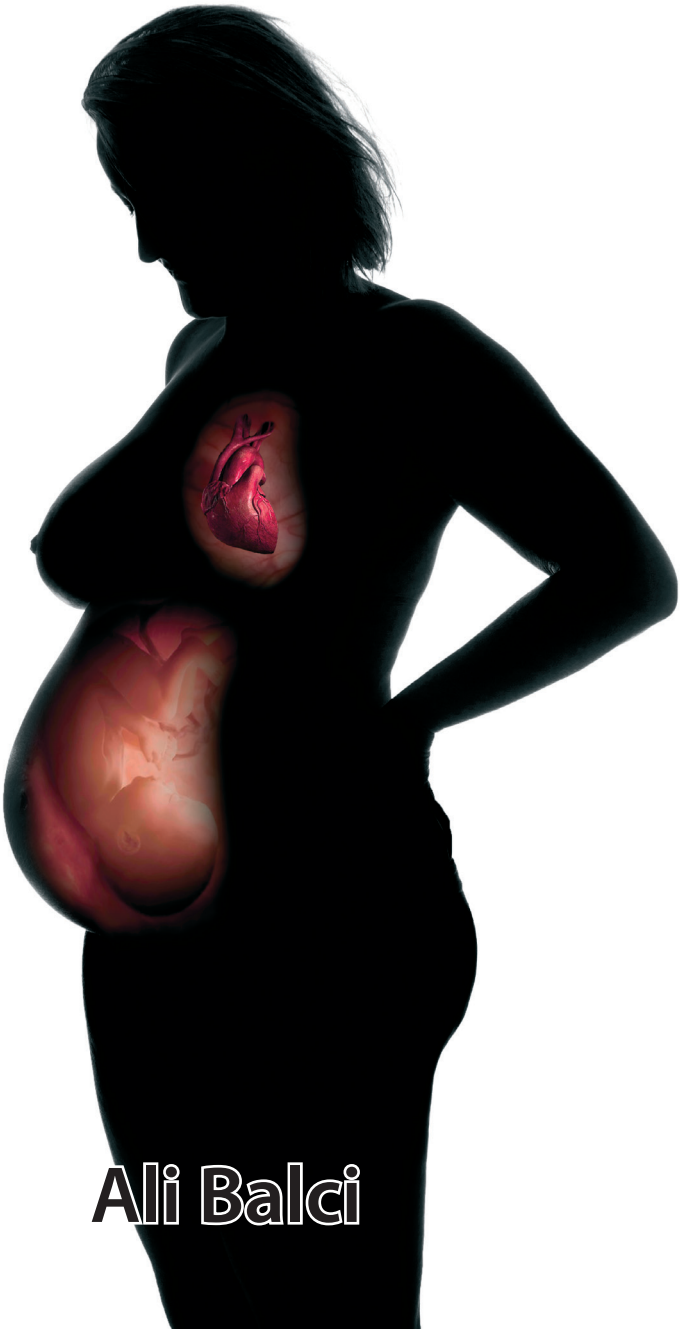
Pregnancy and Outcome in Women with Congenital Heart Disease



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'Voici mon secret.

Il est très simple:

on ne voit bien qu'avec le coeur.

L'essentiel est invisible pour les yeux'

Antoine de Saint-Exupéry

Le Petit Prince

1943

Voor Jeannine & Elin
Aan mijn familie

Contents

Chapter 1 Introduction

Epidemiology

The increasing success of congenital heart surgery allows more and more infants with (complex) congenital heart disease (CHD) to reach adulthood. Congenital heart disease is the most frequently occurring congenital disorder in new-borns, with a birth prevalence of approximately 9/1000 live births worldwide and 8/1000 in Europe.[1] The prevalence of adults with CHD is 4.09 per 1000 adults in Canada and approximately 60% of them are women in the childbearing age, representing the majority of pregnant women with heart disease.[2,3]

Most women with CHD have had corrective or palliative surgery. The majority of these women have residua and sequelae after surgery.[4] Approximately 80% of women who reach childbearing age have a pregnancy wish.[5] Although many women with CHD tolerate pregnancy well, complication rate is considerable.[6,7]

Physiological changes in pregnancy

In order to meet the increased maternal and foetal metabolic demands, pregnancy induces changes in the cardiovascular system including increases in blood volume, cardiac output, heart rate (preload) and decrease in systolic and diastolic blood pressure and systemic vascular resistance (afterload) as well as changes in neurohormonal parameters and a hypercoagulable state.[8]

In normal pregnancy, plasma volume reaches its maximum of 40% above prepregnancy level at the end of the 2nd trimester. Cardiac output (CO) increases during pregnancy up to 50% caused by a rise in stroke volume during early pregnancy, while heart rate becomes the major factor in late pregnancy. Mean heart rate increases with 10-20 beats in the course of pregnancy, peaking in early third trimester.[9,10] (Figure 1) Systemic blood pressure in general falls in early and mid pregnancy due to vasodilatation and may return to prepregnancy values towards the end of pregnancy. There is a fall in systemic vascular resistance between gestational week 5 with a nadir between weeks 20-32. After week 32 of gestation systemic vascular resistance increases again. There is a corresponding decrease in systemic blood pressure in the first trimester reaching its nadir at mid-pregnancy. Thereafter, systemic blood pressure rises again to prepregnancy levels round term.[8,9]

The changes in pre- and afterload are accompanied by remodelling in the ventricles and atria. Both atria and ventricles increase in size. Left ventricular (LV) remodelling also manifests as increase in LV wall thickness and mass.[8,11-13] Mitral, tricuspid, aortic and pulmonic annular diameter increase, which may cause some increase of valve regurgitation. Most women remain in sinus rhythm during pregnancy, however premature atrial and ventricular complexes may become more frequent as a result of increases in chamber size.

The ability of a normal heart to adapt to chronic volume overload prevents the central venous pressure from increasing in healthy women.[14]

In normal pregnancy, deceleration time of the E-wave of trans-mitral flow is longer during the 2nd trimester due to a slightly increased resistance to diastolic flow, caused by an increase in left ventricular mass.[15] In general, diastolic function is much less studied in pregnancy in healthy women, and data in CHD are very rare.

The activated erythropoiesis results in a 20-30% increase in the red blood cell mass to meet the maternal and foetal oxygen needs. However, due to a relative larger increase in plasma volume than red blood cell mass, pregnant women tend to have anaemia due to hemodilution.

Brain natriuretic peptide (BNP) is released in response to ventricular distension due to volume overload in pregnancy.[16] Like BNP, NT-proBNP values are also higher during pregnancy than in non-pregnant controls.[17] In addition, NT-proBNP values reveal a dynamic course during pregnancy. Elevated NT-proBNP values in the first two trimesters probably represent elevated cardiac stress caused by the adaptation of the maternal circulation. The decrease of NT-proBNP beginning in the second trimester may possibly reflect the decrease in vascular resistance during the second trimester.

Pregnancy is associated with several haemostatic changes including a rise in coagulation factors, fibrinogen and platelet adhesiveness, but also a decrease in fibrinolysis. This causes a hypercoagulable state and increases the risk of thromboembolism. Any pre-existing haemostatic disorders associated with the heart defect are at particular risk. These include patients with a Fontan circulation, right-to-left shunt and pulmonary hypertension. Women with mechanical prosthetic valves are also at higher risk of thromboembolism.

Significant rises in central blood volume, blood pressure and cardiac output occur during contractions in labour and due to auto-transfusion in the postpartum period, associated with uterine involution and resorption of leg oedema. Cardiovascular haemodynamic state returns back to prepregnancy state in most women within 6 months postpartum.[18,19]

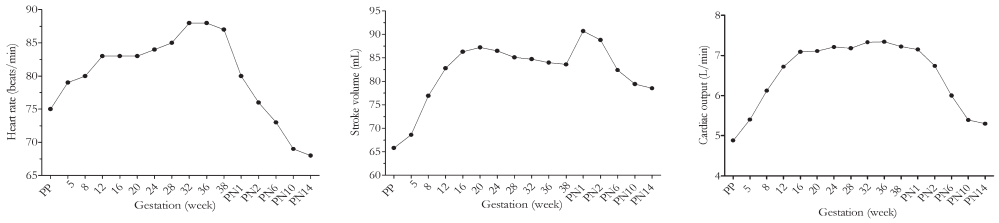

Figure 1. Change in heart rate, stroke volume and cardiac output from the non-pregnancy state, during pregnancy and the first 14 postnatal days. **PP**, prepregnancy; **PN**, postnatal day. (Reproduced from Robson et al.[9,20])

Effect of changes in pregnancy in women with CHD

The cardiovascular changes may not be well tolerated in women with CHD, leading to cardiac events such as heart failure and arrhythmia but also leading to offspring events such as intra uterine growth retardation (IUGR), prematurity and death. Not only volume overload may induce adverse events in the offspring, a reduced plasma volume expansion has also been associated with IUGR and low birth weight.[21]

The required increase in CO aggravates the haemodynamic burden in women with CHD. This is especially important in women with obstructive lesions, since CO in these women is relatively fixed.[22,6,23]

Women with aortic and mitral regurgitation, left to right shunts, as well as women with a right systemic ventricle, may benefit from pregnancy related fall in systemic vascular resistance. However, the fall in systemic vascular resistance may cause right to left shunts to increase during pregnancy, leading to increased dyspnoea and cyanosis as well as adverse events in the offspring. In women with CHD, the pre-existing burden of pressure or volume overload may prevent the ventricles to increase CO or require increased filling pressure to do so, especially when concomitant ventricular dysfunctions exist. This may result in heart failure during pregnancy. Significant ventricular dysfunction already present before pregnancy is associated with a high risk of adverse outcome.[6,23]

Increases in atrial size may contribute to an increase in the frequency of supraventricular arrhythmias. Women with a history of arrhythmia prepregnancy are at increased risk of adverse cardiac events during pregnancy as has been demonstrated in women with tetralogy of Fallot.[5-7,23] BNP levels in women with heart disease are higher than in healthy women. Moreover, BNP levels ≤100 pg/ml have a negative predictive value of 100% for identifying events during pregnancy.[24]

In the peri- and postpartum periods maternal heart failure may develop due to significant rises in blood volume and cardiac output during contractions in labour and auto-transfusion in the postpartum period.

Pregnancy outcome in women with CHD

The haemodynamic changes in the course of pregnancy are associated with increased risk in women with CHD. Heart disease is the most common cause of maternal death and the leading non-obstetric cause in the United Kingdom. However, only 6 per cent of these deaths are related to maternal congenital heart disease.[25,26] In the Netherlands, maternal death caused by cardiovascular diseases is the 2nd most frequent cause after preeclampsia, followed by death as a result of thromboembolism. CHD causes 13% of maternal cardiovascular deaths in the Netherlands.

Outside pregnancy, most frequent cardiac problems in women with CHD are heart rhythm disorders, heart failure, endocarditis, obstructions of conduits and valve dysfunction.[27] Most frequent pregnancy related cardiac problems are heart failure, heart rhythm disorders and thromboembolism. Pregnant women with CHD are not only more susceptible to cardiac complications such as heart failure and arrhythmias, also obstetric complications such as hypertensive disorders of pregnancy (pregnancy induced hypertension and preeclampsia), premature delivery and offspring complications, such as offspring death, small for gestational age and recurrence of CHD in the offspring are more frequent. [6,7,23]

Most adverse events can be prevented, or effectively treated provided risk factors are recognized timely. To do so, it is important to predict potential adverse events in advance both for the mother and the offspring.

Predictors of adverse pregnancy outcome

Several independent risk factors for maternal cardiovascular complications of pregnancy, such as

left heart obstruction, reduced systemic ventricular function and mechanical valve prosthesis, have been identified. Table 1 gives an overview of the predictors of cardiovascular events in pregnancy in women with heart disease, as identified in the world literature. Independent risk factors for offspring events in women with CHD are also found. (Table 2) Not only the specific CHD related risk factors influence pregnancy outcome, generally known predictors for adverse pregnancy outcome such as age, parity, maternal diabetes, hypertensive disorders of pregnancy and smoking also apply to women with CHD. Although predictors may help to identify women at risk for adverse events in pregnancy, it should be kept in mind that the applicability of these predictors depends on the population selected.

Risk stratification

Several models are available to assess the risk of pregnancy in women with CHD. The best know and most widely used model to predict cardiac outcome was introduced by the CARPREG investigators.[6] (Table 1) The CARPREG risk score is based on both CHD and acquired heart disease, resulting in an overestimation of cardiovascular risk of pregnancy in women with CHD. Another way to assess risk of pregnancy is by classification of the complexity of CHD.[28,29] Women with complex congenital heart disease are known to have higher frequencies of cardiovascular events in pregnancy.[7] The complexity of heart disease however does not take into account the current cardiac function, previous events or complicating factors such as aortic diameter in women with bicuspid aortic valve or Marfan's syndrome.

The ESC guidelines recommend that maternal risk should be assessed according to a modified World Health Organization risk classification.[34,35] The group in whom pregnancy should be avoided and the low risk group in whom pregnancy is expected to be well tolerated are well defined. The groups in whom risk of pregnancy is mildly or mildly to moderately elevated is less well defined and sometimes needs an expert to assess. No CHD specific prediction model was available so far.

Table 1. Predictors of maternal cardiovascular complications during pregnancy

Predictor	Study	Population	Risk points
CARPREG			
Prior cardiac event (heart failure, TIA, stroke, arrhythmia)	CARPREG[6]	CHD, AHD	1
NYHA functional class III/IV or cyanosis (SpO2 <90%)	CARPREG	CHD, AHD	1
Left heart obstruction	CARPREG	CHD, AHD	1
(MVA <2 cm^2 or AVA <1.5 cm^2 or peak LVOT gradient >30 mmHg			
Reduced systemic ventricular systolic function (EF <40%)	CARPREG	CHD, AHD	1
ZAHARA			
History of arrhythmia	ZAHARA[23]	CHD	1.50
NYHA functional class III/IV	ZAHARA	CHD	0.75
Left heart obstruction (peak LVOT gradient >50 mmHg or AVA <1.0 cm^2)	ZAHARA	CHD	2.50
Mechanical valve prosthesis	ZAHARA	CHD	4.25
Systemic AV valve regurgitation (moderate/severe)	ZAHARA	CHD	0.75
Pulmonary AV valve regurgitation (moderate/severe)	ZAHARA	CHD	0.75
Cardiac medication before pregnancy	ZAHARA	CHD	1.50
Cyanotic heart disease (corrected and uncorrected)	ZAHARA	CHD	1.00
OTHER STUDIES			
Prior cardiac event (heart failure, TIA, stroke, arrhythmia)	Tanous[24]	CHD, AHD	
Cardiac medication before pregnancy	Tanous	CHD, AHD	
Anticoagulation therapy	Tanous	CHD, AHD	
Maximum BNP >100 pg/ml	Tanous	CHD, AHD	
Right ventricular dilatation	Song[30]	CHD	
Pulmonary arterial hypertension	Song	CHD	
NYHA functional class III/IV	Song	CHD	
NYHA functional class III/IV	Kovavisarach[31]	CHD, AHD	
Smoking history	Khairy[32]	CHD	
Reduced sub-pulmonary ventricular function and/or severe PR	Khairy	CHD	

CARPREG risk score: For each CARPREG predictor that is present, 1 point is assigned to the pregnancy. The risk score is the total number of points. The risk of maternal cardiovascular complications is 5% with 0 points, 27% with 1 point and 75% with ≥1 point.

ZAHARA risk score: For each ZAHARA predictor that is present, a predictor-specific number of points is assigned to the pregnancy, according to the table. The risk of maternal cardiovascular complications is 2.9% with <0.5 points, 7.5% with 0.5–1.5 points, 17.5% with 1.51–2.50 points, 43.1% with 2.51–3.5 points and 70% with >3.5 points.

AHD, acquired heart disease; **AV**, atrioventricular; **AVA**, aortic valve area; **BNP**, B-type natriuretic peptide; **CHD**, congenital heart disease; **EF**, ejection fraction; **LVOT**, left ventricular outflow tract; **MVA**, mitral valve area; **NYHA**, New York Heart Association; **PR**, pulmonary regurgitation, **SpO_2**, Saturation of Haemoglobin with Oxygen as measured by Pulse Oximetry; **TIA**, transient ischemic attack (Adapted from Pieper 2011)[33]

Table 2. Predictors of offspring complications during pregnancy and puerperium

Predictor	Study	Population	Risk points
CARPREG			
NYHA functional class III/IV or cyanosis (SpO_2 <90%)	CARPREG [6]	CHD, AHD	
Heparin / Warfarin use during pregnancy	CARPREG	CHD, AHD	
Smoking during pregnancy	CARPREG	CHD, AHD	
Multiple gestation	CARPREG	CHD, AHD	
Left heart obstruction	CARPREG	CHD, AHD	
(MVA <2 cm^2 or AVA <1.5 cm^2or peak LVOT gradient >30 mmHg			
ZAHARA			
Mechanical valve prosthesis	ZAHARA [23]	CHD	2.50
Twin or multiple gestation	ZAHARA	CHD	1.75
Cyanotic heart disease (corrected and uncorrected)	ZAHARA	CHD	0.75
Cardiac medication before pregnancy	ZAHARA	CHD	0.75
Smoking during pregnancy	ZAHARA	CHD	0.50
OTHER STUDIES			
Subaortic ventricular outflow tract gradient > 30 mmHg	Khairy [32]	CHD	
Myocardial dysfunction*	Gelson [36]	CHD, AHD	
Pulmonary hypertension	Song [30]	CHD	
NYHA functional class III/IV	Song	CHD	

ZAHARA risk score: For each ZAHARA predictor that is present, a predictor-specific number of points are assigned to the pregnancy, according to the table. The risk of offspring complications is 19.9% with <0.5 points, 33.3% with 0.5–1.0 points, 46.7% with 1.00–1.50 points and 59.5% with >1.5 points.

AHD, acquired heart disease; **AVA**, aortic valve area; **CHD**, congenital heart disease; **LVOT**, left ventricular outflow tract; **MVA**, mitral valve area; **NYHA**, New York Heart Association; **PR**, pulmonary regurgitation, **SpO_2**, Saturation of Haemoglobin with Oxygen as measured by Pulse Oximetry
* Unspecified

ZAHARA I study

To give disease specific insights in the complications women with CHD encounter during pregnancy and to investigate the magnitude and determinants of risks associated with pregnancy in specific groups of women with CHD, the first ZAHARA study was set up. For this purpose, a total of 1302 pregnancies in 1802 women with CHD were observed in retrospect.[23] The ZAHARA I study revealed some disease specific predictors of adverse pregnancy outcome.[5,23,37-40] In this thesis, we introduce predictors for maternal cardiovascular and offspring complications in women with tetralogy of Fallot.[5] In addition, we introduce a specific model for pregnancy in women with CHD in general and validate this model. To give a complete overview, this model is included in table 1.

The abovementioned prediction models by the CARPREG investigators and our own prediction model as well as individual predictors found by others (Table 1) may allow refining of risk assessment in women with CHD. It is important that CHD specific risk assessment and counselling is done before women with CHD become pregnant so that a pregnancy management plan, including changes in medication, planning of follow-up visits (during pregnancy) and the mode and location of delivery can be made.

Role of cardiac function in prediction of uteroplacental Doppler flow

In normal pregnancy, a gradual widening of the maternal spiral arteries occurs early in the first trimester due to the invasion of endovascular and interstitial trophoblasts that convert maternal spiral arteries closer to the intervillous space. To maintain adequate organ and uteroplacental perfusion, haemodynamic changes such as increased plasma volume and CO and decreased systemic vascular resistance must take place. During normal pregnancy, blood flow increases in the low impedance uteroplacental circulation, reaching up to 500ml/min at term. Placental flow increase until gestational week 25 and then remains unchanged.[41] Reduced invasion and subsequent remodelling of maternal spiral arteries in the first and second trimester lead to an impaired placental perfusion and release of factors into the maternal circulation resulting in endothelial cell damage leading to hypertensive disorders of pregnancy, which affects 6-10% of pregnancies.[42] Hypertensive disorders of pregnancy, especially preeclampsia, are characterized by impaired trophoblasts invasion and failure of dilatation of spiral arteries, resulting in high uteroplacental vascular resistance, leading to inadequate uteroplacental perfusion and adverse obstetric and offspring outcome.[43,44] Moreover, poor trophoblast invasion and abnormal uteroplacental Doppler flow is associated with cardiovascular dysfunction.[45,46]

Compromised uterine perfusion with placental dysfunction is reflected by abnormal uteroplacental Doppler flow patterns.[47] Uterine artery pulsatility index (PI) and resistance index (RI) are associated with CO, stroke volume, left ventricular isovolumetric relaxation time (IVRT) and systemic vascular resistance.[15] Abnormal uterine artery PI/RI as well as the presence of a notch in early diastolic phase predict preeclampsia, are related to high systemic vascular resistance and low CO, and are associated with adverse outcome in the offspring such as IUGR and small for gestational age, dysmaturity and low birth weight. In CHD, a higher incidence of preeclampsia and IUGR is seen.[6,7,23,32,48,49] This may be related to the impaired cardiac function in women with CHD, leading to a lower CO and to an inadequate uteroplacental perfusion.

Objectives of this thesis

The main objectives of this thesis are to identify predictors of adverse outcome in pregnancies of women with CHD, to assess the best currently available model to predict pregnancy outcome and to elucidate the mechanism behind the high incidence of offspring events in pregnancies of women with CHD, in particular the interaction between the maternal cardiac function and uteroplacental flow.

Outline of this thesis

Part I addresses in retrospect complications and predictors of adverse pregnancy events in women with CHD. In ***chapter two*** pregnancy outcome as well as predictors of adverse outcome are described in women with tetralogy of Fallot; one of the larger groups of CHD patients. In ***chapter three*** an overview is given of complications and predictors for the total group of women with CHD. In addition, the most frequently used prediction model for the estimation of pregnancy risk in women with heart disease is validated and compared with a newly developed CHD-specific pregnancy risk model.

