimmunoassay (BNP-32, Peninsula Laboratories, San Carlos, CA, USA).

Changes in maternal microcirculatory perfusion were assessed sublingually by the sidestream dark field (SDF) imaging technique. We have reported previously on this innovative technique in women with severe PE, in which details on the method, measurement and reliability of the technique are described in depth[35]. In brief, the technique consists of a handheld video microscope (MicroScan Video Microscope, MicroVision Medical, Amsterdam, The Netherlands) which emits stroboscopic green light that is absorbed by hemoglobin of individual red blood cells in superficial vessels of the sublingual mucosa. High-contrast video images of circulating erythrocytes in the microcirculation were recorded and later analyzed with specific software (AVA 3.0). Perfused vessel density (PVD), microvascular flow index (MFI) and a heterogeneity index (HI) for both capillaries (diameter <20 μm) and venules and arterioles (diameter 20–100 μm) were calculated. PVD is a good reflection of functional microvascular density. MFI describes the predominant pattern and HI describes the heterogeneity of the microvascular flow. The microcirculatory characteristics before administration of nicardipine were also included in the previous study on microcirculation in women with severe PE[35].

This study was undertaken as an exploratory pilot. Statistics were performed with IBM SPSS Statistics v. 20.0 (IBM, Armonk, NY, USA). Based on previous results and clinical relevance, CO, TVR, mitral E/A ratio, uterine artery PI, CPR and capillary HI were considered primary outcome parameters[32,35-37]. Measurements obtained before and after nicardipine were compared using non-parametric Wilcoxon signed-ranks test. In view of the number of parameters evaluated, we set $P \leq 0.01$ (two-sided) as the limit of significance.

RESULTS

Mean maternal age was 30 (range, 18–42) years and mean gestational age was 28 (range, 25–34) weeks. An episode of HELLP-syndrome complicated the PE in six women; four occurred at the time of the measurements and two occurred in the following days. The mean 24-h protein excretion was 2.2 g (range, 0.3–6.7 g).

All women had a uterine artery PI≥95th centile, and 80% had early diastolic notches. Nine fetuses had Doppler signs of cerebral redistribution, with CPR≤5^{th} centile, and eight were growth restricted (birth weight <10th percentile). Mean birth weight was 1086 g (range, 540–2120 g). All women delivered by Cesarean section within 6 days of the measurements being obtained (mean, 2.5 days (range, 9 h to 6 days)). Indications for delivery were signs of fetal distress (n = 6), deteriorating maternal condition (n = 2) and failed induction of labor (n = 2), none of which could be related to the administration of nicardipine. All infants were alive at the time of writing.

All women were on concomitant oral antihypertensive medication before inclusion. Eight women were treated with α-methyldopa in various doses ranging from 1500 to 3000 mg. Four women received concomitant nifedipine (dose range, 30–90 mg), two of which were administered in combination with α-methyldopa and one in combination with labetalol (600 mg).

Nicardipine was administered because of insufficient blood pressure control. The mean dose required to achieve the target blood pressures was 3.5mg/h. Seven women required a dose between 1.5 and 3mg/h and achieved the target blood pressures within 1 h from administration. The remaining three women required 4, 6 and 7 mg/h, respectively, and achieved the target blood pressure within 3 h from administration.

Two women experienced complications that could be attributed to nicardipine infusion; one experienced two hypotensive episodes without signs of fetal compromise, which responded well to a fluid challenge and temporary cessation of nicardipine infusion, and another experienced a transient episode of chest pain. Thorough investigations with cardiac enzymes and electrocardiography ruled out ischemia. The pain disappeared and nicardipine was continued. No women developed pulmonary edema.

All paired measurements were performed within 6 h of one another. Paired measurements of all major parameters of systolic and diastolic function, as well as uteroplacental and fetal Dopplers, were obtained in most women. BNP could not be measured reliably in one woman. The SDF-imaging microscope became available only after inclusion into the study of the third patient, and thus sublingual microcirculatory perfusion was analyzed in seven women. The number and results of the paired measurements of maternal hemodynamics, uteroplacental and fetal Dopplers and microcirculatory perfusion are given in Tables 1–3, respectively.

Table 1 Maternal central hemodynamics obtained by radial arterial line and transthoracic echocardiography in 10 pregnant women with pre-eclampsia and hypertensive crisis, before and after administration of nicardipine

Parameter	n	*Before nicardipine*	*After nicardipine*	*Median difference**	P
Maternal systolic function					
Systolic BP (mmHg)	10	188	153	35 (30 to 49)	0.002
Diastolic BP (mmHg)	10	105	83	19 (13 to 25)	0.002
MAP (mmHg)	10	130	105	26 (21 to 28)	0.002
LV end-diastolic diameter (cm)	10	4.85	4.60	0.05 (−0.08 to 0.25)	0.469
LV end-systolic diameter (cm)	10	3.00	2.75	0.25 (−0.15 to 0.68)	0.262
Ejection fraction (%)	10	67	74	−5 (−14 to 2)	0.186
Fractional shortening (%)	10	36	44	−7 (−13 to 2)	0.160
Aortic diameter (cm)	10	2.40	2.30	0.00 (−0.13 to 0.23)	0.642
LVOT diameter (cm)	10	2.00	2.00	0.00	1
LVOT velocity time integral	10	23.00	26.55	−0.85 (−2.80 to 0.73)	0.201
Heart rate (bpm)	10	76	91	−22 (−26 to −14)	0.006
Stroke volume (mL)	10	72	77	−2.5 (−7 to 2)	0.193
Cardiac output (L/min)	10	5.30	6.75	−1.55 (−2.10 to 0.95)	0.004
Total vascular resistance (dynes × s/cm^5)	10	2010	1264	791 (662 to 921)	0.002
Maternal diastolic function					
E (cm/s)	9	90	82	2 (−9 to 27)	0.340
A (cm/s)	9	83	90	−12 (−24 to 11)	0.426
E/A	9	1.1	0.9	0.3 (0.0 to 0.5)	0.125
Deceleration time (ms)	6	160	182	−15 (−46 to 26)	0.688
Isovolumetric relaxation time (ms)	10	88	86.5	0 (−14 to 25)	0.643
Pulmonary vein peak systolic velocity (cm/s)	6	62	71	−6 (−18 to 10)	0.625
Pulmonary vein peak diastolic velocity (cm/s)	6	57	53	7.5 (−9 to 17)	0.281
Pulmonary vein peak atrial reversal velocity (cm/s)	6	29	32	−3 (−6 to 8)	0.906
Diastolic grade	9	0	1	0 (0 to 1)	0.500
Left atrial fractional area change (%)	9	52	55	−1 (−11 to 3)	0.426
Tricuspid valve regurgitation (cm/s)	5	125	121	1 (−6 to 37)	0.813
Pulmonary valve regurgitation (cm/s)	4	163	155	5 (−12 to 20)	0.875
Brain natriuretic peptide (pmol/L)	9	15	12	0 (−8 to 4)	0.945

Data are given as median or median (interquartile range). *Difference calculated as value before nicardipine minus value after nicardipine. A, mitral valve peak velocity during atrial contraction; BP, blood pressure; E, mitral valve peak velocity during early diastole; LV, left ventricle; LVOT, left ventricular outflow tract; MAP, mean arterial pressure.

Table 2 Uteroplacental and fetal Doppler measurements in 10 pregnant women with pre-eclampsia and hypertensive crisis, before and after administration of nicardipine

Parameter	n	*Before nicardipine*	*After nicardipine*	*Median difference**	P
UtA-PI	10	1.58	1.64	0.03 (−0.13 to 0.13)	0.734
UtA-TAMV (cm/s)	10	39	37	−1 (−13 to 6)	0.625
UA-PI	10	1.36	1.43	0.00 (−0.10 to 0.13)	0.941
UA-TAMV (cm/s)	10	18	19	−1 (−4 to 3)	0.902
MCA-PI	10	1.48	1.48	−0.01 (−0.15 to 0.18)	0.980
MCA-TAMV (cm/s)	10	23	25	1 (−4 to 4)	0.922
CPR	10	1.07	1.00	−0.04 (−0.19 to 0.13)	0.770
DV-PI	8	0.70	0.69	−0.02 (−0.20 to 0.34)	0.844
DV-TAMV (cm/s)	8	52	47	−6 (−8 to −1)	0.195

Data are given as median or median (interquartile range). *Difference calculated as value before nicardipine minus value after nicardipine. CPR, cerebroplacental ratio; DV, ductus venosus; MCA, middle cerebral artery; PI, pulsatility index; TAMV, time-averaged maximum velocity; UA, umbilical artery; UtA, mean uterine artery.

Table 3 Parameters of microcirculatory perfusion obtained by sidestream darkfield imaging for small (diameter< 20 μm) and non-small (diameter ≥ 20 μm) vessels in pregnant women with pre-eclampsia and hypertensive crisis, before and after administration of nicardipine

Maternal microcirculation	n	*Before nicardipine*	*After nicardipine*	*Median difference**	P
Perfused vessel density					
Small vessels (/mm)	7	9.9	9.1	−1.4 (−2.7 to 0.9)	0.578
Non-small vessels (/mm)	7	2.4	2.0	0.1 (0.0 to 0.8)	0.469
Microvascular flow index					
Small vessels	7	3.42	3.75	−0.02 (−0.25 to 0.17)	0.813
Non-small vessels	7	3.73	3.75	0.03 (−0.15 to 0.09)	1
Heterogeneity index					
Small vessels	7	0.59	0.27	0.00 (−0.02 to 0.72)	0.438
Non-small vessels	7	0.27	0.25	0.00 (−0.03 to 0.07)	0.688

Data are given as median or median (interquartile range). *Difference calculated as value before nicardipine minus value after nicardipine.

Nicardipine induced a significant afterload reduction (39%) and fall in blood pressure (19%) below targeted values in all women. It triggered a rise in heart rate (25%), which resulted in a significant increase in maternal CO (34%) in all but one woman, who experienced hypotension (Figure 1). She had tachycardia before administration of nicardipine (109 bpm). After the fluid challenge and continuation of nicardipine, the heart rate lowered but CO remained unchanged.

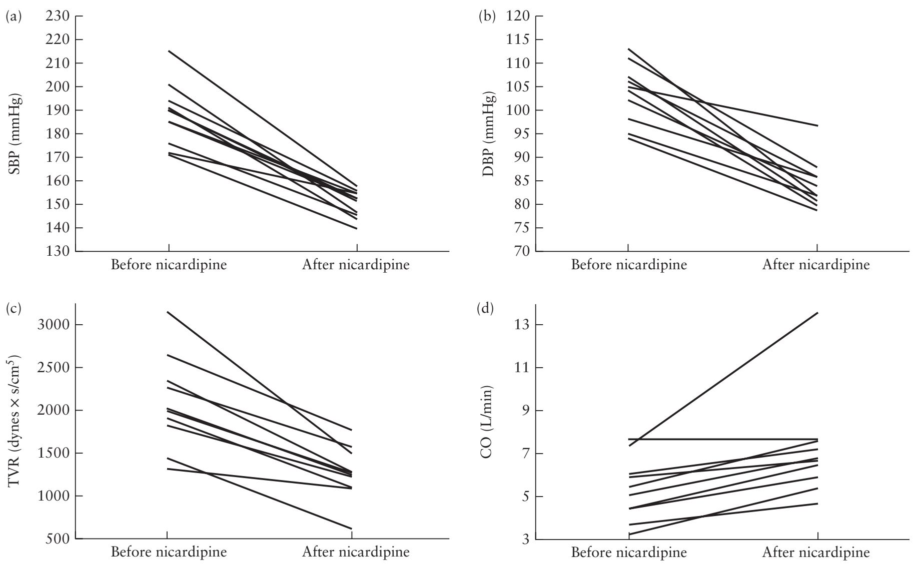

Figure 1 Evolution of: (a) systolic (SBP) and (b) diastolic (DBP) blood pressure, (c) total vascular resistance (TVR) and (d) cardiac output (CO), in 10 pregnant women with pre-eclampsia and hypertensive crisis, before and after stabilization of blood pressure with nicardipine.

There were no significant changes in other parameters of cardiac function, BNP, microcirculatory perfusion and uteroplacental or fetal Dopplers. The mean infusion rate and hemodynamic effects of nicardipine were similar in women with and without the concomitant use of oral nifedipine.

DISCUSSION

Our results indicate that intravenous nicardipine effectively lowers blood pressure through afterload reduction without compromising the maternal or fetal circulations in women with PE and a hypertensive crisis. The baroreceptor-mediated increase in heart rate induces a substantial rise in CO, which assures sufficient tissue perfusion. The uniformity and consistency of this hemodynamic effect in all included women is illustrated in Figure 1 and is remarkable, as previous studies have shown unpredictable hemodynamic responses once any form of treatment is initiated in women with PE[38].

The powerful reduction in peripheral resistance with enhancement of systolic function and preservation of diastolic function is in accordance with observations in animals and non-pregnant subjects. They are specific to nicardipine, as compared with other dihydropiridines[8-10,39]. The increase in CO most likely results from an increase in both heart rate and SV but the latter failed to reach statistical significance. It occurred despite the use of concomitant sympatholytic medication (central α-blockade or β-blockade) in 90% of women. This is comparable to previous studies showing that the combination of nicardipine with sympatholytic drugs (mostly β-blockers) resulted in increased antihypertensive and anti-ischemic potency, while each drug alleviated the negative hemodynamic properties of the other[9,39-43].

Nicardipine has been associated with pulmonary edema and acute cardiac failure in pregnant women[24,29,30]. None of the women in this study developed these complications. Women with PE are prone to developing pulmonary edema when capillary leak is combined with cardiac dysfunction resulting from severe hypertension[44]. The cardioprotective effect we observed in our PE women is therefore reassuring and seems specific to nicardipine as opposed to several other antihypertensive drugs[8].

The absence of uterine artery relaxation remains remarkable. Uterine artery resistance was increased in all women and one would then expect to see an increased sensitivity to a potent vasodilator. Vascular selectivity seems the most plausible explanation for this phenomenon. The reactivity of nicardipine is known to be less in femoral, renal and mesenteric arteries as compared to cerebral and coronary arteries, and could be equally so in uterine arteries[14]. The absence of fetal Doppler changes is also reassuring. It suggests that placental perfusion remains sufficient and transplacental passage is too small to induce fetal responses, even in more susceptible growth-restricted fetuses.

These findings are relevant as human data on uteroplacental and fetal perfusion after treatment of hypertensive crisis with nicardipine are lacking. However, the study design and sample size do not permit the dismissal of all possible fetal side-effects.

Despite the major macrocirculatory changes, we observed neither improvement nor worsening in microcirculatory perfusion. This discrepancy between central hemodynamics and microcirculation is well known from other disease states with hemodynamic imbalance[45,46]. On one hand it is reassuring to observe that microcirculation and end-organ perfusion seem to be maintained, despite a substantial afterload reduction. On the other, the increased output does not automatically imply increased capillary recruitment. The lack of changes might be attributed to the fact that baseline microcirculatory perfusion before nicardipine was relatively normal in our population. We demonstrated previously that sublingual microcirculatory perfusion is disturbed mainly in severe PE with concurrent HELLP syndrome[35]. Only four women in this study had an episode of HELLP syndrome at the time of the microcirculatory measurements. Therefore, vessel densities were within normal ranges with nearly maximal perfusion and normal-to-hyperdynamic flow. Only capillary flow heterogeneity was relatively high in some women, resulting in a high mean score. While the latter improved substantially (lowered), it failed to reach statistical significance. It is highly plausible that our sample size was too small to demonstrate significant changes.

This study highlights the importance and potential of ultrasound for cardiovascular profiling in the study of complex hemodynamic conditions like severe PE. By investigating different components of the cardiovascular system, thereby looking from different angles, one receives a far more accurate, balanced, detailed and complete overview of hemodynamic function of both mother and fetus. This global cardiovascular perspective can be achieved by adding a sector probe and software for transthoracic echocardiography to the readily available obstetric ultrasound devices. Despite our results, we believe that inclusion of microcirculatory assessment is also essential in this concept of cardiovascular profiling. It is the site at which oxygen and nutrient exchange, the ultimate goals of circulation, takes place and research has demonstrated the importance and potential of these parameters[47].

Besides effectively reducing perfusion pressure, nicardipine is known for its selectivity for cerebral and coronary vessels and potency to reduce cardiac and cerebral ischemia[48-50]. In future studies, the inclusion of cerebrovascular Doppler parameters and techniques that enable continuous monitoring should be considered.

Our study is limited by the relatively small number of patients and the concomitant use of other vasoactive medication. The hypertensive emergency warranted minimal treatment delay and immediate availability of the main investigator, which limited the inclusion population. The consistency, magnitude and level of significance of most primary outcomes make it unlikely that our conclusions would be challenged in a larger study population. Furthermore, our results are in accordance with the pharmacological profile of nicardipine in non-pregnant subjects. The study set-up was conceived to observe selectively the short-term effects of nicardipine. The heterogeneity in combination, dose and time since administration prevented detailed analysis of their individual influence of the concomitant medication. Four women were on nifedipine-regulated release tablets in doses of up to 90 mg a day before study inclusion. The efficacy and safety of intravenous nicardipine are remarkable in women who are already on oral nifedipine. This observation confirms our clinical experience and supports the distinctive pharmacological profile and potency of intravenous nicardipine.

Our findings indicate that nicardipine induces a predictive hemodynamic response in women with PE, characterized by an effective control of blood pressure through afterload reduction and increased ventricular performance, without compromising maternal or fetal circulation. Our observations offer theoretical support for the positive experiences seen in previous studies[18,20,23]. Finally, ultrasound can be used for fetomaternal cardiovascular profiling. This concept will become increasingly important for understanding the complex hemodynamic interactions in complicated pregnancies.

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Chapter 4.3

Microcirculation in women with severe pre-eclampsia and HELLP syndrome

a case–control study

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ABSTRACT

Objective To compare microcirculatory perfusion in women with severe pre-eclampsia against that in healthy pregnant women, and secondly in women with severe pre-eclampsia with or without HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets).
Design Case–control study.
Setting University Hospital Rotterdam, the Netherlands.
Population Twenty-three women with severe pre-eclampsia and 23 healthy pregnant controls, matched for maternal and gestational age. Out of the 23 women with severe pre-eclampsia, ten presented with HELLP syndrome.
Methods Microcirculation was analysed sublingually by a non-invasive sidestream dark-field imaging device (SDF).
Main outcome measures Perfused vessel density (PVD), micro-circulatory flow index (MFI), and heterogeneity index (HI) were calculated for both small vessels (∅ < 20 μm; capillaries) and non-small vessels (∅ > 20 μm; venules and arterioles).
Results There were no significant differences between women with severe pre-eclampsia and healthy controls. Women with pre-eclampsia and HELLP syndrome showed a reduced PVD (P = 0.045), MFI (P = 0.008), and increased HI (P = 0.002) for small vessels, as compared with women with pre-eclampsia but without HELLP syndrome.
Conclusions Sidestream dark-field is a novel, promising technique in obstetrics that permits the non-invasive evaluation of microcirculation. We did not observe major differences in sublingual microcirculatory perfusion between women with severe pre-eclampsia and healthy pregnant controls. In women with severe pre-eclampsia, the presence of HELLP syndrome is characterised by impaired capillary perfusion.

INTRODUCTION

The microcirculation is a vast network of small vessels with a diameter below 100 µm. It consists of arterioles that regulate flow to the capillaries, which subsequently drain in venules.[1] Exchange of oxygen and nutrients occurs at the level of the capillaries, which mainly consist of a thin layer of endothelium. With the availability of new imaging modalities, the importance of microcirculatory perfusion in the pathophysiology, prognosis, and treatment of conditions with profound haemodynamic imbalance, like sepsis, shock, and cardiac disease, is emerging. Parameters of microcirculatory perfusion seem independent of global haemodynamic status and appear to be strong predictors of outcome.[1-6] Sidestream dark-field (SDF) imaging is a novel technique enabling direct, non-invasive visualisation of microcirculatory perfusion at the bedside in adults, children, and newborns.[1-3] Severe pre-eclampsia is characterised by a maternal haemodynamic instability caused by generalised endothelial dysfunction.[7] Many of its symptoms and complications strongly suggest microcirculatory dysfunction. A recent study indicates that capillary rarefaction precedes the clinical onset of pre-eclampsia.[8] HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is considered an expression of disease severity.[9,10] Although its exact pathophysiology is not completely understood, the haemolysis, platelet consumption, and liver cell necrosis might reflect a more profound disturbance in microcirculatory function. Our aim was to explore the potential and reliability of SDF in pregnant women, and to analyse microcirculatory perfusion in women with severe pre-eclampsia as compared with that in healthy pregnant women. Secondly, we investigated the influence of HELLP syndrome on microcirculation in women with severe pre-eclampsia.

METHODS

Study setting

The study was conducted from November 2009 to September 2012 at the department of Obstetrics and Prenatal Medicine of the Erasmus Medical Centre of the University of Rotterdam. Twenty-three women with severe pre-eclampsia were included. In ten of these women, pre-eclampsia was complicated by HELLP syndrome. Four women with severe pre-eclampsia had a history of systemic lupus erythematosus or chronic hypertension. Twenty-three healthy pregnant women, matched for maternal and gestational age, were included as controls. Informed consent was obtained from all women and the study protocol was approved by the local medical ethical committee.

Severe pre-eclampsia was defined as pre-eclampsia (hypertension and significant proteinuria) with severe hypertension, and/or with symptoms, and/or with biochemical and/or haematological impairment.[11] HELLP syndrome was defined as the presence of at least two components of either haemolysis (lactate dehydrogenase, LDH ≥ 600 U/l), elevated liver enzymes (aspartate aminotransferase, AST ≥ 70 U/l), or thrombocytopenia (thrombocytes < 100 x 10^9/l).[10] All women with severe pre-eclampsia were categorised into severe pre-eclampsia either with or without HELLP syndrome according to previous definitions after expert agreement by three of the authors (J.C., E.H., and J.D.). Women with severe pre-eclampsia were managed according to our local protocol, as described in Appendix S1.

In women with severe pre-eclampsia we aimed to perform microcirculatory analysis at time points when disease activity was estimated to be maximal and when the interference from treatment was estimated to be as minimal as possible. Therefore, measurements were performed either before intravenous nicardipine, magnesium sulphate bolus, or when laboratory abnormalities consistent with HELLP syndrome occurred, irrespective of other concomitant medication. Age, parity, body mass index (BMI), gestational age, and medical history were obtained for all women.

All measurements were performed in a 15° left lateral tilt. Women were asked to refrain from eating or drinking for 30 minutes before measurements. Blood pressure was determined by manual sphygmomanometry. LDH, AST analysis, and thrombocyte count, as well as haematocrit and haemoglobin counts, were performed as part of the routine clinical procedure in women with severe pre-eclampsia on the day of the measurements.

