Chapter 1

Introduction
EPIDEMIOLOGY

Congenital heart defects (CHD) are the most common congenital defects in newborns, with a birth prevalence of 9/1000 live births worldwide. Due to improved surgical and medical treatment, the majority of these children survive until adulthood. This resulted in a large cohort of adult survivors, mostly still young and of child bearing age. It is important to realize that these women are not cured and that pregnancy can have deleterious effects on cardiac function and patient wellbeing since pregnancy requires major hemodynamic changes.

PHYSIOLOGICAL CHANGES DURING NORMAL PREGNANCY

Pregnancy induces profound changes in the cardiovascular system, in order to meet the increased maternal and fetal metabolic demands. During normal pregnancy, cardiac output increases 30-50% above baseline, starting in early pregnancy and continues to rise until 24 weeks gestation. This augmented cardiac output is maintained until term (figure 1). The increase in cardiac output results from an increase in preload (circulating volume), a decrease in afterload (peripheral vascular resistance) and an increase in heart rate. During labor, delivery and the post-partum period again profound changes in cardiac output occur, because of pain, anxiety, uterine contraction and uterine involution.

The hemodynamic changes described result in progressive left ventricular remodeling. Left ventricular end-diastolic and end-systolic dimensions increase during pregnancy, where ejection fraction remains unchanged. The myocardium becomes hypertrophic as gestation advances and as a result of that, left ventricular mass increases. Despite the morphological changes, diastolic function is not impaired during pregnancy and left ventricular diastolic filling pressures remain unchanged. Studies describing right ventricular remodeling during pregnancy are extremely scarce. The available data suggests that right ventricular systolic function remains stable during pregnancy. Right ventricular diameter appears to increase towards the third trimester of pregnancy.

Figure 1: Hemodynamic changes during pregnancy according to gestational week (modified from Robinson et al.)
PREGNANCY IN WOMEN WITH CONGENITAL HEART DISEASE

Thirteen years of ZAHARA (Zwangerschap bij Aangeboren HARtAfwijkingen, pregnancy in congenital heart disease) research provided valuable insights to the knowledge of pregnancy in women with CHD and the research line evolved from epidemiology focused to more fundamental research focusing on the underlying pathophysiological mechanism of complications.

The first ZAHARA study was conducted between 2002 and 2007 aiming to investigate pregnancy outcome in women with CHD and to identify predictors of cardiac complications during pregnancy retrospectively. Pregnancy in women with congenital heart disease appeared to be associated with increased incidence of cardiovascular, obstetric and neonatal complications\(^{12-22}\). In approximately 7-13% (depending on the underlying heart disease) of the pregnancies in women with CHD, cardiovascular complications occur, with heart failure and arrhythmia being most frequently observed\(^{14,23-25}\). Siu et al. developed the CARPREG (Cardiac disease in pregnancy) risk score, in order to estimate the risk of cardiac complications during pregnancy in women with cardiac disease\(^{24}\). The CARPREG risk score underestimated the risk of cardiac events in a cohort of women with solely CHD, which suggested that modifications in the risk score were needed\(^ {26}\). The ZAHARA study resulted in the development of a new risk estimation model for the occurrence of cardiovascular complications during pregnancy in women with CHD, and also identified new predictors of adverse neonatal outcome\(^ {23}\). The study resulted in the thesis that was defended by Wim Drenthen (2-7-2007).

