Chapter 8

Summary and future perspectives
In part I of this thesis we described the incidence of cardiovascular complications, new predictors of cardiovascular complications during and after pregnancy, and we assessed the impact of pregnancy on cardiac function and remodeling.

Pregnancy in women with CHD is known to be associated with increased incidence of cardiovascular complications, but also obstetric and neonatal complications are common and several risk prediction models have been developed. In chapter 2 we showed that cardiovascular complications occur in 10.3% of the pregnancies in the ZAHARA II study. Women with congenital heart disease had higher Nt-proBNP levels at 20 weeks gestation compared to healthy pregnant women. Women with cardiovascular complications had higher Nt-proBNP levels at 20 weeks gestation compared to women without cardiovascular complications during pregnancy and a Nt-proBNP level > 128 pg/mL at 20 weeks gestation was independently associated with the occurrence of cardiovascular events later in pregnancy. The negative predictive value of Nt-proBNP < 128 pg/mL was 96.9% and Nt-proBNP levels > 128 pg/mL had additional value in predicting cardiovascular complications during pregnancy on top of the other identified predictors. The risk prediction models that are commonly used to predict pregnancy risk, all use preconception parameters. Nt-proBNP levels < 128 pg/mL appear helpful in identifying patients at low risk of cardiovascular complications while they are already pregnant, which provides a helpful additional tool for doctors caring for these patients.

In chapter 3 we demonstrated that no statistically significant changes occur in right and left ventricular function parameters and ventricular dimensions during and after pregnancy in women with CHD. The absolute level of ventricular function parameters and dimensions differs clearly between women with CHD and healthy pregnant women. Fitted longitudinal profiles over time show that the changes seen in women with CHD are comparable to healthy women. This is valuable information during preconception counseling of these women. In this study, visual patterns and model fit criteria suggest non-linear variation in parameters over time; however, there was no statistically significant effect of time for any of these parameters. This might be caused by insufficient power. Follow-up with echocardiography is still valuable, since changes in the individual patient do occur and can be of clinical relevance.

In chapter 4 we described that cardiovascular complications during the first year post-partum are relatively rare. However, women with a cardiovascular event during pregnancy are prone to develop cardiovascular events during the first year post-partum and they have increased subpulmonary ventricular diameters compared with preconception values. These findings underline the importance of post-partum follow-up.

In part II of the thesis we investigated if maternal cardiac dysfunction plays a role in the pathogenesis of obstetric and neonatal complications. Placenta related complications (i.e.
hypertensive disorders of pregnancy and fetal growth restriction) are common in women with congenital heart disease and the ZAHARA II study was designed in order to investigate the effect of impaired maternal cardiac function on the uteroplacental circulation and is relationship with the occurrence of adverse obstetric and offspring outcome. In Chapter 5 we described the main findings of the ZAHARA II study. We found differences in uteroplacental Doppler flow (UDF) parameters between women with CHD and healthy pregnant women. Cardiac dysfunction was associated with an abnormal UDF pattern, while abnormal UDF was associated with neonatal complications. In women with tetralogy of Fallot, we found that abnormal UDF patterns were more prevalent compared to healthy pregnant women. Right and left ventricular dysfunction appeared to be associated with impaired UDF (chapter 6). We confirmed in a smaller, but more homogeneous group of patients the results of the ZAHARA II study. These are important findings, which suggest that maternal cardiac dysfunction is one of the contributors to the occurrence of defective placentation and impaired placenta function, with subsequent poor pregnancy outcome. More fundamental research is required to provide a better understanding of the mechanisms involved.

Finally, several studies have reported impaired cardiac function in healthy women with poor uteroplacental flow and poor pregnancy outcome, which is also present one year post-partum. In chapter 7 we reviewed the literature systematically and we found increasing evidence for an association between pre-existing cardiac dysfunction, poor placentation and poor pregnancy outcome. We postulated that pre-existing cardiac dysfunction, as a result of either known heart disease or a subclinical latent condition is one of the common denominators of poor placentation leading to poor pregnancy outcome.