Sidestream dark-field imaging

The sublingual microcirculation was visualized using SDF (Figure 1A).[12] This hand-held video microscope (MicroScan; MicroVision Medical, Amsterdam, the Netherlands) emits stroboscopic green light (530 nm) from an outer ring of light-emitting diodes (LEDs), which penetrates the tissue to a depth of approximately 3 mm. The light is absorbed by the haemoglobin of individual red blood cells in superficial vessels. A negative image is transmitted back, after 5x optical magnification, to an isolated synchronised charge-coupled device camera in the core of the probe. This allows high-contrast video images of circulating erythrocytes to be recorded with a 286x magnification from the microcirculation of organs covered with a thin epithelial layer. (Figure 1B, Video S1).[5] SDF imaging has been validated against and found to be superior to intravital videomicroscopy.[1,12]

The consensus recommendations on how to best obtain and evaluate SDF measurements were followed.[4,13] After obtaining good image focus and contrast, with specific attention paid to avoiding pressure artefacts by assuring continuous venous perfusion, one investigator (E.H.) recorded three high-quality video clips per measurement, with a duration of at least 20 seconds, each at a different sublingual site (using a high-definition videocassette recorder: GV-HD700; Sony Instruments, Tokyo, Japan).These were digital-

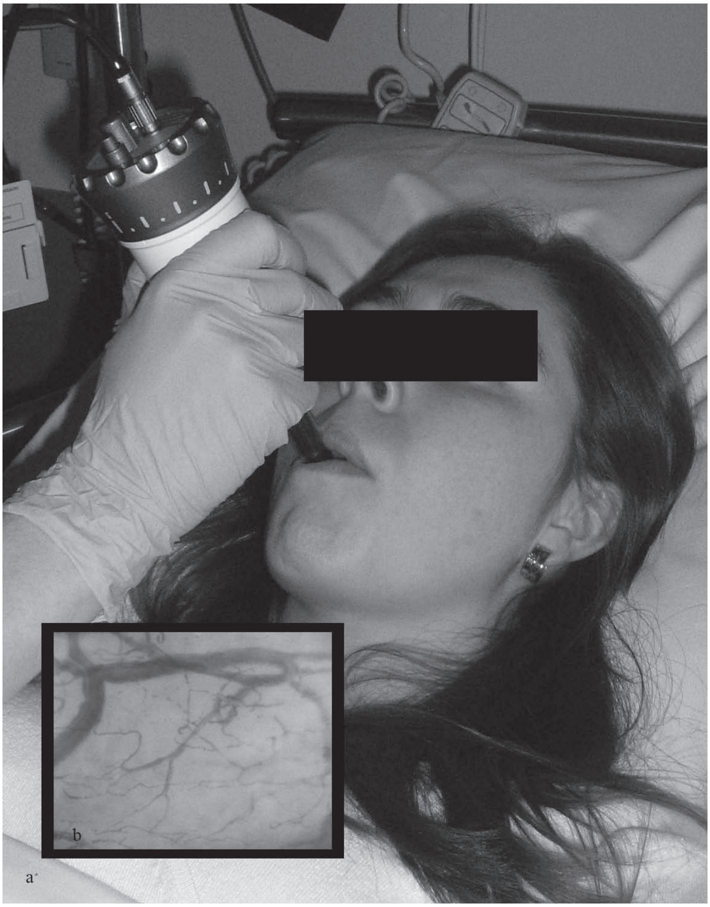

Figure 1 (a) Set-up for a sublingual microcirculatory perfusion measurement with SDF. A disposable sterile plastic cap covers the mouthpiece of the probe. (b) A frozen video-clip image of sublingual microcirculation as viewed with SDF.

ised, blinded, and stored on an external hard drive. After completion of the data set, E.H. performed analysis of the blinded recordings using AVA 3.0 (Automated Vascular Analysis, MicroVision Medical, Amsterdam, the Netherlands).

Inter-observer variability was assessed though separate analysis of the 45 recordings of 15 randomly selected cases by a different investigator (E.B.).

As described in the consensus recommendations, the perfused vessel density (PVD), microcirculatory flow index (MFI), and the heterogeneity index (HI) for MFI were calculated, each reflecting distinctive characteristics of microcirculatory perfusion.[4,13] Each parameter was determined separately for both small vessels ($\varnothing < 20$ µm, capillaries) and non-small vessels (20 µm $\leq \varnothing \leq$ 100 µm, mostly venules and arterioles).[13-15] A detailed description of these parameters and respective methods of calculation is available in Appendix S2.

Statistical analysis

Statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Variables were tested for normality and compared with the Students' t-test or non-parametric Mann–Whitney U-test, as appropriate. The effect of parameters with a known potential to influence haemodynamics (gestational age, use of oral antihypertensive medication), vascular structure (maternal age, BMI, race), or SDF measurements (haematocrit, haemoglobin) was assessed by analysis of covariance (ANCOVA) or by its non-parametric variant (the Quade test), as appropriate.[16-20] The adjusted P values, with $P \leq 0.05$ (two-sided) as the limit of significance, were used without correction for multiple comparisons.

Inter-observer reliability was assessed by calculation of the intraclass correlation coefficients from each parameter (PVD, MFI, and HI), separated for small- and non-small vessels in 15 cases. Inter-observer agreement for PVD was shown in Bland–Altman plots.

In the absence of SDF data on microcirculatory perfusion in pregnancy and severe pre-eclampsia, no power calculation was performed and this study was undertaken as an exploratory pilot.

RESULTS

Adequate recordings and measurements were obtained for all participants. Intraclass correlation coefficients were good for capillary measurements and were moderate for larger vessels (Table 1). Figure 2 shows the inter-observer agreement for PVD in small and non-small vessels. Twelve women with severe pre-eclampsia received concomitant oral antihypertensive medication. This included women with and without HELLP syndrome. All received methyldopa, nifedipine, or a combination of both. One woman received additional oral labetalol.

Table 1. Intraclass correlation coefficients (ICCs) and 95% CIs for inter-observer reliability

ICC (95% CI)	PVD	MFI	HI
Small vessels	0.87 (0.61–0.96)	0.94 (0.77–0.98)	0.96 (0.84–0.99)
Non-small vessels	0.66 (0.05–0.89)	0.88 (0.63–0.96)	0.73 (0.15–0.91)

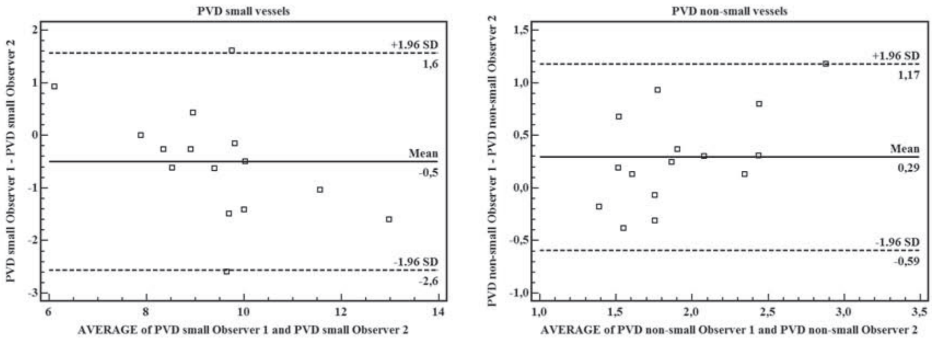

Figure 2 Bland–Altman plots showing interobserver agreement for PVD in small and non-small vessels.

The baseline characteristics of women with severe pre-eclampsia and healthy controls were similar (Table 2). As expected, blood pressure was significantly higher in women with severe pre-eclampsia. Pre-eclampsia was considered to be severe in all women either because of the severity of their hypertension (systolic blood pressure, SBP, ≥ 160 mmHg and/or diastolic blood pressure, DBP, ≥ 110 mmHg) or because of the presence of HELLP.

Table 2. Population characteristics

Characteristics	Women with severe pre-eclampsia (*n* = 23)	Controls (*n* = 23)	*P*
Severe pre-eclampsia versus control pregnancies			
Nulliparous	54.5%	45.5%	ns
Gestational age (weeks)*	33 (21–37)	33 (20–38)	nt
Age (years)	31 (±5)	31 (±5)	nt
BMI*	28 (20–56)	26 (18–41)	ns
Systolic blood pressure (mmHg)*	170 (130–2015)	110 (99–135)	<0.001
Diastolic blood pressure (mmHg)*	102 (76–115)	68 (50–90)	<0.001
Characteristics	**With HELLP (*n* = 10)**	**Without HELLP (*n* = 13)**	***P***
Severe pre-eclampsia with or without HELLP syndrome			
Nulliparous	50%	54%	ns
Gestational age (weeks)*	30 (21–37)	33 (25–37)	ns
Age (years)	31.1 (±3.9)	31.7 (±6.5)	ns
BMI*	26 (20–32)	30 (20–56)	ns
Systolic blood pressure (mmHg)	157 (±31)	174 (±20)	ns
Diastolic blood pressure (mmHg)	96 (±12)	102 (±7)	ns
Oral antihypertensive medication	40%	69%	ns
LDH (U/l)*	850 (602–2964)	426 (265–575)	<0.001
AST (U/l)*	221 (42–1593)	23 (14–52)	<0.001
Thrombocytes (10^9/l)*	99 (41–289)	250 (134–375)	<0.001

ns, not significant; nt, not tested (matching criterion).
Values are expressed as means ± standard deviations or medians with ranges according to normality.
***Non-parametric test** used.

We could not observe any significant differences in sublingual microcirculatory perfusion in women with severe pre-eclampsia, as compared with healthy controls (Figure 3A, B).

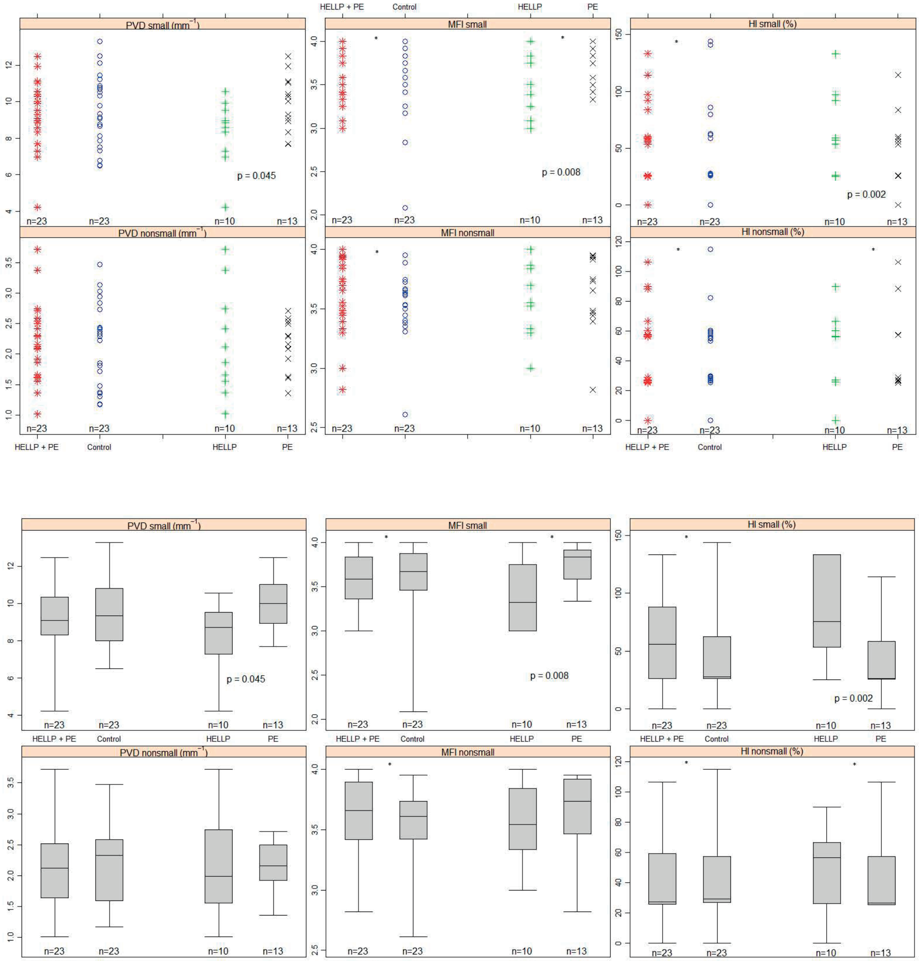

Figure 3 (A) Scatter plots depicting differences in perfused vessel density (PVD), microcirculatory flow index (MFI), and heterogeneity index (HI) for small and non-small vessels between women with severe pre-eclampsia and controls, as well as between women with severe pre-eclampsia with and without HELLP syndrome. *Non-parametric test used. Adjusted *P* values are depicted for comparisons with statistical significant difference; HELLP, severe pre-eclampsia with HELLP syndrome; PE, severe pre-eclampsia without HELLP syndrome. (B) Box plots depicting differences in PVD, MFI, and HI for small and non-small vessels between women with severe pre-eclampsia and controls, as well as between women with severe pre-eclampsia with and without HELLP syndrome. Boxes denote interquartile ranges, bars in boxes represent median values, and error bars represent ranges.

***Non-parametric test** used. Adjusted *P* values are depicted for comparisons with statistical significant difference; HELLP, severe pre-eclampsia with HELLP syndrome; PE, severe pre-eclampsia without HELLP syndrome.

Baseline characteristics between women with severe pre-eclampsia, with or without HELLP, were also comparable, except for the components of HELLP syndrome (Table 2).

Women with HELLP syndrome had significantly lower values of PVD and MFI and significantly higher values of HI for small vessels, as compared with women with severe pre-eclampsia without HELLP (Figure 3A, B). These differences remained significant after adjusting for haemoglobin count, haematocrit, BMI, medication use, pre-existent disease, maternal age, and gestational age.

DISCUSSION

Main findings

In this study we explored microcirculatory perfusion in women with severe pre-eclampsia with SDF, a novel technique in obstetrics.

Microcirculatory research has mainly been hampered by technological limitations. SDF allows the direct recording of high-contrast images and assessment of different aspects of microcirculatory perfusion. In our study, satisfactory images were obtained at the bedside and with minimal discomfort in all women. Inter-observer variability showed good reliability for capillary vessels, but is less evident in non-small vessels given the wide confidence intervals for PVD and HI, despite acceptable intraclass correlation coefficients. These findings are in line with previous results in non-pregnant populations.[4,15,21,22] Fortunately previous research and our results suggest that the capillary compartment is the main area of interest in microcirculatory perfusion. Therefore, SDF seems a preferred method for microcirculatory analysis in obstetrics.[1] Nevertheless, although image recording is relatively straightforwards, off- line analysis still requires substantial human input and remains time consuming. Developments in the most recent version of the SDF camera now permit automatic image analysis, which will further improve reliability, and holds promise for bedside recording and analysis in the future.

Despite the increased blood pressure we did not observe any difference in microcirculatory parameters in women with severe pre-eclampsia, as compared with healthy pregnant controls. Apparently, the major macrocirculatory disturbances of severe pre-eclampsia are not reflected in significant differences in sublingual microcirculatory perfusion. Interestingly, when comparing women with severe pre-eclampsia with or without HELLP syndrome, we observed significant differences in all aspects of capillary perfusion, with a decrease in PVD and MFI and an increased HI in women with HELLP syndrome.

Interpretation and relation to other studies

Previous microcirculation studies described a decreased venular diameter and increased postcapillary (venular) resistance in women with pre-eclampsia using intravital microscopy and plethysmography.[23,24] Although we did not specifically asses changes in vessel diameters and used different techniques in different organ systems, we did not observe major changes in large vessels, which mostly consist of venules and arterioles to a lesser extent. Hasan, using intravital capillaroscopy, reported a reduced capillary density in 11 women with pre-eclampsia, as compared with normal healthy pregnant and non-pregnant women.[25] Houben, using a similar set-up, could not confirm these findings, and Vollebregt, using orthogonal polarisation spectral imaging (OPS), did not find any changes in nail-fold capillary red blood cell velocity.[24,26] Neither did we observe any changes at a capillary level between women with severe pre-eclampsia and healthy pregnant women. This discrepancy may be explained by the use of medication in women with pre-eclampsia, as Hasan performed the measurements before any intervention. Most women in our, Vollebregt's, and Houben's studies had already received some form of antihypertensive therapy, magnesium sulphate, or steroids for fetal lung maturation. These drugs have the potential to infuence capillary perfusion.[27] In further studies, attempts should be made to perform measurements before any treatment; however, this remains difficult, as the maternal condition often does not permit treatment delay in severe pre-eclampsia.

The suggestion of impaired capillary perfusion in women with both pre-eclampsia and HELLP syndrome might explain some aspects of the pathophysiology of HELLP syndrome.[10] The reduced PVD and MFI might be a reflection of microvascular erythrocyte fragmentation and platelet adherence to the damaged endothelial surface in narrowed capillaries.[28] The increased heterogeneity could explain the diffuse pattern of liver cell necrosis in HELLP, where fibrin microthrombi and fibrinogen deposits are often observed both in intact hepatic sinusoids and in areas with hepatocellular necrosis upon histology.[9] Heterogeneity of flow is an important characteristic of impaired microcirculation.[1,4] With heterogeneous flow, a reduced number of capillaries are perfused. Cells close to the capillaries extract the normal quantity of oxygen, but cells too far away become hypoxic. Although the total oxygen delivery is the same, heterogeneous perfusion probably affects tissue oxygenation more than a reduced but homogenous flow.

Future research

Sublingual microcirculation is easily accessible for SDF. It is representative in sepsis, probably because of the embryological and metabolic similarities with the splanchnic mucosa.[1,4] Even so, pre-eclampsia is a complex syndrome that groups a broad clinical spectrum with variable degrees of organ dysfunction. It is therefore questionable whether the endothelial dysfunction is always manifested equally in all vascular beds.

Our results, both in women with and without HELLP, could be explained by the fact that the sublingual microcirculation may not be the most representative site in all pre-eclamptic women. SDF enables microvascular analysis in different areas (e.g. skin, conjunctiva, nail-fold, vagina, cervix, etc.). Further research in obstetrics should explore microcirculatory perfusion at various sites during the haemodynamic adaptation of normal pregnancy, and explore eventual representative areas in pathological conditions.

Besides facilitating (patho) physiological research in larger populations, future improved versions with rapid bedside analysis also offer perspectives for clinical implications. As in sepsis and cardiogenic shock, microcirculatory perfusion analysis has the potential to improve outcome prediction, and assist in the selection of candidates for expectant management or monitoring of medical treatment.[6,29]

Strengths and limitations

This is the largest population of women with pre-eclampsia investigated for microcirculatory changes in a prospective, case-controlled design. Our control group of 23 pregnant women is also one of the largest investigated populations of healthy subjects using SDF. The significant capillary differences in women with HELLP syndrome seem supported by a large effect size. Although it remains controversial whether this exploratory set-up allows for adjustment, significant differences remained, irrespective of adjustment for confounding factors. The absence of clinically relevant spread in the 95% confidence intervals of most parameters suggest that the size of our population was probably sufficient to exclude differences in sublingual microcirculation between healthy women and women with pre-eclampsia. Still, the populations remain small and this study should merely be viewed as an exploratory analysis. Our results certainly need further confirmation in a larger trial, separating women with and without HELLP syndrome, and preferably before any intervention.

CONCLUSION

Sidestream dark-field (SDF) imaging is a promising technique for the study of microcirculatory perfusion in obstetrics. Our study indicates that there are no major differences in sublingual microcirculatory perfusion between women with severe pre-eclampsia and healthy pregnant controls; however, HELLP syndrome is associated with an impairment of all aspects of capillary perfusion.

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SUPPORTING INFORMATION

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

S1. Video clip of sublingual microcirculation by SDF. The moving erythrocytes are clearly visible in both larger and smaller vessels.

Appendix S1. Description of the local clinical management protocol for severe pre-eclampsia.

Appendix S2. Description of microcirculatory perfusion parameters and respective methods of calculation.

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Author's reply re
Microcirculation in women with severe pre-eclampsia and HELLP syndrome
a case control study

J Cornette

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RESPONSE TO 2016-LT-17311

Dear Sir,

In their letter the authors describe a case of placental abruption with fetal demise in a women with severe pre-eclampsia and HELLP syndrome. Despite delivery and supportive treatment, she deteriorated over the following days with occurrence of kidney failure, eclamptic seizures and cardiac arrest, for which CPR was started. Spontaneous circulation was recovered but remained unstable, for which ECMO and hypothermia were initiated with short delays. While experience with extracorporeal cardiopulmonary resuscitation (E-CPR) in pregnancy is limited, evidence in the general population suggests its superiority over conventional CPR.[1] It is probably the prompt action of the team with rapid initiation of ECMO that contributed to the good maternal recovery. As timing is crucial in these circumstances and obstetricians are often first involved, knowledge about these evolutions in E-CPR will probably help in reducing ECMO initiation time, thereby improving outcome.

We also agree with the authors that this case strongly suggests microvascular dysfunction. It can occur independently from the apparent macrocirculatory hemodynamic instability. Yet, it is on this capillary level that the main goal of circulation, the exchange of O_2, nutrients and fluids, for CO_2, and waste products between blood and tissue cells takes place.

We and others have previously demonstrated microcirculatory perfusion problems in women with HELLP.[2,3] While more research is needed on the subject, microvascular assessment has the potential to assist in predicting prognosis and in guiding treatment.

In this case, the clinical condition deteriorated despite delivery and adequate supportive treatment. It highlights that in severe pre-eclampsia, our current management is in essence limited to damage control until the maternal condition spontaneously recovers after delivery. Hypertension control within the safe zone merely prevents cerebrovascular incidents and magnesium sulphate is mainly for seizure prophylaxis. None of these actions substantially improves the pre-eclamptic condition. While intravascular volume depletion is prominent, fluid management remains a controversial issue, given the capillary leak and risk of iatrogenic pulmonary oedema. In the future, assessment of functional microcirculatory haemodynamics with small handheld cameras, might assist in optimising fluid therapy.[4] The main two mechanisms behind oxygen delivery from red blood cells (RBC) to tissues are convection and diffusion. The former depends on RBC velocity, O_2 saturation and O_2 carrying capacity. The latter is mainly dependent on the O_2 gradient and is inversely proportional to the distance between tissues and RBC. Although crystalloids have little inherent capacities to improve O_2 delivery, administration can increase RBC velocity, thereby improving convection and, by opening previously closed capillaries, reducing distance and improving passive interstitial oedema again increases the distance.

Microvascular imaging could assist in achieving optimal convection and diffusion by measuring parameters of RBC velocity and perfused capillary density. While this concept seems promising, it remains experimental at this moment. Extensive research is still needed before its clinical value and benefice can be truly be evaluated in women with severe pre-eclampsia.

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Chapter 5.1

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.

INTRODUCTION

Epidemiology

In the developed world many women with congenital heart disease are reaching child-bearing 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, peripartum 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. Fig. 1 shows the hemodynamic changes. However, some structural changes might never completely be reversed.

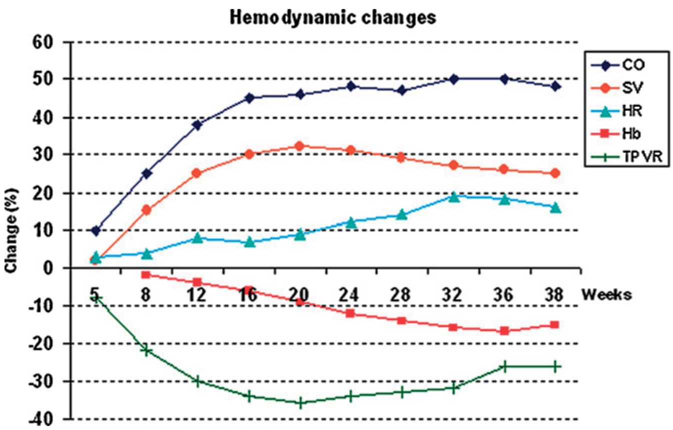

Figure 1 Hemodynamic changes in pregnancy. CO, cardiac output; SV, stroke volume; HR, heart rate; Hb, hemoglobin; TPVR, total peripheral vascular resistance.