Part II covers the prospective assessment of predictors of adverse events in pregnancy in women with CHD. ***Chapter four*** provides the design and rationale of the prospective multicentre ZAHARA II study and in ***chapter five*** the various available risk estimation models are validated and mutually compared using the ZAHARA II population. ***Chapter six*** describes the main outcomes of the ZAHARA II study: the difference in cardiovascular, clinical, biochemical and echocardiographic parameters, the difference in uteroplacental Doppler flow patterns as well as difference in outcome between pregnant women with CHD and healthy pregnant women. In addition, the relation between the maternal cardiac function in women with CHD and the uteroplacental Doppler flow measurements is assessed and predictors of adverse uteroplacental Doppler flow patterns are presented.

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Part I

Complications and predictors of adverse pregnancy outcome in retrospect

Chapter 2

Pregnancy in women with corrected tetralogy of Fallot: Occurrence and predictors of adverse events

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Summary

Background In women with corrected tetralogy of Fallot (ToF), pregnancy is associated with maternal cardiac, obstetric, and offspring complications. Our aim is to investigate the magnitude and determinants of pregnancy outcome in women with corrected ToF.

Methods In this retrospective international multicenter study using 2 congenital heart disease registries, 204 women with corrected ToF were identified. Within this group, 74 women had 157 pregnancies, including 30 miscarriages and 4 terminations of pregnancy. Detailed information on each completed pregnancy (n=123) was obtained using medical records and supplementary interviews.

Results Cardiovascular events occurred during 10 (8.1%) pregnancies, mainly (supra)ventricular arrhythmias. Obstetric and offspring events occurred in 73 (58.9%) and 42 (33.9%) pregnancies, respectively, including offspring mortality in 8 (6.4%). The most important predictor was use of cardiac medication before pregnancy (odds ratio for cardiac events 11.7, 95% CI 2.2-62.7; odds ratio for offspring events 8.4, 95% CI 1.4-48.6). In pregnancies with cardiovascular events, significantly more small-for-gestational-age children were born (P value < 0.01).

Conclusions Cardiovascular, obstetric, and offspring events occur frequently during pregnancies in women with ToF. Maternal use of cardiovascular medication is associated with pregnancy outcome, and maternal cardiovascular events during pregnancy are highly associated with offspring events.

Introduction

Long-term survival after correction of tetralogy of Fallot (ToF) is excellent.[1] Pregnancy is generally well tolerated in women with corrected ToF.[2] Nevertheless, cardiac, obstetric, and offspring events occurred, respectively, during 4.5% to 18%, 11% to 20% and 16% to 27% of completed gestations.[3-7] Predictors of adverse outcome in a cohort with ToF are not known; but in a mixed congenital heart disease (CHD) population, severe pulmonary regurgitation (PR) and right ventricular dysfunction were independent predictors of cardiac events during pregnancy.[5] Whether or not pulmonary valve replacement (PVR) before pregnancy influences pregnancy outcome is unknown. The primary objective of the present study is to determine the magnitude and the nature of events encountered during pregnancy in women with corrected ToF. Secondary objectives are to identify predictors of adverse pregnancy outcome as well as to investigate whether or not cardiac events could influence offspring outcome during the same pregnancy.

Patients and Methods

For the present study, all female patients with ToF aged 18 to 58 years enrolled in the nationwide CONgenital CORvitia (CONCOR) registry and a Belgian tertiary medical center's adult CHD database were identified and asked to participate in the study.[8,9] The institutional review board or ethics committee at each of the participating tertiary centers approved the protocol. Data were obtained from medical records, and supplementary data were retrieved by a questionnaire. Baseline data included basic cardiac anatomy, history, and electrophysiology; prior cardiac events using the European Pediatric Cardiac Coding; noncardiac comorbidity; maternal age at inclusion; prepregnancy New York Heart Association (NYHA) functional class and cyanosis (oxygen saturation <90%); the use of medication; use of cigarettes, drugs, and/or alcohol; and obstetric history including miscarriages (spontaneous fetal loss <20 weeks of gestation) and/or elective abortions.[10-12] Detailed information concerning each completed pregnancy (>20 weeks of gestation) between 1980 and 2007 was recorded: maternal age at conception; mode of delivery; parity; use of cigarettes, drugs, and/or alcohol during pregnancy; use of medication; change in NYHA functional class; 12-leads electrocardiogram; transthoracic echocardiograms; and/or 24-hour electrocardiogram (Holter) registrations. Documented pregnancy-related events were divided into cardiovascular, obstetric, and offspring events (composite endpoints).

Cardiovascular events

Cardiovascular events were defined as follows: documented symptomatic arrhythmia or heart failure requiring treatment (according to attending cardiologist), myocardial infarction, endocarditis, aortic dissection, thromboembolic events, and/or stroke.

Obstetric events

Obstetric events were defined as follows: pregnancy-induced hypertension (PIH, ≥20 weeks of

gestation, ≥140 mmHg systolic and/or ≥90 mmHg diastolic blood pressure, without proteinuria); preeclampsia (PIH with ≥0.3 g of proteinuria in a 24-hours urine sample); eclampsia (preeclampsia with grand mal seizures); hemolysis elevated liver enzymes low platelets syndrome; gestational diabetes[13]; hyperemesis gravidarum (severe, intractable nausea and vomiting leading to dehydration, loss of weight, metabolic disorders, and/or hospitalization); preterm prelabor rupture of membranes (PPROM); assisted delivery (use of forceps or vacuum extraction); caesarean delivery on medical indication; prolongation of cervix ripening (omitted dilatation of the portio vaginalis for ≥20 hours (nullipara) or ≥14 hours (multipara), despite adequate and regular uterus contractions); prolongation of second stage of delivery (primipara >2 hours or multipara >1 hour); premature labor (PL; spontaneous onset of labor at <37 weeks of gestation); postpartum hemorrhage (PPH; blood loss at vaginal delivery ≥500 mL or caesarean delivery ≥1000 mL).

Offspring events

Offspring events were defined as follows: premature birth (birth <37 weeks of gestation); small-for-gestational-age (SGA; birth weight <10th percentile); fetal mortality (intrauterine death ≥20 weeks of gestation); offspring death (within the first year after birth); and/or iteration of CHD.

Statistical analysis

A Clintrial data entry program was used to record information and was converted to SPSS (version 16.0; SPSS Inc, Chicago, IL) for statistical analysis. Descriptive statistics for nominal data are expressed in absolute numbers and percentages. Mean values and SD are presented for normally distributed continuous variables. For nonnormally distributed continuous variables, median and interquartile ranges were computed. Comparison of continuous variables between groups was made by unpaired Student's *t* tests or Mann-Whitney *U* test depending on distribution. For the comparison of dichotomous variables, we used the X^2 test or Fisher exact test, where applicable. All *P* values presented are two-sided. Univariable logistic regression analysis was performed to identify predictors of adverse pregnancy outcome, divided into 3 composite end points (as defined above): cardiac, obstetric, and offspring events. The following prepregnancy baseline variables were assessed: palliative surgery before ToF correction, history of arrhythmias, PVR, use of cardiac prescription medication, NYHA functional class, the presence of a patent shunt, pulmonary atrioventricular valve regurgitation (moderate/severe), pulmonary valve regurgitation (PR; moderate/severe) and/or right ventricular outflow tract obstruction (peak gradient >50 mmHg), and reduced systemic ventricular function. For the classification of valve regurgitation and valve stenosis, we used the classification as recommended by the European Society of Cardiology and the American Society of Echocardiography in their guidelines on valvular heart disease.[14,15] Variables that were associated with an increased incidence of the studied end points (P<0.10) entered the multivariable stage, which at least contained the variables age and parity. The final multivariable model was then constructed by backward deletion of the least significant characteristic until all remaining variables

were significantly (P <0.05) associated with the end point. Because some women went through >1 pregnancy, the validity of treating each pregnancy as an independent event was confirmed by general estimating equation analysis.

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Results

Written informed consent was provided by 204 women (82% of all women who were asked to participate) with corrected ToF. We observed 157 pregnancies in 74 of these patients. One third of the ToF women were enrolled in a pilot study published previously.[3] Of the 157 pregnancies, 30 ended in a miscarriage (19%) and 4 in an elective abortion (2.5%), leaving 123 completed pregnancies (≥20 weeks of gestation, including 1 twin pregnancy) in 69 different patients. From the 16 women who had 30 miscarriages, 13 women later had completed pregnancies. Table 1 shows the baseline characteristics of women with and without completed pregnancies.

Women without completed pregnancies were younger and more often had a mental disability. Most ToF women had a desire for children (168 of 204; 82%). In the childless cohort, the most common reason for being childless at inclusion was that women felt too young (not ready) to have children (n=51; 38%). Thirteen patients reported that anticipated cardiovascular events were the reason they did not pursue pregnancy (9.6%), and 6 of them were advised against pregnancy by their cardiologist. Three women (2.2%) did not have children because of concerns regarding heredity of ToF.

Because the available data concerning the incomplete pregnancies were very limited, we further focused on the 123 completed pregnancies. In Table 2 the baseline characteristics of the 123 completed pregnancies are presented. Of the pregnancies in our cohort, 19.5% was observed before 1990. Between 1990 and 2000, 49.6% and, after 2000, 30.9% of the pregnancies took place. There was no relation between pregnancy period and cardiovascular, obstetric, or offspring outcome. Thirty-three women had undergone PVR at a median age of 23.5 years (range 7-33 years).

None of the patients in our cohort had cyanosis. In 30 of 123 pregnancies (24%), the mother smoked before pregnancy; and in 20 of 123 pregnancies (16%), the mother continued smoking during pregnancy. Details regarding events that were encountered during completed pregnancies are depicted in Table 3. No difference in events was seen between the 2 registries.

Table 1. Patient characteristics for the total cohort and for patients with and without completed pregnancies.

	All patients (N = 204)	Patients without completed pregnancies* (N = 135)	Patients with completed pregnancies* (N = 69)	*P* value†
Mean age at inclusion, y (± SD)	31 ± 7.5	28 ± 6.7	36 ± 5.8	< 0.001
Mean age at repair, y (± SD)	5.1 ± 2.7	4.7 ± 2.5	6.1 ± 2.8	< 0.001
Surgeries before or after repair (%)				
Blalock -Taussig shunt	22 (10.8)	15 (11.1)	7 (10.1)	NS
Waterston shunt	29 (14.2)	14 (10.4)	15 (21.7)	<0.05
Potts Shunt	2 (1.0)	0 (0.0)	2 (2.9)	NS
RVOT procedure	42 (20.6)	24 (17.8)	18 (26.1)	NS
PVR	44 (21.6)	26 (19.3)	18 (26.1)	NS
Valvular dysfunction (%)				
Tricuspid regurgitation‡	27 (18.5)	15 (18.1)	12 (19.0)	NS
RVOT obstruction	46 (31.5)	21 (25.3)	25 (39.7)	NS
Pulmonary valve regurgitation‡	77 (52.7)	39 (47.0)	38 (60.3)	NS
Ventricular septal defect (%)	13 (8.9)	6 (4.4)	7 (11.1)	NS
Mental disability (%)	12 (5.9)	12 (8.9)	0 (0.0)	<0.01

PVR, Pulmonary valve replacement; **RVOT**, Right ventricular outflow tract; **NS**, not significant (*P* >0.05).
* Completed pregnancy, lasting >20 weeks.
† Comparison of women without completed pregnancies versus women with completed pregnancies.
‡ Moderate or severe.[15]

Cardiovascular outcome

The most frequent cardiovascular events were clinically significant arrhythmias needing treatment, which occurred during 8 pregnancies (6.5%); in 4 pregnancies, the mother had atrial fibrillation or flutter; and in the other 4 pregnancies, the mother had symptomatic ventricular tachycardias. Two of these patients had a history of arrhythmias. Heart failure developed during 2 pregnancies (1.6%), both during the third trimester and in the context of severe PR; one of these women had undergone PVR. Pulmonary embolism was diagnosed and subsequently treated with low–molecular weight heparin in one pregnancy. Deterioration of NYHA functional class (≥1 class, between prepregnancy and the third trimester) was documented in 22 completed pregnancies (17.7%) and persisted post pregnancy in 3 pregnancies (2%). Myocardial infarction, stroke, or aortic dissection did not occur in this cohort.

Table 2. Baseline characteristics of the 123 completed pregnancies* in women with corrected ToF.

	N=123
Mean age at inclusion, y (±SD)	36.4 ± 5.6
Mean age at repair, y (±SD)	6.5 ± 4.2
Surgery before/after repair, n (%)	
Blalock-Taussig shunt	12 (9.8)
Waterston shunt	22 (17.9)
Potts shunt	2 (1.6)
RVOT procedure	47 (38.2)
PVR	33 (26.8)
Valvular dysfunction, n (%)	
Tricuspid regurgitation (moderate/severe)[15]	25 (20.3)
RVOT obstruction	54 (43.9)
Pulmonary valve regurgitation (moderate/severe)[15]	69 (56.1)
Ventricular septal defect, n (%)	20 (16.3)
History of arrhythmias, n (%)	5 (4.1)
History of heart failure, n (%)	3 (2.4)
NYHA class ≥II prepregnancy, n (%)	8 (6.5)
Cardiac medication used prepregnancy, n (%)	7 (5.7)
β-Blockers†	1 (0.8)
Calcium-channel blockers	1 (0.8)
Digoxin	3 (2.4)
Amiodarone	2 (1.6)
Vitamin K antagonists, n (%)	2 (1.6)
Mean age at pregnancy, y (±SD)	26.8 ± 4.1
Primipara, n (%)	32 (26.0)
Multipara, n (%)	91 (74.0)
Mean pregnancy duration, wk (±SD)	37.8 ± 4.5

* Completed pregnancy, lasting >20 weeks.
† Stopped using because of pregnancy.

Table 3. Overview of events that occurred during 123 completed* pregnancies in women with corrected ToF.

	N=123	
	ZAHARA N (%)	Healthy population§ (%)
Cardiovascular events	**10 (8.1)**	
Arrhythmias	8 (6.5)	<1
Heart failure	2 (1.6)	<1
Thromboembolic events	1 (0.8)	<0.3
Obstetric events	**73 (58.9)**	
Caesarean delivery	25 (20.3)	6.5
Assisted† vaginal delivery	16 (13.0)	17
PPH	12 (9.7)	2.9
Prolongation of 2nd stage of delivery	10 (8.1)	<2.7
PPROM	8 (6.5)	1.5
PIH	6 (4.8)	10
Prolongation of cervix ripening	5 (4.1)	–
Preeclampsia	4 (3.2)	1.4
Hyperemesis	2 (1.6)	0.6
Solutio placentae	1 (0.8)	<1
Uterus rupture	1 (0.8)	<0.001
Offspring events	**42 (33.9)**	
SGA	23 (18.5)	10
PB	22 (17.7)	10
OM	8 (6.4)	0.9
CHD	3 (2.4)	0.6
Other offspring events‡	3 (2.4)	–

PB, Preterm birth; **OM**, offspring mortality.
* Completed pregnancy, lasting >20 weeks.
† Delivery assisted using forceps or vacuum extraction.
‡ Other offspring events were fetal asphyxia, trisomy 13, and hydrocephalus.
§ Normal population, based on literature.[4,24,25,27-29,32,33]

Table 4. Results of univariable and multivariable logistic regression models and corresponding risk scores for cardiac, obstetric, and offspring events.

Univariable analysis			
	Cardiovascular events*	Obstetric events*	Offspring events*
Palliative surgery	1.3 (0.3-5.1)	0.8 (0.4-1.7)	2.7 (1.1-6.2)‡
History of arrhythmias	9.3 (1.8-46.9)‡	5.2 (0.6-43.6)	2.0 (0.5-8.5)
Prior PVR	3.1 (0.8-11.4)†	2.2 (0.9-5.3)†	1.4 (0.6-3.2)
RVOT obstruction	0.9 (0.2-3.2)	1.2 (0.6-2.4)	1.3 (0.6-2.7)
Pulmonary valve regurgitation§	0.5 (0.1-1.9)	0.5 (0.23-0.99)‡	1.3 (0.6-2.7)
Pulmonary AV valve regurgitation	0.6 (0.1-2.3)	1.4 (0.6-3.4)	2.1 (0.9-5.2)†
Patent shunt	0.8 (0.1-3.8)	2.5 (0.9-6.7)	1.1 (0.4-2.9)
Smoking during pregnancy	0.8 (0.1-3.8)	0.9 (0.4-2.5)	1.4 (0.5-3.7)
Use of cardiac medication prepregnancy	11.8 (2.2-63.3)‡	–	5.5 (1.0-29.2)‡
NYHA class III/IV	0.6 (0.1-5.3)	–	0.3 (0.0-2.7)

Multivariable analysis for endpoints cardiovascular, obstetric and offspring events	
	Odds ratio (95% CI)
Cardiovascular events	
Use of cardiac medication prepregnancy	11.7 (2.2 – 62.7)‡
Obstetric events	
Pulmonary valve regurgitation	0.5 (0.2 – 0.99)‡
Offspring events	
Palliative surgery	3.3 (1.3 – 8.2)‡
Use of cardiac medication prepregnancy	8.1 (1.4 – 48.6)‡

AV, Atrioventricular.
* Expressed as OR (95% CI).
† P <0 .1.
‡ P <0.05.
§ Moderate or severe.[14,15]

Obstetric outcome

Caesarean delivery was the most frequently observed obstetric event and was necessary in 20.3% of completed pregnancies (n=25). A "primary" (planned) caesarean delivery was carried out during 16 gestations, 5 of which were executed based on maternal cardiac indication (moderate/severe pulmonary valve stenosis or regurgitation combined with tricuspid regurgitation and high risk of arrhythmia). Nine "secondary" (unscheduled) caesarean deliveries were performed, all on obstetric indication. Postpartum hemorrhage, hypertensive disorders of pregnancy, and PPROM complicated, respectively, 9.7%, 8%, and 6.5% of completed pregnancies. Forceps were used in 3 pregnancies; and in 13 pregnancies, a vacuum extractor was used to assist vaginal delivery. No significant time effects were found for obstetric outcome.

Offspring outcome

The median birth weight was 3100 g (25th percentile 2755 g; 75th percentile 3400 g). Twenty-three children (19%) were SGA. Delivery was preterm in 22 (18%) of the completed pregnancies. Iteration of CHD was diagnosed in 3 (2.4%) children. In one child, the cardiac defect (atrial septal defect) was associated with a trisomy 13; the other two children had tetralogy of Fallot and atrioventricular septal defect respectively. The overall offspring mortality was 6.4%. Intrauterine demise occurred during 5 gestations, and 3 children died within the first year postpartum. The main reasons for offspring death were immaturity and/or prematurity at birth, intrauterine growth restriction, and recurrence of CHD. Also for offspring outcome, no time effect could be detected. The occurrence of cardiovascular events was associated with a significantly higher number of SGA children (in 5 of 10 pregnancies with cardiovascular events, the offspring was SGA versus 18 of 114 pregnancies without cardiovascular events [P<0.01]).

Predictors

The univariable and multivariable predictors for the composite end points are shown in table 4. Prior PVR was strongly associated with cardiovascular events. Mainly arrhythmias (n=4) complicated pregnancies in the PVR group. In one pregnancy, pulmonary embolism was observed; and one pregnancy in the PVR group was complicated with arrhythmia as well as with heart failure. Arrhythmias before pregnancy were highly associated with cardiovascular events. The most important independent predictor for cardiovascular as well as offspring events was the use of cardiac medication before pregnancy. In pregnancies of women who used any cardiac medication before pregnancy, the risk for SGA babies was almost 7-fold higher compared with pregnancies of women without history of cardiac medication use (odds ratio [OR] 6.8, 95% CI 1.4-32.9, P=0.02). None of the specific cardiac medication used before pregnancy stood out as a culprit. Use of any cardiac medication during pregnancy had a high association with SGA, but this was not statistically significant (OR 4.9, 95% CI 0.9-25.8, P=0.06). No association was found between SGA and other known causes, such as PIH or PE, in our cohort. The use of cardiac medication before pregnancy was associated with PVR: 5 of 7 women who used cardiac medication before pregnancy had previous PVR. Another independent predictor of offspring events was palliative surgical intervention before correction. Women with moderate to severe pulmonary valve regurgitation seem to encounter less obstetric events (35 of 69 vs. 38 of 54, P=0.04).

Discussion

Women with corrected ToF are at increased risk of cardiovascular and obstetric events during pregnancy. Most events are well treatable. The incidence of offspring events is markedly increased. Cardiovascular and offspring outcomes are strongly related with the use of cardiac medication before pregnancy. Surgical status before pregnancy also appears to predict pregnancy outcome. Offspring events are related to maternal cardiovascular events. In our cohort, 19% of the pregnancies

ended in a spontaneous abortion, which is slightly higher than in healthy women (10%-16%) and slightly higher than reported previously in pregnancies of women with ToF.[4,16]

Cardiovascular outcome

The occurrence of cardiovascular events in the present study is comparable to that reported in a recent literature review, which described the outcome of 200 pregnancies in patients with corrected ToF.[4] Arrhythmias were the major cardiac event. Arrhythmias before pregnancy predicted cardiovascular events, as described previously.[6,17-19] Supraventricular and ventricular arrhythmias are well-known long-term sequelae of intracardiac repair of ToF.[20,21] The use of cardiac medication before pregnancy strongly predicted cardiovascular events. This predictor probably reflects a less favorable cardiac condition in terms of ventricular function and arrhythmias. In contrast to others, we did not observe a relationship between severity of PR and more adverse events.[5,7] In previous publications, it was likely that PR was associated with worse pregnancy outcome especially when it was associated with right ventricular dysfunction.[7,22] Heart failure occurred only twice in our population, both times in women with severe PR. The most prevalent complications were arrhythmias, which are related not only to hemodynamics but also to surgical scars and therefore may be encountered also in women with an adequate haemodynamic situation but with a history of surgery, as in women with corrected ToF.

