Pregnancy in women with corrected aortic coarctation: Uteroplacental Doppler flow and pregnancy outcome

Anne S. Siegmund a, Marlies A.M. Kampman a,b, Caterina M. Bilardo c, Ali Balci d, Arie P.J. van Dijk e, Martijn A. Oudijk f, Barbara J.M. Mulder g, Jolien W. Roos-Hesselink h, Gertjan Tj. Sieswerda i, Steven V. Koenen j, Krystyna M. Sollie-Szarynska c, Tjark Ebels k, Dirk J. van Veldhuisen a, Petronella G. Pieper a,e, On behalf of the ZAHARA investigators

a Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
b The Netherlands Heart Institute (ICIN), Utrecht, The Netherlands
c Department of Obstetrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
d Department of Cardiology, Isala, Zwolle, The Netherlands
e Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands
f Department of Obstetrics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
g Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
h Department of Cardiology, Erasmus Medical Center, University of Rotterdam, Rotterdam, The Netherlands
i Department of Cardiology, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands
j Department of Obstetrics, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands
k Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

1. Introduction

Women with a repaired coarctation of the aorta (rCoA), have a relatively low risk of maternal cardiac complications during pregnancy compared to women with other congenital heart diseases (CHD), but hypertensive disorders during pregnancy in these patients are common [1,2]. Hypertensive disorders in pregnant women in the general population are known to be associated with adverse offspring outcome, including preterm delivery, fetal growth restriction and abruptio placentae [3]. In these women who do not have medical disorders before pregnancy, both hypertensive disorders and offspring complications are related to inadequate uteroplacental flow [4,5]. In the ZAHARA II study (Zwangerschap bij Aangeboren HartAfwijkingen, pregnancy in congenital heart disease) we demonstrated that in women with CHD, pregnancy outcome.

Abstract

Objective: Women with repaired coarctation of the aorta (rCoA) are at risk of hypertensive disorders and other complications during pregnancy. Hypertensive disorders in pregnant women are associated with inadequate uteroplacental flow, which is related to adverse offspring outcome. The aim of this study was to investigate the relationship of maternal cardiac function, placental function and pregnancy complications in women with rCoA.

Methods: We included 49 pregnant women with rCoA and 69 controls from the prospective ZAHARA-studies (Zwangerschap bij Aangeboren HartAfwijkingen, pregnancy in congenital heart disease). Clinical evaluation, echocardiography and uteroplacental Doppler flow (UDF) measurements were performed at 20 and 32 weeks gestation. Univariable regression analysis was performed.

Results: Comparison of rCoA and healthy women.

1. Introduction

Women with a repaired coarctation of the aorta (rCoA), have a relatively low risk of maternal cardiac complications during pregnancy compared to women with other congenital heart diseases (CHD), but hypertensive disorders during pregnancy in these patients are common [1,2]. Hypertensive disorders in pregnant women in the general population are known to be associated with adverse offspring outcome, including preterm delivery, fetal growth restriction and abruptio placentae [3]. In these women who do not have medical disorders before pregnancy, both hypertensive disorders and offspring complications are related to inadequate uteroplacental flow [4,5]. In the ZAHARA II study (Zwangerschap bij Aangeboren HartAfwijkingen, pregnancy in congenital heart disease) we demonstrated that in women with CHD,
uteroplacental Doppler flow (UDF) parameters were impaired and were associated with maternal cardiac function before pregnancy [6,7]. In view of these data and the known relation of hypertensive disorders and uteroplacental flow in the general pregnant population, we assessed the relation of cardiac function before pregnancy, UDF and maternal and offspring outcome in women with repaired coartation of the aorta.

2. Methods

This cohort study comprised all pregnant women with rCoA and healthy pregnant women included in the ZAHARA II and ZAHARA III studies [6-8]. These studies are both prospective multicenter observational cohort studies and follow pregnant women with CHD according to identical protocols. Women aged ≥ 18 years with a history of repaired aortic coarctation who presented in one of the participating centers with a pregnancy duration of < 20 weeks and who provided written informed consent were eligible for this study. The healthy controls included in ZAHARA II were recruited from low risk midwife practices in Groningen and Rotterdam. The ZAHARA II and III studies are conducted according to the principles outlined in the Declaration of Helsinki; the study protocols have been approved by the medical ethical committee of all participating hospitals. The complete study design and results of the ZAHARA II study have been reported previously [6-8].