The first ZAHARA study, as well as other reports, revealed that especially placenta-related complications are more frequently observed in women with CHD (ie. hypertensive disorders of pregnancy and fetal growth restriction)\(^ {12-14,27}\). The ZAHARA II study was primarily designed to shed light on a possible underlying mechanism for the increased incidence. In patients with chronic heart failure, worsening cardiac function is associated with dysfunction of other organs\(^ {28,29}\) and a similar mechanism might be present during pregnancy, during which cardiac dysfunction hampers placental development and function leading to adverse pregnancy outcome. We postulated that maternal cardiac dysfunction is responsible for abnormal placental development and placental dysfunction. In pregnant women without underlying heart disease, inadequate adaption of the uteroplacental circulation is responsible for several obstetric and offspring complications. The pathophysiological mechanism is poor trophoblast invasion of the spiral arteries during the placentation process\(^ {30}\), causing failure of the placental-bed arteries to transform from high to low-resistance vessels. Uteroplacental flow investigations (resistance and pulsatility indices of the uterine artery and umbilical artery) provide insight in the placentation process and are commonly used as screening tool to predict the future development of pre-eclampsia, fetal growth restriction, still birth and placental abruption\(^ {31,32}\). In ZAHARA II we investigated the effect of impaired cardiac function...
on the uteroplacental circulation and its relationship with the occurrence of adverse obstetric and offspring outcome. The ZAHARA II study was conducted between March 2008 and August 2011. This study also provided the opportunity to validate the ZAHARA prediction model and to compare it with the other risk prediction models used. It turned out to perform better in a population with CHD compared to the CARPREG risk score. These findings, as well as the study design of ZAHARA II were described in the thesis of Ali Balci, defended at 5-9-2012.

The increased volume load is thought to play an important role in the pathogenesis of the cardiovascular complications and therefore natriuretic peptides (B-type natriuretic peptide (BNP) and amino terminal proBNP (Nt-proBNP)) may be an important predictor of cardiovascular events. Natriuretic peptides are well established predictors of adverse outcome in various cardiac diseases and predict outcome independent of ejection fraction. Data on the predictive role for cardiac event during pregnancy in women with CHD are scarce. Tanous et al. reported a clear association between high BNP values and cardiovascular events during pregnancy, but could not determine the role of BNP in predicting adverse cardiovascular events. Natriuretic peptides can provide a valuable tool for the clinicians caring for these patients in order to identify high risk patients, needing close follow up. The prospective nature of ZAHARA II allowed a comparison of Nt-proBNP between women with CHD and healthy controls. In addition, the role of Nt-proBNP in predicting cardiovascular events during pregnancy could be assessed.

In women with congenital heart disease the progressive cardiac remodeling during pregnancy might have serious repercussions for cardiac function after pregnancy, and therefore might influence their prognosis. Longitudinal data on cardiac remodeling during and after pregnancy in women with CHD is scarce and most of the available research focuses on left ventricular parameters. Data examining longitudinal changes in right ventricular parameters have never been reported in pregnant women with CHD. Several studies indicate that pregnancy can be associated with permanent deterioration in cardiac function and impaired event-free survival. The secondary objective of ZAHARA II was to investigate the incidence of permanent post-partum cardiovascular deterioration in women with CHD, since data is scarce and existing reports mainly describe small retrospective study populations.
AIMS OF THE THESIS

In this thesis we describe the incidence of cardiovascular complications and we report new predictors for cardiovascular complications during and after pregnancy, furthermore we assess the impact of pregnancy on cardiac function and remodeling. Finally, we investigate whether cardiac dysfunction plays a role in the pathogenesis of obstetric and neonatal complications. In part I of this thesis, we focus on the cardiovascular complications during and after pregnancy and we assess the impact of pregnancy on cardiac function and remodeling. In chapter 2 the independent role of Nt-proBNP levels during pregnancy in women with CHD in predicting the occurrence of cardiovascular events will be assessed. Chapter 3 will focus on cardiac adaption during pregnancy in women with CHD compared to healthy pregnant women. The incidence of cardiovascular complications one year post-partum will be described and cardiac function parameters pre-pregnancy and one year post-partum will be compared in chapter 4. In part II of this thesis we investigate the role of cardiac dysfunction in the pathogenesis of obstetric and neonatal complications. Chapter 5 describes the main outcomes of the ZAHARA II study, which assesses the differences in uteroplacental Doppler flow (UDF) patterns as well as the differences in outcome in pregnant women with CHD and healthy pregnant women. The relationship between cardiac dysfunction and uteroplacental Doppler flow patterns will be investigated. Chapter 6 will focus on pregnancy outcome and complications in women with Tetralogy of Fallot. The outcome of the ZAHARA II study will be verified in a homogeneous population. The final chapter of this thesis, chapter 7, reviews the literature systematically in order to investigate all existing evidence for a link between maternal cardiac function, abnormal uteroplacental flow and poor perinatal outcome in women with and without known cardiac disease.
REFERENCES


32. Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abrup-