Pulmonary valve replacement was associated with worse cardiovascular outcome, which is counterintuitive. The use of cardiac medication before pregnancy was strongly associated with PVR (71% of all women who used cardiac medication had PVR), indicating a less favorable cardiac condition in the PVR group. This might be related to late timing of PVR, as all PVRs were performed between 1990 and 2000, when early timing of PVR was not routinely applied. Therefore, in most of these patients, PVR was likely performed when right ventricular function was already compromised. A recent study showed progression of RV dilatation that persisted postpregnancy in women with corrected ToF, which could not be demonstrated in comparable women who did not have pregnancies.[23] In our study, the main events in women after PVR were arrhythmias. These patients may have been vulnerable to arrhythmias because of right ventricular dysfunction, but surgical scars may have also played a role in the occurrence of arrhythmias. In addition, several women had arrhythmias prepregnancy, which is a known predictor for arrhythmias during pregnancy.[6] Unfortunately, our study does not answer the question if timely prepregnancy PVR would have prevented cardiovascular pregnancy events in women with ToF.

Obstetric outcome

The most important obstetric events were PPH and PL based on rupture of membranes, which occurred more frequently than described previously in population-based studies (2.9% and 1.5%, respectively).[24,25] No direct explanation was found; more specifically, no relationship with anticoagulation therapy was detected.[26] Caesarean deliveries were performed more often in our

study (20%) than in the general Dutch population (6.5%), although only 1 in 5 was performed on maternal cardiac indications.[27] Possibly, the threshold for performing caesarean delivery for obstetric/offspring reasons is lower than usual because of caution on the part of obstetricians in these more vulnerable mothers and babies. The other events were in concordance with expected frequencies observed in the general population and mentioned in the literature review.[4]

Offspring outcome

The high offspring mortality (6.4%) by far exceeds expected mortality rates in the general population (0.9%) and also the mortality rate in ToF pregnancies mentioned in the literature (2.0%).[28] Recurrence of CHD, but also premature births with their known associated events, explains, at least in part, this high mortality. The premature birth rate (18%) was substantially higher than expected.[4,29] This was in part attributable to the higher frequency of PL due to rupture of membranes. The incidence of SGA (19%) is also higher than in the general population (by definition 10%), although it is lower than the 35% recently mentioned by Gelson et al.[30] The use of maternal cardiac medication before pregnancy was the most important predictor of offspring outcome. Maternal haemodynamic abnormalities as well as direct effects of maternal cardiovascular medication may undermine placental blood flow and induce placental insufficiency with subsequent intrauterine growth restriction resulting in children born SGA as well as in premature birth. The strong association between maternal cardiovascular events and SGA points in this direction. Palliative surgery before correction appears to influence offspring outcome negatively. Longstanding right ventricular pressure loading and hypoxia in women with a later age at correction may have resulted in more haemodynamic compromise and endothelial dysfunction, compromising placental perfusion and fetal well being.

Limitations

The retrospective study design required very strict definitions for events: all mentioned events had to be documented by medically qualified personnel in the records according to preset definitions before data entry. Heart failure and arrhythmia were only recorded if therapy had been administered. This may have caused underestimation of cardiovascular event rate. In addition, selection bias is introduced by the fact that some patients remained childless because of anticipated/expected risks during pregnancy, which may lead to an underestimation of risks. This study was performed in a survival cohort; thus, no conclusions regarding maternal mortality risk can be made. However, from prospective research, it is known that repaired CHD has a very low risk of maternal death.[6,31] Finally, together with the given sample size and the possible effects of multitesting, for example, inflation of type I error, all conclusions of the present study must be drawn with caution.

Disclosures

Conflicts of interest: None.

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Chapter 3

Predictors of pregnancy complications in women with congenital heart disease

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Summary

Aims Data regarding pregnancy outcome in women with congenital heart disease (CHD) are limited.

Methods and results In 1802 women with CHD, 1302 completed pregnancies were observed. Independent predictors of cardiac, obstetric, and neonatal complications were calculated using logistic regression. The most prevalent cardiac complications during pregnancy were arrhythmias (4.7%) and heart failure (1.6%). Factors independently associated with maternal cardiac complications were the presence of cyanotic heart disease (corrected/uncorrected) (P<0.0001), the use of cardiac medication before pregnancy (P<0.0001), and left heart obstruction (P<0.0001). New characteristics were mechanical valve replacement (P=0.0014), and systemic (P=0.04) or pulmonary atrioventricular valve regurgitation related with the underlying (moderately) complex CHD (P=0.03). A new risk score for cardiac complications is proposed. The most prevalent obstetric complications were hypertensive complications (12.2%). No correlation of maternal characteristics with adverse obstetric outcome was found. The most prevalent neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%). Cyanotic heart disease (corrected/uncorrected) (P=0.0003), mechanical valve replacement (P=0.03), maternal smoking (P=0.007), multiple gestation (P=0.0014), and the use of cardiac medication (P=0.0009) correlated with adverse neonatal outcome.

Conclusion In our tertiary CHD cohort, cardiac, obstetric, and neonatal complications were frequently encountered, and (new) correlations of maternal baseline data with adverse outcome are reported. A new risk score for adverse cardiac complications is proposed, although prospective validation remains necessary.

Introduction

Progress in the fields of diagnostic techniques and surgical intervention has dramatically improved long-term outcome in patients with congenital heart disease (CHD). As a consequence, most patients with congenital cardiac malformations reach childbearing age. Many of these women wish to become pregnant. Pregnancy itself is a circulatory burden, primarily due to volume loading, which has an impact even on a healthy woman's life. In the face of residual lesions or sequelae after correction or an uncorrected maternal congenital heart defect, this burden may have deleterious effects on the health of both the mother and her offspring. Cardiac, obstetric, and neonatal complications all appear to be more prevalent.[1]

It has long been recognized that certain cardiac factors, including prepregnancy NYHA class, the presence of a mechanical valve prosthesis, having pulmonary hypertension/cyanosis, and outflow tract obstruction, adversely influences pregnancy outcome. The 'CARdiac disease in PREGnancy' (CARPREG) investigators were the first to identify predictors of the adverse pregnancy outcome in women with established heart disease. The investigators also were the first to design a risk score, which is now commonly used to 'predict' cardiac complications during pregnancy in the context of maternal CHD. Limitations of the score for patients with CHD are that it is developed based on a cohort that included patients with primary electrical disease as well as acquired heart disease. Moreover, several types of (mainly complex) CHD were underrepresented.[2,3] It is suggested that the CARPREG cardiac risk score therefore needs to be modified to assess the risk of pregnancy in women with CHD.[4]

The primary objective of the present study is to identify patient characteristics associated with adverse pregnancy outcome in a patient cohort consisting of patients with CHD and to propose a modified risk score.

Methods

For the present ZAHARA study, female patients with CHD aged 18–58 years enrolled in the nation-wide CONgenital CORvitia (CONCOR) registry and a Belgian tertiary medical centre's adult CHD database were identified. The databases include patients with CHD >18 years receiving tertiary medical care. The institutional review board or Ethics Committee at each of the seven participating tertiary centres approved the protocol. Patients alive at the time of inclusion (survivors) were contacted by mail and asked to provide written informed consent. The Ethics Committee did not allow review of medical charts without consent. Moreover, we were not allowed to contact family members of deceased patients to retrieve informed consent. Therefore, no information on excluded or deceased patients is available.

Data were retrospectively obtained from medical records as reported by qualified medical personnel and supplemented data were retrieved by a telephonic questionnaire. The questionnaire was mainly used to check data concerning the date of birth/death of offspring, birth weight as recorded in official birth certificates, and to check whether or not external (non-tertiary) medical

personnel was consulted to obtain complete data concerning each pregnancy.

Baseline data including maternal date of birth, parity, age at pregnancy when applicable, basic anatomy, prior surgical procedures, co-morbidity, and medical history (using the European Paediatric Cardiac Coding) were recorded for all women who gave informed consent. Miscarriages and elective abortions were excluded as data concerning these pregnancies are often disputable and unreliable. Besides the baseline data, the following complications were recorded for each completed (>20 weeks of gestation) pregnancy between 1980 and 2007. Cardiac complications (as diagnosed by a tertiary care cardiologist specialist): clinically significant ('requiring treatment at least including drug prescription') episodes of arrhythmia or heart failure, cardiovascular complications (e.a. thrombo-embolic complications, myocardial infarction, and/or cerebrovascular accidents), and endocarditis (including first 6 months post-partum). Obstetric complications: pregnancy-induced hypertension (PIH, new onset hypertension: blood pressure >140 mmHg systolic or >90 mmHg diastolic without proteinuria after 20 weeks of gestation); preeclampsia (PIH with >0.3 g protein in 24h urine sample); eclampsia (preeclampsia with grand mal seizures); haemolysis elevated liver enzymes low platelets (HELLP) syndrome according to the guidelines of the European Society of Gynaecology and Obstetrics premature labour (<37weeks of gestation); post-partum haemorrhage (vaginal delivery. 500 mL, caesarean section >1000 mL). Neonatal outcome: premature delivery (delivery <37 weeks); small-for-gestational-age birth weight (>10th percentile); offspring mortality [demise: in utero (>20 weeks of gestation)—the first-year post-partum].

Data analysis

A Clintrial data-entry program was used to record information and converted to SPSS (version 16.0) and SAS for statistical analysis. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. Mean values and standard deviations were presented for normally distributed continuous variables. For non-normal distributed continuous variables, median and ranges were computed. Univariable logistic regression analysis was performed to identify patient characteristics associated with adverse pregnancy outcome divided into three composite endpoints (as defined above): the cardiac, obstetric complications, and offspring outcome. The following baseline variables were assessed: the presence of patent shunt [atrial septal defect, ventricular septal defect (VSD), persistent ductus arteriosus, and abnormal pulmonary vein connections], surgical status prior to pregnancy (palliation, corrected or uncorrected), history of arrhythmias or cardiac complications (heart failure, cerebrovascular accidents, transient ischaemic attack, myocardial infarction, thrombo-embolic complications, and endocarditis), left heart obstruction [(i) peak aortic gradient >30 mmHg or aortic valve area <1.5 cm^2 or mitral valve area <2 cm^2 and (ii) peak aortic gradient >50 mmHg or aortic valve area <1.0 cm^2], right ventricular outflow tract obstruction >50 mmHg, reduced systemic ventricular function (qualitative ejection fraction or graded quantitative ejection fraction <40% based on echocardiography), presence of cyanosis (oxygen saturation <90%) or pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg),[2]

pulmonary valve regurgitation (moderate or severe), systemic valve regurgitation (moderate or severe), pulmonary atrioventricular (AV) valve regurgitation (moderate or severe), systemic AV valve regurgitation (moderate or severe), aortic dilatation >40 mm (widest diameter), the presence of a mechanical valve prosthesis, the presence of a pacemaker, twin pregnancy, cyanotic heart disease (corrected/uncorrected): CHD which presents at or shortly after birth with cyanosis regardless of subsequent performed palliative corrective interventions, smoking immediately prior to or during pregnancy, alcohol during pregnancy (>0 U/day on average), use of oral anticoagulation and/or other cardiovascular medication during pregnancy, and maternal NYHA class prior to pregnancy. Variables that were associated with an increased incidence of the studied endpoints (P<0.15) entered the multivariable stage. The final multivariable model was then constructed by backward deletion of the least significant characteristic, until all remaining variables were significantly (P<0.05) associated with the endpoint. Because some women underwent one or more pregnancies, the validity of treating each pregnancy as an independent event was determined by general estimating equation analysis.

For each pregnancy, the now widely used CARPREG cardiac risk score was calculated.[2] We subsequently validated this score for the abovementioned combined endpoint cardiac complications. We calculated the *C*-index (concordance index) of the CARPREG risk score, which describes the discriminative capacity, and performed a calibration using the Hosmer–Lemeshow test. The *C*-index has a value between 0.5 (poor discrimination) and 1.0 (perfect discrimination). We then modified the CARPREG risk score using the identified multivariable associations for the composite cardiac endpoint, nevertheless retaining the basic principal of this risk score.[2] In the modified risk score, we use the exponent value to weigh the risk factors and attribute points per risk factor. The developed risk model based on the whole study cohort was further evaluated by drawing 1000 bootstrap samples, with replacement, to estimate the extent to which the predictive accuracy of the model was overoptimistic. We report the mean *C*-index and the corresponding standard error (SEM).

Results

Overall, 1802 women with CHD (82%) provided written informed consent to review their medical records. These patients had 1696 gestations, including 336 miscarriages (19.4%; <20 weeks of gestation) and 58 elective abortions (3.4%). For the present analyses, the data of the 1302 completed pregnancies in 714 individual women were used. Most patients were nulliparous (63%). Mean maternal age at pregnancy was 27.4 (SD±2.6) years. The underlying CHD in the women with completed (>20 weeks of gestation) pregnancies in detail: (un)-corrected atrial septal defect II (n=188), (un)-corrected aortic coarctation including additional cardiac defects (n=160), (un)-corrected VSDs (n=148), pulmonary valve stenosis (n=148; including 21 with >50 mmHg obstruction), corrected tetralogy of Fallot (n=124), Marfan syndrome (n=18; including 32 with aortic root dilatation >40 mm), atrioventricular septal defect (n=89, of which 15 with common orifice), aortic valvar stenosis (n=81, including 18 with >50 mmHg obstruction), atrial or arterial corrected complete transposition

of great arteries (TGA) (n=52, mostly Mustard corrections), (un)-corrected Ebstein malformations (n=22), congenital corrected TGA (n=19), pulmonary atresia with VSD (n=12), Eisenmenger syndrome (n=4), complex cyanotic heart disease (n=9, including patients with Fontan palliation), and other CHD [n=128, including isolated mitral/tricuspid valvular regurgitation (respectively, n=30 and n=1)]. The distribution of complications encountered during these completed (>20 weeks of gestation) pregnancies is illustrated in Table 1. It needs to be stated that, in part, these results are published in the earlier work by our research group and are merely shown for illustrative purposes.[5-14] Main cardiac complications were arrhythmias (4.7%) and heart failure (1.6%), mostly transient in nature and manageable with medical therapy.

Table 1. Complications found during 1302 completed pregnancies organized per category of congenital heart disease.

Congenital heart disease	N	Cardiac complications				Obstetric complications						Neonatal complications		
		AR	HF	CE	EN	PI	PE	EC	HE	PL	PH	PD	SG	MO
Atrial septal defect	188	7	0	2	0	9	12	0	0	12	19	12	33	4
Aortic coarctation	160	2	1	0	1	8	7	0	0	8	19	22	18	6
Ventricular septal defect	148	1	0	1	1	8	9	0	0	7	16	6	16	1
Pulmonary valve stenosis	148	3	1	3	0	12	7	2	1	5	16	20	15	7
Tetralogy of Fallot	124	7	1	1	0	5	4	0	0	9	12	21	20	7
Marfan syndrome	118	1	0	2	0	13	1	0	0	5	11	16	14	8
Atrioventricular septal defects	89	15	3	2	0	9	2	0	0	6	12	10	15	4
Aortic valvar stenosis	81	3	4	0	0	10	3	1	1	5	5	10	9	1
Complete transposition of the great arteries	52	11	4	2	0	7	5	0	1	6	7	16	10	5
Ebstein malformation	22	2	0	1	0	0	0	0	0	0	4	2	1	1
Congenital corrected transposition of great arteries	19	1	2	0	0	2	0	0	2	1	1	1	3	0
Pulmonary atresia	12	3	0	0	0	0	0	1	1	0	0	1	1	0
Pulmonary hypertension or Eisenmengera	4	0	1	0	0	0	0	0	0	0	0	2	0	0
Complex cyanotic heart disease	9	3	2	0	0	1	0	0	0	1	2	6	5	1
Other	128	3	2	0	0	1	0	0	0	1	2	6	5	1
Overall	1302	62	21	17	2	94	57	4	6	76	139	160	180	49

N, number of pregnancies. **AR**, arrhythmias; **HF**, heart failure; **CE**, cardiovascular complications; **EN**, endocarditis; **PI**, pregnancy-induced hypertension; **PE**, preeclampsia; **EC**, eclampsia; **HE**, HELLP syndrome; **PL**, premature labour; **PH**, post-partum haemorrhage; **PD**, premature delivery; **SG**, small for gestational age; **MO**, foetal or neonatal mortality.
a Respectively, ASD related n=2 and VSD related n=2.

The most important obstetric complications were hypertension-related disorders (mainly occurring in uncorrected patients). The most frequently encountered offspring outcomes were born small for gestational age and premature delivery. Maternal cardiac complications and offspring complications were highly correlated (r=0.85, *P*=0.002).

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

Table 2. Results of univariable logistic regression for the composite endpoints: cardiac, obstetric, and offspring complications.

	Cardiac complications	Obstetric complications	Neonatal complications
Patent shunt	0.6 (0.3 – 1.0)	1.0 (0.7 – 1.3)	0.7 (0.5 – 1.0)
Only palliation before pregnancy	**9.8 (2.8 – 34.1)*****	1.7 (0.4 – 7.1)	2.7 (0.7 – 10.9)
Corrected before pregnancy	1.6 (1.0 – 2.7)	1.0 (0.8 – 1.4)	1.3 (1.0 – 1.7)
History of arrhythmias	**5.0 (2.3 – 11.0)*****	0.9 (0.3 – 2.3)	1.2 (0.6 – 2.6)
History of cardiac complications	1.5 (0.4 – 5.0)	1.0 (0.4 – 2.3)	**2.2 (1.0 – 4.7)***
LHO (PG >30mmHg or AVA <1.5 cm^2) + mitral valve stenosis (MVA <2.0 cm^2)[a]	**2.6 (1.2 – 5.5)***	1.0 (0.5 – 1.8)	**0.5 (0.3 – 0.9)***
LHO (PG >50 mmHg or AVA <1.0 cm^2)	**7.4 (2.6 – 21.2)*****	0.4 (0.1 – 1.5)	0.6 (0.2 – 1.6)
Pulmonary ventricular outflow obstruction (PG >50 mmHg)	2.2 (0.9 – 5.7)	1.4 (0.7 – 2.5)	1.2 (0.7 – 2.1)
Reduced systemic ventricular function	**3.3 (1.3 – 8.3)****	0.5 (0.2 – 1.2)	1.6 (0.7 – 3.7)
Cyanosis or pulmonary hypertension	1.9 (0.3 – 12.9)	0.6 (0.1 – 3.9)	3.2 (0.8 – 12.9)
Pulmonary valve regurgitation[b]	1.5 (0.7 – 3.5)	1.2 (0.8 – 2.0)	0.9 (0.5 – 1.4)
Systemic valve regurgitation[b]	1.1 (0.4 – 2.9)	1.0 (0.5 – 1.7)	0.8 (0.4 – 1.5)
Systemic AV valve regurgitation[b]	**2.7 (1.4 – 5.2)****	0.9 (0.6 – 1.5)	1.4 (0.8 – 2.2)
Pulmonary AV valve regurgitation[b]	**2.9 (1.6 – 5.4)*****	0.8 (0.5 – 1.3)	1.4 (0.8 – 2.1)
Aortic dilatation (>40 mm)	1.7 (0.7 – 4.5)	0.8 (0.4 – 1.7)	0.8 (0.4 – 1.6)
Mechanical prosthesis	**37.1 (3.8 – 360.8)****	9.3 (1.0 – 90.1)	9.0 (0.9 – 87.3)
Pacemaker	**4.6 (1.8 – 11.5)****	**2.7 (1.1 – 6.6)****	0.5 (0.2 – 1.5)
Twin or multiple gestation	2.0 (0.6 – 7.0)	2.3 (1.0 – 5.9)	**6.4 (2.3 – 17.8)*****
Cyanotic heart disease (corrected and uncorrected)	**2.8 (1.7 – 4.7)*****	0.9 (0.6 – 1.3)	**2.0 (1.4 – 2.9)*****
Smoking before pregnancy	0.9 (0.5 – 1.5)	0.9 (0.6 – 1.2)	1.4 (1.0 – 1.9)
Smoking during pregnancy	1.1 (0.6 – 2.0)	0.7 (0.4 – 1.0)	**1.6 (1.1 – 2.3)****
Alcohol during pregnancy	1.2 (0.6 – 2.6)	1.2 (0.7 – 2.0)	0.7 (0.4 – 1.2)
Oral anticoagulation	**5.7 (2.4 – 13.5)*****	1.9 (0.8 – 4.7)	2.7 (1.0 – 7.2)
Other cardiac medication before pregnancy	**4.2 (2.3 – 7.8)*****	1.0 (0.6 – 1.8)	**2.1 (1.4 – 3.3)*****
NYHA	**3.1 (1.6 – 6.0)*****	0.8 (0.4 – 1.4)	1.1 (0.7 – 1.8)

AV, atrioventricular; **AVA**, aortic valve area; **LHO**, left heart obstruction; **MVA**, mitral valve area; **NYHA**, New York Heart Association; **PG**, peak gradient. Values are expressed as odds ratio (95% Confidence Interval).
a None of the patients had a **MVA** of <2.0 cm^2.
b Moderate/severe.
* *P*<0.05; ***P*<0.01; ****P*<0.001. The bold entries are the statistical significant data, which makes interpretation simpler.

The event rate per characteristic is reported in Table 3.

Table 3. Event rate per characteristics in absolute numbers (percentages) for the three composite endpoints: cardiac, obstetric, and offspring complications.