2.1. Baseline data and follow up

The pre-pregnancy baseline data of all pregnant women were collected during the first ante-partum visit using medical records. Baseline data included diagnosis of CHD, prior cardiovascular interventions, recoarctation, previous cardiac events, obstetric history, maternal age, medication use, blood pressure, history of hypertension (defined as present if reported in the patients records), New York Heart Association (NYHA) functional class, modified WHO risk class for maternal risk of cardiovascular complications according to ESC guidelines [9], ECG, laboratory results and echocardiographic recordings. All included pregnant women visited the outpatient clinic at 20 and 32 weeks of gestation and at 1 year postpartum for clinical evaluation (including NYHA class assessment), standardized echocardiographic recordings, ECG and NT-proBNP measurement. UDF registrations (pulsatility and resistance indices of the umbilical and uterine arteries and the presence of early diastolic notch) were performed at the prenatal care outpatient clinic at 20 and 32 weeks of gestation. UDF measurements were evaluated according to the guidelines of the International Perinatal Doppler Society [10,11]. All echocardiograms were performed according to disease specific protocols and evaluated off-line in the University Medical Center Groningen, the Netherlands. Assessment of diastolic and systolic ventricular function, chamber quantification and valvular function were performed according to the current guidelines [12–14].

2.2. Cardiac, obstetric and neonatal outcome

During pregnancy and up to 6 months post-partum, cardiovascular, obstetric and offspring events in all included women were evaluated. Primary cardiovascular events were defined as: need for an urgent invasive cardiovascular procedure, heart failure (according to the guidelines of the European Society of Cardiology and documented by the attending physician [15]), new onset or symptomatic tachy- or bradyarrhythmia requiring new or extended treatment, thromboembolic events, myocardial infarction, cardiac arrest, cardiac death, endocarditis and aortic dissection [6,7]. Primary obstetric events included: instrumental vaginal delivery (vacuum or forcipal-extraction), Cesarean section (planned or emergency), pregnancy induced hypertension (PIH), pre-eclampsia (PIH combined with proteinuria), eclampsia (pre-eclampsia with grand mal seizures), gestational Diabetes Mellitus, HELLP syndrome (haemolysis, elevated liver enzymes, low platelet syndrome), hyperemesis gravidarum, non-cardiac death, placental abruption, postpartum hemorrhage, preterm labour and preterm premature rupture of membranes (before 37 weeks gestation) [6]. Offspring events were fetal death (intra-uterine death ≥ 20 weeks gestation), perinatal death (number of stillbirths from 20 weeks gestation and death up to 28 days post-partum), intra-ventricular hemorrhage, neonatal respiratory distress syndrome, preterm birth (before 37 weeks gestation), occurrence of congenital heart disease, small for gestational age (birth weight < 10th percentile) and low birth weight (< 2500 g) [6,7].

2.3. Statistical analysis

We used SPSS (IBM SPSS Statistics, version 23.0, IBM SPSS Statistics, IBM corporation Armonk, NY) for statistical analysis. Continuous variables with normal distribution are presented as mean with standard deviation (± SD), nonnormally distributed variables as median with interquartile ranges, and dichotomous variables are presented as absolute numbers with percentages. Comparison of continuous variables between groups was performed with the Student t-test or Mann-Whitney U test, depending on distribution. Longitudinal comparison of continuous variables within CHD and healthy pregnancy groups at 2 time points (20 and 32 weeks) was performed by using the paired t-test. For the comparison of dichotomous variables, we used the χ² test or Fisher exact test, as appropriate. Univariable linear regression was used to assess associations between cardiac function parameters and UDF parameters. The following predefined preconception parameters were assessed: maternal age at conception, parity, recoarctation, open-heart surgery, left ventricular ejection fraction (LVEF), right ventricular (RV) function (tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (RVFAC)) and aortic stenosis (peak gradient ≥ 36 mm Hg); and the following parameters at 20 weeks of gestation: left ventricular ejection fraction, TAPSE, RVFAC, aortic stenosis, high NT-proBNP (~95th percentile of the NT-proBNP values at 20-week and 32-week gestation in healthy women) and β-blocker use [6]. Interaction terms were constructed and added to the model to test for confounding variables. Multivariable linear regression analysis was not performed, due to the relative small number of patients. Instead, multivariable Lasso regression with penalized selection of variables was performed to identify the most parsimonious model and to confirm results of the univariable analyses. Logistic regression analysis was used to assess associations between cardiac, obstetric, offspring complications and UDF. A P value of < 0.05 was considered statistically significant and all P values are 2-sided.