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 [7-9].

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.

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

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].

Complications during pregnancy

The type of complication depends on the specific cardiac pathology (Table 2). 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].

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
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)

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 1 shows the safety profile of commonly used cardiovascular drugs during pregnancy.

Interventional treatment: An 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 50–100 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 14-33% 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].

MANAGEMENT OF 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 h 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 5.2

Pregnancy outcomes in women with aortic valve substitutes

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ABSTRACT

Young women who require aortic valve replacement (AVR) need information on the potential cardiac and obstetric complications of pregnancy for the different available valve substitutes. We therefore assessed pregnancy outcome in women who received an autograft, homograft, or mechanical valve in the aortic position. Women who were pregnant after surviving AVR in our institution between 1987 and 2011 were included. Information on cardiac status and pregnancy outcome was obtained through hospital medical records and by means of an extensive patient questionnaire. Forty women experienced 67 pregnancies of which 55 (82%) completed pregnancies, 6 (9%) miscarriages, and 6 (9%) terminations of pregnancy. Eighteen (45%) women had a pulmonary autograft, 13 (32%) a homograft, and 9 (23%) a mechanical valve. Mean age at first pregnancy was 30.0 ± 5.7 years. There was no maternal mortality, but 1 fetal death (1.8%) and 1 neonatal death (1.8%) occurred. Maternal cardiac complications occurred in 13% and obstetric complications in 38% of the completed pregnancies. Heart failure (9%), arrhythmias (7%), hypertension-related disorders (7%), preterm delivery (24%), and small for gestational age infants (15%) were most often encountered. Mechanical valve recipients had the highest incidence of both cardiac and obstetric complications. In conclusion, pregnancy-associated complications after AVR were common and human tissue valves should be considered in the discussion for the optimal aortic valve substitute in a young female. However, careful obstetric monitoring is mandatory.

When a young woman requires aortic valve replacement (AVR), it is important to incorporate reliable information on potential pregnancy complications and pregnancy outcome when considering the available surgical options. In mechanical valve recipients, complications due to anticoagulation therapy represent a threat for both mother and her unborn child.[1-3] Accelerated valve dysfunction due to degeneration may be a point of concern in biological valve substitutes although more recent studies report that pregnancy does not increase structural deterioration or reduce survival.[4-6] There is limited evidence available on the rate of cardiac and obstetric complications in young women who become pregnant after AVR. Most available information concerns mechanical –mainly mitral- valve recipients and shows increased risks of anticoagulation-related complications and increased maternal and fetal mortality and morbidity.[1, 2, 5, 7-10] Also for human tissue valve recipients, reports on pregnancy related outcomes are scarce.[5, 10-12] In this perspective, the aim of the present study was to determine the occurrence of cardiac and obstetric complications in women who experienced a pregnancy after implantation of an autograft, homograft, or mechanical valve in the aortic position in our institution.

METHODS

Women who were pregnant after surviving an AVR with a pulmonary autograft, a homograft, or a mechanical valve prosthesis in the Erasmus University Medical Center, were aged 50 years or younger at time of surgery, were operated between April 1987 and January 2011, and were at least 16 years at the last clinical follow-up, were invited to participate. The study protocol was approved by the Institutional Review Board (MEC 2010-272) and informed consent was obtained. All patients who receive a human tissue valve substitute in our institution are followed prospectively (MEC 2000-813). Eligible patients were identified through our prospective cohort study of human tissue valve recipients and through our departmental patient information system.[13, 14]

Information on pregnancy and cardiac status of the patients until January 1st, 2011 was obtained through hospital medical records and structured patient questionnaire that was conducted between December 1st 2010 and September 1st, 2011. We collected data on underlying valve etiology at last surgery, hemodynamic diagnosis, previous surgical/interventional procedures, age at surgery, type (and size) of aortic valve substitute, concomitant procedures, time from surgery to first pregnancy, age at conception, and preconceptional systolic left ventricular function (LVF), maximum aortic jet velocity (Vmax), and peak pulmonary artery pressure (PAP).

Pregnancy was defined as positive HCG test or obstetric ultrasound. Miscarriage was defined as spontaneous loss of pregnancy <20 weeks of gestation. Information about each completed pregnancy (duration >20 weeks of gestation) included: New York Heart Association (NYHA) functional class, medication, physical examination, pregnancy duration, mode of delivery. For each baby, gender, birth weight, and APGAR score was registered.

Registered cardiac complications were: arrhythmia (symptomatic sustained documented arrhythmia), heart failure (requiring treatment), persistent NYHA functional class deterioration (≥1 year postpartum), syncope, thrombo-embolic complications, aortic dissection, and/or endocarditis. Obstetric complications included: pregnancy-induced hypertension (PIH; de novo onset of hypertension after ≥20 weeks of gestation), preeclampsia (hypertension and proteinuria), eclampsia (preeclampsia with grand mal seizures), Hemolysis Elevated Liver Enzymes Low Platelets (HELLP) syndrome, preterm premature rupture of membranes (membrane rupture <37 weeks gestation), premature labor (spontaneous onset of labor <37 weeks gestation), postpartum hemorrhage (>1000 ml), placental abruption, premature delivery (<37 weeks of gestation), small-for-gestational-age (birth weight <10th percentile), fetal death (≥20 weeks of gestation), and neonatal death (<30 days postpartum).[15] The incidence of complications and mode of delivery in this study was compared to data derived from the 2008 Dutch Perinatal Registry. In this registry, maternal and fetal data of all deliveries occurring in the Netherlands are recorded (about 180,000; 96% complete). It included both home as well as hospital deliveries and contained information on the presence of cardiovascular disease in the mother (no further specification) and neonatal congenital defects (cardiac 0.41%; non-cardiac 2.38%).[16]

Anticoagulation therapy administered in our institution to mechanical valve recipients was according to our local protocol and initiated in close collaboration with the hematologist.[17] As soon as pregnancy was confirmed, acenocoumarol was changed to a weight adjusted therapeutic dose of low molecular weight heparin (LMWH) until the end of the first trimester and when necessary monitored with anti-Xa levels. Acenocoumarol was then restarted until 36 weeks of gestation. Hereafter a therapeutic dose of LMWH was given until spontaneous onset of labor or the day before induction of labor or elective cesarean section. After delivery, LMWH was initiated again, along with acenocoumarol until 2 consecutive appropriate INR levels were reached.

Normality of the distribution of continuous data was tested with the Kolmogorov-Smirnov test with Lilliefors correction. Continuous data are displayed as means with standard deviations or in case of a skewed distribution, as medians with interquartile ranges and were compared using the one-way analysis of variance test or the Kruskal-Wallis test. Discrete data are presented as absolute numbers and percentages and compared using the Pearson's Chi-Square test or Fisher's exact test.

Univariable logistic regression analysis was performed to identify possible factors associated with the incidence of pregnancy-related complications. Missing values were imputed by the mean. Age at surgery, maternal age at first pregnancy, valve type, time from surgery until first pregnancy, duration of pregnancy, caesarean section, preconceptional LVF, Vmax, and PAP were considered as co-variables in the univariable model for cardiac and obstetric events. For comparison of the event incidence with the general Dutch population the Chi squared test was used. All statistical tests were two-sided and a p-value ≤ 0.05 was considered significant. For data analysis SPSS 17.0 for Windows (SPSS, Chicago, Illinois) was used.

RESULTS

Forty patients experienced at least 1 pregnancy after AVR in our institution (Table 1). There were 67 singleton pregnancies in these 40 women. Fifty-five pregnancies continued beyond 20 weeks (47% males) in 35 women. All 6 spontaneous miscarriages were <14 weeks of gestation. Six pregnancies were terminated (Table 1). The only termination of pregnancy for maternal cardiac reason was performed in a mechanical valve recipient with pulmonary hypertension, tricuspid insufficiency, and moderate stenosis of the mechanical prosthesis in aortic position of 3.3 m/s. One termination was performed in a fetus with spina bifida. There were no acenocoumarol associated embryopathies. Table 2 displays the mode of delivery for the 55 completed pregnancies differentiated by type of valve substitute; Figure 1 illustrates the modes of delivery in comparison to the Dutch general population. There was no maternal mortality.

Heart failure was the most common cardiac complication with a persistent NYHA deterioration in 3 patients (Table 3). One mechanical valve recipient with permanent atrial fibrillation developed prosthetic valve thrombosis and subsequent heart failure at 33 weeks gestation. Anticoagulation was converted to intravenous heparin and the woman underwent a caesarean section at 36 weeks. A girl of 2,150 g was born. Five weeks later she underwent a re-AVR with another mechanical valve.

The most common obstetric complications concerned hypertension-related disorders, preterm delivery, and small-for-gestational-age infants (Table 3; Figure 2). Five of the 13 pregnancies which ended prematurely were induced before 37 weeks for cardiac indication: congestive heart failure in 2 patients (1 mechanical valve prosthesis; 1 pulmonary autograft), prosthetic valve thrombosis (mechanical valve prosthesis), Marfan syndrome (homograft), and dilated aortic root with aortic and pulmonary regurgitation (pulmonary autograft).

There was 1 fetal death in a mechanical valve recipient at 20 weeks and 4 days which presented with absent heart rate, growth restriction, and fetal hydrops on ultrasound. A macerated male infant (190 gram) with a placenta of 30 gram was born. Fetal autopsy

Table 1 Patient characteristics

Variable	All (n = 40)	Autograft (n = 18)	Homograft (n = 13)	MP (n = 9)	p Value
Intervention or surgery before aortic valve replacement					
0	23 (58%)	10 (56%)	9 (69%)	4 (44%)	0.46
1	8 (20%)	2 (11%)	4 (31%)	2 (22%)	0.46
>1	9 (23%)	6 (33%)	0	3 (33%)	0.07
Diagnosis					
Aortic stenosis	15 (38%)	10 (56%)	4 (31%)	0	0.02
Aortic regurgitation	13 (33%)	3 (17%)	6 (46%)	5 (55%)	0.10
Mixed	12 (30%)	5 (28%)	3 (23%)	4 (44%)	0.61
Etiology					
Congenital	26 (65%)	16 (89%)	8 (62%)	2 (22%)	<0.01
Rheumatic	12 (30%)	2 (11%)	4 (31%)	6 (67%)	0.01
Aneurysm or dissection	2 (5%)	0	1 (8%)	1 (11%)	0.49
Age at last surgery (yrs)	25.4 ± 7.7	21.5 ± 6.6	26.9 ± 5.0	31.2 ± 9.0	<0.01
Concomitant procedures					
None	28 (70%)	16 (89%)	8 (62%)	4 (44%)	0.04
Coronary bypass	3 (8%)	1 (6%)	0	2 (22%)	0.23
Mitral valve surgery	6 (15%)	0	3 (23%)	3 (33%)	0.04
Prosthesis size (mm)	—	—	22 (21−22)	21 (21−23)	
Interval from surgery to first pregnancy (yrs)*	3.1 (1.6−6.1)	5.5 (1.8−9.4)	2.3 (1.4−4.6)	2.1 (1.5−4.6)	0.14
Total pregnancies	67	33	22	12	0.39
1	40 (60%)	18 (55%)	13 (59%)	9 (75%)	0.46
2	20 (30%)	11 (33%)	6 (27%)	3 (25%)	0.83
3	7 (10%)	4 (12%)	3 (14%)	0	0.46
Pregnancy age (yrs)*					
First (n = 40)	30.0 ± 5.7	27.0 ± 4.1	30.2 ± 4.6	35.7 ± 5.9	<0.01
Second (n = 20)	30.9 ± 4.7	30.0 ± 3.9	31.9 ± 5.0	32.1 ± 8.0	0.75
Third (n = 7)	32.1 ± 5.5	32.7 ± 7.0	31.3 ± 4.0	—	0.86
Preconceptional left ventricular function (n = 66)					
Good	64%	61%	77%	50%	0.18
Moderate	36%	39%	23%	50%	0.18
Preconceptional pulmonary artery pressure (mm Hg) (n = 62)	6 (3−15)	13 (9−18)	3 (2−3)	4 (1−11)	<0.01
Preconceptional maximum aortic jet velocity (m/s)*					
First pregnancy (n = 38)	1.78 ± 0.69	1.36 ± 0.42	1.85 ± 0.60	2.60 ± 0.55	<0.01
Second pregnancy (n = 19)	1.70 ± 0.54	1.41 ± 0.46	2.01 ± 0.36	2.23 ± 0.38	0.01
Third pregnancy (n = 7)	1.83 ± 0.80	1.41 ± 0.48	2.39 ± 0.87	—	0.23
Completed pregnancies	55 (82%)	28 (85%)	20 (91%)	7 (58%)	0.05
Miscarriage	6 (9%)	3 (9%)	0	3 (25%)	0.05
Pregnancy terminated	6 (9%)	2 (6%)	2 (9%)	2 (17%)	0.64
Social reasons	4 (6%)	2 (6%)	2 (9%)	0	0.70
Maternal cardiac indication	1 (1%)	0	0	1 (17%)	0.18
Fetal spina bifida	1 (1%)	0	0	1 (8%)	0.18

Data are presented as n (%), mean ± SD (continuous variables), or median (interquartile range; continuous variables).

MP = mechanical aortic valve prosthesis.

*** All** 67 pregnancies, including miscarriages and terminations.

Table 2 Mode of delivery for 55 completed pregnancies in 35 women

Variable	All (n = 55)	Autograft (n = 28)	Homograft (n = 20)	MP (n = 7)	p Value
Vaginal delivery*	42 (76%)	19 (68%)	17 (85%)	6 (86%)	0.32
Spontaneous	11 (20%)	3 (11%)	5 (25%)	3 (43%)	0.25
Assisted delivery	13 (24%)	7 (25%)	5 (25%)	1 (14%)	0.67
Epidural anesthesia	11 (20%)	4 (14%)	5 (25%)	2 (29%)	0.80
Induction of labor	20 (36%)	11 (39%)	7 (35%)	2 (29%)	0.53
Elective cesarean section	8 (15%)	5 (18%)	2 (10%)	1 (14%)	0.89
Maternal cardiovascular risk	5 (9%)	3 (11%)	2 (10%)	0	0.72
Prosthetic valve thrombosis	1 (2%)	0	0	1 (14%)	0.13
Fetal presentation	1 (2%)	1 (4%)	0	0	1.00
Fetopelvic disproportion	1 (2%)	1 (4%)	0	0	1.00
Emergency cesarean section	5 (9%)	4 (14%)	1 (5%)	0	0.42
Fetal distress†	2 (4%)	1 (4%)	1 (5%)	0	1.00
Placental abruption	1 (2%)	1 (4%)	0	0	1.00
Fetopelvic disproportion	2 (4%)	2 (7%)	0	0	0.62

Data are presented as n (%).

*** Overlapping** categories.

† Deceleration on cardiotocography.

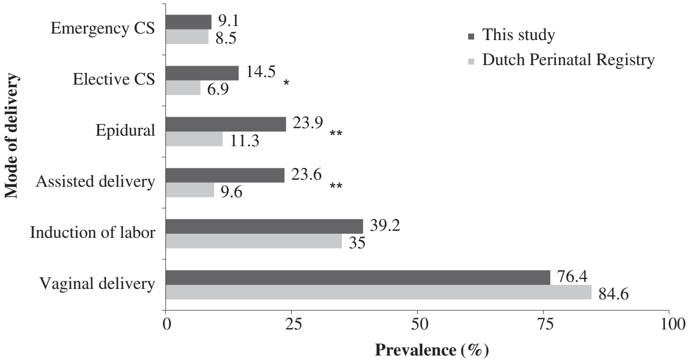

Figure 1 *Mode of delivery of 55 completed pregnancies compared to Dutch Perinatal Registry. CS = cesarean section.*

Table 3 Outcome of 55 completed pregnancies in 35 women

Variable	All (n = 55)	Autograft (n = 28)	Homograft (n = 20)	MP (n = 7)	p Value
Pregnancy duration (weeks)	38 (36−40)	38 (35−40)	39 (38−40)	36 (31−39)	0.20
Birth weight (kg) (n = 54)	3.0 (2.5−3.3)	3.0 (2.4−3.3)	3.1 (2.9−3.3)	2.7 (1.9−3.0)	0.11
Birth weight percentile (n = 54)*	31 (14−54)	30 (11−54)	34 (21−54)	16 (11−80)	0.47
APGAR score ≥8 at 5 minutes	94%	96%	95%	86%	0.55
Cardiac complications†	7 (13%)	4 (14%)	1 (5%)	2 (29%)	0.21
Heart failure	5 (9%)	2 (7%)	1 (5%)	2 (29%)	0.20
Supraventricular arrhythmia	4 (7%)	1 (4%)	1 (5%)	2 (29%)	0.09
Persistent New York Heart Association deterioration	3 (5%)	1 (4%)	1 (5%)	1 (14%)	0.71
Valve thrombosis	1 (2%)	0	0	1 (14%)	0.13
Obstetric complications†	21 (38%)	11 (39%)	6 (30%)	4 (57%)	0.50
Hypertension-related disorders	4 (7%)	0	4 (20%)	0	0.02
Pregnancy-induced hypertension	2 (4%)	0	2 (10%)	0	0.14
Preeclampsia	2 (4%)	0	2 (10%)	0	0.14
Premature labor	4 (7%)	3 (11%)	0	1 (14%)	0.33
Preterm premature rupture of membranes	3 (5%)	3 (11%)	0	0	0.26
Placental abruption	1 (2%)	1 (4%)	0	0	1.00
Preterm delivery	13 (24%)	8 (29%)	2 (10%)	3 (43%)	0.14
Spontaneous	5 (9%)	4 (14%)	0	1 (14%)	0.24
Cardiac maternal indication	5 (9%)	2 (7%)	1 (5%)	2 (29%)	0.20
Obstetric indication	3 (5%)	2 (7%)	1 (5%)	0	1.00
Small-for-gestational age	8 (15%)	5 (18%)	3 (15%)	0	0.67
Fetal death	1 (2%)	0	0	1 (14%)	0.13
Postpartum hemorrhage	2 (4%)	2 (7%)	0	0	0.36
Postpartum blood loss (ml)	300 (200−425)	300 (200−650)	350 (300−400)	200 (200−500)	0.48
Neonatal death	1 (2%)	1 (4%)	0	0	1.00

Data are presented as number of pregnancies (%) or median (interquartile range; continuous variables).
*** Adjusted** for gestational age, fetal gender, and parity.
† Overlapping categories.

was declined by the parents. Placental pathology showed severe placental insufficiency. One postnatal death occurred in a pulmonary autograft recipient who was on oral anticoagulation therapy because of a protein C deficiency and prior deep venous thrombosis. At 19 weeks, she had preterm premature rupture of membranes and fetal growth restriction. Despite the poor prognosis the woman opted for expectant management. At 30 weeks, she spontaneously delivered a 600 g boy who died on the first postnatal day due to lung hypoplasia.

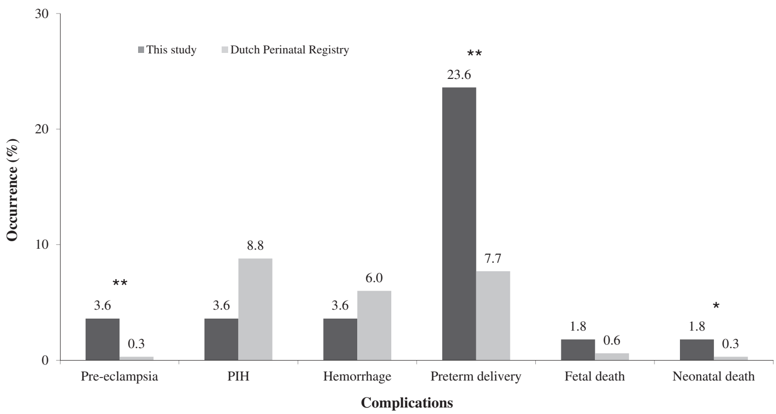

Figure 2 Incidence of obstetric and perinatal complications of 55 completed pregnancies compared to Dutch Perinatal Registry.16 PIH = pregnancy-induced hypertension.

No potential predictors of cardiac complications could be identified. Obstetric complications were more common in patients with cardiac complications during pregnancy (OR 13.2; 95% CI 1.5-119.5; p=0.02). There was no correlation between preconceptional Vmax over the aortic valve and birth weight (r -0.01; p=0.95).

Two women with a completed pregnancy were not treated according to the current ESC guidelines for the use of anticoagulation in pregnant mechanical valve patients.[17] One patient received an insufficient dose of oral anticoagulation therapy and developed a prosthetic valve thrombosis. The other patient was treated with a combination of acenocoumarol and LMWH until a healthy girl was born by spontaneous vaginal delivery at 40 weeks.

DISCUSSION

Pregnancy in patients after AVR with a human tissue valve or a mechanical valve substitute was associated with serious maternal cardiac and obstetric complications in half of the patients in our study. However, all patients survived pregnancy. Human tissue valve recipients had a lower incidence of cardiac maternal and obstetric complications than patients with mechanical valve prostheses. Mechanical valve recipients were at risk for miscarriage, supraventricular arrhythmias, heart failure, and preterm delivery.

Pregnancy elicits major hemodynamic changes.[18, 19] In addition, pregnancy induces alterations in the maternal coagulation cascade which makes it difficult to provide sufficient anticoagulation therapy in mechanical valve recipients and is therefore associated with maternal morbidity and mortality.[1, 9, 10] However, more intensive anticoagulation may lead to hemorrhage. A recent review of maternal mortality considers care as sub-optimal when there has been inappropriate management of anticoagulation, which can contribute to maternal cardiac death.[20] A Danish cohort study describes 2 maternal deaths in 107 mechanical valve recipients of which 1 was anticoagulation related.[1] The mechanical valve patient in our cohort who developed a prosthetic valve thrombosis failed to comply with het anticoagulation therapy leading to inadequate anticoagulation. While appropriate dosing of oral anticoagulation can be challenging in pregnancy, patient compliance has also to be taken into account.

Another important cardiac complication in our study population was symptomatic heart failure during pregnancy which occurred in 5 patients, of whom 3 experienced a persistent New York Heart Association (NYHA) deterioration after 1 year. Heart failure is described as a serious complication in pregnant patients who underwent prior valve replacement.[1, 21-23] It has been the cause of maternal death,[1] but also an indication for termination of pregnancy.[22] Two of the 5 patients with heart failure in our study were advised against pregnancy prior to conception; both had persistent NYHA deterioration after pregnancy. Although preconceptional counseling has the intention to reduce the risk on severe maternal cardiac events during pregnancy, it is the patient and her family who finally decides to pursue or decline a pregnancy based on the informed wishes and expectations.

In the present study, hypertensive related disorders occurred significantly more often in homograft recipients. Of the reports on pregnancy outcomes in homograft patients,[2, 10, 21, 24, 25] only 1 study describes a case of pre-eclampsia.[24] The aortic gradient increases significantly in homograft patients during pregnancy, but this is also seen in mechanical valve recipients,[21] and probably reflects the increased cardiac output (increased stroke volume) and decrease in systemic vascular resistance. Unfortunately, we could not identify a specific reason for the increase in hypertensive related disorders among homograft patients.