	N	Cardiac complications, N (%)	Obstetric complications, N (%)	Neonatal complications, N (%)
Overall	1302	99 (7.6)	313 (24.0)	331 (25.4)
Patent shunt	306	14 (4.6)	72 (23.5)	65 (21.2)
Only palliation before pregnancy	9	**4 (44.4)**	3 (33.3)	4 (44.4)
Corrected before pregnancy	683	65 (9.5)	166 (24.3)	189 (27.7)
History of arrhythmias	39	**12 (30.8)**	9 (23.1)	12 (30.8)
History of cardiac complications	33	3 (9.1)	7 (21.2)	**13 (39.4)**
LHO (PG >30 mmHg or AVA <1.5 cm^2) + mitral valve stenosis (MVA < 2.0 cm^2)[a]	71	**11 (15.5)**	16 (22.5)	**11 (15.5)**
LHO (PG >50 mmHg or AVA <1.0 cm^2)	22	**7 (31.8)**	2 (9.1)	4 (18.2)
Pulmonary ventricular outflow obstruction (PG >50 mmHg)	68	10 (14.7)	21 (30.9)	20 (29.4)
Established reduced systemic ventricular function	35	**7 (20.0)**	5 (14.3)	14 (40.0)
Cyanosis or pulmonary hypertension	9	1 (11.1)	1 (11.1)	5 (55.6)
Pulmonary valve regurgitation[b]	109	11 (10.1)	29 (26.6)	24 (22.0)
Systemic valve regurgitation[b]	76	6 (7.9)	16 (21.1)	16 (21.1)
Systemic AV valve regurgitation[b]	106	**17 (16.0)**	24 (22.6)	34 (32.1)
Pulmonary AV valve regurgitation[b]	105	**18 (17.1)**	21 (20.0)	33 (31.4)
Aortic dilatation (>40 mm)	58	6 (10.3)	13 (22.4)	12 (20.7)
Mechanical prosthesis	4	**4 (100.0)**	3 (75.0)	3 (75.0)
Pacemaker	29	**8 (27.6)**	**14 (48.3)**	4 (13.8)
Twin or multiple gestation	17	2 (11.8)	7 (41.2)	**11 (64.7)**
Cyanotic heart disease (corrected and uncorrected)	198	**31 (15.7)**	45 (22.7)	**75 (37.9)**
Smoking before pregnancy	313	21 (6.7)	70 (22.4)	96 (30.7)
Smoking during pregnancy	192	14 (7.3)	34 (17.7)	**66 (34.4)**
Alcohol during pregnancy	89	7 (7.9)	22 (24.7)	16 (18.0)
Oral anticoagulation	24	**10 (41.7)**	10 (41.7)	12 (50.0)
Other cardiac medication before pregnancy	96	**21 (26.2)**	21 (26.2)	**34 (42.5)**

AV, atrioventricular; **AVA**, aortic valve area; **LHO**, left heart obstruction; **MVA**, mitral valve area; **NYHA**, New York Heart Association; **PG**, peak gradient.
a None of the patients had a **MVA** of <2.0 cm^2.
b Moderate/severe.
The bold entries are the statistical significant data, which makes interpretation simpler.

The multivariate model correlating the composite endpoints of cardiac and neonatal complications is shown in Table 4. New independent (multivariable) factors associated with cardiac complications

were the presence of a moderate-to-severe pulmonary or systemic AV valve regurgitation, cyanotic heart disease (corrected/uncorrected), and the presence of mechanical valve prosthesis. A history of arrhythmias, maternal NYHA functional class, the presence of left ventricular outflow tract obstruction, and the use of cardiac drugs also proved to be independent predictors of cardiac complications in concordance with previous studies.

Table 4. Multivariable model for the composite endpoints of cardiac and neonatal complications corrected for maternal age and parity.

	Odds ratio (95% CI)	*P* value
CARDIAC COMPLICATIONS		
History of arrhythmias	4.3 (1.8 – 10.2)	0.0011
Other cardiac medication before pregnancy	4.2 (2.1 – 8.6)	<0.0001
NYHA functional class	2.2 (1.1 – 4.5)	0.0298
LHO (PG >50 mmHg or AVA <1.0 cm^2)	12.9 (3.9 – 42.3)	<0.0001
Syst AV valve regurgitation (moderate/ severe)	2.0 (1.0 – 4.0)	0.0427
Pulm AV valve regurgitation (moderate/ severe)	2.3 (1.1 – 5.0)	0.0287
Mechanical valve prosthesis	74.7 (5.3 – 1057)	0.0014
Cyanotic heart disease (corrected and uncorrected)	3.0 (1.7 – 5.0)	<0.0001
NEONATAL COMPLICATIONS		
Twin or multiple gestation	5.4 (1.9 – 15.2)	0.0014
Smoking during pregnancy	1.7 (1.2 – 2.4)	0.0070
Cyanotic heart disease (corrected and uncorrected)	2.0 (1.4 – 2.9)	0.0003
Mechanical valve prosthesis	13.9 (1.2 – 157)	0.0331
Other cardiac medication before pregnancy	2.2 (1.4– 3.5)	0.0009

AV, atrioventricular; **AVA**, aortic valve area; **LHO**, left heart obstruction; **NYHA**, New York Heart Association; **PG**, peak gradient; **Pulm**, pulmonary; **Syst**, systemic.

None of the investigated patient characteristics were associated with adverse obstetric complications. The presence of multiple gestations, the presence of at birth cyanotic heart disease, the presence of mechanical valve prosthesis, smoking during pregnancy, and the use of cardiac medication other than anticoagulation regimes were independently associated with adverse neonatal complications. In Table 5, the details regarding the encountered cardiac complications are described, including the underlying CHD. The performance of the CARPREG cardiac risk score was limited with a *C*-index of 0.656 for the composite cardiac endpoint. Figure 1 shows the alternative risk score and the corresponding cardiac risk during pregnancy. The mean *C*-index of this risk model, as obtained in the 1000 bootstrap samples, was 0.762 with a SEM of 0.026. This implies some over-optimism in the estimated predictive accuracy of the model. In the future, this new cardiac risk index needs to be externally validated in a prospective study.

Discussion

The present, and thus far largest, study investigates the pregnancy complications in women with CHD. Complications were frequently encountered. Several new associations with adverse cardiac and neonatal pregnancy complications were identified. On the basis of these associations, a new risk index was designed, which seems to enhance discrimination and calibration compared with the existing CARPREG risk score. External validation of this risk score in a large prospective study, however, remains necessary.

Predicting cardiac complications

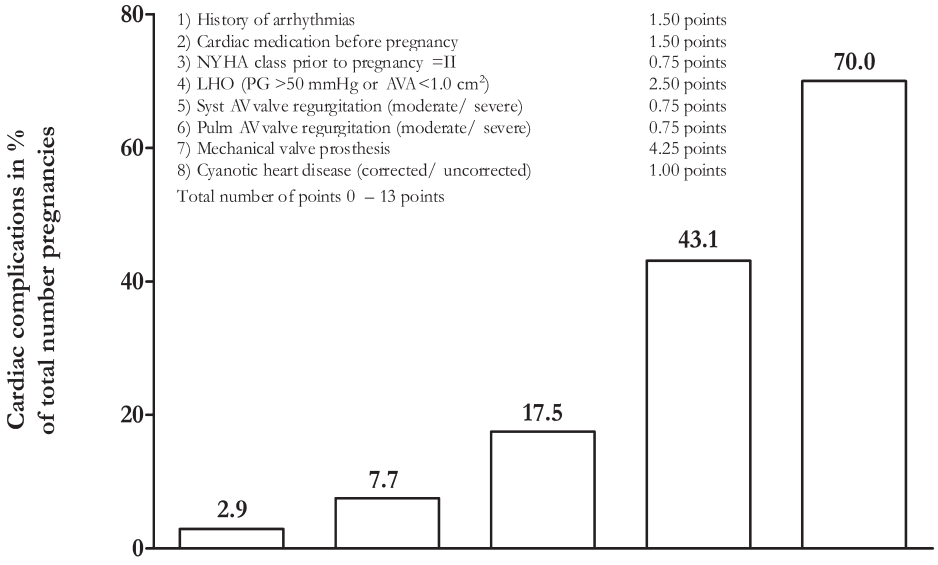
In our study, cardiac complications occurred during 7.6% of completed pregnancies, slightly lower than the 11% reported in our recent review.[1] Clinically significant episodes of arrhythmias (4.7%) and heart failure (1.6%) were the most important of cardiac complications. The lower prevalence of cardiac complications was largely attributable to the lower incidence of heart failure (1.6 vs. 4.8%).[1] As heart failure is difficult to distinguish from 'normal' physiological developments associated with pregnancy, including malleolar edema, shortness of breath during exercise, and increased nocturnal urination frequency, we used a strict definition. The occurrences of other cardiac complications were in line with expectations.

Table 5. Presence of predictors and the number of complications encountered in these patients.

Risk factor	N	Cardiac complications	Underlying CHD in pregnancies with complications
History of arrhythmias	39	AR (n= 8); HF (n= 1); CE (n= 3); EN (n= 0)	TGA 3; ASD 2; ccTGA 1; AOS 1; TOF 1; VSD 1; AVSD 1; PS 1; UVH 1.
Other cardiac medication before pregnancy	80	AR (n= 16); HF (n= 4); CE (n= 4); EN (n= 0)	TGA 6; AVSD 5; TOF 3; Marfan 2; MR 1, AOR 1; VSD 1; ASD 1.
NYHA functional class	7	AR (n= 1); HF (n= 1); CE (n= 0); EN (n= 0)	PAVSD 1; AOR 1.
LHO (PG >50 mmHg or AVA <1.0 cm^2)	22	AR (n= 2); HF (n= 2); CE (n= 0); EN (n= 0)	AOS 5; AVSD 1; CoA 1
Syst AV valve regurgitation[d]	106	AR (n= 7); HF (n= 8); CE (n= 1); EN (n= 0)	AVSD 9; TGA 3;ccTGA 1;MVP 1; AOS 1; Eisenmenger 1.
Pulm AV valve regurgitation[d]	105	AR (n= 10); HF (n= 3); CE (n= 2); EN (n= 1)	AVSD 6; Ebstein 3; PAVSD 3; DORV 1; TOF 1; VSD 1; Eisenmenger 1.
Mechanical valve prosthesis[a]	6	AR (n= 3); HF (n= 2); CE (n= 2)*; EN (n= 0)	AOS 3; AOR 1; MR 2
Cyanotic heart disease (corrected and uncorrected)	198	AR (n= 24); HF (n= 8); CE (n= 3); EN (n= 0)	TGA 13; TOF 9; PAVSD 3; UVH 3; DORV 1; AOS 1;Eisenmenger 1.
		Neonatal complications	
Twin or multiple gestation	18	PD (n= 10); SG (n= 4); MO (n= 1)	
Smoking during pregnancy	192	PD (n= 28); SG (n= 40); MO (n= 8)	
Cyanotic heart disease (corrected and uncorrected)	198	PD (n= 46); SG (n= 34); MO (n= 13)	
Mechanical valve prosthesis[c]	6	PD (n= 3); SG (n= 1); MO (n= 0)	
Other cardiac medication before pregnancy	80	PD (n= 22); SG (n= 14); MO (n= 7)	

AOR, aortic valve regurgitation; **AOS**, aortic valve stenosis; **AR**, arrhythmias; **ASD**, atrial septal defect; **AV**, atrioventricular; **AVA**, aortic valve area; **AVSD**, atrioventricular septal defect; cc**TGA**, congenital corrected transposition of great arteries; **CE**, cardiovascular complications; **CoA**, aortic coarctation; **DORV**, double outlet right ventricle; **EN**, endocarditis; **HF**, heart failure; **LH**, left heart; **Marfan**, Marfan syndrome; **MO**, foetal or neonatal mortality; **MR**, isolated mitral valve regurgitation; **MVP**, mitral valve prolaps; **NYHA**, New York Heart Association; **PAVSD**, pulmonary atresia with VSD; **PD**, premature delivery; **PG**, peak gradient; **PS**, pulmonary valve stenosis; Pulm, pulmonary; **SG**, small for gestational age; Syst, systemic; **TGA**, atrial complete transposition of great arteries; **TOF**, Tetralogy of Fallot; **UVH**, univentricular heart; **VSD**, ventricular septal defect.

a Position of mechanical valve: 4 aortic, 2 mitral; type of mechanical valve: all bileaflet, except 1 Björk-Shiley mitral valve.
b Both cardiovascular complications were mechanical valve thrombosis occurring at 12 and 14 weeks of gestation shortly after switch of full dose subcutaneous low molecular weight heparin back to oral anticoagulation (one aortic bileaflet prosthesis; one Björk shiley mitral valve prosthesis). No other risk factors for thrombotic complications were present during these pregnancies. One of these patients had two additional episodes of thrombosis during the same pregnancy, which were not analysed separately.
c Including the two pregnancies complicated by mechanical valve thrombosis.
d Moderate/severe.



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

Figure 1. The modified risk score for cardiac complications during completed (>20 weeks of gestation) pregnancies in women with congenital heart disease (expressed as % of the total number of completed pregnancies). **AV**, atrioventricular; **AVA**, aortic valve area; **LHO**, left heart obstruction; **NYHA**, New York Heart Association; **PG**, peak gradient; **Pulm**, pulmonary; **Syst**, systemic.

New associations with adverse cardiac complications were: (i) the presence of moderate/severe systemic or pulmonary AV valve regurgitation, (ii) the presence of mechanical valve prosthesis, and (iii) 'at birth' cyanotic CHD. (i) The presence of significant AV valve regurgitation is known to cause volume loading and atrial distension. These factors are subsequently linked with the development of heart failure and supraventricular arrhythmias. In patients with significant pulmonary AV valve regurgitation, the majority of complications were arrhythmias. The vulnerability to develop arrhythmias is a well-known long-term complication in these patients even outside pregnancy. Up till now, due to the decrease in systemic vascular resistance, the importance of systemic AV valve regurgitation during pregnancy was thought to be limited. Therefore, our finding that moderate/severe systemic AV valve regurgitation independently predicts maternal complications is important, in particular as half of the complications consisted of heart failure. Importantly, we need to realize that in a significant proportion of patients, the moderate-to-severe AV valve regurgitation was associated with (moderately) complex CHD, and concomitant ventricular dysfunction and/

or dilatation may have been involved in the development of complications. This risk factor should therefore be interpreted in the context of the associated heart disease and ventricular function. (ii) The fact that the presence of a mechanical valve correlated with adverse cardiac outcome is not surprising. Several case series and reports have described important cardiac complications including maternal mortality, heart failure, arrhythmias, and mechanical valve thrombosis.[15-17] Especially, although not exclusively, patients with old generation valves in mitral valve position appeared at greater risk for valve thrombosis.[15] In all our patients with mechanical valves, cardiac complications occurred (Table 4), including mechanical valve thrombosis during two pregnancies, one in a woman with a high-risk mechanical prosthesis (mitral Björk Shiley) but the other in a woman with a bileaflet aortic valve. Both events presented shortly after switching therapy from subcutaneous full fixed dose low molecular weight heparin to oral anticoagulation consisting of acenocoumarol. At present, the anticoagulation regime best used during pregnancy in women with mechanical valves is still a subject of debate. The used schedule is not advocated in the official ESC guideline.[18] Moreover, in our patients, anti-factor *X*a levels were not monitored; this may well have negatively affected the occurrence of valve thrombosis. (iii) The fact that patients with at birth cyanotic heart disease appear to be at greater risk for cardiac complications most likely reflects the complexity of the underlying heart condition. Patients with more complex heart disease need more interventions and are more prone to develop complications outside pregnancy.[19] The burden of pregnancy may accelerate the development of adverse cardiac complications.

In concordance with the CARPREG and other investigators, we identified NYHA functional class >II, left heart obstructive lesions, and a history of arrhythmias to be independent predictors of maternal cardiac complications.[20,21] It needs to be added that arrhythmias were the most common cardiac complication in women with a history of arrhythmias. Silversides *et al.*[22] reported earlier that in women with pre-existing cardiac rhythm disorders, exacerbation of arrhythmic episodes during pregnancy was common.

In contrast to the CARPREG report, a decreased systemic ventricular function was a univariate but not multivariate predictor of cardiac complications. In this retrospective study, we had to use a less accurate definition for decreased left ventricular function (subjective mostly echocardiographic estimation vs. measurement of ejection fraction in the CARPREG study) which may in part explain this difference. The association between significant systemic AV valve regurgitation and decreased systemic ventricular function (e.g. in patients with a systemic right ventricle) may be another part of the explanation, as systemic AV valve regurgitation emerged as an independently associated characteristic in our study. Cyanosis and a history of cardiac complications also did not correlate with adverse cardiac outcome. The low incidence of these variables may at least be in part the explanation. Cyanotic women are often advised against pregnancy.[23]

Predicting obstetric complications

Obstetric complications were observed during 24% of completed pregnancies. Hypertensive

disorders of pregnancy were the most important obstetric complication occurring in 12.2% (including preeclampsia in 4.4%). No plausible associations with adverse obstetric outcome were found.

Predicting neonatal complications

Neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%), overall complicating 25% of completed pregnancies. In comparison with the results summarized in our literature review, the occurrence of small for gestational age and offspring mortality is higher, which could be mainly attributed to the relatively higher percentage of complex CHD.

New associations were the use of cardiac medication, 'at birth' cyanotic heart disease, and mechanical valve prosthesis. The fact that at birth cyanotic heart disease and the use of cardiac medication predicted neonatal complications most probably reflects the severity of the underlying heart disease. Mechanical valve prosthesis mainly resulted in premature delivery which may be the result of precautions taken by the attending physician as most deliveries were induced prematurely (possibly because of maternal cardiac complications). In several case series, similar observations were done.[16,17]

In the CARPREG study, predictors for neonatal complications were NYHA functional class or cyanosis, left heart obstructive lesions, smoking during pregnancy, multiple gestations, and the use of anticoagulation during pregnancy. In our population, the maternal functional class >II or cyanosis did not appear to be a risk factor, probably at least in part due to the low prevalence in our population. Also patients with left heart obstruction did not appear to be at greater risk for offspring complications. In correspondence with the report by Siu *et al.*, in our study, women with a twin gestation and those who smoke during pregnancy were at a higher risk for offspring complications (Table 5). The most important risk associated with multiple gestations is spontaneous preterm delivery, which is subsequently related with increased perinatal mortality and morbidity.[24,25] Smoking during pregnancy is also a well-known risk factor that affects neonatal outcome.[26]

Risk scores

The CARPREG risk score performed inadequately in our population and largely overestimated risk, in line with other reports.[27,28] The differences between the populations that we pointed out may in part explain the poor performance of the CARPREG cardiac risk score in our population. In addition, the incidence of cardiac complications appears relatively low (7.6%) in comparison to 13 and 19.4% reported by Siu *et al.*[2,3,29] and Khairy et al.[4] However, the cardiac complication rate in the CARPREG study in patients with CHD is 7.1% (32 in 445 pregnancies). Apparently, acquired or arrhythmic heart disease patients are at higher risk. The cohort investigated by Khairy *et al.* had an overrepresentation of complex CHD, which may explain the higher cardiac complication rate. Nonetheless, the different definition of heart failure (therapeutic interventions had to be performed) that we needed to use in this retrospective study could also in part explain this discrepancy. The

incidence of cardiac complications in our study, however, is comparable to the frequency found in a recently published literature review.[1] The modification of the risk index (as explained in the Results section) seems to enhance discrimination and calibration. Importantly, both risk scores have significant limitations restricting indiscriminative use. The representation of risk factors in the population determines which risk factors emerge. Important risk factors such as pulmonary arterial hypertension are likely to be underrepresented in contemporaneous cohorts, preventing such risk factors to be identified. Therefore, it is important to underline that the calculation of risk scores should be only a part of prepregnancy risk assessment. We advocate a prepregnancy evaluation in an outpatient setting, including physical examination, laboratory evaluation, and an echocardiography according to a predefined protocol by an expert in the field. In addition to weighing predictors found in ZAHARA and CARPREG and calculating risk scores, disease-specific information should always be used when estimating pregnancy risk in order to avoid over-simplification implied by risk calculation. Also existing guidelines and expert articles should be consulted.[30] External validation of our modified risk score in a large prospective study remains necessary, before use in everyday practice is possible.

Limitations

Most of the limitations of the present study are related to the retrospective design. First and most importantly, the present study lacks a historical 'matching' control population. This is, however, not as straightforward and simple exercise, as the vast majority of healthy women in the Netherlands and Belgium deliver at home with the help of a midwife. Therefore, the women consulting gynecological hospital care are a selected population with (mainly obstetric or neonatal) complications or at higher risk for these complications. Moreover, the concept of a control population is, in our opinion, only sustainable, when both cohorts are followed in an identical fashion according to a predefined protocol. Therefore, a prospective study would be the best option, on the other hand, to collect the number of pregnancies provided in the present study; data collection would take at least 10 years and interfere with the contemporaneous applicability. A second limitation is the possibility of underreporting. Because data-retrieval was retrospective, only documented complications (by medically educated personnel) were included. Third, we need to take into account that for the present study, a survivor cohort was selected, therefore not allowing the investigation of maternal mortality. Moreover, patients thought to be at high risk based on earlier studies, e.g. Eisenmenger syndrome and many Fontan patients, are generally advised against pregnancy or mainly patients at relatively good health achieve pregnancy. The risk of pregnancy in women with these complex heart diseases can therefore be underestimated in this study; nevertheless, it represents today's policies regarding pregnancy. Another limitation concerns the impossibility in this retrospective study to accurately quantify the severity of systemic and pulmonary ventricular volumes and function. Also the exclusion of miscarriage and abortion pregnancies may result in an underestimation of certain risks. For example, the reason for elective abortion in one patient was a clinically significant

supraventricular arrhythmia with secondary heart failure. To include these pregnancies in the analyses would, however, lead to an underestimation of other complications that incorporated a certain gestational age to develop, i.e. hypertensive disorders. Moreover, the limitations associated with the low-risk contrast, the still relatively small cohort, and the lower incidence of complications and subsequent impossible internal validation need to be taken into account. The present cohort is representative for a CHD population receiving tertiary medical care, including patients with complex heart disease; caution, however, is needed when extrapolating the results to populations with another CHD distribution. In summary, the results should be interpreted with caution.