3. Results

3.1. Baseline characteristics

During the study period 49 pregnant women with rCoA and 69 healthy pregnant controls were included. Baseline characteristics are shown in Table 1. No significant differences were found between women with rCoA and healthy controls regarding age at conception and parity. Significantly more healthy women smoked prior to pregnancy than women with rCoA (33.3% versus 16.7%, P = 0.04). History of hypertension was only reported in women with CoA and 50% of these women used antihypertensive medication < 6 months before pregnancy. A diastolic ‘run-off’ pattern had been noticed before pregnancy in the descending aorta in one rCoA woman and in the abdominal aorta in five rCoA women. Only one of these women had hypertension before pregnancy. However, neither hypertension nor a diastolic run-off pattern were present during pregnancy in these women.

3.2. Pregnancy outcome

Data regarding cardiovascular, obstetric and offspring events were available in all pregnancies. One woman with rCoA developed non-sustained ventricular tachycardia during pregnancy for which hospital admission and metoprolol therapy was needed. Only in women with rCoA (N = 4) NYHA functional class deterioration (≥ 2 classes) was observed (P = 0.024). NT-proBNP levels were higher in women with rCoA than in healthy women at 20 and 32 weeks gestation (125 ± 134 ng/L versus 53 ± 36 ng/L, P = 0.001 and 111 ± 90 ng/L versus 43 ± 25 ng/L, P < 0.001). Women with rCoA had significantly higher mean arterial pressure (MAP) than healthy women (85.0 ± 9.5 mm Hg vs. 77.8 ± 7.9 mm Hg, P < 0.001 at 20 weeks and 85.0 ± 7.0 mm Hg vs. 79.7 ± 7.2 mm Hg, P = 0.001 at 32 weeks gestation). Only rCoA women needed antihypertensive medication (22.4% versus 0%, P = 0.001 at 20 weeks and 28.6% versus 0%, P < 0.001 at 32 weeks gestation).

Obstetric and offspring events are presented in Fig. 1. The overall obstetric event rate was not statistically different between women with rCoA and healthy women (P = 0.62). Women with rCoA received more often assistance during delivery (P = 0.023) and had shorter gestational age at delivery (38.7 ± 1.8 versus 39.8 ± 1.5 weeks, P = 0.001). In women with rCoA, PIH was associated with a history of hypertension before pregnancy (β = 1.748, P = 0.034). Offspring events occurred in 14.3% of women with rCoA compared to 11.5% of healthy women (P = 0.67). In women with rCoA, there was one perinatal death 4 days after birth due to perinatal asphyxia. Offspring of women with rCoA had lower Apgar scores after 1 and 10 min than offspring of healthy women (P = 0.023 and P = 0.006). Birth weight of offspring of rCoA women was lower compared to offspring of healthy women (3232 ± 522 g versus 3578 ± 553, P = 0.001) and was associated with β-blocker use during pregnancy (β = −418.0, P = 0.012). Offspring of women with rCoA who used β-blocker during pregnancy (26.5%) had significant lower birth weight than offspring of women with rCoA who did not use β-blocker (2925 ± 634 g versus 3343 ± 433, P = 0.012). Birth weight of offspring of women with rCoA,
both with and without β-blocker use during pregnancy, differed from birth weight of offspring of healthy women (2925 ± 634 g versus 3578 ± 553 g, P < 0.001; and 3343 ± 433 g versus 3578 ± 553, P = 0.029).

In women with rCoA, regression analysis of UDF and pregnancy complications revealed that pulsatility index of the umbilical artery at 32 weeks of gestation was associated with offspring events (β = 0.270, P = 0.018) and resistance index of the umbilical artery at 32 weeks of gestation was associated with pregnancy induced hypertension (β = 0.122, P < 0.001).

