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

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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. In women with rCoA, tricuspid annular plane systolic excursion (TAPSE) decreased during pregnancy (25.7 mm to 22.8 mm, $P = 0.006$). UDF indices and pregnancy complication rates were similar in both groups. Offspring of rCoA women had lower birth weight (3233 g versus 3578 g, $P = 0.001$), which was associated with β-blocker use during pregnancy ($\beta = -418.0$, $P = 0.01$).
Association of cardiac function and UDF. Right ventricular (RV) function before pregnancy (TAPSE) and at 20 weeks gestation (TAPSE and RV fractional area change) were associated with impaired UDF indices (umbilical artery pulsatility index at 20 weeks $\beta = -0.02$, $P = 0.01$, resistance index at 20 and 32 weeks $\beta = -0.01$, $P = 0.02$ and $\beta = -0.02$, $P = 0.01$ and uterine artery pulsatility and resistance index at 20 weeks gestation $\beta = -0.02$, $P = 0.05$ and $\beta = -0.01$, $P = 0.02$).
Conclusions: Women with rCoA tolerate pregnancy well. However, RV function is altered and is associated with impaired placentation.

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,

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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 coarctation 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 echocardiogram, ECG and NT-proBNP measurement. UDF registrations (pulsatility and resistance indices of the umbilical and uterine arteries and the presence of early diastolic notching) 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 χ^2 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 [16]. 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 = 0.066). 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,

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