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Part II

Prospective assessment of complications and predictors of adverse events

Chapter 4

Associations between cardiovascular parameters and uteroplacental Doppler (blood) flow patterns during pregnancy in women with congenital heart disease: Rationale and design of the Zwangerschap bij Aangeboren Hartafwijking (ZAHARA) II study

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Summary

Background Previous research has shown that women with congenital heart disease (CHD) are more susceptible to cardiovascular, obstetric, and offspring events. The causative pathophysiologic mechanisms are incompletely understood. Inadequate uteroplacental circulation is an important denominator in adverse obstetric events and offspring outcome. The relation between cardiac function and uteroplacental perfusion has not been investigated in women with CHD. Moreover, the effects of physiologic changes on pregnancy-related events are unknown. In addition, long-term effects of pregnancy on cardiac function and exercise capacity are scarce.

Methods Zwangerschap bij Aangeboren Hartafwijking (ZAHARA) II, a prospective multicenter cohort study, investigates changes in and relations between cardiovascular parameters and uteroplacental Doppler flow patterns during pregnancy in women with CHD compared to matched healthy controls. The relation between cardiovascular parameters and uteroplacental Doppler flow patterns and the occurrence of cardiac, obstetric, and offspring events will be investigated. At 20 and 32 weeks of gestation, clinical, neurohumoral, and echocardiographic evaluation and fetal growth together with Doppler flow measurements in fetal and maternal circulation are performed. Maternal evaluation is repeated 1 year postpartum.

Implications By identifying the factors responsible for pregnancy-related events in women with CHD, risk stratification can be refined, which may lead to better prepregnancy counseling and eventually improve treatment of these women.

Background

Because of improved long-term survival, most women with congenital heart disease (CHD) reach child-bearing age and many pursue pregnancy. In women with uncorrected maternal congenital heart defects or with residual sequelae after correction, the haemodynamic changes in pregnancy can have negative effects on the health of both mother and her (unborn) child. Cardiac events are rare in healthy women (<1%), while arrhythmias occur in 4.5% and heart failure in 4.8% of women with CHD.[1] In complex CHD, cardiac event rate can be even higher.[1-4] Women with CHD are not only more susceptible to cardiac events, but obstetric and offspring events are also more prevalent.[1-3] Important obstetric events are postpartum hemorrhage (8%, up to 29%), pregnancy-induced hypertension (5.5%, up to 13%), preeclampsia (PE; 3.2%, up to 10%), and preterm delivery (16%, up to 65%); whereas in healthy pregnant women, the prevalence of these events is much lower.[1] Frequently observed events in offspring of women with CHD are intrauterine growth restriction (IUGR), prematurity, and mortality.[1-3] The magnitude of these risks depends, at least in part, on the type and severity of maternal CHD. In the general population, both IUGR and PE are associated with a lower cardiac output (CO), an elevated total vascular resistance (TVR), and abnormal uterine and umbilical artery Doppler waveform patterns.[5,6] These parameters can be used to identify women at risk for PE and IUGR. The higher incidence of these events in women with CHD may be caused by inadequate maternal haemodynamics, resulting in insufficient uteroplacental circulation.[7,8] Nevertheless, the interaction between echocardiographic, haemodynamic, and neurohumoral parameters on one side and uteroplacental Doppler flow patterns on the other side in relation to pregnancy outcome have not been studied in women with CHD and have not been compared to those in healthy pregnant women. In addition, although some studies identified predictors of cardiac events in women with both acquired and CHD, prospective data relating echocardiographic parameters of ventricular or valvular function to maternal cardiac events are still scarce and little is known about the long-term effects of pregnancy on cardiac function or exercise capacity in women with CHD.[2,3,9] The mid- and longterm effects of pregnancy on cardiovascular haemodynamics have been described in a few select subgroups.[10,11] In these studies, however, exercise capacity or cardiac biomarkers were not assessed. In this article, we will introduce the study design and describe the rationale of the ZAHARA II study.

Methods

Study objectives

The primary objective of the present study is to compare cardiovascular, neurohumoral, and uteroplacental Doppler flow changes during pregnancies of women with CHD with age- and parity-matched healthy controls and to relate these changes to the occurrence of cardiovascular and obstetric events and to offspring outcome. The secondary objective of this study is to evaluate the incidence of permanent postpartum cardiovascular deterioration in women with CHD.

Study design

This is an observational prospective multicenter cohort study.

Study population

Women with any morphological CHD with a pregnancy of <20 weeks duration, presenting in the participating centers, who meet all the inclusion and none of the exclusion criteria are eligible (Table 1). During a 3-year period, a minimum of 160 women with CHD are enrolled, and simultaneously, 60 healthy, age- and parity-matched women are recruited from a low-risk midwife practice in Groningen and in Rotterdam, the Netherlands, to serve as controls. We will use a subclassification for our cohort where appropriate, using division in disease complexity, the adapted World Health Organization classification for estimating pregnancy risk, or clustering of the morphological and functional comparable diseases as in previous studies.[2,9,12,13]

Table 1. Inclusion and exclusion criteria of ZAHARA II

WOMEN WITH CHD
Inclusion criteria
Age ≥18 y
Morphological **CHD**
Presentation at ≤20 wk of gestation
Presentation in one of the participating medical centers
Exclusion criteria
Miscarriage or termination of pregnancy <20 wk of gestation
Alcohol abuse
Illicit drugs use
HEALTHY CONTROLS
Inclusion criteria
Age ≥18 y
Presentation at ≤20 wk of gestation
Exclusion criteria
Miscarriage or termination of pregnancy <20 wk of gestation
Women who are on chronic medication
Women who are under specialist control
Alcohol abuse
Illicit drugs use

Measurements

Baseline data are recorded at the first prenatal visit using medical records and include underlying heart disease, prior interventions, cardiac sequelae, prior cardiac events, comorbidity, and obstetric

history. Maternal age, parity, present cardiac status (including New York Heart Association functional class, physical examination, oxygen saturation, and echocardiographic data), use of medication, intoxications, educational status, and current employment are also recorded. Clinical evaluation at gestational weeks 20 and 32 as well as at 1 year postpartum is performed for follow-up data and for registration of events. During follow-up echocardiograms, electrocardiograms and 24-hour electrocardiographic registrations as well as obstetric evaluation and blood and urinalysis are conducted.

Echocardiography

Standardized echocardiograms according to disease-specific protocols are performed at 20 and 32 weeks of gestation and at 1 year postpartum. Echocardiograms are evaluated off-line in the University Medical Center Groningen, Groningen, the Netherlands. Morphological left and right ventricular size and function (if feasible, ejection fraction according to Simpson's rule), atrial size, valvular function (quantification of regurgitation and stenosis of all valves) as well as disease-specific evaluation (i.e., presence and location of intracardiac shunts, evaluation of conduits, or baffles) are performed according to current recommendations and guidelines.[14-20] Blood pressure and heart rate are measured during echocardiography to calculate CO and TVR as described previously.[15,17,19] Prepregnancy routinely performed echocardiograms (available in most of the patients) are analyzed for comparison.

Obstetric evaluation

Fetal biometry is assessed by ultrasound and uteroplacental perfusion is studied by Doppler flow measurements of uterine arteries. Umbilical artery pulsatility index, resistance index, and uterine artery flow and early diastolic notching are evaluated at 20 and 32 weeks of pregnancy according to the guidelines of the International Perinatal Doppler Society.[5,21] Evaluation of the digitally stored (Doppler) ultrasound registrations is performed in the University Medical Center Groningen.

Blood and urinalysis

Haematologic parameters, renal and hepatic function, haemoglobin A1c as well as nonfasting glucose, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) are assessed from blood samples at 20 and 32 weeks of gestation and 1 year postpartum and compared with the values before pregnancy, if available. Proteinuria is quantitatively assessed at 20 and 32 weeks of gestation.

Cardiopulmonary aerobic capacity testing

Cardiopulmonary aerobic capacity testing is performed 1 year postpartum in patients who underwent this test <2 years before pregnancy.[22]

Adverse events

Clinical adverse events in ZAHARA II are subdivided in cardiac, obstetric, offspring, and general adverse events (Table 2). We define cardiovascular events as described in previous studies (Table 2). In addition, we assess changes in NT-proBNP levels and in echocardiographic findings in patients with CHD compared to those in healthy controls. We define abnormal echocardiographic changes in pregnancies as a significant deterioration in size or function of subpulmonary or sub-aortic ventricle; new onset or aggravation of valve regurgitation ≥1 grade (mild to moderate or severe, or moderate to severe) during pregnancy and/or persisting 1 year postpartum; persistent (≥1 year) significant aggravation of valve stenosis (mild to moderate or severe, or moderate to severe); significant increase in aortic dimensions (≥5 mm) during pregnancy and/or 1 year postpartum. Furthermore, pulsatility index >95th centile in umbilical artery, uterine artery resistance index >95th centile, umbilical artery resistance index >0.58 or >90th centile, or early diastolic notching in uterine artery is considered abnormal in obstetric ultrasound evaluation.[23] Finally, a significant deterioration in functional capacity and/or exercise capacity 1 year postpartum in all patients compared with pre-pregnancy values is considered abnormal.

Statistical and ethical considerations

Sample size calculation. One of the primary aims of the ZAHARA II study is to compare the uteroplacental Doppler flow, expressed as pulsatility index in the umbilical artery, during pregnancy between women with CHD and healthy controls. A sample size of 160 patients and 60 controls achieves a power of 80% at a significance level of 0.05 to detect a difference of 5% higher mean pulsatility index in women with CHD.
Statistical analysis. Continuous variables with normal distribution will be presented as mean (±SD), nonnormally distributed variables as median (with 25th and 75th percentile), and dichotomous variables will be presented as absolute numbers and percentages. Comparison of continuous variables between groups will be made by independent t-tests or the Mann-Whitney U test, depending on their distribution. For the comparison of dichotomous variables, we will use the X^2 test or Fisher exact test, where applicable. Uni- and multivariable logistic regression analyses will be performed to identify predictors of adverse pregnancy outcome. For the analysis of repeated measures within the women with CHD, between the women with CHD, as well as between the women with CHD and the healthy controls, we will use multivariate general linear models.

Ethical considerations. The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen). The study design, all research aims, and the specific measurements in the ZAHARA II Study have been approved by the medical ethical committee of all participating hospitals. New measurements will only be embedded in the study after approval of the medical ethical committee. All participants are asked for their written informed consent after having received written and oral information about the study.

Table 2. Adverse events as defined in ZAHARA II
Primary cardiovascular events during pregnancy, up to 6 m postpartum
Need for urgent invasive cardiovascular procedures
Heart failure: according to the guidelines of the European Society of Cardiology and documented by the attending physician[40]
Any documented new-onset or symptomatic tachy- or bradyarrhythmia requiring new/extended treatment
Thromboembolic events: deep vein thrombosis, pulmonary embolism, intracardiac thrombosis, arterial thrombosis, systemic arterial embolisms or TIA
Myocardial infarction
Cardiac arrest
Cardiac death
Endocarditis: according to the Duke criteria[41]
Aortic dissection
Secondary cardiovascular events during pregnancy, up to 6 m postpartum
NYHA class deterioration: decline of 2 points in NYHA functional class during pregnancy or within 6 m postpartum, compared with prepregnancy NYHA class or a persisting deterioration in NYHA functional class postpartum
Primary obstetric events
Assisted delivery: use of forceps, use of a vacuum extractor, or the performance of a cesarean section for delivery on maternal cardiac and medical indication, on maternal obstetric indication, or on fetal indication
PIH: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or an increase of systolic (>30 mmHg) or diastolic (>15 mmHg) blood pressure, in the absence of proteinuria, occurring after ≥20 wk of gestation
PE: PIH with ≥0.3 g/24 h proteinuria
Eclampsia: PE with grand mal seizures
Mild gestational diabetes mellitus: a fasting blood glucose <140 mg/dL (7.8 mmol/L) and 2-h postprandial 140-198 mg/dL (7.8-11 mmol/L)
Severe gestational diabetes mellitus: a random serum glucose value >200 mg/dL (11.1 mmol/L) or a fasting blood glucose value >126 mg/dL (7.0 mmol/L)
HELLP: hemolysis (LDH >250 U/L), elevated liver enzymes (ASAT >40 U/L and ALAT >45 U/L), low platelets (<1.0 × 10.6/mm^3) syndrome
Hyperemesis gravidarum: severe, intractable nausea and vomiting, leading to dehydration, loss of weight, metabolic disorders, and hospitalization
Noncardiac death: all cause mortality, except cardiac mortality
Postpartum hemorrhage: blood loss >500 mL (vaginal delivery) or >1000 mL (cesarean section), requiring transfusion or leading to a drop in hemoglobin >20 g/L (1.24 mmol/L)
Premature labor: spontaneous onset of labor <37 wk of gestation
Preterm premature rupture of membranes: spontaneous rupture of membrane before the onset of uterine contractions and before 37 wk of gestation
Abruptio placentae: premature detachment of the placenta from the wall of the uterus
Secondary obstetric events
Amniotomy: mechanical/artificial rupture of membranes
Induction of labor
Prolongation of cervix ripening: omitted dilatation of the portio vaginalis during ≥20 h (nullipara) or ≥14 h (multipara), despite adequate and regular uterine contractions
Prolongation of second stage of delivery (primipara >2 h; multipara >1 h)
Placenta previa: localization of the placenta partially or completely above the internal ostium of the cervix

Table 2 (continued). Adverse events as defined in ZAHARA II
Offspring events
Fetal death: intrauterine death >20 wk of gestation
Extended perinatal death: the number of stillbirths from 20 wk of gestation and neonatal death up to 28 d postpartum
Early neonatal death: within 6 d after birth
Late neonatal death: within 7-28 days after birth
Infant death: >28 d and within 1 y after birth
Perinatal death: the total number of stillbirths from 20 wk of gestation and death up to 7 days postpartum
Offspring death: the total number of stillbirths from 20 wk of gestation and death up to 1 y postpartum
Intraventricular hemorrhage: bleeding in the fetal cerebral ventricles
Neonatal respiratory distress syndrome: respiratory insufficiency caused by a developmental insufficiency of surfactant production and structural immaturity in the lungs in premature infants
Infections leading to hospital admission
Premature birth: birth <37 wk gestation
Occurrence of CHD
Occurrence of other congenital disease
Small for gestational age: birth weight below the 10th percentile adjusted for gestational age and based on population values
Low birth weight: birth weight <2500 g
Meconium stained amniotic fluid
General events
Anemia: between 18 wk of gestation until 1 wk postpartum: 6.5 mmol/L or 10.5 g/dL[42]
Hospitalization: all cause hospitalization for more than 1 night
Fever: ≥38.5°C during pregnancy up to 6 m postpartum requiring medical treatment
Infection: infections during pregnancy up to 6 m postpartum requiring medical treatment
ALAT, Alanine aminotransferase; **ASAT**, aspartate aminotransferase; **LDH**, lactate dehydrogenase; **NYHA**, New York Heart Association; **PIH**, pregnancy-induced hypertension; **TIA**, transient ischemic attack.

Data management and privacy protection. Data are directly entered onto written case record forms (CRF) and manually entered into an electronic database by 2 researchers. Random samples of all entered data are double checked by other research members to monitor the quality of this manual data entry process. Open text fields are copied into the electronic database exactly as they are filled in on the CRF. All measurements will be checked by examination of the data including their ranges, distributions, means, SD, outliers, and logical errors. Data outliers and missing values will be checked on the original CRF. All information in these data sets that enables identification of a participant will be excluded. The CRF as well as the data sets include subject unique identification numbers that enable feedback about one subject to the data manager but do not enable identification of that particular subject.

Discussion

In the present study, we assess whether changes in cardiovascular, hemodynamic, neurohumoral

parameters, and uteroplacental Doppler flow patterns during pregnancy of women with CHD differ from age- and parity-matched healthy controls. We also assess the interaction of these changes with the occurrence of cardiovascular, obstetric, and offspring events. In addition, we evaluate the incidence of permanent changes in cardiovascular parameters 1 year postpartum in women with CHD and compare these with matched healthy controls.

During normal pregnancy, considerable haemodynamic changes occur.[24] Total vascular resistance decreases, mainly due to peripheral arterial vasodilatation, mediated by progesterone and vasodilators such as nitric oxide as well as a low-resistance flow in the uteroplacental circulation.[25,26] In normal pregnancy, a gradual widening of the maternal spiral arteries occurs early in the first trimester due to the invasion of endovascular and interstitial trophoblasts that convert maternal spiral arteries closer to the intervillous space. As a consequence, plasma volume, heart rate, and CO gradually increase in the first 2 trimesters of pregnancy to maintain adequate organ and uteroplacental perfusion while TVR decreases.[24,26] Blood pressure drops in the first trimester of pregnancy, reaching its lowest point at the end of the second trimester, around 20 weeks of gestation, and returns to near prepregnancy levels around term.[24,27] Together with the rise in plasma volume, the CO rises, which is reflected by an increase in both atrial and ventricular volumes, ventricular wall thickness, and the rise of heart rate.[24] In normal pregnancy, an increased NT-proBNP level can be measured.[28] Cardiovascular haemodynamic state returns back to prepregnancy state in most women within 6 months postpartum.[24,29]

In women with CHD, haemodynamic changes in pregnancy can exceed the compensatory possibilities of their compromised circulation, resulting in cardiac complications such as heart failure, arrhythmias, and other cardiovascular events. Known predictors of maternal cardiovascular events are related to underlying disease as well as to prepregnancy haemodynamic and functional status.[2,3,9] However, detailed information about changes in ventricular and valvular function as well as in CO and TVR and their relationship to the occurrence of cardiovascular events in pregnancy is not available. Echocardiographic evaluation before, during, and after pregnancy in our population with CHD and in matched healthy pregnant controls will clarify some of the confusion. NT-proBNP is a well-known marker of heart failure severity.[30,31] In women with CHD, NT-proBNP has been incompletely evaluated, even outside pregnancy. However, it has been shown that NT-proBNP correlates positively with New York Heart Association functional class deterioration as well as with cyanosis and inversely with ventricular ejection fraction, even in asymptomatic women with CHD.[32,33] As these parameters predict pregnancy complications in women with CHD, it is plausible to hypothesize that NT-proBNP may be an easy and useful method for stratification of cardiovascular risk in pregnancy.[1-3,9] Moreover, NT-proBNP levels are divergent in hypertensive disorders of pregnancy, with a graded increase from normal pregnancy to gestational hypertension and PE.[34] The frequency of these disorders is increased in women with CHD, and NT-proBNP levels may provide further insight in the relation of cardiovascular status and the occurrence of these complications.[4,35]

Hypertensive disorders of pregnancy, especially PE, are characterized by impaired trophoblast invasion and failure of dilatation of spiral arteries, resulting in high uteroplacental vascular resistance, leading to inadequate uteroplacental perfusion and adverse obstetric and offspring outcome, including IUGR and PE.[6,7] Compromised uterine perfusion with placental dysfunction is reflected by abnormal uteroplacental Doppler waveform patterns.[5] Abnormal uterine artery pulsatility index and notching in early diastolic phase predicts PE, is related to high TVR and low CO, and is associated with IUGR and small for gestational age.[5] In CHD, a higher incidence of PE and IUGR is seen.[1-4,35,36] This may be related to a lower CO and higher incidence of heart failure in these women that may lead to inadequate uteroplacental perfusion. Therefore, uteroplacental flow patterns may differ in women with CHD compared to healthy women and abnormal uteroplacental perfusion may be associated with cardiovascular status as well as with offspring outcome.

Late effects of pregnancy in CHD Long-term effects of pregnancy in women with CHD are incompletely described. In a cohort of women with aortic stenosis, requirement of cardiac intervention was the most important late cardiac event after pregnancy.[10] In a small group of women after Mustard correction, permanent deterioration in functional class, dilatation of right ventricle, right ventricular dysfunction, and tricuspid valve regurgitation have been demonstrated.[11] In women with atrioventricular septal defect, persisting deterioration of atrioventricular valve regurgitation was found as well as persisting deterioration of functional class.[37]

Unfortunately, most data are retrospective, and for many defects, no data on mid- and late-term outcome after pregnancy are available. In the present study, echocardiographic and clinical follow-up will be at least 1 year post pregnancy for all women with CHD. In normal pregnancy, exercise capacity declines in the early postpartum period.[38,39] Despite the improvement in the following 6 months, the pre-pregnancy level is not reached. Whether exercise capacity in women with CHD declines more than in healthy pregnant women is uncertain and will be studied in our cohort.

Conclusion

The current ZAHARA II study is the first "in vivo" study in women with CHD to evaluate the effect of compromised cardiac performance on the uteroplacental circulation and its relationship with the occurrence of obstetric events and adverse offspring outcome. By identifying the components responsible for pregnancy-related events in women with CHD, we will refine risk stratification that will lead to better prepregnancy counseling and may eventually improve treatment of these women.

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Appendix. Supplementary Data

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Chapter 5

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

Submitted

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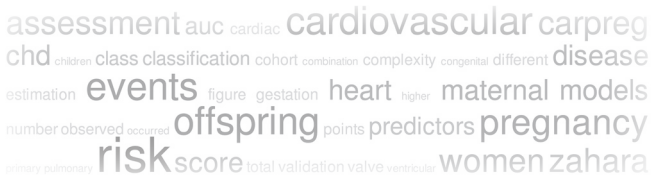


Summary

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

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

Results Maternal cardiovascular events occurred during 19 (9.9%) pregnancies. Offspring events occurred during 63 pregnancies (33.0%). Both cardiovascular and offspring event rate increased with higher risk scores, higher TPc or TPo, higher WHO class and greater DC. The highest area under the curve (AUC) for cardiovascular risk was achieved by the WHO class (AUC: 0.79). CARPREG and ZAHARA I offspring risk scores and TPo performed comparably in estimating offspring risk (AUC: 0.67, 0.66 and 0.68 respectively). A combination of different risk estimation systems resulted in a slightly higher AUC for both maternal and offspring risk.