Almost all newborns of mechanical recipients were vaginally delivered without excessive maternal hemorrhage during labor or caesarean section (Figure 2). The Danish cohort on the other hand reports a postpartum bleeding incidence of 12% and reported 1 fatal bleeding.[1] This underlines the importance of careful anticoagulation monitoring during delivery. Our study illustrates that through careful anticoagulation monitoring during delivery it is possible for mechanical valve recipients to deliver a baby without extensive bleeding.

There was 1 fetal death and 1 postnatal death, both in patients on oral anticoagulation therapy. Although the risks appears to be decreasing in the last few decades, mechanical valve recipients still have up to 9% fetal death risk.[1, 9, 26] Perinatal death risk is reported to be up to 6% in mechanical valve recipients,[9, 26, 27] and up to 8% in the mostly small cohorts of human tissue valve recipients.[10-12, 21, 24, 25] Dore and Somerville report 1 perinatal death among 14 pregnancies in pulmonary autograft patients, although not directly related to cardiac reasons.[11]

Preterm delivery occurred more often (24%) in our study population as compared to the general Dutch population, especially in mechanical valve recipients. This high rate of preterm delivery was also found in the Danish cohort which found a rate of 49%.[1] Of the 13 cases of preterm delivery in the current study, 8 were induced on medical indication of which 5 due to cardiac reasons. As preterm delivery is the leading cause of infant mortality and morbidity, it is crucial to understand which risk factors are associated with preterm delivery.[28] Maybe the treating physicians are too cautious with this particular patient group and therefore it is mainly a doctors decision' to intervene earlier as compared to the normal Dutch population. Perhaps with good advice how to guide the anticoagulant management during delivery (new ESC guidelines) and some reinsurance, based on our findings, less preterm deliveries could be reached.

The counseling of young female patients who require AVR and may contemplate pregnancy, requires a multidisciplinary discussion including several important issues. These patients should be individually informed about the (dis)advantages of the different available valve substitutes and corresponding potential pregnancy-associated maternal and fetal complications.[3] The high incidence of preterm delivery and valve thrombosis in mechanical valve recipients illustrates that these valves are far from ideal in patients during pregnancy. On the other hand, the curious finding of a high incidence of hypertension related disorders in homograft recipients calls for further studies and indeed careful monitoring of the last stage of pregnancy in this patient group. Although human tissue valves needs careful obstetric monitoring, they provide female patients a biological solution that eliminates the daily burden of anticoagulation, in particular during pregnancy, and their durability is not influenced by pregnancy.[29] Therefore, human tissue valves should be considered as aortic valve substitute of choice in young patients with severe aortic valve disease who are planning to start a family.

Just as with most studies on this topic, patient numbers in the present study are relatively small and treatment took place in a tertiary hospital, necessitating careful interpretation of the results.

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Chapter 5.3

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.

1. 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.

2. 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.

2.1. 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 [20].

Birthweight centiles, corrected for gestational age, maternal race, parity and fetal sex were derived from the Dutch national reference curves [21]. 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) [22].

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.

2.1.1. 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 [23].

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 [24]. Left ventricular mass (LVmass) was calculated using the Devereux formula [25]. 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.

2.2. 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 [26]. 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 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) [27]. 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.

3. 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.

Fig. 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

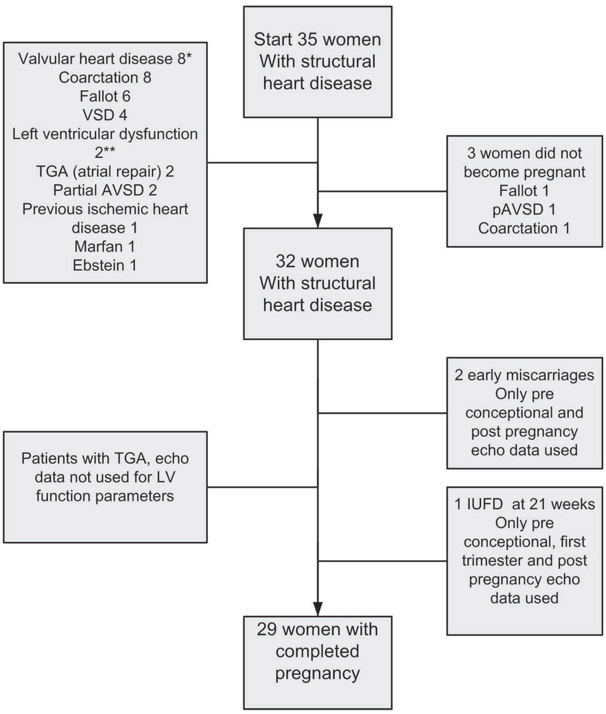

Figure 1 Organogram of the study population with details on cardiac diagnosis. * Five women with mechanical aortic and/or mitral valve. ** One woman after previous chemotherapy and one woman with a dilated cardiomyopathy.

the 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

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 (2×), St Judes MVR//TV plasty (2×)	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 44 mm	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 (2×), balloon dilatation recoarctation	Mild rest coarct, mild PS, no HT	2
VSD, subvalvular aortic membrane	Closure VSD (2×), 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
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 2×//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 (2×), VSD (2×), MV plasty (2×) 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

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 Fig. 2 and 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.

Table 2 Details of maternal and obstetric complications and outcomes.

Complications	N	%	WHO 1–2 (n)	WHO 3–4 (n)	Remarks
Cardiac			21	11	
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	
Cesarean 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	$34^{3/7}$	$41^{6/7}$
Birthweight (g)	3156	587	3319	2792	3255	1810	4100
Apgar 5 minute	9	1	9.40	9.56	10	8*	10

* **Excluding** the intrauterine death at 21 weeks.

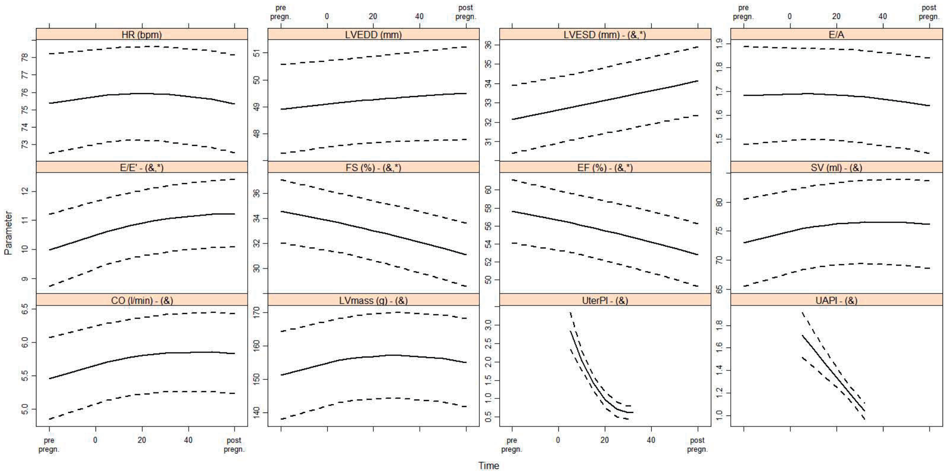

Figure 2 Fitted longitudinal profiles of each parameters for the whole population. The dashed lines denote 95% point-wise confidence intervals. The symbol '&' denotes parameters for which there was a significant time effect, and the symbol '*' parameters for which there was a significant difference between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

Table 3 Estimated regression coefficients per parameter 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

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 Fig. 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 Fig. 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.

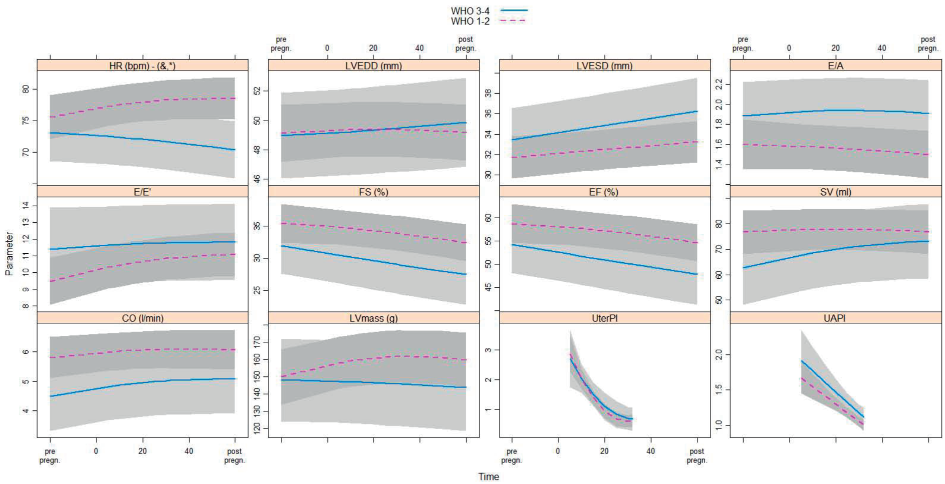

Figure 3 Fitted longitudinal profiles for each parameter divided according to the severity of the cardiac condition. The dark gray area surrounding the dashed red line and lighter gray area surrounding the full blue line denote the 95% pointwise confidence intervals for the WHO1–2 group and WHO3–4 group 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.

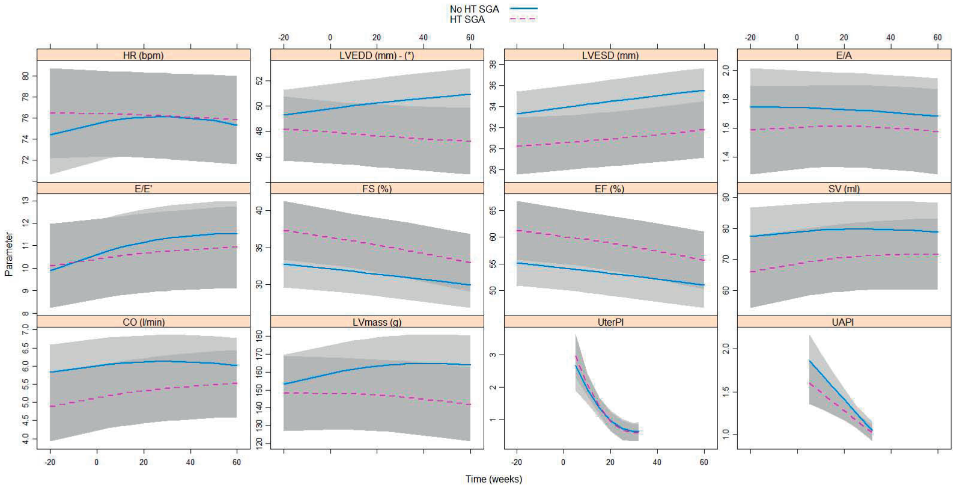

Figure 4 Fitted longitudinal profiles for each parameter divided according to the occurrence of hypertension and/or small for gestational age fetus. The dark gray area surrounding the dashed red line and lighter gray area surrounding the full blue line denote the 95% pointwise confidence intervals for 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.

4. 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 [10,11,13-15,28].

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 [13,17,29]. 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 [11,30].

When assessing the influence of severity of cardiac disease on cardiac adaptation we observed a similar pattern between WHO1–2 and WHO3–4 groups. While the trend seems visually more pronounced for the severe group (WHO 3–4) in Fig. 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 adaptive potential in high risk groups (Fig. 3) and thus requires further investigation in a larger population.

A similar effect is observed for the influence of HT/SGA in Fig. 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 [31,32]. 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 [33].

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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Response to letter
Assessment of the right ventricle in pregnant women with and without structural heart disease

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Dear Editor,

We would like to thank the authors for their valuable comments on our manuscript and certainly welcome the suggestion for more interest in right ventricular function in pregnant women with structural heart disease [1,2].While evaluation of its functioning seems evident in lesions with right sided involvement, it is probably essential in all types of structural heart disease as it becomes more and more evident that left sided dysfunction often involves or induces right ventricular dysfunction [3].While the latter is often less apparent, it is indeed not less important.

The problem remains that there are no data on normal right ventricular function during uncomplicated pregnancy for comparison. It then becomes difficult to discern between physiological changes related to pregnancy and pathological changes due to the structural defect.

The neglection of right ventricular assessment can largely be attributed to the difficulties in obtaining straightforward representative measurements with ultrasound. Even more than for its left counterpart, most parameters only crudely reflect aspects of right ventricular function. Interpretation is then highly dependent of underlying structural abnormalities and changing loading conditions [4].

Assessment of volume and ejection fraction with 2-D ultrasound is severely hampered by the anterior position and complex shape of the right ventricle [4]. The gold standard remains cardiac magnetic resonance (CMR). 3-D is promising but still remains challenging in patients with structural heart defects [5,6].

In assessing other parameters of right ventricular systolic function, one has to bear in mind that the interplay between intrinsic myocardial performance and loading conditions is even more complex as for the left ventricle. Therefore, development of load independent markers of right ventricular function, especially with changing conditions during pregnancy, is essential [3].

As suggested, several parameters like tricuspidal annular plane systolic excursion (TAPSE), Tissue Doppler velocities as well as strain, strain rate and myocardial acceleration during myocardial contraction (IVA), the latter being less load dependent, are promising [4,7]. Still most of them also have their intrinsic limitations and normal values for pregnancy are lacking for comparison.

We performed CMR of the right ventricle in a subgroup of our population and will soon submit our data. Unfortunately we did not asses right ventricular function by ultrasound in a systematic way [2]. We think that more research on normal values of both ventricles with the latest ultrasound techniques is primordial in healthy pregnant women and agree that parameters of right ventricular function should then be included in studies of pregnant women with heart disease. Only then will we be able to truly asses the influence of pregnancy on global heart function in these women.

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Chapter 5.4

Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease

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ABSTRACT

Background

Pregnant women with congenital heart disease (CHD) are susceptible to cardiovascular, obstetric, and offspring complications. In women with CHD, cardiac dysfunction may compromise uteroplacental flow and contribute to the increased incidence of obstetric and offspring events.

Methods and Results

We performed a prospective multicenter cohort study of pregnant women with CHD and healthy pregnant women. We compared clinical, laboratory, echocardiographic, and uteroplacental Doppler flow (UDF) parameters at 20 and 32 weeks gestation, and pregnancy outcome. We related cardiovascular parameters to UDF parameters and pregnancy outcome in women with CHD. We included 209 women with CHD and 70 healthy women. Cardiovascular parameters (N-terminal pro-B-type natriuretic peptide, left and right ventricular function) differed between both groups. UDF parameters were impaired in CHD women (umbilical artery pulsatility and resistance index at 32 weeks in CHD versus healthy women, P=0.0085 and P=0.017). The following cardiovascular parameters prepregnancy and at 20 weeks gestation were associated with UDF (umbilical artery resistance index) at 32 weeks at multivariable analysis: (1) right ventricular function (tricuspid annular plane systolic excursion) (P=0.002), (2) high N-terminal pro-B-type natriuretic peptide (P=0.085), (3) systemic (P=0.001), and (4) pulmonary (P=0.045) atrioventricular valve regurgitation. Women with CHD had more obstetric (58.9% versus 32.9%, P<0.0001) and offspring events (35.4% versus 18.6%, P=0.008) than healthy women. Impaired UDF was associated with adverse obstetric and offspring outcome.

Conclusions

UDF parameters are abnormal in pregnant women with CHD. Cardiovascular function is associated with an abnormal pattern of UDF. Compromised UDF may be a key factor in the high incidence of offspring and obstetric complications in this population.

Congenital heart disease (CHD) occurs in ≈1% of newborns, and 50% of these children are female. The extensive evolution of cardiac surgery for CHD has resulted in a large population of adult women with CHD. Many of them pursue pregnancy. Pregnancy in these women is associated with cardiovascular complications, which occur in ≈10% of pregnancies. Moreover, obstetric and offspring complications are also more prevalent than in healthy pregnant women.[1-5] In women with CHD, offspring complications are related to maternal cardiac function.[5] However, the underlying pathophysiology of this relationship is not completely unraveled. In healthy women with intrauterine growth restriction or hypertensive disorders of pregnancy, the process of placentation is often disturbed, resulting in abnormal uterine and umbilical artery Doppler flow patterns.[6] Such abnormal uteroplacental Doppler flow (UDF) patterns are validated markers of adverse offspring outcome. Moreover, coexisting maternal cardiac and vascular function abnormalities have been demonstrated.[7-9] Whether these abnormalities may be explained by damage caused by circulating angiogenic factors secreted by the placenta, or abnormal placentation and offspring outcome are caused by (subtle) underlying cardiac and vascular disease, is unknown. In women with CHD, the relation between cardiac function (as expressed in N-terminal pro-B-type natriuretic peptide [NT-proBNP] levels and echocardiographic parameters), UDF patterns, and offspring complications has not been investigated. We hypothesized that preexisting cardiac dysfunction in pregnant women with CHD results not only in cardiovascular complications, but also can lead to disturbed placentation with abnormal UDF patterns, thus compromising normal growth and development of the fetus and contributing to offspring complications in pregnancy. To confirm this hypothesis, we performed a prospective study in women with CHD and healthy women. The primary objectives of this study are (1) to compare the cardiovascular clinical, biochemical, and echocardiographic parameters, and UDF patterns, as well, of pregnant women with CHD with healthy pregnant women, and (2) to relate maternal cardiovascular parameters in women with CHD to UDF patterns. The secondary objective is to relate UDF patterns to obstetric and offspring outcome. This study will give insight in the pathophysiology of offspring complications in women with CHD.

PATIENTS AND METHODS

Design and Setting

This prospective observational multicenter cohort study was conducted between March 2008 and August 2011. The extensive study design of the Zwangerschap en Aangeboren HARtAfwijkingen (ZAHARA) II study was published previously and is summarized below.[10]

Patient Selection

Female patients with structural CHD (aged ≥18 years) reporting pregnancy with a duration ≤20 weeks who provided written informed consent and who were followed in 1 of the 8 participating tertiary hospitals participated in the study. In the Netherlands, pregnancies of all healthy women are routinely handled by midwives, regardless of socioeconomic status. Therefore, simultaneously, healthy pregnant women were recruited from midwifery practices. Miscarriages or termination before 20 weeks gestation and twin pregnancies were excluded, as were women with known illicit drug or alcohol abuse. The study was approved by the Medical Ethics Committee of all participating hospitals.

Sample Size Calculation

One of the primary aims of the ZAHARA II study was to compare the UDF, expressed as pulsatility and resistance indices in the uterine and umbilical artery, during pregnancy between women with CHD and healthy controls. A total sample size of 240 subjects (160 patients and 60 [healthy] controls) achieves 80% power to detect a difference of 0.05 in pulsatility index (25% of the expected standard deviation) among the means versus the alternative of equal means by using an independent samples t test with a 0.05 significance level. The common standard deviation within a group is assumed to be 0.20. The sample size for comparison of pulsatility index (PI) was based on an effect size of 0.25. For resistance index (RI), we would use the same assumption and therefore arrive at a similar sample size.

Preconception Characteristics

Baseline data were recorded at the first prenatal visit and included maternal age, obstetric history, cardiovascular history, comorbidity, prepregnancy cardiac status and echocardiographic recordings (including systemic and pulmonary ventricular function and valvular function), use of medication, and alcohol and smoking history.

Evaluation at 20 and 32 Weeks

At 20 and 32 weeks gestation, participants underwent clinical and laboratory evaluation (including serum hemoglobin and NT-proBNP), echocardiographic examination, and UDF registration (PI and RI of the umbilical artery and of the right and left uterine artery, and the presence of early diastolic notching). All echocardiographic recordings were made on commercially available Philips or Vingmed General Electric ultrasound equipment. Echocardiograms were evaluated off-line by 3 experienced cardiologists (each of them reviewed a part of the echocardiograms). A fourth cardiologist checked the consistency and accuracy of the echocardiography data. Chamber quantification and ventricular and valvular function were assessed according to current guidelines.[11–14]

Because Tricuspid Annular Plane Systolic Excursion (TAPSE) and ejection fraction by Simpsons rule are not validated in patients with single ventricles and systemic right ventricles, these measurements were not performed in these patient groups.

Obstetric and Offspring Events

Extensive definitions of obstetric and offspring events were published previously and are summarized below.[10]

Obstetric events were noncardiac death, pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes mellitus, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet syndrome), hyperemesis gravidarum, assisted delivery, postpartum hemorrhage, preterm labor, preterm premature rupture of membranes, and abruptio placentae.

Offspring events were fetal death, neonatal death, intraventricular hemorrhage, neonatal respiratory distress syndrome, infections leading to hospital admission, neonatal intensive care unit admission, premature birth, occurrence of CHD, occurrence of other congenital disease, small for gestational age, and low birth weight.

Statistical Analysis

We used SPSS (IBM SPSS Statistics, version 19.0, IBM SPSS Statistics, IBM Corporation, Armonk, NY) and STATA (version 12.0, StatCorp LP, College Station, TX) for statistical analysis. Continuous variables with normal distribution are presented as mean with standard deviation (±standard deviation), nonnormally distributed variables as median with interquartile ranges, and dichotomous variables are presented as absolute numbers with percentages. Cardiovascular parameters and UDF parameters at 20 and 32 weeks gestation, and pregnancy outcome, were compared between women with CHD and healthy women. Comparison of continuous variables between groups was performed with the Student t test or Mann-Whitney U test, depending on distribution, with and without logarithmic transformation. Longitudinal comparison of continuous variables within CHD and healthy pregnancy groups at 2 time points (20 and 32 weeks) was performed by using the paired t test. We compared the PI and RI within the groups CHD and healthy women and compared these measurements of the CHD group with measurements of healthy women at 20 weeks and at 32 weeks, as well. For the comparison of dichotomous variables, we used the χ^2 test or Fisher exact test, as appropriate. A P value of <0.05 was considered statistically significant and all P values are 2-sided. Uni- and multivariable linear and logistic regression analyses were performed to assess associations between cardiovascular parameters and UDF parameters during pregnancy and between UDF parameters and obstetric and offspring outcome, as well, in women with CHD. The following predefined variables were assessed in univariable analysis: age, disease complexity,[15] risk of cardiovascular complications according to modified World

Health Organization class,[16] body surface area, body mass index, New York Heart Association functional class, resting heart rate, heart rhythm, mean arterial pressure, smoking during pregnancy, cardiac medication use, prepregnancy hypertension, anemia, high NT-proBNP, valve dysfunction (stenosis and regurgitation), left ventricular diastolic diameter/body surface area, left ventricular mass/body surface area, left ventricular ejection fraction, mean left ventricular systolic tissue velocity (S′) (septal-lateral), left atrial volume, left ventricular early to atrial mitral inflow velocity ratio, left ventricular mitral inflow deceleration time, mean left ventricular early diastolic tissue velocity (E′) (septal-lateral), right ventricular diastolic diameter, right ventricular function (TAPSE), and right ventricular systolic tissue velocity (S′).

In addition, variables at 20 weeks gestation were adjusted for prepregnancy values that were significantly associated with the studied end points ($P<0.05$), and variables at 32 weeks gestation were adjusted for values that were significantly associated with the studied end points prepregnancy and at 20 weeks gestation. Variables that were strongly associated with the studied end points ($P<0.10$) or variables considered relevant ($P>0.10$) entered the multivariable model. The final multivariable model was constructed by backward deletion of the least significant characteristic, with a criterion for deletion of $P\geq0.10$. When performing the multivariable model, we used pairwise deletion of cases to deal with missing values.