**DISCUSSION**

In order to reduce the burden of cardiovascular complications during pregnancy in women with congenital heart disease, it is of utmost importance to counsel patients and their partners about the risks during pregnancy, and it is essential to have an adequate follow-up plan during pregnancy.

Current European Society of Cardiology (ESC) guidelines on management of cardiovascular disease during pregnancy state that regular follow-up of women with CHD during pregnancy is indicated. The frequency of follow-up depends on modified WHO risk classification (see further). However, since publication of the guidelines in 2011, important new insights were reported. Integrating the new insights gathered in this thesis into the current knowledge on pregnancy in women with CHD, I propose a new follow-up algorithm, as displayed in figure 1. It should be noticed that several very high risk patients, i.e. those with a mechanical valve or with severe aortic dilatation are excluded from this algorithm, since monthly follow-up is indicated irrespective of the findings during follow-up.
Preconceptional risk assessment

Modified WHO risk class

WHO I
- Follow-up second trimester
  - Clinical assessment
  - Echocardiogram
  - Nt-proBNP measurement
  - Refer all patients to obstetrician: UDF at 20 & 32 weeks gestation.

WHO II
  - Discuss termination of pregnancy.
  - Continuing pregnancy?
    - Yes: Follow-up during third trimester with clinical assessment, Nt-proBNP and echocardiogram.
    - No: Nt-proBNP value?
      - Nt-proBNP > 128 pg/mL: Follow-up during third trimester with clinical assessment, Nt-proBNP and echocardiogram.
      - Nt-proBNP < 128 pg/mL: Follow-up postpartum.

WHO III
  - Follow-up first trimester
    - Clinical assessment
    - Echocardiogram
    - Refer all patients to obstetrician: UDF at 20 & 32 weeks gestation.

WHO IV
  - Deteriorating cardiac / valvular function and/or ventricular dilatation?
    - Yes: Bimonthly follow-up with clinical assessment and echocardiogram.
    - No:
      - No: Next follow-up at 20 weeks gestation.

Deteriorating cardiac / valvular function and/or ventricular dilatation on echocardiogram?

Figure 1: Proposed follow-up algorithm for pregnant women with congenital heart disease. Ideally performed before conception. When patient presents for the first time when already pregnant, perform risk assessment as soon as possible.
Adequate follow-up starts with the assessment of maternal cardiac risk during pregnancy, which should be expressed according to the modified WHO risk classification. This classification integrates all known risk predictors, co-morbidities, and current cardiac condition (figure 2), and it has recently proven to be superior to other prediction models in predicting the pregnancy risk of women with CHD.

According to the current guidelines, the follow-up frequency depends on the modified WHO risk class, but should at least be done once every trimester with performance of an echocardiogram. A recent report from the European registry on pregnancy and cardiac disease (ROPAC) shows that most of the cardiovascular events were encountered by women in modified WHO risk class III and IV, with heart failure being the most frequent observed complication. Heart failure tends to develop more frequently during the late second or early third trimester and post-partum period, with modified WHO risk class ≥ III being an important risk factor. A recent report from the ZAHARA II study also shows that cardiovascular events are more prevalent in women in modified WHO risk classes III and IV, with no cardiovascular complications at all in women with modified WHO risk class I. Based on these reports, it should be considered for women in modified WHO risk class I to monitor them only once during the second and the third trimester (figure 1).
As can be seen in figure 1, an echocardiogram should be performed during every visit to the outpatient clinic and follow-up should be intensified when deterioration is present. When echocardiography is not sufficient for adequate follow-up (i.e. determination of aortic dimensions), other imaging modalities (MRI/CT without contrast) should be used. Cornette et al. showed that cardiac output, stroke volume and E/E' ratio increased during pregnancy and that left ventricular ejection fraction decreased. In chapter 3 of this thesis, visual patterns and model-fit criteria did also suggest non-linear variation over time, but it did not reach statistical significance in our study. This might be caused by insufficient power. However, since changes in cardiac function can occur and the changes seen might be of clinical relevance for individual patients, follow-up with echocardiography is indicated during pregnancy in women with CHD.