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

Introduction

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

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

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

Patients and Methods

Design and setting

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

Inclusion and exclusion criteria

Pregnant women with structural CHD (≥18 years) followed in any of 8 participating tertiary centers who provided written informed consent were included in the study at 20 weeks gestation.

Miscarriage or pregnancy termination prior to 20 weeks gestation was reason for exclusion, as were drugs and alcohol abuse.

Baseline characteristics

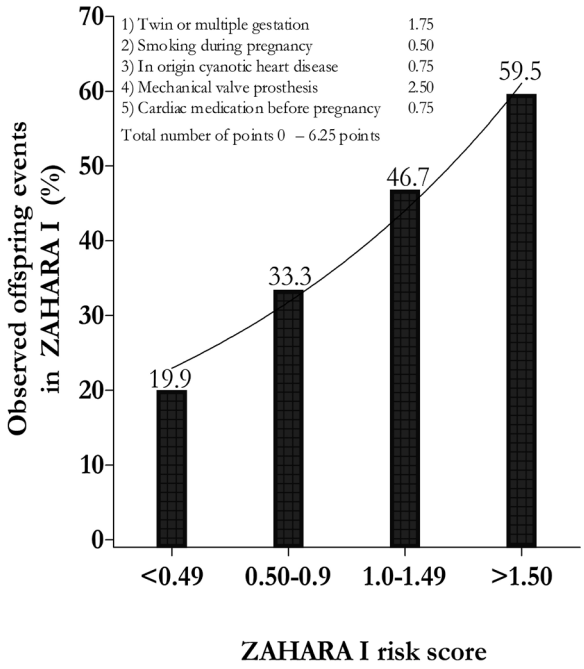
Baseline data recorded at the first prenatal visit at the cardiology outpatient clinic (at 20 weeks gestation) included: maternal age, obstetric history (including parity), underlying heart disease, prior interventions, cardiac sequelae, prior cardiovascular events, co-morbidity, prior and present cardiac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

Risk assessment

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

Endpoints

We scored maternal cardiovascular and offspring events for each pregnancy according to the definitions used in the CARPREG and ZAHARA I studies. Primary cardiovascular events were: cardiovascular mortality, clinically significant (needing treatment) arrhythmia, clinically significant (needing treatment) heart failure, thrombo-embolic events (e.g. pulmonary embolism, valve thrombosis or deep venous thrombosis), vascular events (e.g. cerebrovascular accidents, myocardial infarction and dissection), need for urgent or invasive cardiovascular intervention up to 6 months post partum and endocarditis.[2,7] Secondary cardiac events were: NYHA class deterioration ≥2 points compared to baseline. Offspring events were: premature delivery (delivery <37 weeks gestation), small for gestational age birth weight (<10th percentile), respiratory distress syndrome and/or sepsis; intracerebral (intraventricular) hemorrhage; recurrence of congenital heart disease and offspring mortality (demise in utero [>20 weeks gestation] till the first year postpartum).



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

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

Statistical analysis

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

Ethical Considerations

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

Results

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

Maternal cardiovascular events

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

Offspring events

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

Table 1. Maternal baseline characteristics (prior to pregnancy) at inclusion. N = 191 pregnancies.

	N	(%)
DEMOGRAPHICS		
Maternal age at conception (years ± SD)*	29.3	(±4.4)
Parity status		
0	124	(64.9)
1	50	(26.2)
≥ 2	17	(8.9)
CLINICAL SITUATION		
NYHA class I	189	(99.0)
PAST MEDICAL HISTORY		
History of arrhythmias	14	(7.3)
Left heart obstruction (PG > 30 mmHg or AVA < 1.5cm2 or MVA < 2 cm^2)	14	(7.3)
Left heart obstruction (PG > 50 mmHg or AVA < 1.0 cm^2)	2	(1.0)
Systemic ventricular ejection fraction < 40%	2	(1.0)
Cardiac medication before pregnancy†	27	(14.1)
Systemic AV valve regurgitation#	6	(3.1)
Pulmonary AV valve regurgitation#	9	(4.7)
Mechanical valve prosthesis	11	(5.8)
Cyanotic heart disease**	50	(26.2)
Severe PR and/or depressed subpulmonary ventricular ejection fraction	22	(11.5)
Smoking history	34	(17.8)
Pacemaker / ICD	5	(2.6)
Congestive heart failure	2	(1.0)
Cerebrovascular accident	3	(1.6)
MEDICATION USE PRECONCEPTION		
None	164	(85.9)
Diuretics	0	(0.0)
Antiplatelet drugs	0	(0.0)
Vitamin K antagonists/Heparin	14	(7.3)
Digoxin	2	(1.0)
Beta-adrenoreceptor blocker	23	(12)
Calcium channel blocker	5	(2.6)
Angiotensin-converting enzyme inhibitor	1	(0.5)
Antiarrhythmic drugs	2	(1.0)

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

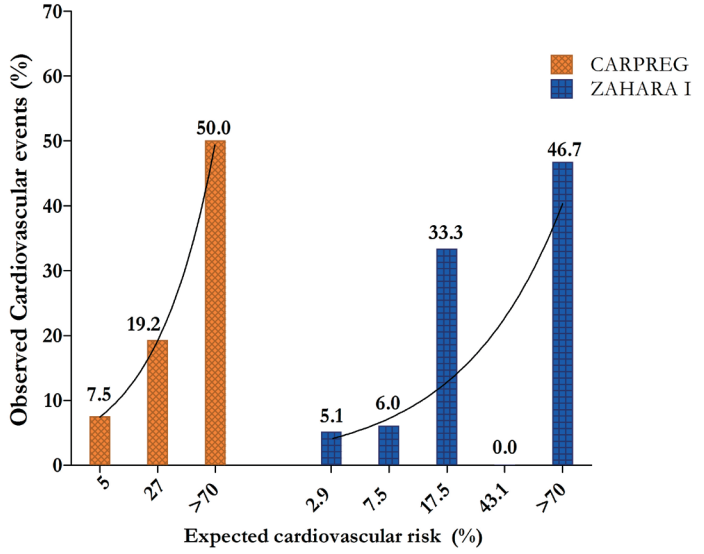
Table 2. Distribution of cardiovascular and offspring events by primary type of congenital heart disease in 191 completed pregnancies.

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

Values are number of pregnancies. **AoS/BiAoV**, congenital aortic valve stenosis or bicuspid aortic valve; **APVR**, Anomalous pulmonary venous return; **PCE**, primary cardiovascular events; **SCE**, secondary cardiovascular events; **TGA**, Transposition of the great arteries.
* 1 Loeys Dietz, all others Marfan.
† All corrected; 2 double-outlet right ventricle (Fallot type).
‡ Pulmonary atresia with combined atrial and ventricular septal defects; truncus arteriosus.
§ Isolated cleft mitral valve, corrected with mechanical valve (St Jude 25mm).
** 1 twin pregnancy
†† 66 offspring events in 191 pregnancies; including three twin pregnancies.

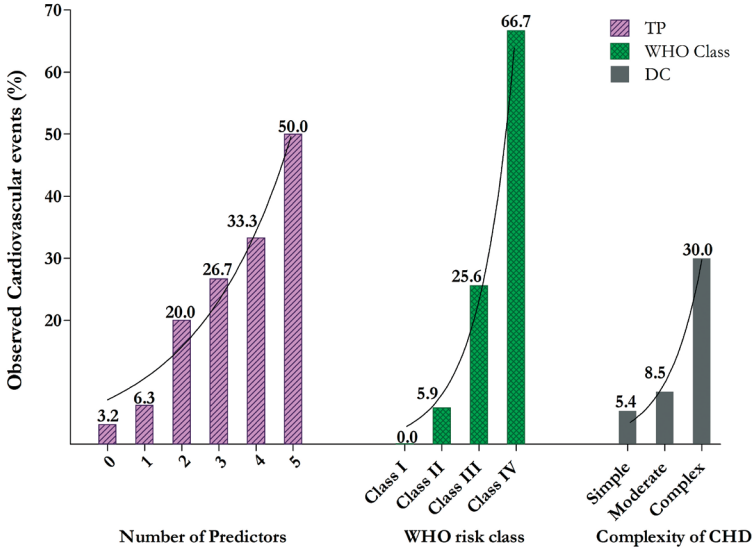
Validation of risk scores and comparison of different risk assessment techniques

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



Number of events	12	5	2	5	4	3	0	7
Pregnancies at risk	161	26	4	98	67	9	2	15
Percentage of total cohort (%)	32.5	13.6	2.1	51.3	35.1	4.7	1.0	7.9

Figure 2a. Expected and Observed cardiovascular events for the ZAHARA I and CARPREG risk scores.



Number of events	2	5	6	4	1	1	0	6	11	2	3	9	6
Pregnancies at risk	62	79	30	15	3	2	43	102	43	3	56	106	20
Percentage of total cohort (%)	32.5	41.4	15.7	7.9	1.6	1.0	22.5	53.4	22.5	1.6	29.3	55.5	10.5

Figure 2b. Observed cardiovascular event percentages for Total number of Predictors, WHO Classification and for Disease Complexity.

Figure 3a shows the ROC for cardiovascular events for the different risk assessment and estimation models. All ROC curves of cardiovascular events deviate significantly from the diagonal line (no discrimination), with exception of the CARPREG risk score (AUC 0.62; 95% CI 0.47-0.77; *P* =0.081). The AUC for the ZAHARA I cardiovascular risk score was 0.73 (95% CI 0.59-0.87; *P* =0.010).

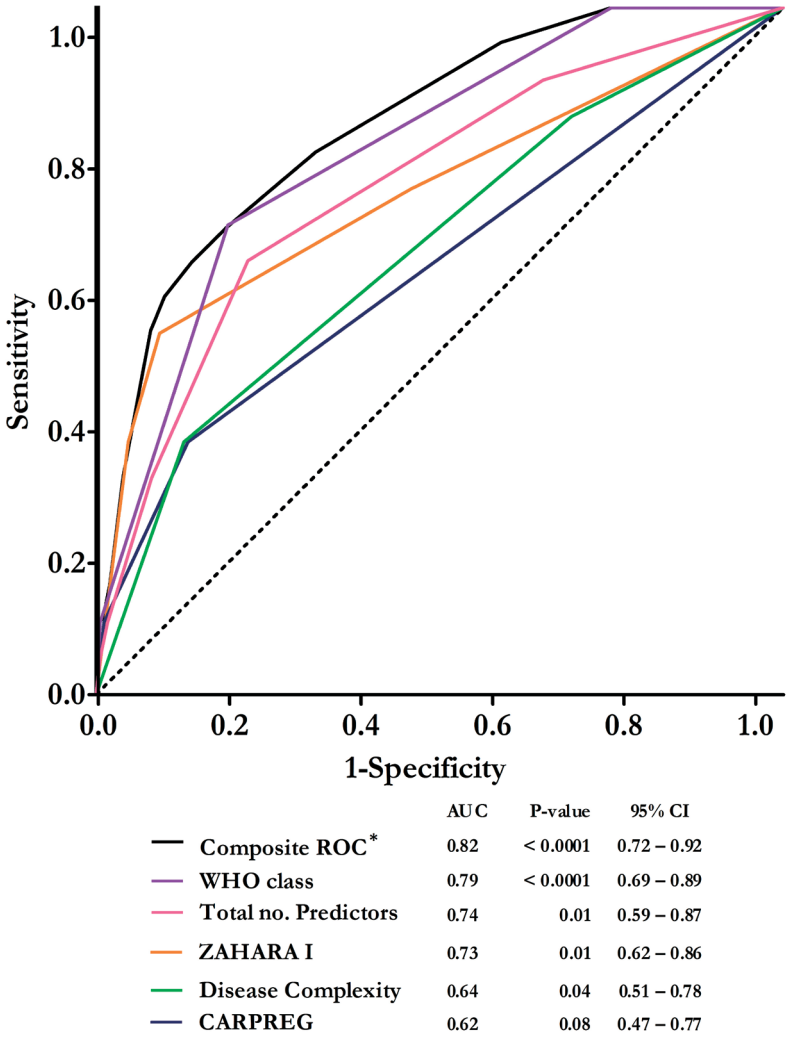
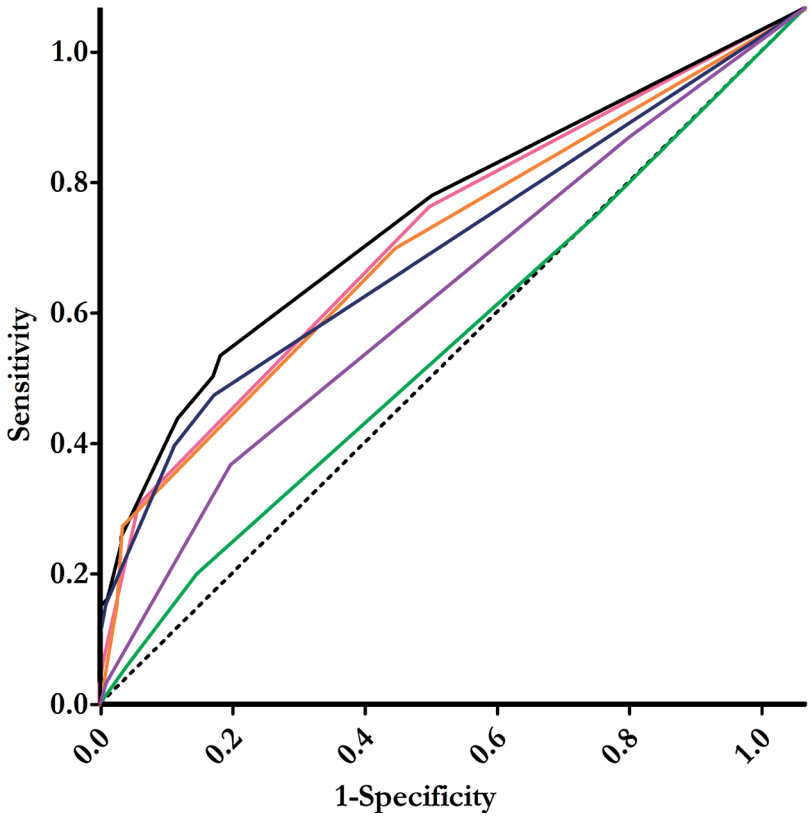


Figure 3a. Receiver Operating Characteristic Curves of cardiovascular events for the different cardiovascular risk assessment and estimation models.

*Composite ROC: optimal combination of risk assessment models (WHO class, total no. cardiac predictors and DC).The AUC differs significantly between WHO class and 1) CARPREG [*P*=0.0065] and 2) disease complexity [*P*=0.0093]; as well as between CARPREG and total number of cardiovascular predictors [*P*=0.035].

Of the 5 cardiovascular risk assessment models, WHO classification had the highest AUC for prediction of maternal cardiovascular events (AUC 0.79; 95% CI 0.69-0.89; *P* <0.0001). A combination of WHO classification, TPc and DC had a slightly higher AUC: 0.82; 95% CI 0.72-0.92; *P*<0.0001).



	AUC	P-value	95% CI
Composite ROC*	0.70	0.040	0.62 –0.78
Total no. offspring predictors	0.68	< 0.0001	0.59 – 0.76
CARPREG	0.67	< 0.0001	0.59 – 0.76
ZAHARA I	0.66	< 0.0001	0.58 – 0.75
WHO Class	0.59	0.041	0.50 – 0.67
Disease Complexity	0.50	0.941	0.42 – 0.59

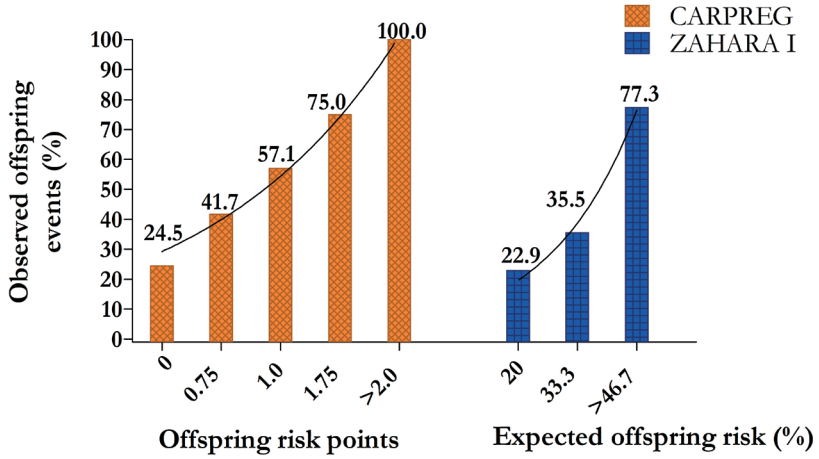
Figure 3b. Receiver Operating Characteristic Curves of offspring events for the different offspring risk assessment and estimation models.

*Composite ROC: optimal combination of risk assessment models (ZAHARA I offspring risk score and CARPREG offspring risk points). The AUC differs significantly between disease complexity and 1) total no. of offspring predictors [*P*=0.0008], 2) ZAHARA I [*P*=0.0013], and 3) CARPREG [*P*=0.012]; as well as between total no. of offspring predictors and WHO class [*P*=0.025].

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

Discussion

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



Number of events	35	5	16	3	7	22	27	17
Pregnancies at risk	143	12	28	4	7	96	76	22
Percentage of total cohort (%)	18.0	2.6	8.2	1.5	3.6	11.3	13.9	8.8

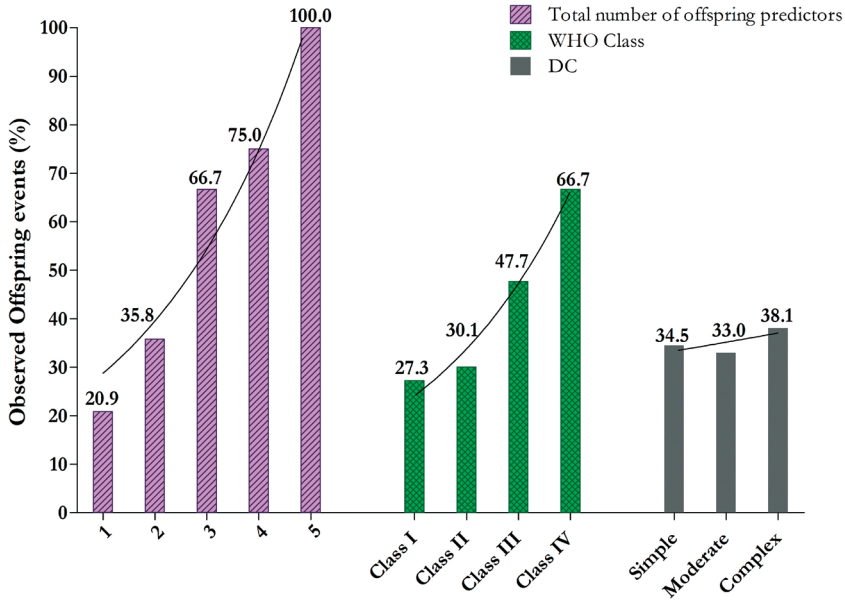
Figure 4a. Expected and Observed offspring events for the ZAHARA I risk score and Observed cardiovascular event percentage for CARPREG risk points.

Maternal cardiovascular events

Our study indicates that pregnancy in women with CHD is relatively safe. The cardiac event rate in our cohort is low compared to some other studies.[5,18-20] The difference in observed cardiovascular events is mainly due to differences in study population and in definition of primary and secondary cardiovascular events. Several other studies found comparable cardiovascular event rates.[1,2,4,7,21,22] Our cohort is a relative low risk cohort, with 99% of women in NYHA class I prepregnancy and no women with cyanosis or pulmonary arterial hypertension. Well organized prepregnancy counseling in the tertiary centers in the Netherlands prevents most high risk women from becoming pregnant, which can explain the relatively low event rate in our cohort.

Validation of cardiovascular risk assessment models

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



Number of events	20	30	15	3	2	13	33	22	2	21	36	9
Pregnancies at risk	86	81	21	4	2	44	103	44	3	58	106	21
Percentage of total cohort (%)	44.3	41.8	10.8	2.1	1.0	22.7	53.1	22.7	1.5	29.9	54.6	10.8

Figure 4b. Observed offspring events percentages for Total number of offspring predictors, WHO Classification and for Disease Complexity.

The CARPREG risk score overestimates maternal cardiovascular risk in our cohort, in line with other studies.[4,5,21,22]

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

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

Offspring events

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

Validation of offspring risk assessment models

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

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

Limitations and strengths

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

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Conflict of interest: none declared.

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Chapter 6

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

Submitted

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Summary

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 We compared clinical, laboratory, echocardiographic and uteroplacental Doppler flow (UDF) parameters at 20 and 32 weeks of gestation, and pregnancy outcome in women with CHD and healthy women. We related cardiovascular parameters to UDF parameters and pregnancy outcome in women with CHD.

Results We included 209 women with CHD and 70 healthy women. Cardiovascular parameters (N-terminal pro-B-type natriuretic peptide (NT-proBNP), 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). Women with CHD had more obstetric and offspring events than healthy women (58.9% versus 32.9%, P<0.0001; and 35.4% versus 18.6%, P=0.008). Impaired UDF was associated with adverse obstetric and offspring outcome. At multivariate analysis, cardiovascular parameters prepregnancy and at 20 weeks were associated with UDF (umbilical artery resistance index at 32 weeks): right ventricular function (tricuspid annular plane systolic excursion) (P=0.002), high NT-proBNP (P=0.085), and systemic (P=0.001) and pulmonary (P=0.045) atrioventricular valve regurgitation.