RESULTS

Prepregnancy Baseline Characteristics

We recruited 234 pregnant women with CHD. Twenty-five women were excluded because of miscarriage (n=11), serious protocol violation (n=6), twin pregnancy (n=4), or withdrawal of informed consent (n=4). Simultaneously, 70 healthy, age and parity-matched pregnant control women with a singleton pregnancy were recruited.

No significant difference was observed between women with CHD and healthy pregnant women with respect to maternal age at conception (28.7±4.4 versus 29.2±4.5, P=0.44), parity (64.1% versus 62.9% nulliparous, P=0.46), ethnic origin (95.7% versus 97.1% white, P=0.35), and prepregnancy body mass index (23.5±3.9 versus 23.1±3.9, P=0.56). More healthy women smoked prepregnancy than CHD women (33.3% versus 20.7%, P=0.03). None of the women had impaired glucose tolerance or hypertensive disorder of pregnancy at the time of recruitment. Table 1 shows prepregnancy cardiovascular data of the CHD cohort. None of the women had uncorrected cyanotic disease or SpO_2 <90%; mean oxygen saturation was 98.5±1.5% at 20 weeks gestation. Of patients with shunt lesions, 78% had a history of correction of the defect. Cardiac medication was used before pregnancy by 15.8% of women with CHD; 7.2% were on anticoagulation

Table 1. Maternal Prepregnancy Characteristics in Women With CHD (n=209)

	n	%
Underlying CHD		
Left-sided lesions	57	27.3
Aortic stenosis/bicuspid aortic valve	*29*	*50.9*
Aortic coarctation	*26*	*45.6*
Other	*2*	*3.5*
Right-sided lesions	64	30.6
Ebstein anomaly	*4*	*6.3*
Pulmonary stenosis	*21*	*32.8*
Tetralogy of Fallot	*39*	*60.9*
Shunt lesions	60	28.7
Abnormal pulmonary venous return	*6*	*10*
Atrial septal defect	*20*	*33.3*
Atrioventricular septal defect	*8*	*13.3*
Ventricular septal defect	*26*	*43.3*
Connective tissue disease	9	4.3
Marfan syndrome	*8*	*88.9*
Loeys–Dietz syndrome	*1*	*11.1*
Complex CHD	19	9.1
Transposition of great arteries (Mustard/Senning operation)	*11*	*57.9*
Transposition of great arteries (arterial switch operation)	*2*	*10.5*
Congenitally corrected transposition of great arteries	*1*	*5.3*
Fontan circulation	*3*	*15.8*
Other complex CHD	*2*	*10.5*
Disease complexity*		
Simple	59	28.2
Moderate complex	131	62.7
Complex	19	9.1
Modified WHO classification (risk of pregnancy)		
Class 1 (low risk)	43	20.6
Class 2 (moderately high risk)	117	56.0
Class ≥3 (high risk)	49	23.4
Medical history		
History of heart failure	5	2.4
History of arrhythmia	19	9.1
History of hypertension	14	6.7
History of diabetes mellitus	2	1.0
Pacemaker	7	3.3
Mechanical valve prosthesis	11	5.3
Biological valve prosthesis	20	9.6
Medication use prepregnancy		
Cardiac medication	33	15.8
β-Blockers	26	12.4
Other cardiac medication	16	7.7
Vitamin K-antagonists/heparin	15	7.2
		(*Continued*)

NYHA functional class		
Class I	159	76.1
Class II	49	23.4

In underlying heart disease, several groups are mentioned (ie, left sided lesions, right sided lesions, etc). The n and % in roman are then a % for such a group. Within each group, subdiagnoses are mentioned (ie, aortic stenosis, aortic coarctation, other). The n and % of subdiagnoses are shown in italics. CHD indicates congenital heart disease; NYHA, New York Heart Association; and WHO, World Health Organization.
***Disease complexity:** according to Warnes et al.[15]

therapy and 12.4% used a β-blocker. Sinus rhythm was present in 88% (n=185). Systemic ventricular ejection fraction was known in 161 CHD women and was below 45% in 8.1% of these women. Prepregnancy right ventricular (RV) function (TAPSE) was known in 138 CHD women; RV dysfunction (TAPSE < 16 mm) existed in 14.5% of these women. Three women conceived through intracytoplasmic sperm injection. Six women had a history of thyroid dysfunction; however, thyroid stimulating hormone was normal preconception.

Comparison of Cardiovascular and UDF Parameters Between Pregnant Women With CHD and Healthy Pregnant Women

New York Heart Association functional class deterioration >1 class at 32 weeks in comparison with prepregnancy occurred only in CHD and not in healthy women: 10.1% versus 0%, P=0.003. We compared laboratory, echocardiographic, and UDF parameters between CHD and healthy cohorts at 20 and 32 weeks gestation (Table 2). NT-proBNP was higher throughout pregnancy in women with CHD and decreased during pregnancy in both groups; the decrease was significantly greater in CHD women (P=0.04). Systemic ventricular mass corrected for body surface area was higher and increased (P<0.005) only in women with CHD. Systemic ventricular ejection fraction did not change significantly in both groups. Several diastolic systemic ventricular function parameters were significantly worse in CHD women: systemic ventricular annular velocity (E′) was lower and diastolic filling pressure (E/E′) higher; change during pregnancy was comparable between both groups. RV systolic function (represented by TAPSE and systolic annular

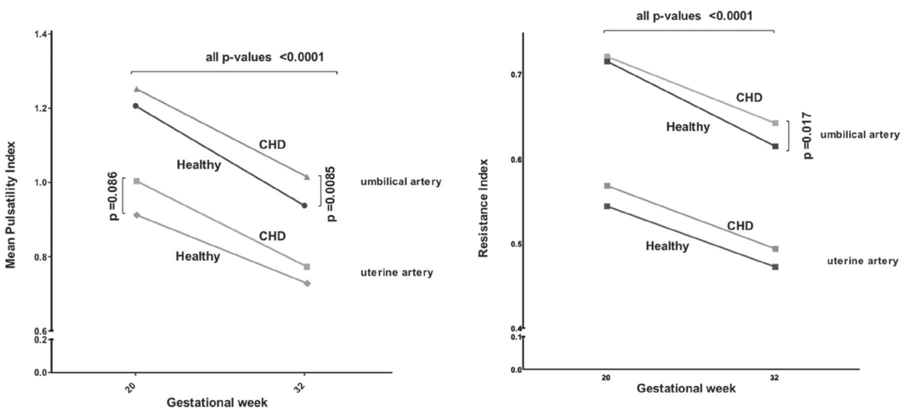

Figure 1 Uteroplacental Doppler flow parameters: pulsatility index and resistance index of mean of right and left uterine artery and of umbilical artery at 20 and 32 weeks of pregnancy, in women with CHD and healthy women. Mean PI (left) and mean RI (right) differed significantly between 20 and 32 weeks, in both uterine and umbilical artery and in healthy controls and CHD patients (as represented by the horizontal line indicating all *P* values <0.0001). Significant differences in separate analyses comparing groups at 20 weeks and at 32 weeks are indicated by vertical lines with *P* values. CHD indicates congenital heart disease; PI, pulsatility index; and RI, resistance index.

Table 2. Comparison of Women With CHD (n=209*) With Healthy (n=70*) Women During Pregnancy

	Gestational Week 20					Gestational Week 32				
	CHD		Healthy			CHD		Healthy		
		n		n	*P* Value		n		n	*P* Value
General parameters										
Smoking during pregnancy	10.0%		2.9%		0.077	10.0%		2.9%		0.077
Cardiac medication	11.0%		0 %		0.002	13.9%		0%		<0.0001
NYHA class I	53.1%		58.6		0.069	39.6%		37.1%		0.005
NYHA class II	39.7%		41.4%			46.4%		62.9%		
NYHA class III	7.2%		0 %			14.0%		0%		
MAP, mm Hg	81.4±8.7	178	77.8±7.8	69	0.003	83.1±8.0	168	79.7±7.1	65	0.003
Laboratory parameters										
Hb, mmol/L	7.5±0.6	192	7.5±0.5	67	0.59	7.4±0.7	184	7.4±0.5	64	0.62
NT-proBNP, pg/mL	111.5 (58.7–171.4)	166	51.0 (23.5–67.0)	49	<0.0001	64.0 (47.7–120.0)	159	24.5 (14.1–41.5)	48	<0.0001
Systemic ventricular size, mass and systolic function†										
Systemic ventricular end-diastolic diameter	47.4±5.6	182	48.0±3.8	68	0.29	48.4±6.3	172	48.4±3.6	66	0.83
Systemic ventricular mass/BSA, g/m²	49.7±14.3	177	42.0±7.2		<0.0001	53.9±14.4	166	43.9±8.1	65	<0.0001
Systemic ventricular ejection fraction, %	57.4±8.6	182	61.3±5.9	67	<0.0001	56.9±8.4	167	60.0±6.2	65	0.003
Systemic ventricular diastolic function†										
LA volume, mL‡	40.2±14.1	157	42.64±10.2	66	0.20	43.3±14.0	153	41.61±11.1	65	0.39
E/A ratio	1.8 (1.4–2.2)	151	1.7 (1.4–2.2)	64	0.89	1.5 (1.2–1.8)	144	1.5 (1.2–1.7)	62	0.72
E deceleration time, ms	193.5 (162.8–237.3)	150	186.5 (169.5–217.3)	64	0.49	184.0 (155.5–217.0)	141	191.0 (159.0–224.0)	59	0.44
Mean E (septal-lateral), cm/s	11.0 (10.1–12.5)	133	12.5 (11.3–13.3)	66	<0.0001	9.96 (9.06–11.5)	132	11.1 (9.76–12.5)	58	0.056
E/E	9.2 (7.7–11.9)	114	7.3 (6.6–8.2)	62	<0.0001	8.8 (7.0–11.3)	113	7.2 (6.1–8.0)	55	<0.0001
Right ventricular size and function†										
Right ventricular diastolic diameter, cm	39.0±7.3	161	35.6±4.1	58	<0.0001	39.0±7.0	155	35.7±4.7	53	0.0002
TAPSE, mm	22.5±5.6	169	26.3±3.4	64	<0.0001	21.4±6.4	164	25.3±3.8	66	<0.0001
Right ventricular S , cm/s	9.7±2.8	126	11.2±1.9	54	<0.0001	9.3±3.2	135	11.3±2.0	51	<0.0001

BSA indicates body surface area; CHD, congenital heart disease; E, early passive filling velocity of systemic ventricular inflow; E′, early diastolic tissue Doppler velocity of systemic ventricular annular ring; E/A ratio, early to atrial mitral inflow velocity ratio; Hb, serum hemoglobin; LA, left atrium; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; Right ventricular S′, systolic tissue Doppler velocity of tricuspid annular ring; and TAPSE, tricuspid annular plane systolic excursion.
***Numbers different** from n=209 or n=70 are shown separately.
†Women with systemic right ventricle heart were only excluded from this specific analysis.
‡LA is the atrium receiving pulmonary venous flow; volume not measured in women with atrial correction of transposition and in Fontan patients.

velocity) was worse in CHD and decreased significantly in CHD women only (P=0.017 and P=0.009, respectively). Figure 1 shows UDF parameters at 20 and 32 weeks. Uterine and umbilical artery PI and RI were higher throughout pregnancy in the CHD group and decreased in both groups. Uterine artery PI and RI were both measured in 139 women at 20 weeks, and umbilical artery PI and RI were both measured in 157 women at 32 weeks, whereas 51 women did not have any uterine artery UDF measurement at 20 weeks, and

Table 3. Associations of Preconception and 20 Weeks Variables With Umbilical Artery RI 32 Weeks Entering the Multivariable Models

	n*	B	95% CI	*P* Value
Association of 20 weeks variables with umbilical artery RI 32 weeks entering model 1				
Age at conception	157	0.003	0.00043 to 0.006	0.025
Parity	157	0.003	–0.012 to 0.018	0.68
Smoking during pregnancy	157	0.039	–0.002 to 0.079	0.063
High NT-proBNP†	129	0.027	–0.001 to 0.054	0.058
Systemic AV valve regurgitation	149	0.059	0.021 to 0.096	0.002
LVEF, %	139	-0.0002	–0.02 to –0.001	0.77
TAPSE, mm	131	-0.002	–0.004 to –0.0005	0.124
Association of preconception variables with umbilical artery RI 32 weeks entering model 2				
Disease complexity	157			0.115
Simple (reference)		…	…	…
Moderate complex		0.025	–0.004 to 0.053	0.092
Complex		0.044	–0.004 to 0.093	0.071
Age at conception	157	0.003	0.00043 to 0.006	0.025
Parity	157	0.003	–0.012 to 0.018	0.68
Pacemaker	157	0.046	–0.02 to 0.112	0.174
Sinus rhythm	134	–0.030	–0.071 to 0.010	0.135
LVEF, %	118	–0.001	–0.003 to 0.0002	0.091
TAPSE, mm	100	–0.005	–0.008 to –0.002	<0.001
Aortic stenosis (moderate/severe)	122	–0.047	–0.103 to 0.009	0.097
Systemic AV valve regurgitation	127	0.037	–0.004 to 0.078	0.079
Pulmonary AV valve regurgitation	123	0.040	0.008 to 0.072	0.015
Association of 20 weeks variables with umbilical artery RI 32 weeks entering model 2				
Smoking during pregnancy	157	0.039	–0.002 to 0.079	0.063
High NT-proBNP*	129	0.027	–0.001 to 0.054	0.058
LVEF, %	139	–0.0002	–0.02 to –0.001	0.77

For the full list of variables that were assessed in univariable analysis, see Methods. AV indicates atrioventricular; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RI, resistance index; and TAPSE, tricuspid annular plane systolic excursion.
***Because the** number of measurements of umbilical artery RI at 32 weeks is limited to 157, n cannot exceed this number.
†High NT-proBNP: >95th percentile of healthy controls (>128 ng/L).

23 women did not have any of umbilical artery measurements at 32 weeks. Missing measurements were mainly attributable to logistic reasons.

Relation of Cardiovascular Parameters and UDF Indices in Women With CHD

We related maternal cardiovascular to UDF parameters. PI and RI were not both measured in all patients. Because results were comparable, we present RI data, in accordance with previous studies presenting data on the relation of UDF parameters with cardiac function in healthy women.[17] RI was available in 141 women for the uterine artery at

Table 4. Multivariable Regression Analysis for the Prediction of Umbilical Artery RI at 32 Weeks of Gestation

	n*	B	95% CI	*P* Value
Model 1: Association of 20 weeks variables with umbilical artery RI 32 weeks (degrees of freedom=128)				
Age at conception	157	0.004	0.001 to 0.008	0.006
Smoking during pregnancy	157	0.045	−0.000 to 0.090	0.051
High NT-proBNP†	129	0.024	−0.003 to 0.050	0.085
Systemic AV valve regurgitation	149	0.068	0.027 to 0.109	0.001
Model 2: Association of 20 weeks variables with umbilical artery RI 32 weeks after adjusting for preconception variables (degrees of freedom=99)				
Age	157	0.003	0.000 to 0.007	0.040
Pulmonary AV valve regurgitation preconception	127	0.035	0.001 to 0.067	0.045
TAPSE preconception	100	−0.004	−0.007 to −0.002	0.002
Systemic AV valve regurgitation 20 weeks	149	0.056	−0.011 to 0.101	0.016

AV indicates atrioventricular; CI, confidence interval; NT-proBNP, N-terminal pro B-type natriuretic peptide; RI, resistance index; and TAPSE, tricuspid annular plane systolic excursion.
***Because the** number of measurements of umbilical artery RI at 32 weeks is limited to 157, n cannot exceed this number.
†High NT-proBNP: >95th percentile of healthy controls (>128 ng/L).

20 weeks gestation and in 157 women for the umbilical artery at 32 weeks. Univariable analysis revealed the following baseline (prepregnancy) variables to be associated with uterine artery RI (20 weeks): parity, preconception heart rate, systemic atrioventricular valve regurgitation, and left atrial volume. Heart rate, use of cardiac medication, and TAPSE at 20 weeks were also associated with uterine artery RI (20 weeks). Hypertension was not significantly associated with UDF in our cohort (B=0.028, P=0.28). Multivariable analysis rendered parity (B=0.04, P=0.048), resting heart rate at 20 weeks (B=−0.002, P=0.006), and use of cardiac medication at 20 weeks (B=0.08, P=0.035) significant. Univariable analysis and multivariable models for the prediction of umbilical artery RI (32 weeks) are presented in Tables 3 and 4.

Pregnancy Outcome in CHD and Healthy Women and Relation of Outcome to UDF

Cardiovascular events occurred in 10.0% in the CHD and 0% in the healthy group. UDF parameters were not significantly associated with cardiovascular events.

Obstetric events occurred in 58.9% of CHD and 32.9% of healthy women (P<0.005). CHD women had more planned cesarean deliveries (13.4% versus 1.4%, P=0.003) and assisted vaginal deliveries (47.4% versus 25.7%, P=0.001). The secondary cesarean delivery rate did not differ between both groups (10.0% versus 11.4%). Several obstetric events occurred more often in CHD women without the differences reaching statistical significance: hypertensive disorders of pregnancy (17.7% versus 11.4%), preeclampsia

(5.7% versus 1.4%), and preterm premature rupture of membranes (6.7% versus 2.9%). Postpartum hemorrhage occurred in both groups in 8.6%. In women with CHD, high umbilical artery RI (>90th percentile of healthy group) at 32 weeks was associated with obstetric events (P=0.049).

CHD women had shorter gestational age at delivery than healthy women (38.3 versus 39.7 weeks, P<0.005) and their babies had lower birth weight (3036 versus 3578 g, P<0.005). More babies of CHD women had an Apgar score of <9 (8.7% versus 0%, P=0.009) 10 minutes after birth.

Offspring events occurred more often in CHD women than in healthy women: 35.4% versus 18.6% (P=0.008); offspring events excluding the small number of women with isolated CHD in the offspring: 34.4% versus 18.6, P=0.012. More children of women with CHD were small for gestational age (16.3% versus 4.3%, P=0.008). Congenital heart disease occurred in 4.8% of offspring of CHD women versus 0% of healthy women's

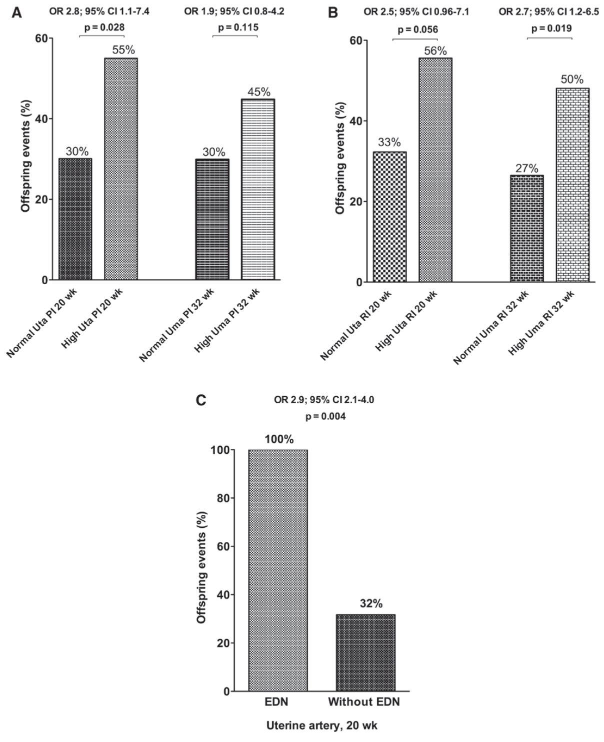

Figure 2 Relation of uteroplacental Doppler flow parameters and offspring outcome. **A**, Uterine and umbilical artery PI and offspring events. **B**, Uterine and umbilical artery RI and offspring events. **C,** Uterine artery early diastolic notch and offspring events. Reported are the percentage of offspring events within, respectively, the groups uterine artery PI and RI at gestational week 20 and the groups umbilical artery PI and RI at gestational week 32, and within the groups with and without early diastolic notch. CI indicates confidence interval; EDN, early diastolic notch; OR, odds ratio; PI, pulsatility index; RI, resistance index; RR, relative risk; Uma, umbilical artery; and Uta, uterine artery.

offspring (P=0.176). Offspring death occurred in 2.9% of the CHD group and 0% of the healthy group. Causes of death were pregnancy termination because of spina bifida or complex heart disease in 2 pregnancies, intrauterine death in 2 patients because of hydrops fetalis and placental insufficiency, and postpartum death because of respiratory insufficiency in 2 pregnancies. Premature birth occurred in 12.4% versus 5.7% (P=0.18). UDF patterns of women with CHD were associated with offspring events (Figure 2). This association was also significant when offspring CHD was excluded from the total number of offspring events.

DISCUSSION

Our study is the first to compare UDF parameters of pregnant women with CHD and healthy pregnant women and to relate these to cardiovascular parameters in pregnant women with CHD.

Our data show that UDF and cardiovascular parameters differ between women with CHD and healthy women. In women with CHD, ventricular function, and valvular function, is related to UDF. As expected (because this is known in the general pregnant population), UDF is associated with obstetric and offspring events.

Adequate uteroplacental blood flow is necessary for normal pregnancy outcome. Vascular remodeling of the uteroplacental circulation guarantees sufficient blood flow throughout pregnancy. This remodeling is characterized by vascular widening of the uterine circulation, which is mediated by endovascular trophoblast invasion of uterine spiral arteries, increased shear stress, and angiogenic and humoral factors.[18] The remodeling process results in a low resistance in the uteroplacental circulation. Abnormalities in the placentation process can result in elevated resistance and pulsatility indices, which are associated with adverse maternal and offspring outcome, particularly hypertensive disorders and intrauterine growth restriction.[5,19] In our study, women with CHD had significantly more obstetric and offspring complications than healthy women. This included a 4-fold increase in the incidence of preeclampsia and of children born small for gestational age. The increased incidence of these complications in women with CHD is in line with previous studies.[1,3-5,20-22]

The association of abnormal UDF patterns and obstetric and offspring outcome, which is well established in the general population, was also present in our women with CHD. More important, UDF indices indicated a higher resistance in the uteroplacental circulation throughout pregnancy in women with CHD than in healthy women. We demonstrated that UDF abnormalities in women with CHD were related to cardiac function, both before and during pregnancy. Cardiac parameters associated with UDF in the multivariable model included preconception RV function but not left ventricular function. The likely explanation is the higher prevalence of RV dysfunction in our population. We used the TAPSE as a measure of RV function, because it is a reproducible simple measurement that is associated with RV function and symptoms in patients with CHD.[23,24]

Healthy pregnant women demonstrated a relatively high New York Heart Association functional class during pregnancy, reflecting the normal symptoms of pregnancy that can resemble heart failure. Functional class deteriorated more in women with CHD than in healthy women, which may indicate a less favorable adaptation of women with CHD to the hemodynamic changes of pregnancy.

Not surprisingly, NT-proBNP was higher throughout pregnancy in women with CHD than in healthy women. NT-proBNP decreased during pregnancy in both groups, as has been demonstrated previously in healthy women,[25] and as can be explained by an increasing glomerular filtration rate during pregnancy. We found elevated NT-proBNP to be weakly associated with abnormal UDF. NT-proBNP and BNP are well-established biomarkers of heart failure, and BNP is a predictor of maternal cardiovascular pregnancy complications.[26] NT-proBNP or BNP have not previously been investigated in relation to UDF in women with heart disease. Prepregnancy NT-proBNP was unfortunately not available. NT-proBNP may become a useful tool in pregnancy risk estimation in women with heart disease, but its role needs further investigation.