It would be helpful for doctors caring for pregnant women with CHD, to have an additional tool to determine the risk of future cardiovascular complications while the patient is already pregnant. Tanous et al. were the first to report on B-type natriuretic peptide (BNP) during pregnancy in women with heart disease. They found that women with heart disease had higher values of BNP during pregnancy and that high levels were associated with cardiovascular complications during pregnancy. BNP levels > 100 pg/mL had a sensitivity of 100% and a specificity of 70% of identifying women with cardiovascular events during pregnancy. Tanous et al. were the first to report on B-type natriuretic peptide (BNP) during pregnancy in women with heart disease. They found that women with heart disease had higher values of BNP during pregnancy and that high levels were associated with cardiovascular complications during pregnancy. BNP levels > 100 pg/mL had a sensitivity of 100% and a specificity of 70% of identifying women with cardiovascular events during pregnancy. In chapter 2 of this thesis, we described that Nt-proBNP > 128 pg/mL at 20 weeks gestation was independently associated with the occurrence of cardiovascular events later in pregnancy and had additional value in predicting the occurrence of cardiovascular events on top of other identified predictors. Nt-proBNP levels > 128 pg/mL at 20 weeks gestation had a sensitivity of 81.3% and a specificity of 61.8% for cardiovascular complications later in pregnancy. The findings of both studies underline that natriuretic peptide levels can be helpful in identifying patients at risk of cardiovascular complications during pregnancy. The negative predictive value of Nt-proBNP < 128 pg/mL is very high. Therefore, it seems justifiable to perform follow-up only once during pregnancy (at 20 weeks gestation) for women in modified WHO risk class I, with Nt-proBNP < 128 pg/mL, and no deterioration of cardiac or valvular function at 20 weeks gestation and no dilatation of ventricular dimensions. It should be kept in mind that the predictive value of a test is strongly dependent on the prevalence of cardiovascular complications. Therefore, it seems reasonable to use Nt-proBNP levels to increase follow-up frequency in women with modified WHO III-IV risk class, since they are at highest risk of cardiovascular complications.

As discussed in chapter 1, women with CHD are prone to develop obstetric complications and have higher risk of adverse neonatal outcome during pregnancy. In particular more placenta-related complications (i.e. hypertensive disorders of pregnancy, fetal growth restriction) are observed. In chapter 5 we described the main results of the ZAHARA II study. We found dif-
ferences in UDF patterns between pregnant women with CHD compared to healthy women and cardiac function was associated with abnormal UDF patterns. TAPSE preconception (as a measure of systolic subpulmonary ventricular function), as well as pulmonary AV valve regurgitation preconception, and systemic AV valve regurgitation at 20 weeks gestation, were associated with abnormal UDF patterns in a multivariable analysis. In a cohort of 55 patients with tetralogy of Fallot, right and left ventricular function parameters were associated with abnormal UDF patterns (chapter 6). These findings suggest that pre-existent cardiac dysfunction, as well as cardiac dysfunction during pregnancy might influence placental development and placental function. However, the underlying mechanism remains unclear. After systematically reviewing the literature (chapter 7), we found increasing evidence for an association between pre-existing cardiac dysfunction, poor placentation, and poor pregnancy outcome. At this moment, uteroplacental Doppler flow measurements are not routinely performed during follow-up of women with CHD. I recommend referring all pregnant women with heart disease to an obstetrician, in order to routinely investigate uteroplacental flow at 20 and 32 weeks gestation. Early recognition of abnormal UDF patterns in these women might reduce the burden of obstetric and fetal complications. With early detection of placental insufficiency, adequate fetal monitoring can be started. When indicated, premature labor can be induced or therapy can be initiated.