3.3. Uteroplacental Doppler flow measurements and cardiac function

No significant differences were observed between patients and healthy controls in pulsatility and resistance indices of the umbilical and uterine arteries or in the presence of early diastolic notchting at 20 and 32 weeks. Associations of umbilical artery pulsatility and resistance indices at 20 weeks of pregnancy and cardiovascular maternal parameters of rCoA women are reported in Table 2. TAPSE at 20 weeks of pregnancy was associated with umbilical artery pulsatility and resistance indices and TAPSE preconception was associated with umbilical artery resistance index at 32 weeks gestation (β = −0.016, P = 0.010). Additionally, RVFAC at 20 weeks gestation was associated with uterine artery pulsatility and resistance indices at 20 weeks (β = −0.016, P = 0.050 and β = −0.005, P = 0.030). Lasso regression analysis including all parameters (as mentioned in methods section) at 20 weeks selected TAPSE and RVFAC at 20 weeks gestation in the aforementioned models. In women with rCoA, mean TAPSE preconception was 23.2 ± 4.6 mm and 20.5% had an absolute value below 20 mm. Fig. 2 presents changes in left and right ventricle function parameters of rCoA women during pregnancy. A significant decrease in TAPSE from 20 to 32 weeks gestation was only noticed in women with rCoA (25.7 mm to 22.8 mm, P = 0.006). At 32 weeks gestation, TAPSE was significantly lower in women with rCoA compared to healthy women (23.4 ± 5.3 mm versus 25.3 ± 3.8 mm, P = 0.036) and more women with rCoA had an absolute value of TAPSE below 20 mm compared to healthy women at 32 weeks gestation (31.7% versus 3.0%, P < 0.001). LVEF was also significantly lower in rCoA women compared to healthy women during pregnancy (57.9 ± 6.0% versus 61.1 ± 6.0%, P = 0.006 at 20 weeks and 57.2 ± 6.3% versus 60.0 ± 6.2%, P = 0.025 at 32 weeks gestation). Changes in LVEF and RVFAC during pregnancy were not significant. Open-heart surgery was associated with TAPSE preconception and at 20 weeks gestation (β = −4.237, P = 0.020 and β = −4.246, P = 0.020). A history of open heart surgery did not affect the association between TAPSE and UDF parameters. LVEF, β-blocker use and open-heart surgery were not associated with higher pulsatility or resistance indices.

4. Discussion

The main novel finding of our study is that in pregnant women with rCoA, which is a left sided heart defect, right ventricular function is altered and is associated with impaired UDF indices. This was found in a rCoA population with a very low incidence rate of cardiac complications during pregnancy. Furthermore, offspring and obstetric events and mean values of UDF parameters did not statistically differ from healthy pregnant women.

Of all women with rCoA, only one woman had a primary cardiovascular event (ventricular arrhythmia). This low event rate is in line with the literature review of Drenthen et al., who found 1% heart failure and 0.3% of other cardiovascular events in women with rCoA during pregnancy [1]. However, Krieger et al. conducted a large population-based study and found a higher rate of cardiovascular events in women with rCoA (4.8%). The latter authors also found a high rate of pre-eclampsia (4.3%) in pregnancy in women with rCoA [17]. It has been demonstrated that pre-eclampsia in women with cardiovascular disease is strongly associated with heart failure during pregnancy [18]. Therefore the high cardiac event rate in the study of Krieger et al. may be related to their high rate of pre-eclampsia. Even though our cardiac event rate was low, it must be underlined that it is important to carefully monitor women with rCoA and preeclampsia for development of heart failure. Most authors report that hypertensive complications are common in pregnant women with rCoA [1,2,7,17]. Although in our study the incidence of hypertensive complications did not differ significantly...
between women with rCoA and healthy controls, absolute percentages were higher in women with rCoA and similar to the literature [1,17]. The lack of significance is likely due to our relatively small number of women with rCoA. Nevertheless in our study, PIH is associated with a history of hypertension and with impaired UDF in women with rCoA. This indicates that monitoring of blood pressure is important in women with rCoA during pregnancy.

The rate of offspring complications was low compared to other CHD [1], which is in line with previous studies of rCoA women [1,2]. Furthermore, the incidence rate of offspring complications in rCoA women did not differ from healthy women in our study which demonstrate a good neonatal outcome in women with rCoA. However, offspring of rCoA women had lower birth weight than offspring of healthy women. An association with β-blocker use was found, which is consistent with other studies [7,19]. Offspring of women with rCoA who used β-blocker during pregnancy had statistically lower birth weight than offspring of women who did not use β-blocker, with a mean difference of 418 g. This difference is even higher than found by the ROPAC investigators and may well be of clinical importance [20]. Moreover, offspring of rCoA women who did not use β-blocker during pregnancy still had lower birth weight than offspring of healthy women. This indicates that β-blockers are not the only negative influence on birth weight in rCoA women, but the use of β-blocker appears to have an additional negative effect on fetal growth. Our previous research indicated that cardiac medication, mainly β-blockers, negatively affects uteroplacental flow, and thus affects offspring outcome [20,21]. However, in our rCoA population we could not confirm an association between β-blocker use and impaired UDF parameters.