Cardiac medication was related to uterine artery RI. The use of cardiac medication is also a predictor of maternal cardiac complications and is probably a marker of disease severity.[5] Most medications were β-blockers, which are known to be associated with lower birth weight, which may be mediated by a negative effect on placental blood flow. Interestingly, both systemic and pulmonary atrioventricular valve regurgitation were associated with UDF parameters. Atrioventricular valve regurgitation is regarded as relatively harmless for the mother and her child, because the decrease in vascular resistance that accompanies pregnancy may reduce regurgitation. However, recent research indicates that mitral regurgitation does predict maternal cardiovascular complications and induces unfavorable cardiac remodeling.[5,27] A recent study demonstrated that mitral prolapse is associated with preterm delivery.[28] Therefore, atrioventricular valve regurgitation cannot be regarded as completely innocent. Our results indicate that placental flow may be compromised by atrioventricular valve regurgitation. This association may be caused by a direct hemodynamic effect or by a common developmental disorder. Valve stenosis did not predict UDF, which might be explained by a lower prevalence than regurgitant lesions. In addition to cardiac parameters, parity, age, and smoking were also associated with UDF.

Our results support the hypothesis that prepregnancy cardiac dysfunction is related to UDF abnormalities, which are indicative of abnormal placentation. This finding is linked to the increased incidence of obstetric and offspring complications in women with CHD.

Evidence from the literature indicates a relationship in the general population between previous hypertension during pregnancy, preeclampsia, or intrauterine growth restriction and the later occurrence of acquired cardiovascular disease in the mother.[29-31] A recent study revealed an association of uterine artery RI during pregnancy with prepregnancy uterine artery blood flow.[32] Based on these data, it has been hypothesized that pregnancy complications, particularly preeclampsia and intrauterine growth restriction, reveal latent cardiovascular abnormalities that may already be present before pregnancy. Our study adds evidence to support this hypothesis, because, in our women with CHD, cardiac function prepregnancy is related to abnormal UDF and adverse offspring outcome.

Strengths and Limitations

Our study is the first to investigate UDF in pregnant women with cardiac disease. Several limitations must be considered. We designed our study to include pregnant women with various underlying congenital cardiac diseases. The heterogeneity of our population may have caused underrepresentation not only of individual diseases, but also of specific cardiac dysfunctions. This may have impacted the robustness of our prediction models. Moreover, because the study included women when they were already pregnant, collection of prepregnancy data was retrospective, and missing data were inevitable (mainly prepregnancy echocardiography data).

Additionally, in this multicenter study, deviation from the protocol sometimes occurred, whereas complex disease often prevented accurate measurements of chamber size and function. Cardiac output could therefore not be measured reliably, and not all data were available in all patients. Technical limitations prevented the digital storage of UDF patterns, which were therefore measured by the different caregivers. Our composite outcome variable combined all offspring events. Because some offspring events (eg, CHD) may not be influenced by UDF or may be influenced through a different mechanism, we repeated the analysis without offspring CHD, which did not significantly alter outcome. We did not have data available on the course of intrauterine growth and could not report on intrauterine growth restriction. Therefore, we used small for gestational age as a parameter of offspring growth. There might be some inclusion bias because we did not include patients from regional hospitals. Because the composition of our population is comparable with the Dutch national congenital database (CONCOR), this bias can be regarded unimportant. Because of the significant number of missing data from echocardiography in the preconception period, we chose to make a prediction model by using data at 20 weeks gestation. Where possible, we assessed the influence of the known prepregnancy data. Despite these limitations, we were able to demonstrate that cardiac function in women with CHD is associated with an abnormal pattern of UDF and adverse pregnancy outcome. Our study results lead to an improved understanding of the pathophysiology of offspring events in women with CHD, and may also contribute to a better insight in the pathophysiology of offspring complications in the general population.

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CLINICAL PERSPECTIVE

Women with congenital heart disease (CHD) are not only at risk of maternal cardiovascular complications during their pregnancies, but they also have an increased risk of obstetric and offspring complications. Offspring complications such as small for gestational age and premature birth are related to maternal cardiac function, but the mechanism underlying this relationship is unknown. In this clinical study, in 209 pregnant women with CHD and 70 healthy women, we demonstrated that uteroplacental Doppler flow parameters (uterine and umbilical artery pulsatility and resistance indices) are worse in pregnant women with CHD than in healthy women and are related to maternal cardiovascular function parameters, such as right ventricular function, valvular regurgitation, heart rate, and prepregnancy need for cardiac medication. Uteroplacental flow parameters were related to offspring outcome, as is also known in the general pregnant population. Therefore, we concluded that in women with CHD, uteroplacental flow may be compromised by maternal cardiac dysfunction and that impaired uteroplacental flow may be a key factor in the high incidence of obstetric and offspring complications. Our study improves the understanding of the pathophysiology of offspring events in women with CHD and may also contribute to a better insight into the pathophysiology of offspring complications in the general population. The results of this study are of importance for counseling of women with CHD who are contemplating pregnancy and will improve risk stratification leading to more adequate monitoring of pregnancies in these women.

Chapter 5.5

Contraception and cardiovascular disease

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ABSTRACT

Contraceptive counselling should begin early in females with heart disease, preferably directly after the start of menstruation. In coming to a decision about the method of contraception, the following issues should be considered: (i) the risk of pregnancy for the mother and the consequences of an unplanned pregnancy; (ii) the risks of the contraceptive method; (iii) failure rates; (iv) the non-contraceptive benefits; (v) the availability; (vi) the individual's preferences; (vii) protection against infection; and (viii) costs. In some women with heart disease, the issues may be complex and require the input of both a cardiologist and an obstetrician (or other feto-maternal expert) to identify the optimal approach. No studies have been performed in women with heart disease to investigate the relative risks and benefits of different contraceptive methods.

INTRODUCTION

The success of cardiac surgery and the medical management of women with congenital and acquired heart disease means that most will reach puberty and could become pregnant, as most become sexually active even with severe heart disease.[1,2] However, pregnancy is high-risk in at least some of these women and needs careful planning.[1 – 3] In the large international prospective registry of pregnant patients with cardiac disease (ROPAC), 38% of 1321 women was defined to be high risk and 4% had a contraindication for pregnancy.[2] Effective contraception is essential especially in those with a contraindication for pregnancy. In other women, effective contraception is crucial to allow counselling and optimal timing of pregnancy, improving the chances of an uncomplicated pregnancy. In addition, women with cardiac disease may use medication that is teratogenic (i.e. ACE-inhibitors), consequently, effective contraception is essential. However, the provision of contraceptive advice to these women is sporadic. One study reported that nearly 35% of 49 women had not been advised on the use of contraceptives, while counselling in another 30% had been inappropriate.[4] Another study reported the widespread use of oestrogen-containing formulations (33%), despite their association with an increased risk of thrombo-embolic disease, even in women with a contraindication for oestrogen-use, while the safer progesterone-only alternatives were used relatively infrequently (1.3%).[5]

Large population-based sexual health studies have all reported a decrease in median age at first intercourse over the past 50 – 60 years. In the western world, the median age of menarche is around 12 – 13 and the age at first sexual intercourse for women around 17 years, with 2 – 30% having sexual intercourse before the age of 15.[6] The mean age at first intercourse of women with heart disease is similar to that of the general population.[7] Clearly general practitioners, (paediatric) cardiologists, obstetricians, and other doctors caring for these women should offer appropriate contraceptive advice early, preferably soon after menstruation starts.

Medically, the key issues relate to reliability and the thrombosis- and infection risk of each possible method. The most reliable methods are those that are the most straight forward to use, the implant and the intrauterine device (IUD). The thrombotic risk is greatest with oestrogen-containing compounds and the copper IUD has the greatest risk of pelvic infection, while all non-barrier contraceptives at best have a limited benefit through thickening of the cervical mucous or not protective benefit at all in preventing infection. A good approach is the use of a long-acting reversible form of contraception combined with a male condom for prevention of sexually transmitted diseases.

From a health economic perspective, contraception is cost saving to society by preventing the costs and emotional distress associated with unintended pregnancies and terminations.[8] This is even more pronounced in women with medical conditions like heart disease.

Subdermal implants, IUDs, and sterilization are more cost effective than other methods.[8] This is related to their contraceptive efficacy, high continuation rate, additional medical benefits (e.g. decreased menstrual bloodloss, low thrombotic risk), and long duration of action.

However, the discussion on contraception should not be limited to the safest and most efficient way to avoid pregnancy, but should encompass other issues like menstrual regulation, reduction of uterine blood loss and menstrual discomfort, as well as the possibility of treatment for endometriosis, PCOS, acne, ovarian cysts, and other conditions. While these issues might be considered less important, they affect the daily comfort and wellbeing of women. The chances of a woman continuing to use contraception are much greater if the method used also makes her feel well.[3] Given the complexity of each request, we prefer an individualized approach where the contraceptive and non-contraceptive benefits and the risks of each method are matched with the patient's desire, after appropriate counselling. In this article, we will discuss the relative risks and benefits of different contraceptive methods in the context of a woman with heart disease.

TYPE OF CONTRACEPTION

To find the best type of contraception, issues such as risks, failure rates, non-contraceptive benefits, individual preferences, and protection against infection should be considered (Figure 1). In some women with heart disease, the issues may be complex and require the input of both a cardiologist and an obstetrician to identify the optimal approach. The risks and consequences of pregnancy, planned as well as unplanned, can be estimated based upon the Modified WHO classification of maternal cardiovascular risk.[9] For the risks of each contraceptive method, the detailed WHO medical eligibility criteria (WHO-MEC) for contraceptive use offer guidance in women with specific medical conditions.[10] The WHO developed this practical system of recommendations with four categories for each contraceptive method and each medical condition including heart disease (Table 1). The guidelines are developed and regularly updated by a panel of international experts, primarily based on scientific evidence where available and expert opinion where it is not. As no studies on contraception have been performed in women with heart disease most recommendations are based on extrapolation of data from studies in women without heart disease. Several national guidelines are based on this system, adapted to the local situation.[11,12]

The efficacy of a contraceptive method is based on its intrinsic mechanism of action, but is also highly dependent on its correct use. It is therefore often expressed as an optimal efficacy, reflecting its theoretical efficacy and a typical efficacy, based on what is observed in real life. Table 2 shows these efficacies along with the most important risks and benefits.

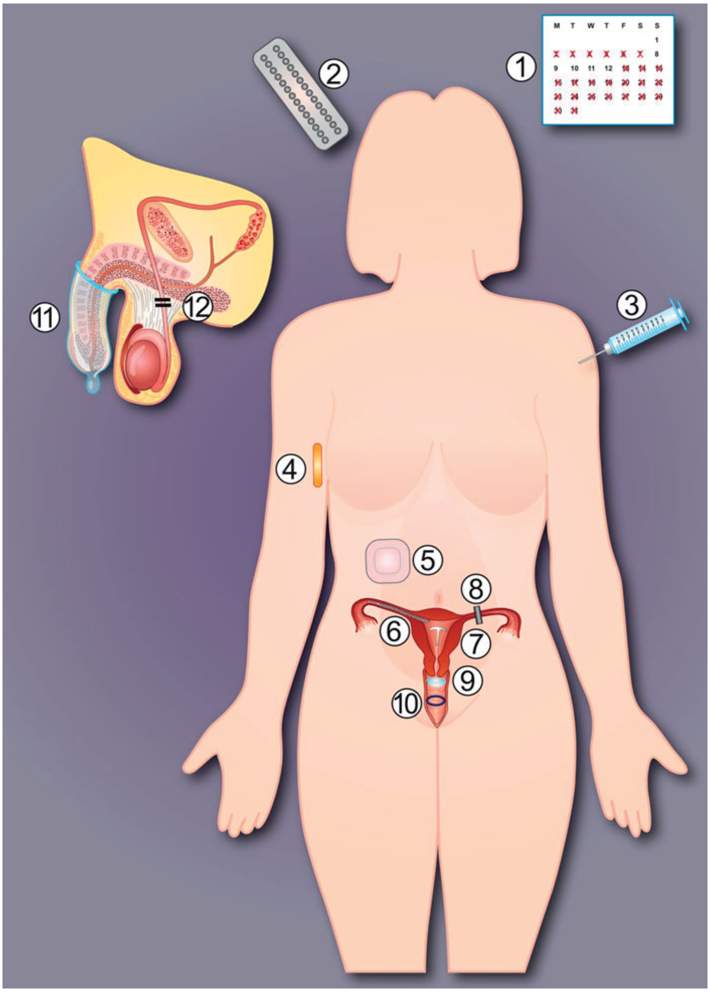

Figure 1 Sketch illustrating different types of contraceptives. (1) Safe period, (2) oral contraceptive (COC or POP), (3) injectable (DMPA), (4) implant, (5) patch, (6) hysteroscopic tubal occlusion, (7) intrauterine contraceptive device, (8) tubal ligation, (9) diaphragm, (10) vaginal ring, (11) male condom, (12) vasectomy.

Table 1 WHO eligibility criteria for widely used contraceptive methods

1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

Table 2 The percentage of women who will experience an unplanned pregnancy within the first year of use of a given contraceptive method (typical and optimal usage), together with the percentage of continued use after 1 year, the risk of thrombosis and of infection associated with the methods use. Modified from13,14

Group	Contraceptive type	Failure (typical, %)	Failure (optimal, %)	Continued use at 1 year (%)	Thrombosis risk	Infection risk
Highly effective (<1%) Reversible	Implant	0.05	0.05	84	May be slightly increased risk	Minimal
	IUCD	0.2 (LNG)	0.2	80	No increased risk	Transient bacteraemia at insertion, increased PID
		0.8 (Copper)	0.6	78		
Highly effective (<1%) Irreversible	Vasectomy	0.15	0.1	100	No increased risk	Post-operative
	Tubal Occlusion	0.5 (abdominal, laparoscopic, or hysteroscopic)	0.5	100	No increased risk	Post-operative
Moderately effective (3–12%)	Injectable	Depo-Provera 3% Combined injectable 3%	Depo-Provera 0.3% Combined injectable 0.05%	56	Depo-provera: increased risk Combined injectable: increased risk	Minimal, but no protection from PID
	Combined oral contraceptive	8	0.3	68	Increased risk	Minimal, but no protection from PID
	Desogestrel containing progesterone-only pill	8	0.3		No increased risk	Minimal, but no protection from PID
	Patch	8	0.3	68	Increased risk	Minimal, but no protection from PID
	Ring	8	0.3	68	Increased risk	Minimal, but no protection from PID
Poorly effective (18–28%)	Male Condom	15	2	53	No increased risk	Reduced PID
	Diaphragm	16	6	57	No increased risk	Reduced PID
	Female Condom	21	5	49	No increased risk	Reduced PID
	Sponge	16–32 (nulliparous vs. parous)	9–20 (nulliparous vs. parous)	46–57 (parous vs. nulliparous)	No increased risk	No protection from PID
	Safe Period	25	3–5	51	No increased risk	No protection from PID
	Withdrawal	27	4	43	No increased risk	No protection from PID
	Spermicide	29	18	42	No increased risk	No protection from PID
No contraception		85	85			

Barrier methods, calendar methods, and withdrawal

Barrier forms of contraception (including condoms, diaphragms, and cervical caps), calendar methods, or withdrawal before ejaculation are usually considered insufficient due to their substantial failure rate.[13] It consistently seems that humans are not invariably rational or practical when passionate. Nevertheless, a male condom protects against sexually transmitted diseases in non-monogamous relationships and might prove valuable as an additional contraceptive method.

Combined oestrogen and progesterone contraceptives

Combined oestrogen and progesterone contraceptives combine either ethinylestradiol or estradiol valerate with various progestins (progestogens). They are mostly used as tablets with regular stop periods, but they can be delivered by a vaginal ring, injection, or transdermal patch. Combined oral contraceptives are divided in four generations depending on the progestin used and the type and dose of the oestrogen component. The oestrogen component in combined oral contraceptives significantly increases the risk of venous thrombosis (2–7-fold) irrespective of the type of progestin used although the risk is small in absolute numbers (8–10/10 000 women-years exposure).[15,16] This risk of an unplanned pregnancy must be weighed against the risks of the combined contraceptives. Besides venous thrombosis, combined oral contraceptives increase the risk of arterial thrombosis and hypertension.[17,18] Therefore, combined oral contraceptives are not recommended (WHO-MEC 3) or even contraindicated (WHO-MEC4) in women with cardiac disease (especially those with an increased thrombotic risk, either venous or arterial), ischaemic heart disease or hypertension. Combined oral contraceptives inhibit ovulation, thicken the cervical mucus, preventing sperm penetration, and prevent implantation by altering endometrial receptivity. Theoretically, contraceptive efficacy is high, but this is completely dependent on its correct usage.[13,19] Some medication may influence their efficacy. For instance, Bosentan, taken in the management of pulmonary hypertension, increases the metabolism of contraceptive steroids, decreasing their efficacy and in this circumstance, a supplementary method, like a condom, should be used.[11,20,21] Combined oral contraceptives usually improve cycle control by making periods regular, less painful, and lighter.[22,23] Women often reduce the frequency of withdrawal bleeds, by continuous intake for 2 or 3 months.[24] Combined oral contraceptives can also be used for the treatment of ovarian cysts, polycystic ovary syndrome, and features of mild hyperandrogenism like acne or hirsutism.[25]

Progesterone-only contraceptives

Progesterone-only methods of contraception come in a variety of formulations. Depending on the method used, the contraceptive mechanism of action is a combination of cervical mucus thickening, preventing sperm penetration, and reduction of endometrial receptivity, preventing implantation. The higher dose formulations also inhibit ovulation.[19,26-30] Most importantly, progestins probably do not increase the risk of thrombosis, although discussion exists, as some papers have reported an increased risk of thrombosis in patients using Depo-provera, while others have not.[31-34] Progesterone-only pills, commonly known as 'mini-pills' contain various types of progestogens and are used daily without a break. Most have a limited efficacy as contraceptive but were traditionally used as a contraceptive supplement to lactation.

Desogestrel (Cerazette) containing progesterone-only pill is the only one to effectively inhibit ovulation and has a similar safety window (12 h) and contraceptive effectivity as the combined oral contraceptives. It is therefore the only progesterone-only pill recommended in women with (severe) cardiac disease.[11,20,21,28,35]

Depot-medroxyprogesterone acetate (DMPA) can be used for intramuscular or subcutaneous injection and offers contraceptive protection for at least 13 weeks. While its effect usually last much longer, adherence to the 13-weekly interval (with a 4-week grace period) is recommended in order to be able to rely on its contraceptive efficacy.[36]

Subdermal implants containing etonogestrel or Levongestrel keep their contraceptive efficacy for 3–5 years and are easily inserted after simple local infiltration in the medial groove between the biceps and triceps. The rare failures due to unnoticed loss of the implant at insertion and problems of implant retrieval at removal with the etonogestrel containing implants have largely been overcome by a new inserting device and incorporation of a radioactive filament.[26,36] A large Danish population study including 1 626 158 women, suggested a potential slightly increased thrombotic risk with subdermal implants (relative risk 1.4).[32] However, the study failed to reach statistical significance (95% CI 0.6–3.4).and with other studies assessing the influence on haemostatic parameters being reassuring, there is little evidence of increased thrombosis risk with their use.[32,37-39] Prolonged exposure to progestagens induces endometrial atrophic changes. This results in an irregular and unpredictable bleeding pattern, often with reduced blood loss, duration, and menstrual frequency (occasionally amenorrhea).[40-43] However, it is also sometimes characterized by continuous spotting.[26,44] The exact mechanism responsible for this remains to be understood but may be related to vascular fragility of the atrophic endometrium. While most women welcome the reduction in vaginal blood loss, the unpredictable nature or continuous spotting can be bothersome in others. Creating realistic expectations during counselling often greatly contributes to patient satisfaction and acceptance of undesirable side effects.[29,30,45]

Intrauterine contraceptive device and intrauterine system

The two most common forms of reversible intrauterine contraceptives are the banded copper containing intrauterine device (copper-IUD) and Levonogestrel-releasing intrauterine system (IUS) (Levonogestrel-IUS = Mirena). Copper is toxic to the ova and sperm and the device induces an endometrial inflammation preventing implantation, thereby offering safe contraception for 10 years. For the Levonogestrel-IUS, the gradual, local release of progesterone induces endometrial atrophy and the formation of a cervical mucus plug, which impedes sperm penetration offering safe contraception for 5 years. It suppresses ovulation for the 1st two cycles thereafter the cycle returns to normal.[46] Progesterone containing subdermal implants and Levonogestrel-IUS and copper-IUD are considered long-acting reversible contraceptives. By eliminating the dependency on patient adherence, their efficacy is excellent even exceeding sterilization and fertility rapidly returns upon removal.[13,26,47]

While menstrual blood loss and discomfort might be increased after insertion of a copper-IUD, the Levonogestrel-IUS, after a 3–4-month period of irregular light loss, usually reduces blood loss and, in the majority, results in complete amenorrhea. An IUD can be used in both nulli- and parous women and have no effect on thrombogenic risk.[48] Insertion is facilitated during menstruation, offering immediate contraception , but can be performed at any point in the cycle and even postpartum.[49] Uterine perforation occurs but is rare. The risk of pelvic infection is increased for the 3 months after insertion of IUD and women should be warned to report fever or other worrying symptoms promptly. Transient bacteraemia has been documented at replacement but is rare during simple insertion or removal.[50,51] Guidelines for infective endocarditis prophylaxis during placement of these devices has changed considerably over the past decade across Europe and Northern America. The most recent recommendations from the American Heart Association (2008) and the National Institute for Clinical Excellence (2008) no longer advise routine use of antibiotic prophylaxis for genito-urinary instrumentation in women with cardiac disease (including valvular heart disease, congenital heart disease, and cyanotic congenital heart disease) irrespective of their underlying risk of endocarditis, or those with a high risk of adverse outcomes associated with endocarditis.[52,53] These guidelines have been driven by four large randomized trials, which were reviewed in a Cochrane collaboration meta-analysis by Grimes et al.[54-58] These randomized controlled trials were designed to explore the peri-procedural infective risk to the upper genito-urinary tract associated with instrumentation during IUD implantation. Pelvic inflammatory disease within 90 days was the primary outcomes in all four trials. Other secondary outcomes included removal of the IUD (in two of the trials) for reasons apart from ‘spontaneous’ expulsion of the device. Unscheduled visits were another secondary outcome measure. Overall these trials demonstrated that prophylactic doxycycline or azithromycin compared with placebo or no treatment conferred additional benefit (OR 0.89 (95% CI 0.53–1.51).[54] Sinei et al.,[56] using doxycycline prophylaxis, showed a significant reduction in non-scheduled visits following IUD insertion in those having received antiobiotic prophylaxis, but failed to show a significant reduction in rates of pelvic inflammatory disease following IUD insertion. Ladipo et al.,[55] replicating this methodology in a Nigerian population, were unable to demonstrate any difference in unscheduled visits or infection following IUD insertion. Walsh et al.[57] and Zorlu et al.[58] also failed to demonstrate any significant benefit for prophylactic antibiotics on pelvic inflammatory disease. However, a recent retrospective study evaluated the effect on endocarditis prevalence associated with the introduction of the new guidelines over the period 2004–13 (i.e. before and after introduction of the new guidelines). By March 2013, 35 more cases per month of endocarditis were reported than would have been expected.[59] These results do not establish a causal relationship, but call for further systematic evaluation of the specific benefit of antibiotic prophylaxis in high-risk women. Currently, the guidelines states that antibiotic prophylaxis for the placement of an IUD or IUS is not recommended, however, the administration of prophylactic antibiotics (ampicillin 2 g and gentamicin 80 mg given intravenously 1 h before IUD insertion) prevents bacteraemia and may be wise in high-risk women (e.g. with a prosthetic valve) given the increasing incidence of endocarditis since introduction of the new guidelines, while endocarditis is associated with high morbidity and mortality and the incidence or serious side-effects of prophylactic antibiotics is relatively low.[60]

Sterilization

Sterilization in a patient with a contraindication for pregnancy or after a couple has completed their family is not unreasonable.[11,21,61] Vasectomy, is a highly effective approach to contraception and poses no risk to a woman with heart disease, but may not be ideal in the context of a woman with a high chance of early demise as it compromises the fertility of the man in eventual future relationships. Laparoscopic or open tubal ligation and hysteroscopic insertion of intratubal stents may be the best sterilization option as long as the woman understand that such procedures should be considered irreversible. If a pregnant woman is to be delivered by caesarean section and has completed her family, then the option of a sterilization at the same time should be discussed mentioning that the regret and failure rate might be slightly higher and the possibility of reversal lower than for the standard laparoscopic approach.[62,63] Not unreasonably, many women are unwilling to be sterilized as a primary form of contraception, even if they have severe heart disease and pregnancy would carry a very high risk.