Conclusion UDF parameters differ between healthy and CHD women. UDF parameters are associated with cardiovascular function and obstetric and offspring outcome in women with CHD. Compromised UDF may be a mechanism involved in the high incidence of adverse offspring and obstetric outcome in women with CHD.

Introduction

The extensive evolution of cardiac surgery for congenital heart disease (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. Moreover, also obstetric and offspring complications are 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 incompletely unraveled. In healthy women with intrauterine growth restriction or hypertensive disorders of pregnancy, the process of placentation is disturbed resulting in abnormal uterine and umbilical artery Doppler flow patterns.[6] Co-existing cardiac function abnormalities have been demonstrated.[7,8] However, 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), uteroplacental Doppler flow (UDF) patterns and offspring complications has not been investigated. We hypothesized that cardiac dysfunction in women with CHD results not only in cardiovascular complications, but also leads to disturbed placentation with abnormal UDF patterns, thus compromising normal growth and development of the fetus and contributing to complications in pregnancy. The objective of the present study is therefore to compare cardiovascular clinical, biochemical and echocardiographic parameters as well as UDF patterns of pregnant women with CHD with healthy pregnant women. Moreover, we relate maternal cardiovascular parameters in women with CHD to UDF patterns, and relate these to obstetric and offspring outcome.

Patients and Methods

Design and setting

This prospective observational multi-centre cohort study was conducted between March 2008 and August 2011. The study design was published previously and is summarized below.[9]

Patient selection

Female patients with structural CHD (age ≥ 18 years) reporting pregnancy with a duration ≤20 weeks and followed in one of the 8 participating tertiary hospitals who provided written informed consent participated in the study. 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.

Preconception characteristics

Baseline data recorded at the first prenatal visit (20 weeks gestation) included: maternal age, obstetric history, cardiovascular history, co-morbidity, prepregnancy cardiac status and echocardiographic recordings (including systemic and pulmonary ventricular function as well as valvular function), use of medication, alcohol and smoking history.

Evaluation at 20 and 32 weeks

Participants underwent at 20 and 32 weeks of gestation clinical and laboratory evaluation (including serum haemoglobin and NT-proBNP), echocardiographic examination, as well as uteroplacental Doppler flow registration (pulsatility index (PI) and resistance index (RI) of umbilical artery and of right and left uterine artery, and presence of early diastolic notching (EDN)). All echocardiographic recordings were made on commercially available Philips or Vingmed General Electrics ultrasound equipment. Echocardiograms were evaluated off-line by 3 experienced investigators and chamber quantification, ventricular and valvular function were assessed according to guidelines.[10-13]

Obstetric and offspring events

Extensive definitions of obstetric and offspring events were published previously and are summarized below.[9]

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

Offspring events: 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, SPSS Inc., Chicago, Illinois, USA) and STATA (version 12.0, StatCorp LP, College Station, Texas, USA) for statistical analysis. Continuous variables with normal distribution are presented as mean with standard deviation (±SD), non-normally distributed variables as median with interquartile ranges (IQR)), and dichotomous variables are presented as absolute numbers with percentages. Cardiovascular parameters and UDF parameters at 20 and 32 weeks gestation as well as pregnancy outcome were compared between women with CHD and healthy women. Comparison of continuous variables between groups was performed with Student's t test or Mann-Whitney U test, depending on distribution, with and without logarithmic transformation. For the comparison of dichotomous variables, we used the X^2 test or Fisher exact test, as appropriate. A P value <0.05 was considered statistically significant and all P values are two-sided. Uni- and multivariable linear and logistic regression analyses were performed to assess associations between cardiovascular parameters and UDF parameters as well as between UDF parameters and obstetric and offspring outcome. In addition, variables at 20 weeks gestation were adjusted for prepregnancy variables that were significantly associated with the studied endpoints (P<0.05) and variables at 32 weeks gestation were adjusted for variables that were significantly associated with the studied endpoints prepregnancy and at 20 weeks gestation. Variables that were

strongly associated with the studied endpoints (P<0.10) entered the multivariable model. The final multivariate model was constructed by backward deletion of the least significant characteristic, with a criterion for deletion of P≥0.10.

Results

Prepregnancy 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.

CHD and healthy cohorts were well balanced 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% Caucasian, P=0.35) and prepregnancy body mass index (BMI) (23.5±3.9 versus 23.1±3.9, P=0.56). More healthy women smoked prepregnancy compared to CHD women (20.7% versus 33.3%, P=0.03). Table 1 shows prepregnancy data of the CHD cohort. Cardiac medication was used prepregnancy by 15.8% of women with CHD, 7.2% were on anticoagulation therapy and 12.4% used a beta-blocker. Sinus rhythm prepregnancy 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 (tricuspid annular plane systolic excursion (TAPSE)) was known in 138 CHD women; RV dysfunction (TAPSE <16 mm) existed in 14.5% of these women.

Cardiovascular and UDF parameters in pregnant women with CHD and healthy pregnant women

NYHA functional class deterioration ≥2 class at 32 weeks compared to prepregnancy occurred more often in CHD than 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 in both cohorts, the decrease was significantly more in CHD women (P=0.04). Systemic ventricular mass/body surface area (BSA) was higher and increased (P<0.005) only in women with CHD.

Table 1. Maternal prepregnancy characteristics in women with CHD (N=209)		
	N	(%)
CHD DISEASE COMPLEXITY		
Simple	59	28.2
Moderately complex	140	67.0
Complex	10	4.8
LESIONS		
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's 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
MEDICAL HISTORY		
History of heart failure	5	2.4
History of arrhythmia	19	9.1
History of hypertension	14	6.7
History of diabetes	2	1.0
Pacemaker	7	3.3
Mechanical valve prosthesis	11	5.3
Biological-valve prosthesis	20	9.6
NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASS		
NYHA functional class I	159	76.1
NYHA functional class II	49	23.4
NYHA functional class III	1	0.5

CHD, congenital heart disease; **NYHA**, New York Heart Association.

Table 2. Comparison of women with CHD with healthy women during pregnancy.

	Gestational week 20			Gestational week 32		
	CHD	Healthy	*P* value	CHD	Healthy	*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%	<0.001
NYHA class I NYHA class II NYHA class ≥III	53.1% 39.7% 7.2%	58.6% 41.4% 0 %	0.069	39.6% 46.4% 14.0%	37.1% 62.9% 0%	0.005
MAP (mmHg)	80.0 (75.0 – 86.7)	76.7 (72.3 – 82.3)	0.003	83.2 (78.0 – 87.7)	78.0 (74.0 – 84.3)	0.003
LABORATORY PARAMETERS						
Hb (mmol/l)	7.45 (7.10 – 7.80)	7.50 (7.20 – 7.80)	0.59	7.40 (7.00 – 7.90)	7.50 (7.20 – 7.80)	0.62
NT-proBNP (ng/l)	111.5 (58.7 – 171.4)	51.0 (23.5 – 67.0)	<0.001	64.0 (47.7 – 120.0)	24.5 (14.1 – 41.5)	<0.001
SYSTEMIC VENTRICULAR SIZE, MASS AND SYSTOLIC FUNCTION*						
Systemic ventricular enddiastolic diameter	47.0 (45.0 – 50.0)	48.0 (45.3 – 51.0)	0.16	48.0 (44.0 – 52.0)	48.0 (46.0 – 51.0)	0.65
Systemic ventricular mass/BSA (g/m^2)	46.7 (38.1 – 55.9)	39.2 (36.1 – 45.4)	<0.001	51.1 (43.6 – 59.2)	42.2 (36.1 – 48.6)	<0.001
Systemic ventricular ejection fraction (%)	58.0 (50.0 – 64.0)	60.0 (59.0 – 65.0)	0.002	58.0 (51.0 – 61.0)	60.0 (56.0 – 62.5)	0.012
SYSTEMIC VENTRICULAR DIASTOLIC FUNCTION*						
LA volume (ml)	38.0 (30.2 – 48.0)	43.1 (34.1 – 49.5)	0.20	42.0 (33.4 – 50.2)	39.6 (34.6 – 49.3)	0.39
E/A ratio	1.8 (1.4 – 2.2)	1.7 (1.4 – 2.2)	0.89	1.5 (1.2 – 1.8)	1.5 (1.2 – 1.7)	0.72
E deceleration time (ms)	193.5 (162.8 – 237.3)	186.5 (169.5 – 217.3)	0.49	184.0 (155.5 – 217.0)	191.0 (159.0 – 224.0)	0.44
Mean E′ (sep-lat) (cm/s)	11.0 (10.1 – 12.5)	12.5 (11.3 – 13.3)	<0.001	9.96 (9.06 – 11.5)	11.1 (9.76 – 12.5)	0.025
E/ E′	9.2 (7.7 – 11.9)	7.3 (6.6 – 8.2)	<0.001	8.8 (7.0 – 11.3)	7.2 (6.1 – 8.0)	<0.001
RIGHT VENTRICULAR SIZE AND FUNCTION*						
Right ventricular diastolic diameter (cm)	38.5 (34.0 – 44.0)	36.0 (31.0 – 38.2)	0.001	39.0 (34.0 – 42.0)	36.0 (32.0 – 40.0)	0.002
TAPSE (mm)	22.0 (18.0 – 26.0)	26.0 (24.0 – 28.0)	<0.001	20.0 (17.0 – 25.0)	26.0 (22.0 – 27.0)	<0.001
Right ventricular S′ (cm/s)	10.0 (7.72 – 12.0)	11.4 (10.6 – 12.3)	<0.001	9.30 (7.11 – 11.9)	11.1 (10.1 – 12.5)	<0.001

CHD, congenital heart disease; **NYHA**, New York Heart Association; **Hb**, serum hemoglobin; **MAP**, mean arterial pressure; **NT-proBNP**, N-terminal pro B-type natriuretic peptide; **LA**, left atrium, **E**, Early passive filling velocity of systemic ventricular inflow; **E′**, early diastolic tissue Doppler velocity of systemic ventricular annular ring; **TAPSE**, tricuspid annular plane systolic excursion; Right ventricular **S′**, systolic tissue Doppler velocity of tricuspid annular ring.
* Excluding systemic right ventricles

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 groups. RV systolic function (represented by TAPSE and systolic annular velocity) was worse in CHD and decreased significantly in CHD women only (P=0.017 and P=0.009, respectively).[5]

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.

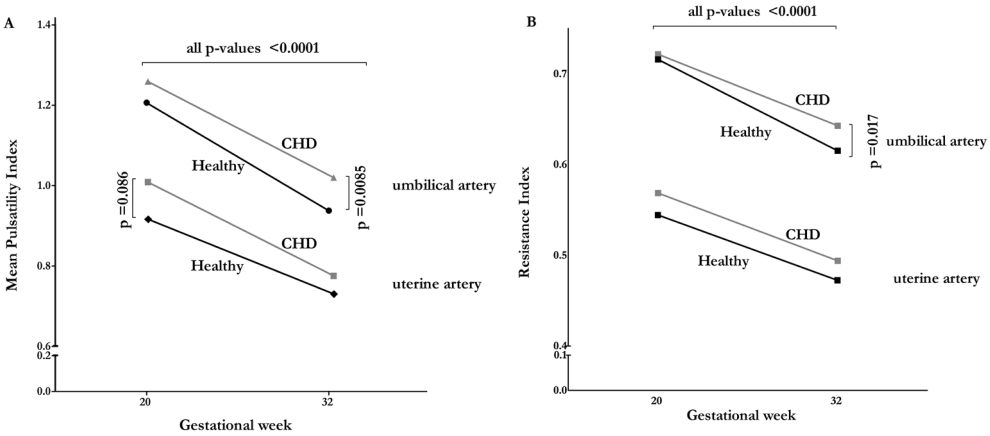

Figure 1. Uteroplacental Doppler flow parameters: pulsatility index and resistance index of mean of right and left uterine artery and of umbilical artery at 20 and 32 weeks of pregnancy, in women with CHD and healthy women.

Pregnancy outcome in CHD and healthy women

Cardiovascular events occurred in 10.5% 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 caesarean sections (13.4% versus 1.4%, P=0.003) and assisted deliveries (47.4% vs 25.7%, P=0.001). Several obstetric events occurred more often in CHD women without the differences reaching statistical significance: hypertensive disorders of pregnancy (17.7% versus 11.4%), pre-eclampsia (5.7% versus 1.4%) and PPROM (6.7 versus 2.9%). 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 gram, P<0.005). Offspring events occurred more often in CHD than in healthy women: 35.4% versus 18.6%, (P=0.008). 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 offspring (P=0.176). Offspring death occurred in 2.9% of the CHD group and 0% of the healthy group, 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). Multivariate predictors of offspring events, corrected for age and parity, were: preconception use of anticoagulation therapy (OR 6.29, 95% CI 1.55-25.4, P=0.010) and severe pulmonary regurgitation (OR 2.88, 95% CI 1.08-7.72, P=0.035); at 20 weeks gestation: uterine artery PI (OR 3.28, 95% CI 1.19-9.02, P=0.021 and mean arterial pressure (OR 1.06, 95% CI 1.01-1.11, P=0.021); at 32 weeks gestation: NT-proBNP > twice the upper limit of normal (>256 ng/l) (OR 10.3, 95% CI 2.00-53.5, P=0.005) and aortic stenosis (peak velocity >3m/s)(OR 5.91, 95% CI 1.01-34.5, P=0.049. In a final multivariate model including all of the abovementioned parameters simultaneously, all effects remained significant.

Relation of cardiovascular parameters and UDF indices

We related maternal cardiovascular parameters to UDF parameters. PI and RI were not measured both in all patients. Univariate analysis revealed the following variables to be associated with uterine artery RI (20 weeks): parity, preconception heart rate, systemic atrioventricular valve regurgitation and left atrial volume; and at 20 weeks heart rate, use of cardiac medication and TAPSE. Multivariate analysis rendered parity (β=0.04, P=0.048), resting heart rate at 20 weeks (β=-0.002, P=0.006) and use of cardiac medication at 20 weeks (β=0.08, P=0.035) significant. Multivariate models for prediction of umbilical artery RI (32 weeks) are presented in table 3.

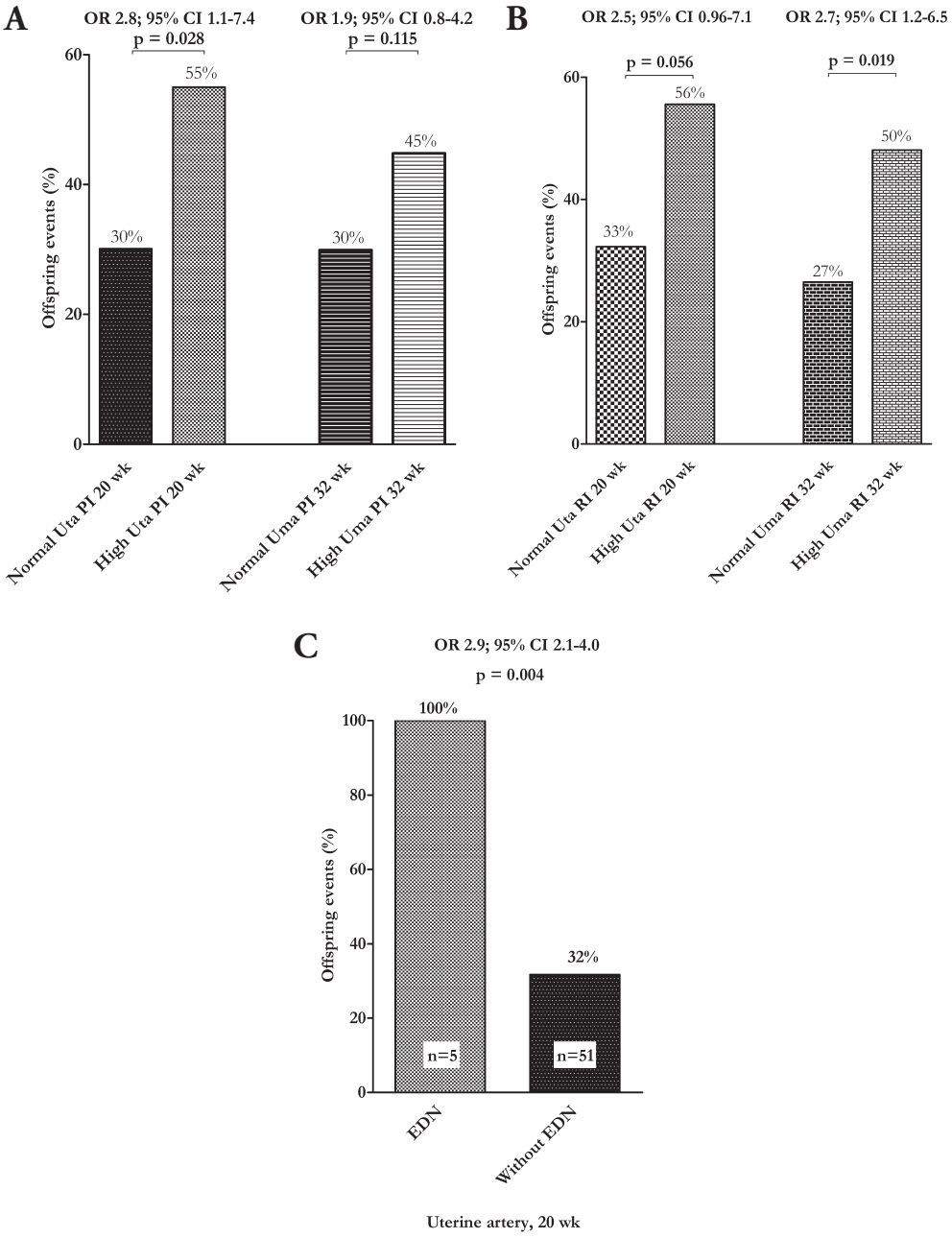

Figure 2. Relation of uteroplacental Doppler flow parameters and offspring outcome. **A:** Uterine and umbilical artery PI and offspring events. **B:** Uterine and umbilical artery RI and offspring events. **C:** Uterine artery early diastolic notch and offspring events. **Uta,** Uterine artery; **Uma,** umbilical artery; **EDN,** early diastolic notch; **PI,** pulsatility index; **RI,** resistance index.

Table 3. Univariate and multivariate regression analysis for the prediction of umbilical artery RI at 32 weeks of gestation

	β	95% CI	*P*
Association of 20 wk variables with umbilical artery RI 32 wk			
Age	0.004	0.001 – 0.008	0.006
Smoking during pregnancy	0.045	-0.000 – 0.090	0.051
High NT-proBNP*	0.024	-0.003 – 0.050	0.085
Systemic AV valve regurgitation	0.068	0.027 – 0.109	0.001
Association of 20 wk variables with umbilical artery RI 32 wk after adjusting for preconception variables			
Age	0.003	0.000 – 0.007	0.040
Systemic AV valve regurgitation 20 weeks	0.056	-0.011 – 0.101	0.016
Pulmonary AV valve regurgitation preconception	0.035	0.001 – 0.067	0.045
TAPSE preconception	-0.004	-0.007 – -0.002	0.002

RI, resistance index; **NT-proBNP**, N-terminal pro B-type natriuretic peptide; **AV**, atrioventricular; **TAPSE**, tricuspid annular plane systolic excursion.
*High NT-proBNP: >95th percentile of healthy controls (>128 ng/l)

Discussion

Our study is the first to compare UDF parameters of CHD and healthy women and relate these to cardiovascular parameters and to events and outcome 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 as well as valvular function are related to UDF, while UDF is predictive of obstetric and offspring events.

Adequate uteroplacental blood flow is necessary for normal pregnancy outcome. Vascular remodeling of the uteroplacental circulation guarantees sufficient flow throughout pregnancy. This remodeling is characterized by vascular widening of the uterine circulation, which is mediated by endovascular trophoblast invasion of uterine arteries, increased shear stress, and angiogenic and humoral factors.[14] 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 pre-eclampsia and intrauterine growth retardation.[5,15] In our study women with CHD had significantly more obstetric and offspring complications than healthy women. This included a four-fold increase in the incidence of pre-eclampsia and of children born small for gestational age. The increased incidence of these complications is in line with previous studies[1, 3-5,16-18] 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 compared to 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 multivariate model included preconception right ventricular function and NT-proBNP. NT-proBNP and BNP are well-established biomarkers of heart failure and BNP is a predictor of maternal cardiovascular pregnancy complications.[19] NT-proBNP or BNP have not previously been investigated in relation to offspring outcome in women with heart disease. We found elevated NT-proBNP to be associated with both abnormal UDF and offspring complications. Prepregnancy NT-proBNP was unfortunately not available. NT-proBNP may become a useful tool in pregnancy risk estimation in women with heart disease. Cardiac medication was related to uterine artery RI. The use of cardiac medication is also a predictor of maternal cardiac complications and is probably related to disease severity.[5] 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 remodelling.[5,20] A recent study demonstrated that mitral prolapse is associated with preterm delivery.[21] Therefore, atrioventricular valve regurgitation cannot be regarded as completely innocent. Our results indicate that placental flow may be compromised by atrioventricular valve regurgitation, possibly by reducing cardiac output. Valve stenosis did not predict UDF, which might be explained by a lower prevalence than regurgitant lesions. In addition to cardiac parameters, also parity, age and smoking were associated with UDF.

Our results confirm the hypothesis that prepregnancy cardiac dysfunction is involved in the pathogenesis of abnormal placentation. The importance of this finding reaches beyond explanation of the high obstetric and offspring complication rate in women with CHD.