Not specified in figure 1 is the role of holter monitoring during follow-up. The role of performing holter monitoring routinely in every patient has never been investigated. However, several specific defects have a high a-priori risk of arrhythmia or conduction disorders (i.e. women with atrial repair of transposition of the great arteries). An increased risk of arrhythmia is also present in women with a history of arrhythmia. Holter monitoring, at least once during the third trimester, in these type of patients seems justifiable, since most of the hemodynamic changes have reached a steady state by then. It provides also useful information for management during delivery. In patients reporting complaints of palpitations or dizziness holter monitoring should be performed at least once during pregnancy. When symptomatic arrhythmia is present, therapy should be induced.

For the post-partum period, I recommend follow-up with clinical assessment and the performance of an echocardiogram one year post-partum, in particular for women with cardiovascular complications during pregnancy. Chapter 4 of this thesis, as well as other studies, showed that pregnancy is associated with worsening cardiac function afterwards, and women with cardiovascular complications during pregnancy are prone to develop cardiovascular complications after pregnancy. Close follow-up post-partum is therefore warranted in these patients. Women with a high mortality risk after delivery should be kept in hospital during the first two to six weeks. Thereafter, weekly follow-up is indicated. For women classified in modi-
ified WHO risk class IV follow-up should be performed one month post-partum. For women in modified WHO risk class III during pregnancy, scheduled follow-up three months after delivery is recommended. Follow-up as early as six weeks post-partum should be considered for women with considerable deterioration in cardiac function during pregnancy.

In conclusion, this thesis added valuable new insights to the knowledge of cardiovascular risk in women with congenital heart disease during and after pregnancy, and some elucidation was brought about the pathogenesis of the increased obstetric and neonatal complication rate.

Recommendations for integration of these findings into daily clinical practice have been discussed, but its final place should be addressed in future revisions of the ESC guideline management of cardiovascular disease during pregnancy.

FUTURE RESEARCH

An important problem that remains in the management of pregnancy in women with CHD is the management of women with mechanical valve prosthesis. In chapter 2 we identified mechanical valve prosthesis again as an important predictor of cardiovascular complications, with valve thrombosis being the most important, and potentially life-threatening, complication. There is no ideal anticoagulation regimen, as every approach has inherent risks and benefits for both mother and fetus. A recent report of the ROPAC registry showed again that there is no clear evidence in support of one approach over another. It is highly recommended to perform a large, prospective observational study, in which the outcomes of different anticoagulation regimens can be compared. Adding strict protocols for monitoring the level of anticoagulation in the different regimens should be considered (INR / peak-/ through anti Xa levels or both). This will be the only way to see which anticoagulation regimen is superior and what kind of monitoring should be recommended to that regimen.

It would also be valuable to perform a study which investigates whether or not it is useful to measure Nt-proBNP levels in women with modified WHO risk class II. With the current evidence it does not seem appropriate to remove third trimester follow-up from the schedule, but this specific research may be helpful to make an evidence based decision. The predictive role of Nt-proBNP before pregnancy in predicting cardiovascular complications during pregnancy could also be a valuable addition to preconception counseling, in particular for the risk of the development of heart failure and arrhythmia.

Another intriguing issue that should be addressed in future research is the role of the right ventricle during pregnancy in women with CHD. We identified right ventricular dysfunction as an independent predictor of complications during pregnancy (chapter 2) and the right ventricle tends to dilate in women with complications during pregnancy (chapter 4). Interest-
ingly, right ventricular dysfunction (TAPSE) was also associated with impaired uteroplacental flow in women with congenital heart disease. Future research should focus on potential mechanisms of how right ventricular dysfunction influences the placentation process. A part of the explanation might be sought in increased venous pressure, which was described previously as a potential mechanism for disturbed placentation. The association between systemic and pulmonary atrioventricular valve regurgitation and impaired uteroplacental circulation might also point in this direction. Histological examination of placental tissue combined with extensive uteroplacental Doppler investigations will be necessary to elucidate the patho-physiological mechanism further. Before this, it would be of interest to investigate whether uteroplacental Doppler flow is already disturbed in the first trimester of pregnancy. This would provide more fundamental evidence that cardiac dysfunction influences placental development. These are essential first steps before we can even speculate about influencing pregnancy outcome in women with CHD. Until then, watchful waiting with regular follow-up is warranted.
REFERENCES