Some women will struggle to accept the finality of no longer being able to have children. There are risks associated with the procedure itself and, although rare, it does have a failure rate, and definite adverse effect psychological impact on the patient. Recently, the role of sterilization has been reduced by the availability of other highly reliable and reversible contraceptive techniques, such as subdermal implants and Levonogestrel-IUS.

Emergency contraception

Emergency contraception can be a valuable back-up in case of unprotected intercourse. A single dose of 1.5 mg of Levonogestrel is very efficient with a 1.1% failure rate if taken within 72 h after unprotected intercourse.[64] Its mechanism of action is mainly through delaying ovulation. Therefore, its efficacy is limited once ovulation has occurred.[65] A single dose of Mifeprostone 25 mg and Ulipristal acetate 30 mg, two progesterone receptor modulators, seem to be more effective than Levonogestrel and can be taken up to 120 h after unprotected intercourse. In addition to the inhibition of ovulation, these agents may also prevent implantation and reduce tubal motility.[64-66] Besides minor side effects like nausea, vomiting, and headache, these methods are generally considered safe, even in women with heart disease. Patients should be made aware that menstruation is often delayed. The most effective approach remains the insertion of a copper-IUD within 120 h after intercourse (0.09% failure rate), which, as well as preventing pregnancy, will offer long-term contraception.[67]

Two doses of levonorgestrel (750 mg) have a small effect on blood clotting parameters with an increase in fibrinogen at 24 and 48 h and a reduction in anti-thrombin III lasting from 2–12 h post treatment (oestrogen-based methods have a more marked effect).[68] However, despite these changes, there was no evidence of an increased risk of thrombosis in users of post-coital contraception.[69] On the contrary, a case report described a potentiation of warfarin by levonorgestrel, perhaps by the displacement of warfarin from its main transport protein, α1-acid glycoprotein.[70] Indeed, there may exist a strong and potentially dangerous interaction between high-dose levonorgestrel and warfarin urging the need for extra INR control in the first days. Consequently, it may be better to insert a copper IUD for post-coital contraception in a woman taking warfarin.

CONTRACEPTIVE ADVICE IN WOMEN WITH SPECIFIC CARDIAC LESIONS

There is a paucity of published information and very little evidence about contraception in women with all forms of heart disease. These women are a heterogeneous group, meaning that risk stratification and contraceptive advice has to be individualized and should be based not only on the nature of the cardiac problem, but also on the presence of other medical conditions, the age of the woman and her partner, number of previous children, cultural and religious beliefs, and individual wishes.

Compromised cardiac function

Pregnancy in women with previously diagnosed idiopathic, familial, or peripartum cardiomyopathy carries a risk of heart failure and occasionally death. Deterioration of left-ventricular function is reported in up to 50% of cases in the peripartum period, despite optimal medical therapy.[71,72] Maternal mortality figures typically include deaths that occur during pregnancy or in the first 42 days after delivery. However, deaths related to peripartum cardiomyopathy may occur after this limit and the linkage with the preceding pregnancy lost. The cause of death can be intractable heart failure, sudden death due to ventricular arrhythmia or due to a thrombo-embolic event, occurring as a result of the poorly contractile left and/or right ventricles.[73] Therefore, pregnancy is high-risk in women with a left-ventricular ejection fraction (LVEF) below 45% (WHO Class III) and is contraindicated if LVEF is below 30% (WHO Class IV).[9]

In patients with peripartum cardiomyopathy, the occurrence of heart failure has been reported even after a termination of pregnancy or stillbirth, further supporting the need for reliable contraception to prevent unplanned pregnancies. Therefore, in these women, effective contraception is essential and while there is no absolute contraindication to use of any method, an individualized approach should be taken, which includes consideration of the risk of thromboemboli, the use of anticoagulation, and the occurrence of arrhythmias. Although some fluid retention may occur, there is no evidence that the contraceptive steroid hormones aggravate heart failure. However, combined oral contraceptives are contraindicated in women who have a reduced ejection fraction after a myocardial infarction, especially when other risk factors, such as smoking and hypertension, are present.

Contraception in women with heart disease requiring anticoagulation

Women with mechanical valves, Fontan-circulation, and pulmonary hypertension have an increased risk of thrombosis, which is commonly managed using Vitamin K antagonists. In these women, the cardiovascular and thrombogenic risks of (unplanned) pregnancy often outweigh the inherent risks of most contraceptive methods. However, in women on anticoagulation, the incidence of heavy and prolonged menstrual bleeding as well as intermenstrual and postcoital bleeding is increased.[7,74,75] They can even experience ovarian haemorrhage at ovulation, potentially leading to severe abdominal bleeding on a rare occasion.[76,77]

Both oestrogens and progestins can potentiate the anticoagulative effects of coumarines, necessitating a re-evaluation of the INR several weeks after initiation.[21,70,78] Therefore, in the context of a woman taking anticoagulants, a reliable contraceptive method without increased thrombotic risk, that reduce menstrual blood loss and inhibits ovulation would be most suitable. Progesterone-only methods, especially the long-acting reversible contraceptives and the Levonogestrel-IUS are therefore the method of choice in these women, although being on anticoagulants may increase the tendency to irregular bleeding patterns, most women would experience a reduction in vaginal blood loss. Indeed, this approach is sometimes used in anticoagulated women solely to reduce menstrual blood loss, despite earlier sterilization.[40-43] While DMPA injections induces some fluid retention and can be complicated by intramuscular haematoma, it rarely seems to be of clinical significance, even in patients on anticoagulation.[11,20,21,61] There are no good data on whether the increased thrombogenic risk of combined oral contraceptives is controlled by appropriate anticoagulation.[74,79,80] Given this uncertainty, and the severe consequences of a thrombotic event in this patient population, most guidelines state that combined oral contraceptives are contraindicated (WHO-MEC4) in women with a history of thrombosis, a mechanical heart valve (particularly the older single leaflet valves like the Bjork Shiley or Starr Edwards), Fontan operation, cyanotic heart disease, pulmonary hypertension, coronary artery disease, or atrial fibrillation despite appropriate anticoagulation.[10-12,21] Nevertheless, there is debate among experts about these recommendations as scientific support is lacking and combined oral contraceptives offer important non-contraceptive benefits such as improved cycle control, particularly in women who wish to discontinue progesterone-only methods due to unpredictable bleeding.[61,81]

While certainly not first choice, we believe that combined oral contraceptives can be considered in these women after appropriate counseling.

Contraceptive interventions in high-risk women

The pain and cervical manipulation during insertion and removal of an IUD can elicit a vagal reaction in as many as 5% of women.[11,20,21,61,79,82] While this is usually benign in most women, it is potentially dangerous in those with pulmonary hypertension or a Fontan repair. Consequently, we recommend that insertion and removal of an IUD in these women occurs in a setting with cardiovascular monitoring, with anaesthetic support on standby, and using appropriate pain relief, either paracervical block or systemic opioids, to prevent a vagal reaction. Taking this into account, Levonogestrel-IUS may therefore be less suited in these women when compared with subdermal implants. Subdermal implants have a superior contraceptive efficacy to sterilization and are easily inserted, only requiring local anaesthetic and are a very option for women with a mechanical valves, pulmonary hypertension, or Fontan repair.[11,20,21,26,29,31,61,83] As in the case of desogestrel containings progresterone-only-pills, these subdermal implants require an additional contraceptive measures in women taking Bosentan. Sterilization through laparoscopic tubal ligation requires the creation of a pneumoperitioneum and is therefore contraindicated in women with pulmonary hypertension or Fontan repair. If desired, an open or laparoscopic procedure with minimal inflation under general, spinal/epidural, or even local anaesthesia can be considered, but it also requires temporary cessation of the anticoagulation and contains a procedure inherent risk of haemorrhage and thrombosis.[11,21,61,84]

The new methods of tubal occlusion, achieved by hysteroscopic insertion of tubal stents, have been used successfully in a group of women with severe heart disease and may be a good option. Ultrasound assessment of tubal patency after several months is required before effective contraception can be expected.[21,61,85-87] As for IUD insertion, antibiotic coverage can be considered despite the current guidelines and adequate monitoring and pain relief to prevent an eventual vagal reaction should be assured in these women. Sterilization does not offer the non-contraceptive benefits (e.g. reduction in menstrual blood loss) of other methods. With the contraceptive efficacy of Levonogestrel-IUS and subdermal implants implants exceeding that of sterilization, the indications for the latter is limited in this patient population.

Contraception in women with arrhythmias

Women with arrhythmias often use medication that is teratogenic (i.e. amiodarone), consequently, effective contraception is essential. When a change of antiarrhtyhmic medication is decided upon, it should be implemented when the mother is still using contraception, since this allows time to judge the tolerance and effectiveness of the new medication. In the case of anticoagulant medication, the change can be made in early pregnancy.

A small increase in heart rate was demonstrated in women using oestrogen-containing contraceptives,[88] but not with oestradiol alone.[89] Theoretically, an increase in heart rate could reduce myocardial perfusion and promote cardiac arrhythmias, however, the rise in heart rate in these studies was minor and is therefore unlikely to be of clinical significance. There is no other evidence that contraception of any kind triggers the occurrence of arrhythmias. Therefore, the most important issue is the elevated thrombo-embolic risk with use of combined contraceptives in women with an arrhythmia. In women with isolated arrhythmias (i.e. isolated supraventricular or ventricular extra beats, AVNT, or VT's in long QT-syndrome), combined contraceptives can be used. However, when atrial flutter or fibrillation is present, either paroxysmal or permanent, caution in the use of combined hormonal contraceptives is advised, because of elevated risk of thrombo-embolism (WHO-MEC 3).[11,61,90,91]

CONCLUSION

Contraception is a delicate, sometimes difficult issue, which carries many ethical, moral, and medical dilemmas. Contraceptive counselling should begin early, and the choice of method based on the impact of (an unplanned) pregnancy, the risks, and benefits of the contraceptive type and the individual's preferences. Complex cases will require the input of both a cardiologist and an obstetrician and the absence of any good quality studies mean that the decision is almost always based on expert opinion. In many situations, the ease of use and efficacy of the progestogen-only long-acting reversible contraceptive methods make them a good method for patients with cardiovascular disease.

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Chapter 6

Discussion

DISCUSSION

In this thesis we assessed the potential of non-invasive hemodynamic monitoring in pregnant women. Normal pregnancy is accompanied by substantial hemodynamic changes which are necessary to permit the normal development of a fetus. In healthy pregnant women the cardiovascular system is already intensely challenged [1, 2]. It is even more so in most pregnancy complications or in women with pre-existent cardiovascular disease. In fact, the cardiovascular system is predominantly implicated in all major causes of maternal and fetal mortality and severe morbidity being either hypertensive disease, fetal growth restriction, cardiac disease, sepsis, hemorrhage or preterm birth [3-9]. While its importance is well acknowledged, the cardiovascular system is not as intensively studied as often assumed. Many beliefs on cardiovascular adaptation which are commonly accepted in research and relied on in clinical practice are based on old data using dated techniques in small number of subjects. As an example, current ideas on changes in cardiac output during labor and delivery are almost exclusively based on echocardiographic continuous wave Doppler measurements obtained at the pulmonary valve in 15 women and published in 1987 [10]. Also, the level of hemodynamic monitoring is usually rather basic in pregnant women, even in complex conditions. In mothers, blood pressure and pulse oximetry are currently often used as sole surrogates of the cardiovascular condition. In the fetus, monitoring is mostly limited to umbilical and middle cerebral artery Dopplers along with fetal heart rate monitoring. While these parameters are evidently important, they merely offer a crude reflection of the feto-maternal cardiovascular condition. This might have contributed to the fact that progress in our understanding and management of these complex conditions has been limited in the last two decades.

Advances in the care for pre-eclampsia have mainly been achieved by a policy of damage control along with improvements in neonatal care. Maternal complications have decreased thanks to stricter blood pressure control, liberal use of magnesium sulphate and lower threshold for delivery but no substantial breakthrough has been achieved in altering the disease course [11, 12]. In growth restriction, advanced fetal monitoring strategies incorporating heart rate variability and venous Dopplers have failed to show their superiority and experiences with interventions to improve placental perfusion show conflicting results [13]. Fluid and transfusion protocols in postpartum hemorrhage and puerperal sepsis are still usually based on local tradition or expert opinion at best, but are rarely hemodynamically guided according to the individual patient needs.

Pioneer work from the late forties until the seventies of last century using invasive catheterization and dye dilution techniques explored the substantial changes in cardiac output, stroke volume and vascular resistance that accompany normal pregnancy in experimental settings [14-20]. With the availability of Swan-Ganz catheters, invasive monitoring of maternal hemodynamics was introduced in clinical obstetrics in the eighties and nineties [9, 21-33]. These experiences greatly contributed to our current pathophysiological understandings and pointed towards the potential of hemodynamic monitoring in the management of critically ill pregnant women. Hemodynamic guided fluid management and treatment showed its benefits in women with severe pre-eclampsia, pulmonary edema and oliguria [22, 25]. However their invasive nature limited their use to only a few severe conditions. After the controversies about increased mortality with their use in intensive care settings, the enthusiasm for Swan-Ganz catheters faded in obstetrics around the millennium change [34-37]. Doppler ultrasound then promised to be an non-invasive alternative for hemodynamic monitoring [38-41]. While Doppler echography of the uteroplacental and fetal vasculature became the cornerstone for both scientific and clinical assessment of fetal hemodynamics, maternal echocardiography remained a non-invasive research alternative for dedicated aficionados only, but failed to reach widespread popularity in clinical obstetrics [42-45]. Alternative techniques like bio-impedance and pulse contour analysis are not commonly used either as validation in pregnancy remained an issue due to a lack of an available comparative gold standard [46-48]. Yet the previous experiences with invasive techniques in severe conditions clearly suggest the potential of non-invasive hemodynamic monitoring, which could be used in a larger population.

In this thesis we initially validate cardiac output measurements using transthoracic echocardiography against the gold standard of pulmonary artery catheterization in pregnant women [49]. With cardiac output being the most prominent parameter of cardiac function, it highlights the feasibility and potential of transthoracic echocardiography for non-invasive hemodynamic monitoring. Importantly it also offers a new golden standard for validation and introduction of newer techniques for hemodynamic monitoring in pregnancy. The validation issue in the absence of an applicable gold standard, which has too often been the subject of discussion amongst interested can now be resolved. The potential of magnetic resonance is addressed for analysis of cardiac function in general and of the important but often neglected right heart in particular [50, 51]. Detailed volume analysis by MRI of both left and right atria and ventricles permits to deduct the respective contribution of caval (preload) and aortic (afterload) compression by the gravid uterus in dorsal decubitus with advancing pregnancy.

Sidestream Darkfield Imaging (SDF) is introduced and validated for the assessment of the microvascular perfusion in pregnant women [52]. The microcirculation is the largest compartment of the cardiovascular system and the site where its ultimate goal, the exchange of oxygen, nutrients and fluid for carbon dioxide and waste products with cells takes place. In severe pre-eclamptic women, we show that microvascular perfusion is unaffected despite major macrovascular disturbances. It reflects the complex interaction between the micro- and macrocirculation, which is characteristic for hemodynamic unstable conditions. It also revealed microcirculatory perfusion disturbances in women with HELLP syndrome which concur with the capricious pathophysiology of the condition. The non-invasive macrovascular (transthoracic echocardiography) and microvascular (SDF) techniques for maternal cardiovascular evaluation are combined and detailed uteroplacental and fetal Dopplers added. As such a hemodynamic profile is created. It offers a global picture of the pregnant woman and her products of conception in addition to a view on the complex interactions between these individual components of the challenged cardiovascular tree. The importance of this concept of non-invasive hemodynamic profiling in investigating and managing several pregnancy complications and its feasibility in both healthy and diseased pregnant women is demonstrated. Despite the absence of apparent changes in blood pressure, nifedipine tocolysis induces a substantial drop in vascular resistance in normotensive pregnant women [53]. A compensatory rise in cardiac output sustains the rest of the cardiovascular function and the uteroplacental and fetal perfusion in healthy women. It offers a detailed answer to the long debated cardiovascular risks and safety of nifedipine tocolysis . The same concept is applied for a detailed investigation of the hemodynamic effects of nicardipine in severe pre-eclamptic women with a hypertensive crisis [54]. The selective nature of the arterial relaxation and compensatory increase in cardiac output allow effective and safe blood pressure reduction while maintaining maternal cardiac function as well as uterine, microvascular, placental and fetal perfusion.

In women with heart disease, cardiovascular function along with uteroplacental perfusion and the interactions between them are investigated in both a single center and nationwide cohort [55, 56]. Cardiovascular adaptation to pregnancy is attenuated with a blunted rise in cardiac output, signs of progressive systolic and diastolic dysfunction and decreased uteroplacental perfusion. A relation between reduced cardiac function and impaired uteroplacental flow is established which is associated with adverse obstetric and neonatal outcomes. It still remains to be answered which pathophysiological mechanisms leads to the impairment in uteroplacental perfusion. Is it either a defective placentation occurring early in pregnancy, a mismatch between a failing cardiovascular perfusion potential and increasing placental perfusion requirements that occur with advancing gestation or a combination of both? Nevertheless, both studies show substantially increased incidences of cardiac, pregnancy or offspring complications in women with heart disease. Assessment of pregnancy outcomes in women with aortic valve substitutes in particular highlight the increased complication rate with mechanical valves [57]. As such, human tissue valves, despite their limited sustainability, should strongly be considered when counseling young non-pregnant women for optimal aortic valve substitutes. Optimal preconception care in women with heart disease also includes appropriate contraceptive advise. It requires an individual approach taking effectivity, safety, the particularities of the specific cardiac condition and the women's preferences into account. It is often complex and is best attended in time by a dedicated multidisciplinary specialized team. Our review offers guidance on the subject [58].

All our studies showed that ultrasound is the cornerstone for maternal, uteroplacental and fetal hemodynamic assessment. While uteroplacental and fetal ultrasound are well integrated into daily obstetric routine, maternal ultrasound is much less so and merits specific attention. The available obstetric ultrasound devices can easily be upgraded with cardiovascular software and probes. Given the similarities with fetal echocardiography, training of feto-maternal specialists is within reach. It would well fulfill with the true meaning of this subspecialty name. Along with obstetric anesthesiologists, maternal medicine internists, congenital cardiologists and neonatal intensivist they can form a dedicated feto-maternal critical care team where one a can further share and exchange ones expertise on an equivocal base. It also enables the further development of the field of Obstetric Critical Care. Finally maternal cardiovascular ultrasound protocols drafted and endorsed by the obstetric cardiovascular and ultrasound societies would further help to promote and implement maternal cardiovascular ultrasound into obstetric care.

Our studies in normal pregnant women, pre-eclamptic women and women with cardiac disease also showed that that the concept of hemodynamic profiling can help to elucidate the complex interactions between the several components of the cardiovascular tree.

Therefore it has a potential for permitting breakthroughs in the study and management of various pregnancy complications. This approach could be employed to address research questions in various domains like comparisons of different hypertensive drugs, effects of NO donors in fetal growth restriction or optimal amount of fluids required in postpartum hemorrhage and puerperal sepsis.

Still, this profile is neither yet offering a complete overview nor is it easily obtained. Cardiac and advanced obstetric ultrasound are operator and hardware dependent. They also provide single or intermittent measurements. Despite improvements with successors (Incident Dark Field (IDF)) of the SDF, analysis of microcirculatory images still remains time consuming [59, 60]. As such the concept needs further fine tuning and evolution. Dopplers from other core organs like the brain, kidneys and liver and venous system could relatively easily be obtained with the available systems and incorporated in the concept [61-63]. With evolutions in ultrasound devices probably being comparable to evolutions in personal computers, we have by far not employed the full potential offered by the newer generation ultrasound systems. Tissue Doppler and speckle tracking can help to quantify ventricular function independent of load and to reveal subtle differences [6, 64-67].

The former is important considering the continuous changes in loading conditions with evolving pregnancy. The relevance of the latter lies in the knowledge that subtle subclinical diastolic dysfunction often precedes later overt failure [68]. Epidemiological data show that pregnancy complications like pre-eclampsia, despite apparent postpartum recovery, remain associated with an increased risk of cardiovascular disease later in life [69, 70]. Recent studies using advanced echocardiography unmasked persistent systolic and diastolic dysfunction despite apparent clinical recovery after severe pre-eclampsia [68, 71]. It is still unknown whether pre-eclampsia is a symptomatic expression revealed by the cardiovascular stress of pregnancy or the cause of this increased cardiovascular risk. Either way, it offers a window of opportunity for screening and targeted interventions in these women.

While tissue Doppler and speckle tracking become mainstream in adult cardiology they still remain experimental in fetal cardiac assessment [72]. Given the clear limitations of current uteroplacental and fetal Dopplers and changing loading conditions during fetal life, these techniques might have an additional potential in reflecting fetal wellbeing, cardiac adaptation to chronic stress and response to medication [73].