Evidence from the literature indicates a relationship in the general population between previous pre-eclampsia or intra-uterine growth restriction and the later occurrence of acquired cardiovascular disease in the mother.[22,23] A recent study revealed an association of uterine RI during pregnancy with prepregnancy uterine blood flow.[24] Based on these data it has been hypothesized that pregnancy complications, particularly pre-eclampsia and intra-uterine growth restriction, reveal latent cardiovascular abnormalities that may be already present before pregnancy. Our study adds strong evidence to support this hypothesis, since in our women with CHD cardiac function prepregnancy 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, since the study included women when they were already pregnant, collection of prepregnancy data was retrospective, and missing data were inevitable. Additionally, in this multicentre study, sometimes deviation from the protocol occurred, while complex disease often prevented accurate measurements of chamber size and function; therefore not all data were available in all patients. Our composite outcome variable combined all offspring events. However, some offspring events may not be influenced by UDF (i.e. recurrence of congenital heart disease). Despite these limitations, we were able to demonstrate that cardiac function in women with CHD is associated with UDF and 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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Chapter 6

Chapter 7

Summary &

Future perspective

Nederlandse samenvatting

Dankwoord

Chapter 7

Summary & Future perspective

Nederlandse samenvatting

Dankwoord

Summary

In the last decades the number of women with congenital heart disease (CHD) reaching childbearing age is steadily increasing. Most of these women have a pregnancy wish and although many women with CHD tolerate pregnancy well, complication rate is still considerable. Due to the great diversity of the CHD population, outcome of pregnancy in women with CHD is not easy to predict. In this thesis we focus on the identification of predictors of adverse pregnancy outcome in women with CHD. Our data are meant to give guidance to recognize women at increased risk timely so adverse outcome can be prevented or at least limited to a minimum.

In the **FIRST PART** we addressed in retrospect complications and predictors of adverse pregnancy events in women with CHD.

Chapter 1 gave an overview of the prevalence and clinical significance of pregnancy related adverse outcome in women with CHD. We described the normal physiology of pregnancy and the pathophysiological consequences of haemodynamic changes of pregnancy for women with CHD. In addition, we reviewed the known predictors of adverse outcome that can be used for risk stratification in women with CHD. In ***chapter 2*** we focused on pregnancy and outcome in women with tetralogy of Fallot. We identified women with tetralogy of Fallot using 2 congenital heart disease registries. Within this cohort, 123 pregnancies occurred, that lasted longer than 20 weeks. Cardiovascular events occurred in 8% of pregnancies, while obstetric and offspring events occurred in 59% and 34% of pregnancies. Offspring death occurred in 6% of pregnancies. We identified several predictors of adverse cardiac and offspring outcome in pregnancies of women with tetralogy of Fallot. The most important independent predictor for both cardiovascular and offspring events was the use of cardiac medication before pregnancy. Palliative surgery before correction was also an independent predictor of adverse offspring outcome. In addition, we found that the occurrence of maternal cardiovascular events during pregnancy was highly associated with offspring events. In ***chapter 3*** we gave an overview of complications during pregnancy and predictors of adverse pregnancy events in the largest group of women with CHD ever assessed (n=1302). The most prevalent cardiac complications during pregnancy in women with CHD were arrhythmias (5%) and heart failure (2%). Factors independently associated with maternal cardiovascular events were the presence of cyanotic heart disease (corrected or uncorrected), the use of cardiac medication before pregnancy, left heart obstruction, presence of a mechanical valve and systemic or pulmonary atrioventricular valve regurgitation. The most prevalent obstetric complications were hypertensive disorders of pregnancy (12%). The most prevalent neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%). Cyanotic heart disease, presence of a mechanical valve, maternal smoking, multiple gestations and the use of cardiac medication were independent predictors of adverse offspring outcome. In addition, the most widely used model for the estimation of pregnancy risk in women with heart disease (CARPREG risk score) was validated.

We found that the CARPREG risk score overestimated the risk of cardiovascular events in women with CHD and proposed a new CHD-specific prediction model for the prediction of adverse cardiovascular events in women with CHD.

The **SECOND PART** of this thesis covered the prospective assessment of predictors of adverse events in pregnancy in women with CHD.

Chapter 4 described the design and rationale of the prospective ZAHARA II study that was designed to assess whether changes in cardiovascular, haemodynamic, neurohumoral parameters, and uteroplacental Doppler flow patterns during pregnancy in women with CHD differed from age- and parity-matched healthy controls. Another aim of the ZAHARA II study was to assess the interaction of these changes with the occurrence of cardiovascular, obstetric, and offspring events. Finally the ZAHARA II study was designed to compare and validate the existing risk estimation models in a prospective cohort of women with CHD. In ***Chapter 5*** the various available risk estimation models were validated and mutually compared using the ZAHARA II population. In this prospective study, we determined the outcomes of 191 pregnancies. The ZAHARA I and CARPREG cardiovascular risk scores were calculated for each pregnancy, as was the total number of cardiovascular or offspring risk predictors from these and other studies combined. Pregnancies were also classified according to the modified World Health Organization (WHO) classification of maternal cardiovascular risk and according to disease complexity. Maternal cardiovascular events occurred in 10% of pregnancies. Offspring events occurred in 33% of pregnancies. Both cardiovascular and offspring event rate increased with higher ZAHARA I or CARPREG risk scores, higher total number of cardiovascular or offspring risk predictors, higher WHO class and greater disease complexity. When comparing the 5 individual risk assessment models, the modified WHO classification provided the most adequate individual assessment of cardiovascular risk in the ZAHARA II cohort. For the assessment of offspring events, the difference in area under the curve was very small between the total number of offspring predictors, the ZAHARA risk score and the CARPREG risk points. A combination of the risk factors from ZAHARA I and CARPREG provided the highest area under the curve for the assessment of offspring events. In ***Chapter 6*** the main outcome of the ZAHARA II study was described. To prove that in women with CHD cardiac dysfunction compromises uteroplacental flow and contributes to the increased incidence of events, we compared cardiovascular clinical, biochemical and echocardiographic parameters as well as uteroplacental doppler flow patterns of pregnant women with CHD with healthy pregnant women and related these parameters to maternal and offspring outcome in women with CHD. We included 209 women with CHD and 70 healthy women. Cardiovascular parameters (NT-proBNP, left and right ventricular function) differed between both groups. Uteroplacental Doppler flow parameters were impaired in women with CHD compared to in healthy women. Women with CHD had more obstetric and offspring complications than healthy women (58.9% versus 32.9%, $P<0.0001$; and 35.4% versus 32.9%, $P=0.008$).

An impaired uteroplacental Doppler flow was associated with adverse obstetric and offspring outcome in women with CHD. Abnormal cardiovascular parameters prepregnancy and at 20 weeks were associated with impaired uteroplacental Doppler flow: high NT-proBNP, decreased tricuspid annular plane systolic excursion, mitral and tricuspid regurgitation predicted a higher umbilical artery resistance index at 32 weeks. Therefore a compromised uteroplacental Doppler flow may be a mechanism involved in the high incidence of offspring and obstetric events in women with CHD.

Future perspective

Until now, most research concerning pregnancy in women with congenital heart disease focused on the incidence of pregnancy complications. Some studies identified predictors of adverse outcome. In the present thesis we added some new predictors as well as new prediction models to provide aid in the assessment of women at increased risk. We also compared several risk assessment models and methods to further improve risk assessment and thereby outcome of pregnancy in women with CHD. To improve risk assessment in the future it is important to further specify predictors and develop risk models for specific subgroups of women with different CHD. For this purpose larger multicentre cohort studies are essential; therefore researchers should join forces.

Cardiac parameters are not only associated with cardiac outcome in pregnancy. We also demonstrated in the ZAHARA II study that cardiac dysfunction in women with CHD affects uteroplacental flow. In the general pregnant population, inadequate uteroplacental circulation is strongly associated with adverse obstetric and offspring outcome, and this was also confirmed in our CHD population. Further studying the relation of cardiac function as well as of vascular/endothelial function and uteroplacental Doppler flow in women with CHD may further elucidate the mechanism of adverse obstetric and offspring events in these women.

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Samenvatting

In de laatste decennia is het aantal vrouwen met een aangeboren hartafwijking die de vruchtbare leeftijd bereikt gestaag toegenomen. De meeste van deze vrouwen hebben een zwangerschapswens en hoewel een zwangerschap door de meeste vrouwen met een aangeboren hartafwijking goed wordt verdragen, is het aantal complicaties toch aanzienlijk. Door de grote diversiteit in de populatie van patiënten met een aangeboren hartafwijking zijn zwangerschapscomplicaties bij vrouwen met een aangeboren hartafwijking niet eenvoudig te voorspellen. In dit proefschrift richten we ons op de identificatie van voorspellers van zwangerschapscomplicaties bij vrouwen met een aangeboren hartafwijking. Het doel van onze bevindingen is om een handvat te geven in het tijdig herkennen van vrouwen met een verhoogd risico, zodat zwangerschapscomplicaties kunnen worden voorkomen of tenminste tot een minimum kunnen worden beperkt.

In het **EERSTE DEEL** van dit proefschrift hebben we ons in retrospect gericht op complicaties en voorspellers van zwangerschapscomplicaties bij vrouwen met een aangeboren hartafwijking.

Hoofdstuk 1 geeft een overzicht van de prevalentie en de klinische relevantie van zwangerschap gerelateerde complicaties bij vrouwen met een aangeboren hartafwijking. We hebben de normale fysiologie van de zwangerschap en de pathofysiologische gevolgen van de hemodynamische veranderingen van een zwangerschap voor vrouwen met een aangeboren hartafwijking beschreven. Bovendien, hebben we de bekende voorspellers van zwangerschapscomplicaties besproken die gebruikt kunnen worden voor risicostratificatie van vrouwen met een aangeboren hartafwijking. **Hoofdstuk 2** richt zich op zwangerschap en uitkomst bij vrouwen met de tetralogie van Fallot. We hebben vrouwen met de tetralogie van Fallot geïdentificeerd in 2 registraties voor personen met een aangeboren hart afwijking. Binnen dit cohort vonden 123 zwangerschappen plaats die langer stand hielden dan 20 weken. Cardiovasculaire complicaties traden op bij 8% van de zwangerschappen, terwijl obstetrische complicaties en complicaties bij het kind bij respectievelijk 59% en 34% van de zwangerschappen plaatsvonden. In 6% van de zwangerschappen overleed het kind. We hebben diverse voorspellers van cardiale complicaties en complicaties bij het kind geïdentificeerd voor zwangerschappen van vrouwen met de tetralogie van Fallot. De belangrijkste onafhankelijke voorspeller voor zowel cardiovasculaire complicaties als complicaties bij het kind was het gebruik van cardiale medicatie vóór de zwangerschap. Een palliatieve operatie voorafgaand aan een correctie bij de moeder was ook een onafhankelijke voorspeller van complicaties bij het kind. Tenslotte hebben we gevonden dat het vóórkomen van cardiovasculaire complicaties bij de moeder tijdens de zwangerschap sterk gerelateerd was aan het vóórkomen van complicaties bij het kind. In **hoofdstuk 3** hebben we een overzicht gegeven van complicaties rond de zwangerschap en voorspellers van deze complicaties in de grootste groep vrouwen met een aangeboren hartafwijking die ooit was bestudeerd (n=1302). De meest voorkomende cardiale complicaties tijdens de zwangerschap bij vrouwen met een aangeboren hartafwijking waren hartritmestoornissen (5%) en

hartfalen (2%). Factoren die onafhankelijk geassocieerd waren met cardiovasculaire complicaties bij de moeders waren de aanwezigheid van cyanotische hartafwijkingen (zowel gecorrigeerd als ongecorrigeerd), het gebruik van cardiale medicatie vóór de zwangerschap, obstructie van de linker harthelft, de aanwezigheid van een mechanische kunstklep en een systemische of pulmonale atrioventriculaire klep insufficiëntie. De meest voorkomende obstetrische complicatie was een hypertensieve aandoening van de zwangerschap (12%). De meest voorkomende complicaties bij het kind waren vroeggeboorte (12%), een te laag geboortegewicht voor de duur van de zwangerschap (14%) en sterfte (4%). Onafhankelijke voorspellers van complicaties bij het kind waren: moeders met cyanotische hartafwijkingen, de aanwezigheid van een mechanische kunstklep bij de moeder, rokende moeders, een meerling zwangerschap en het gebruik van cardiale medicatie door de moeder. Voorts werd het meest gebruikte model voor de schatting van het zwangerschapsrisico bij vrouwen met een hartaandoening (CARPREG risico score) gevalideerd. We vonden dat de CARPREG score het risico op cardiovasculaire complicaties bij vrouwen met een aangeboren hartafwijking overschat en stelden een nieuw predictie model voor, dat voor vrouwen met een aangeboren hartafwijking meer specifiek is.

Het **TWEEDE DEEL** van dit proefschrift beslaat de prospectieve beoordeling van voorspellers van complicaties tijdens de zwangerschap bij vrouwen met een aangeboren hartafwijking.

Hoofdstuk 4 beschreef het ontwerp en de ratio achter de prospectieve ZAHARA II studie, die werd ontworpen om te beoordelen of veranderingen in de cardiovasculaire, hemodynamische, neurohumorale parameters en uteroplacentale Doppler flow patronen tijdens de zwangerschap bij vrouwen met een aangeboren hartafwijking verschilden van gezonde vrouwen, die vergelijkbaar waren qua leeftijd en het aantal doorgemaakte zwangerschappen. Een ander doel van de ZAHARA II studie was om de interactie te onderzoeken van deze veranderingen met het voorkomen van cardiovasculaire en obstetrische complicaties evenals complicaties bij het kind. Ten slotte werd de ZAHARA II studie ontworpen om de bestaande risicoschattingsmodellen te vergelijken en prospectief te valideren in een cohort vrouwen met een aangeboren hartafwijking. In **hoofdstuk 5** werden de verschillende beschikbare risicoschattingsmodellen gevalideerd en onderling vergeleken aan de hand van de ZAHARA II populatie. In deze prospectieve studie hebben we de uitkomst van 191 zwangerschappen bepaald. De ZAHARA I en CARPREG cardiovasculaire risico scores werden berekend voor elke zwangerschap, evenals het totaal aantal cardiovasculaire of kind risico voorspellers van deze en andere studies gecombineerd. Zwangerschappen werden ook ingedeeld volgens de gemodificeerde indeling van de Wereld Gezondheid Organisatie (WHO) voor maternale cardiovasculair risico en volgens ziekte complexiteit. Maternale cardiovasculaire complicaties vonden plaats in 10% van de zwangerschappen. Bij 33% van de zwangerschappen vond een complicatie bij het kind plaats. Zowel cardiovasculaire complicaties als complicaties bij het kind namen toe met toename van de 'ZAHARA I' en de 'CARPREG´ risico scores, een hogere totaal aantal 'cardiovasculaire' of 'kind' risico

voorspellers, hogere 'WHO klasse' en grotere 'complexiteit van de hartafwijking'. Bij het vergelijken van de 5 individuele risicoschattingsmodellen, bleek de gemodificeerde WHO classificatie het meest adequate individuele risicoschattingsmodel voor de beoordeling van het cardiovasculaire risico in de ZAHARA II cohort. Bij de vergelijking van risicoschattingsmodellen voor het voorspellen van complicaties bij het kind was het verschil in 'area under the curve' zeer klein tussen totaal aantal kind complicatie voorspellers, ZAHARA I risicoscore en totaal aantal CARPREG risico punten. Een combinatie van de risicofactoren van ZAHARA I en CARPREG gaf de grootste 'area under the curve' voor het voorspellen van complicaties bij het kind. In **hoofdstuk 6** werden de hoofdresultaten van de ZAHARA II studie beschreven. Om aan te tonen dat bij vrouwen met een aangeboren hartafwijking de uteroplacentale doorbloeding wordt gecompromitteerd door de cardiale dysfunctie en bijdraagt aan de toegenomen incidentie van complicaties, hebben we klinische (cardiovasculaire), biochemische en echocardiografische parameters evenals uteroplacentale doppler flow patronen van zwangere vrouwen met een aangeboren hartafwijking vergeleken met die van gezonde zwangere vrouwen en deze parameters tevens gerelateerd aan maternale en kind complicaties bij vrouwen met een aangeboren hartafwijking. We hebben 209 vrouwen met een aangeboren hartafwijking en 70 gezonde vrouwen geïncludeerd in deze studie. Cardiovasculaire parameters (NT-proBNP, linker en rechter ventrikel functie) verschilden tussen beide groepen. Uteroplacentale Doppler flow parameters waren slechter bij vrouwen met een aangeboren hartafwijking dan bij gezonde vrouwen. Vrouwen met een aangeboren hartafwijking hadden vaker obstetrische complicaties evenals meer complicaties bij hun kinderen dan gezonde vrouwen (58,9% versus 32,9%, $P<0,0001$ en 35,4% versus 32,9%, $P=0,008$). Een verminderde uteroplacentale Doppler flow was geassocieerd met een slechtere obstetrische en kind uitkomst bij vrouwen met een aangeboren hartafwijking. Een aantal abnormale cardiovasculaire parameters preconceptie en bij 20 weken zwangerschap waren geassocieerd met een verminderde uteroplacentale doorbloeding: een verhoogde NT-proBNP, een verminderde rechter kamer functie ('tricuspid annular plane systolic excursion' (TAPSE)) en systemische en pulmonale atrioventriculaire klepinsufficiëntie voorspelden een hogere arteria umbilicalis 'resistance index' bij 32 weken zwangerschap. Een gecompromitteerde uteroplacentale doorbloeding zou dus een van de mechanismen kunnen zijn, betrokken bij de hogere incidentie van complicaties bij moeder en kind bij vrouwen met een aangeboren hartafwijking.

Toekomstperspectieven

Tot nu hebben de meeste onderzoeken met betrekking tot zwangerschap bij vrouwen met een aangeboren hartafwijking zich gericht op de incidentie van zwangerschapscomplicaties. Sommige studies hebben zelfs voorspellers van een negatieve zwangerschapsuitkomst gevonden. In dit proefschrift zijn enkele nieuwe voorspellers toegevoegd aan de bestaande voorspellers. Daarnaast zijn er nieuwe risicoschattingsmodellen gemaakt die kunnen helpen bij de beoordeling van vrouwen die een verhoogd risico hebben op complicaties in de zwangerschap. Er zijn ook diverse risicoschattingsmodellen onderling vergeleken zodat de optimale risicoschatting verder verbeterd kan

worden en daardoor de zwangerschapsuitkomst bij vrouwen met een aangeboren hartafwijking. Om de risicoschatting bij vrouwen met een aangeboren hartafwijking verder te verbeteren in de toekomst is het belangrijk om voorspellers verder te specificeren en risicomodellen te verder te ontwikkelen voor de verschillende specifieke subgroepen van vrouwen met een aangeboren hartafwijking. Om dit te bereiken zijn grotere multicentrische cohort studies essentieel; daarom is het essentieel dat onderzoekers hun krachten bundelen.

Cardiale parameters zijn niet alleen geassocieerd met cardiale uitkomst tijdens de zwangerschap. We hebben in de ZAHARA II studie ook aangetoond dat cardiale dysfunctie bij vrouwen met een aangeboren hartafwijking de uteroplacentale doorbloeding beïnvloedt. In de algemene zwangere bevolking is een abnormale uteroplacentale doorbloeding sterk geassocieerd met complicaties bij moeder en kind. Dit werd ook bevestigd in onze populatie zwangere vrouwen met een aangeboren hartafwijking. Verder onderzoek naar de relatie tussen de hartfunctie, danwel de vasculaire/endotheliale functie met de uteroplacentale doorbloeding bij vrouwen met een aangeboren hartafwijking zou het mechanisme achter de vele complicaties bij vrouwen met een aangeboren hartafwijking en hun kind verder kunnen verhelderen.

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Lieve Elin, de 'fakkel' in ons leven. Zonder het zelf te beseffen ben jij mijn mooiste inspirator. Je hebt mij doen beseffen dat er meer is in het leven!

Hivyo, sasa ni wakati wa sherehe!

Zwolle, 12 juni 2012

Stellingen

Behorende bij het proefschrift:

Pregnancy and Outcome in women with Congenital Heart Disease

door

Ali Balci

1. Vrouwen met een gecorrigeerde tetralogie van Fallot hebben een verhoogd risico op cardiovasculaire en obstetrische complicaties tijdens de zwangerschap. (Dit proefschrift)

2. Foetale en neonatale complicaties zijn bij vrouwen met een gecorrigeerde tetralogie van Fallot geassocieerd met cardiovasculaire complicaties in de zwangerschap. (Dit proefschrift)

3. De CARPREG risico score overschat het risico op complicaties in een populatie vrouwen met een structureel aangeboren hartafwijking. (Dit proefschrift)

4. De gemodificeerde WHO classificatie is het best beschikbare risicoschattingsmodel voor het inschatten van het cardiovasculaire risico bij zwangere vrouwen met een aangeboren hartafwijking. (Dit proefschrift)

5. De aanwezigheid van een mechanische klepprothese bij vrouwen met een aangeboren hartafwijking is sterk geassocieerd met cardiale complicaties in de zwangerschap. (Dit proefschrift)

6. Zwangere vrouwen met een aangeboren hartafwijking hebben een hogere weerstand in de uteroplacentale vaten en slechtere cardiovasculaire parameters dan gezonde zwangere vrouwen. (Dit proefschrift)

7. De weerstand in de uteroplacentale vaten is bij vrouwen met een aangeboren hartafwijking gerelateerd aan de cardiovasculaire functie van de moeder en tevens een voorspeller van complicaties bij moeder en kind. (Dit proefschrift)

8. Hiç bilenlerle bilmeyenler bir olur mu? (Kur'an-ı Kerim, 39:Zümer;9)

9. Varium et mutabile semper femina (Publius Vergilius Maro, Aeneas 4, 569-570)

10. Vergissen is menselijk. Volharden is des duivels (Seneca 4 v. Chr.-65 n. Chr.)

11. Liefde vermenigvuldigt zich als je het deelt; net als kennis.

12. Leren 'Nee' zeggen is een belangrijk onderdeel van het promotietraject.

13. Mistakes are all right, but failure is not. Failure is jus a mistake you cannot recover from. (NASA, lessons in project management)

14. An expert is a man who has made all the mistakes that can be made in a very narrow field. (Niels Bohr, 1885-1962)