Although no differences were found in neonatal event rate between offspring of rCoA and healthy women, there is an association between obstetric and offspring complications and impaired UDF, which is in line with other literature [7,22,23].

Interestingly, in this rather small population the only maternal cardiac parameters that showed a fairly consistent association with abnormal UDF parameters at different time points were RV function parameters (TAPSE and RVFAC). Recent evidence suggests that in women with congenital heart disease pre-pregnancy cardiac dysfunction is related to impaired placentation, reflected by UDF abnormalities [7,22,24]. Increased
prevalence of left and right ventricular dysfunction has been demonstrated in healthy women who developed high uteroplacental resistance and had poor pregnancy outcome [24]. Ventricular dysfunction limits cardiac output resulting in suboptimal uterine perfusion and defective placentalation [23]. It is of interest that in our rCoA population parameters for RV function were associated with impaired UDF parameters instead of the expected left ventricular (LV) function parameters.

Evidence that RV dysfunction plays a prominent role in placental development and uteroplacental flow regulation is increasing. We previously demonstrated the association of RV function and UDF parameters even more significant in a heterogeneous population of women with CHD and in women with a right-sided heart disease [7,22]. The observation of the same association in a population with left sided disease further reinforces the importance of the right ventricle in uterine flow and in placental development. It is known that left and right ventricular functions are related. In conditions associated with left sided heart defects or systemic hypertension, impairment of LV function has been reported [25,26]. This has also been demonstrated in patients with rCoA where RV systolic and diastolic mechanics were impaired [27]. Our database only allowed analysis of TAPSE and RVFAC as RV function parameters. We found a significant lower value of TAPSE at 32 weeks gestation in women with rCoA compared to healthy pregnant women, and a significant decrease in TAPSE from 20 to 32 weeks in rCoA women, which seems to indicate subclinical RV dysfunction, even though absolute values were still in the normal range. Possibly this subtle, subclinical RV dysfunction is already present earlier in pregnancy or even before pregnancy but other, more sensitive RV parameters may be needed to prove this [25–27]. Our study confirms that indeed also in a left sided heart defect (i.e. repaired CoA) pregnancy complications are associated with RV subclinical dysfunction. The underlying mechanisms of RV function impairment in patients with rCoA remains uncertain. It has been demonstrated that despite successful repair of coarctation of the aorta, late after repair increased LV mass and LV afterload persist [27,28]. Possibly, these LV abnormalities affect RV function through LV-RV interaction.

It has been suggested that TAPSE may not be valid for RV function after open-heart surgery since longitudinal contraction may be impaired with preserved global RV function [29,30]. In our study, TAPSE remained correlated with worse UDF indices even after correction for open-heart surgery.

In contrast to our previous studies on UDF in CHD women, no significant differences were observed between UDF parameters in rCoA and healthy women [7,22]. However, these studies reported more cardiac function abnormalities in pregnant women with CHD than in this study on women with rCoA, which may explain the different results, in combination with the relatively small size of the study population.

4.1. Strengths and limitations

Our study is the first to compare uteroplacental flow parameters of women with rCoA to healthy women and our results add to existing evidence that cardiac function before and during pregnancy is related to uteroplacental flow and offspring outcome. Due to the study protocol, pre-pregnancy data collection was retrospective. For this reason, missing data were unavoidable. Furthermore, the study population was relatively small, hampering multivariate linear regression analyses. However, Lasso regression confirmed our findings from the univariable analyses.
5. Conclusion

In pregnant women with repaired aortic coarctation, it appears that right ventricular function is altered compared to healthy women and might affect uteroplacental flow and fetal growth. Furthermore, blood pressure regulation is important during pregnancy. Birth weight in offspring of women with rCoA is lower than in offspring of healthy women, which is partly explained by the use of β-blockers. However, in most women pregnancy outcome is favourable and the risk of defective placentaion and adverse pregnancy outcome is not significantly increased. This study indicates again the importance of further exploration of the relationship between cardiac function and uteroplacental flow and its relation to pregnancy outcome.

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Competing interest

None.

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