Like women, pregnancy and its complications can be intriguingly complex. Despite some apparent similarities, the wide pallet of subtle interactions and interindividual variations which make them interesting can also render them difficult to understand and unpredictable, even for dedicated professionals. Hoping for simple solutions is therefore not realistic or fair. It is unlikely that evident changes in occasional measurements of a single parameter will offer a comprehensive answer. However, there could be a role for continuous concurrent measurements of several maternal, uteroplacental and fetal macro- and microvascular parameters, taking the concept of hemodynamic profiling to a next level. Dynamic trends and subtle changes can be observed within the individual. Large amounts data can be dredged and analyzed with modern software for apparent discrete but significant patterns and interactions. A personalized medicine approach is reached by assessing variations within one's individual profile. Ideally these parameters should be obtained with an non-invasive, continuous, easy to use, affordable, validated and operator independent method. Collection of basic physiological parameters like heart rate, blood pressure and arterial oxygen saturation are already common but physical connection to a device usually limits the subjects mobility. Continuous registration in different settings would allow to assess variability, reactivity and interaction with other parameters and rule out white coat interference. This will be facilitated by the explosion in the evolution of mobile smart devices and apps in the form of wearables like watches, glasses, lenses, clothes and chips. Besides peripheral arterial blood pressure, pulse wave analysis of peripheral artery wave form also permits the calculation of central blood pressure and markers of vascular stiffness like pulse wave velocity, augmentation index and to estimate cardiac output. For cardiac output measurements the third generation bio-impedance devices equally seem promising. Measurements can be obtained with minimal discomfort by simple application of chest electrodes. The signal quality and stability is sufficient for use during intense efforts and a wireless design permits measurements in ambulant subjects. As such, it does not require the presence of a high skilled health worker and can be used in a variety of situations and populations like laboring women, obstetric critical care settings, standard obstetric wards or healthy pregnant women. Validation can now be performed against transthoracic echocardiography in pregnant women and facilitated by comparing changes within the individual rather than absolute values. Inclusion of continuous cerebral monitoring is possible thanks to new devices allowing continuous cortical oximetry using NIRS and simultaneous EEG recordings with only a few sensors applied on the forehead. Continuous microvascular tissue perfusion and oxygen supply can be investigated with the O2C technology combining laser Doppler flow and tissue spectrophotometry in a single small probe. Rapid progressions also occur in the development of wearable electrodes or chips that allow, easy and continuous fetal heart rate monitoring while being mobile (Pure trace®, Monica Novii®, Pregsense®, Modoo®,…). By improving filtering techniques, additional information on fetal heart rate variability and fetal ECG becomes realistic.

With current smartphones capacities surpassing most older PCs, all these wireless measured physiological parameters could be recorded, stored, and integrated on them. As such, besides in acutely ill, hospital bed bound patients, continuous hemodynamic profiling could soon be employed for less severe conditions and in an ambulatory setting.

In conclusion this thesis shows that ultrasound becomes indispensable for advanced and integrated feto-maternal medicine and research. It permits non-invasive hemodynamic profiling which encompasses both the mothers', uteroplacental and fetal circulatory system and thus offers a complete overview. This concept can be used to unravel pathophysiological mechanisms, monitor treatment or to predict outcome. A multitude in evolutions of devices for wireless and continuous monitoring offers new perspectives to further integrate hemodynamic profiling in obstetric care, in- and outside the hospital. It could take the concept of hemodynamic profiling to a next level.

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Chapter 7

Summary

Samenvatting

SUMMARY

This thesis addresses the hemodynamics in several pregnancy complications. After the introduction (chapter 1), we start in chapter 2 by providing a general overview of normal hemodynamic adaptation to pregnancy. In order to permit a successful pregnancy outcome for both mother and child, the cardiovascular system must undergo substantial changes during pregnancy, labor, delivery and in the postpartum period. In chapter 2.1 adaptations in the various components of the cardiovascular tree during normal pregnancy are described in detail. In chapter 2.2 we further focus on the microcirculation. It is the largest albeit a lesser studied component of the cardiovascular system. Here, exchange of oxygen and nutrients for carbon dioxide and waste products with tissues takes place, which is the ultimate goal of circulation. In this chapter we describe the anatomy and physiology of the microcirculation along with the techniques, importance and potential of microvascular assessment in pregnant women.

In chapter 3 several techniques of non-invasive cardiovascular monitoring are addressed. In a meta-analysis of combined data from a prospective trial and systematic review, cardiac output measurements using transthoracic echocardiography showed excellent agreement with pulmonary artery catheterization in pregnant women (chapter 3.1). These results offer the opportunity to consider transthoracic echocardiography as an alternative reference technique. In chapter 3.2, the effects of left lateral and supine positioning on maternal cardiac function are described in each trimester of pregnancy. By using the ability of cardiac magnetic resonance to accurately assess cardiac volumes, the respective contributions of caval obstruction and aortic compression by the gravid uterus are determined.

In chapter 4 we address the potential of cardiovascular profiling by combining cardiac and obstetric ultrasound for maternal, uteroplacental and fetal hemodynamic monitoring in several pregnancy complications. The profile is further elaborated by including sidestream darkfield imaging to assess microvascular perfusion.

In chapter 4.1 we show that nifedipine tocolysis induces profound hemodynamic changes. A substantial reduction in systemic vascular resistance is balanced by an opposing rise in cardiac output thereby maintaining blood pressure, uteroplacental and fetal perfusion (chapter 4.1). In severe pre-eclamptic women with a hypertensive crisis, nicardipine effectively reduces blood pressure through selective afterload reduction. A compensatory increase in cardiac output assures uteroplacental, fetal and microvascular perfusion. This hemodynamic response is uniform and predictable (chapter 4.2). In chapter 4.3 we validated sidestream darkfield imaging in obstetrics. We did not observe major differences in sublingual microcirculatory perfusion between women with severe

pre-eclampsia and healthy pregnant controls. However HELLP syndrome is characterized by impaired capillary perfusion.

In the fifth chapter we focus on women with cardiac disease. With improvements in in medical and surgical care, most women with heart disease reach reproductive age. In chapter 5.1, a general overview is provided of pregnancy and delivery management in these women. A retrospective study reflecting 25 years of experience showed that cardiac and obstetric problems frequently complicate pregnancies of women with aortic valve replacements. As these complications occur more often with mechanical valves, human tissue valves should be considered in young women (chapter 5.2). By using obstetric and cardiac ultrasound we show in chapter 5.3 that 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 also suggest a persistent reduction in systolic and diastolic cardiac function after pregnancy in women with structural heart disease. Uteroplacental Doppler flow is impaired in women with heart disease. This impairment is associated with certain parameters of cardiac function. Obstetric and off spring complications frequently occur in women with heart disease and are often related to uteroplacental dysfunction (chapter 5.4). Preventing unintended pregnancies is equally important in women with heart disease. Early personalised contraceptive advise by a multidisciplinary team, where efficacy, inherent risks and benefits are evaluated in relation to the particularities of the cardiac condition and the women`s individual preference should be considered as an integral part of standard treatment. In many situations, progestogen-only long-acting reversible contraceptives are most suited for women with cardiovascular disease (chapter 5.5).

In chapter 6 we discuss our findings. With continuous evolutions and innovations in techniques for hemodynamic monitoring, we reflect on the potential of hemodynamic profiling in the near future. Finally, an English and Dutch summary is provided in chapter 7.

SAMENVATTING

Dit proefschrift beschrijft de hemodynamiek bij verschillende zwangerschapscomplicaties. Na de introductie (hoofdstuk 1) wordt in hoofdstuk twee een algemeen overzicht gegeven van de normale hemodynamische adaptatie aan de zwangerschap. Tijdens de zwangerschap, durante partu en in het kraambed moet het cardiovasculaire systeem substantiële veranderingen ondergaan om een goede uitkomst voor moeder en kind te realiseren. In hoofdstuk 2.1 worden aanpassingen in de verschillende componenten van het cardiovasculaire systeem gedurende de normale zwangerschap in detail beschreven. In hoofdstuk 2.2 wordt er toegespitst op de microcirculatie. Het is de grootste maar minder bestudeerde component van het cardiovasculaire systeem. Ter hoogte van de weefsels wordt hier zuurstof en nutriënten uitgewisseld voor koolstofdioxide en afvalproducten; in essentie het ultieme doel van de circulatie. In dit hoofdstuk worden naast de anatomie en fysiologie van een microcirculatie ook de verschillende technieken, het belang en potentieel van microvasculair onderzoek bij zwangere vrouwen aangekaart.

Hoofdstuk 3 gaat over verschillende technieken voor non-invasieve cardiovasculaire monitoring. In een meta-analyse die gegevens combineert van een prospectief onderzoek en een systematische review, tonen we aan dat cardiac output bepalingen door middel van transthoracale cardiografie zeer goed overeen stemmen met metingen verkregen door catheterisatie van de pulmonaal arterie bij zwangere vrouwen (hoofdstuk 3.1). Deze resultaten laten ons nu toe om transthoracale echocardiografie als alternatieve referentie techniek te beschouwen. In hoofdstuk 3.2 worden de effecten van rugligging en linker zijligging op de maternale cardiale functie beschreven in elk trimester van de zwangerschap. De eigenschap van cardiale magnetische resonantie om nauwkeurig volumes te bepalen wordt aangewend om de respectievelijk contributie van vena cava obstructie en aorta compressie door de zwangere uterus in kaart te brengen.

In hoofdstuk vier wordt het potentieel van cardiovasculaire profilering aangekaart. Cardiale en obstetrische echografie worden gecombineerd voor maternale, uteroplacentaire en foetale hemodynamische monitoring bij verschillende zwangerschapscomplicaties. Het profiel wordt verder aangevuld met sidestream darkfield imaging voor onderzoek van de microvasculaire perfusie.

In hoofdstuk 4.1 tonen we aan dat tocolyse met nifedipine belangrijke hemodynamische veranderingen induceert. Een substantiële reductie van de systemische vasculaire weerstand wordt opgevangen door een stijging in cardiac output waardoor de bloeddruk, uteroplacentaire en foetale perfusie behouden blijven. Bij ernstige pre-eclamptische vrouwen met een hypertensieve crisis wordt de bloeddruk met nicardipine effectief verlaagd door selectieve afterload reductie. Een compensatoire toename in cardiac output verzekert de uteroplacentaire, foetale en microvasculaire perfusie. Deze hemodynamische respons is uniform en voorspelbaar (hoofdstuk 4.2). In hoofdstuk 4.3 valideren we sidestream darkfield imaging in de obstetrie. Er werden geen majeure verschillen geobserveerd in de sublinguale microcirculatoire perfusie tussen vrouwen met ernstige pre-eclampsie en gezonde zwangere controles. Het HELLP-syndroom wordt gekenmerkt door een verstoorde capillairen perfusie.

Het vijfde hoofdstuk gaat over vrouwen met een hartziekte. Door verbetering in medische en heelkundige zorg bereiken de meeste vrouwen met een hartziekte de vruchtbare leeftijd. In hoofdstuk 5.1 wordt een algemeen overzicht aangeboden over het beleid tijdens de zwangerschap en de bevalling bij deze vrouwen. Een retrospectief onderzoek over 25 jaar toont aan dat cardiale en obstetrische problemen frequent optreden bij zwangere vrouwen met aortaklep vervanging. Aangezien deze complicaties vaker voorkomen bij mechanische kleppen, moeten humane weefselkleppen ernstig in overweging worden genomen bij jonge vrouwen met potentiële kinderwens (hoofdstuk 5.2). Aan de hand van obstetrische en cardiale echografie tonen we in hoofdstuk 5.3 aan dat het karakteristieke patroon van hemodynamische adaptatie aan de zwangerschap is afgevlakt bij vrouwen met structurele hartziekte. De volume belasting door de zwangerschap induceert een toename in diastolische dysfunctie. Onze bevindingen suggereren ook dat de reductie in systolische en diastolische functie persisteert na de zwangerschap. Uteroplacentaire Doppler flow is gestoord bij vrouwen met hartziekte. Deze verstoring is geassocieerd met bepaalde cardiale parameters. Obstetrische complicaties en complicaties bij de kinderen komen frequenter voor bij vrouwen met hartziekte en zijn vaak gerelateerd aan de uteroplacentaire dysfunctie (hoofdstuk 5.4). Het voorkomen van een ongeplande zwangerschap is belangrijk bij vrouwen met hartziekte. Het vereist een vroeg en gepersonaliseerd contraceptief advies door een multidisciplinair team. Hierbij worden effectiviteit, inherente risico's en voordelen meegenomen evenals de bijzonderheden van de cardiale conditie en de persoonlijke voorkeur van de vrouw. Dit gewogen contraceptief advies maakt integraal deel van de standaard zorg voor vrouwen met een hartziekte. Vaak zijn reversibele, lang werkende contraceptieve methodes die enkel progesteron bevatten het meest aangewezen voor vrouwen met een hartziekte.

In hoofdstuk zes worden de bevindingen bediscussieerd. Gezien de continue evolutie en innovatie in technieken voor hemodynamische monitoring, reflecteren we op het potentieel van hemodynamische profilering in de nabije toekomst. Hoofstuk zeven bestaat uit een Engelse en Nederlandse samenvatting.

Chapter 8

PhD portofolio

Curriculum vitae

Publications

Authors and affiliations

Dankwoord

PHD PORTFOLIO

Name PhD candidate: J.M.J. Cornette
Erasmus MC Department: Obstetrics & Gynaecology
PhD period: 2007-2016
Promotor: Prof. dr. E.A.P. Steegers
Prof. dr. J.W. Roos-Hesselink
Co-promotors: dr. J.J. Duvekot

1.PhD training	Year	ECTS
<u>International conferences, workshops and presentations</u>		
- Obstetrical critical care symposium, Rotterdam	2016	1
1 presentation		
-.European congress of perinatal medicine (ECPM), Maastricht	2016	3
2 presentations, moderator		
- Second international congress on maternal hemodynamics, Rome	2016	3
1 presentation, moderator, organizing committee		
- Cursus prenatale geneeskunde voor de gynecoloog, Rotterdam	2016	1.5
1 presentation		
- Developmental origin of health and disease congress (DOHAD), Cape-Town	2015	1.5
1 presentation		
- International society for the study of hypertension in pregnancy congress (ISSHP), Budapest	2015	1
- 20e Nederlands-Vlaams Doelen congres, Rotterdam	2015	1.5
moderator		
- Cardiologie in zwangerschap, Ede	2015	0.25
-.First international congress on maternal hemodynamics, Hasselt	2014	3
3 presentations, moderator, organizing committee		
- Maternale ziekten en management van ernstige maternale complicaties, Leiden	2014	3
2 presentations, moderator, organizing committee		
-.Priorities in perinatal medicine, Cape Town	2014	1.5
1 presentation		
-.Cardiac problems in pregnancy congress (CPP), Venice	2014	1
- Gynaecongres//cardiocongres NVOG,VVOG en NVCC, Amersfoort, Papendal, Breda, Gent, Antwerpen	2007-2016	1.5
1 presentation at the NVCC		
- 12th World congress in fetal medicine (FMF), Marbella	2013	1
- Nederlands-Vlaams Doelen congres, Rotterdam	2009-2013	0.5
- Boerhaeve foetale geneeskunde, Leiden	2009-2013	1.5

1.PhD training	Year	ECTS
1 presentation		
-.Second European congress on preconception care and health Rotterdam	2013	0.5
-.Workshops on maternal hemodynamics, Cambridge, Rome, Rotterdam, London, Cardiff	2009-2016	4
5 presentations , organization of the Rotterdam meeting, organizing committee		
- Prisma in de praktijk, Rotterdam	2012	0.5
- ISUOG World Congress on Ultrasound in Obstetrics and Gynecology, Kopenhagen	2012	2
1 presentation		
- Foetale neurosonografie cursus, Utrecht	2012	0.25
- ISSHP, Rome	2011	2
1 presentation and 1 poster		
- Society of gynecological investigations (SGI), Miami	2011	1.25
2 poster presentations		
-. CPP, Valencia	2010	1
- Zwangerschap en cardiovasculaire, Utrecht afwijkingen,	2009	0.25
-.Maternal intensive care congres, Antwerpen	2009	1
1 presentation		
- Gezondheidsaspecten bij prenatale zorg en partus anno 2009, Antwerpen	2009	0.25
- ISSHP, Washington	2008	1.25
1 poster		
- 8th World Congress of Perinatal Medicine, Florence	2007	1
-. Robotica in de Gynaecologie, Antwerpen	2007	0.25
-. 3D echocardiografie cursus, Eindhoven	2007	0.25
-. 3D echgrafiecursus obstetrie, Rotterdam/Zwolle	2007	0.25
-. Refereeravonden Rotterdamse cluster, Rotterdam	2007	0.5
4 presentations, 1 organization local meeting		
-. Regional obstetric consortium (Bella Obstetrica)., Rotterdam	2007-2016	1
Total		**45**

2. Teaching activities		
Didactic Skills		
- Generic instructor course (GIC), Tilburg	2007	1
- Managing obstetrical emergency and trauma (MOET) Intructor, Tilburg	2008-2016	5
- Generic Instructor course instructor, Tilburg	2015	1
- Teach the teacher, Rotterdam	2008	0.5
Teaching		
- Lectures,practicals and minor obstetrics, Rotterdam School of medicine (EUR)	2007-2016	4
- National Training days for registrars in O&G (NVOG)	2009-2016	5
- Lectures Obstetrics, School for Midwifery and School for Nurses (HRO)	2007-2016	1
Supervising Master's theses		
- Clinical Obstetrics, I.Herrewijnen (HR0)	2013-2015	3

1.PhD training	Year	ECTS
- Clinical Obstetrics, R van Dijk (HRO)	2010-2012	1
- Medicine, J.Erkamp (EUR)	2012	3
- Medicine, E Herzog (EUR)	2010	3
- Medicine, C Jacobs (EUR)	2016	3
- Medicine, S Wanders (EUR)	2016	3
- PhD Dominique Mannaerts	2007-2016	1
- Mentorship of registrars	2007-2016	1
Total		**35.5**
3. Other activities		
- Guest editor Journal of Pregnancy	2012	1
- Reviewer BJOG, Ultrasound in Obstetrics and Gynecology, Gynecologic and Obstetric Investigations, Journal of Obstetrics and Gynaecology, Journal of Pregnancy, Fetal Diagnosis and Therapy, Circulation, Heart, European Journal of Epidemiology, Fetal and Maternal Medicine Review, Obstetrics and Gynaecology Research, International Journal of Biological and Chemical Sciences, NTVG, NTOG	2007-2016	3
- Jury member PhD defense Anneleen Staelens, Universiteit Hasselt	2016	1
Total		**5**

Total ETCS points: 85.5

CURRICULUM VITAE

Jérôme Cornette was born as the oldest of four children on the 28th of December 1974 in Antwerp, Belgium. After attending his primary school at the St-Stanislas college and secondary school at the Onze-Lieve-Vrouw-van-Lourdescollege, he starts his medicine studies at the University of Antwerp. He graduates as an M.D. in 1999 and starts his specialty training in Obstetrics and Gynaecology at the University Hospital of Antwerp (UZA) followed by a registrarship at the Kalafong Hospital from the University of Pretoria (South Africa) and at the St-Augustinus Ziekenhuis in Antwerp.

From 2004 to 2006 he accomplishes a subspecialty training in Perinatal Medicine (Maternal and Fetal Medicine) at the Erasmus MC in Rotterdam (The Netherlands). Since then he works there as a consultant with special interest in obstetric critical care, congenital cardiology and prenatal diagnosis. His research in hemodynamics was initiated at the Kalafong Hospital with a research grant from the MRC and was continued at the department of Obstetrics in close collaboration with the department of Cardiology from the Erasmus MC.

Jérôme Cornette lives in Brasschaat (Belgium) with Maite Zorita Diaz, and together they have son and daughter, Noah and Camille.

PUBLICATION LIST

1. Wilms FF, Vis JY, Oudijk MA, Kwee A, Porath MM, Scheepers HC, et al. The impact of fetal gender and ethnicity on the risk of spontaneous preterm delivery in women with symptoms of preterm labor. J Matern Fetal Neonatal Med. 2016 Nov;29(21):3563-9.
2. van Hagen IM, Cornette J, Johnson MR, Roos-Hesselink JW. Managing cardiac emergencies in pregnancy. Heart. 2016 Sep 14.
3. Srebniak MI, van Zutven LJ, Petit F, Bouquillon S, van Heel IP, Knapen MF, et al. Interstitial 6q21q23 duplication - variant of variable phenotype and incomplete penetrance or benign duplication? Mol Cytogenet. 2016;9:43.
4. Erkamp J, Cornette J. Contraception and Cardiovascular Disease. Book chapter in: Pregnancy and Congenital Heart Disease. London: Springer; 2016.
5. Cornette J, Laker S, Jeffery B, Lombaard H, Alberts A, Rizopoulos D, et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheters in severely ill pregnant women. A prospective comparative study and systematic review. Ultrasound Obstet Gynecol. 2016 Jul 12.
6. Cornette J, Buijs EA, Duvekot JJ, Herzog E, Roos-Hesselink JW, Rizopoulos D, et al. Hemodynamic effects of intravenous nicardipine in severely pre-eclamptic women with a hypertensive crisis. Ultrasound Obstet Gynecol. 2016 Jan;47(1):89-95.
7. Cornette J, Brückman A. The microcirculation: physiology and measurements. Book chapter in: Maternal Hemodynamics. Cambridge Cambridge University Press; 2016.
8. Cornette J. Author's reply re: Microcirculation in women with severe pre-eclampsia and HELLP syndrome: a case control study. BJOG. 2016 Sep;123(10):1710-1.
9. Bruijn MM, Hermans FJ, Vis JY, Wilms FF, Oudijk MA, Kwee A, et al. Which Factors Contribute to False-Positive, False-Negative, and Invalid Results in Fetal Fibronectin Testing in Women with Symptoms of Preterm Labor? Am J Perinatol. 2016 Jul 21.
10. Brückman A, Cornette J. Microvascular findings in pathological pregnancies. Book chapter in: Maternal Hemodynamics. Cambridge Cambridge University Press; 2016.
11. Wilms FF, van Baaren GJ, Vis JY, Oudijk MA, Kwee A, Porath MM, et al. Prescribing patterns of antenatal corticosteroids in women with threatened preterm labor. Eur J Obstet Gynecol Reprod Biol. 2015 Sep;192:47-53.
12. Vis JY, van Baaren GJ, Wilms FF, Oudijk MA, Kwee A, Porath MM, et al. Randomized comparison of nifedipine and placebo in fibronectin-negative women with symptoms of preterm labor and a short cervix (APOSTEL-I Trial). Am J Perinatol. 2015 Apr;32(5):451-60.
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surement in the prediction of preterm delivery in symptomatic women? Eur J Obstet Gynecol Reprod Biol. 2015 Sep;192:79-85.
14. Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, Vasario E, Gaisin IR, Iung B, et al. Is a planned caesarean section in women with cardiac disease beneficial? Heart. 2015 Apr;101(7):530-6.
15. Roos-Hesselink JW, Cornette J, Sliwa K, Pieper PG, Veldtman GR, Johnson MR. Contraception and cardiovascular disease. Eur Heart J. 2015 Jul 14;36(27):1728-34, 34a-34b.
16. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet. 2015 May 30;385(9983):2162-72.
17. Laubach M, Cornette J. Organisatie van de verloskundige zorg in Vlaanderen en Nederland. Handboek verloskunde: Acco Uitgeverij; 2015. p. 64-6.
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19. Bruijn M, Vis JY, Wilms FF, Oudijk MA, Kwee A, Porath MM, et al. Quantitative fetal fibronectin testing in combination with cervical length measurement in the prediction of spontaneous preterm delivery in symptomatic women. BJOG. 2015 Dec 15.
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22. Cornette J, van der Wilk E, Janssen NM, van der Weiden RM, Jenninkens SF, Pattynama P, et al. Uterine artery pseudoaneurysm requiring embolization during pregnancy. Obstet Gynecol. 2014 Feb;123(2 Pt 2 Suppl 2):453-6.
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24. Cornette J, Herzog E, Buijs EA, Duvekot JJ, Rizopoulos D, Hop WC, et al. Microcirculation in women with severe pre-eclampsia and HELLP syndrome: a case-control study. BJOG. 2014 Feb;121(3):363-70.
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