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Major adverse maternal cardiovascular-related events in those with aortopathies. What should we expect?

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ABSTRACT

Major adverse maternal cardiovascular-related events (MAMCRE) in aortopathy patients undergoing pregnancy are poorly defined. The aim was to assess for MAMCRE in pregnant patients with aortopathy or aortic enlargement in conotruncal defects (CTD), and determine if there are differences between groups.

We conducted a single-center retrospective review of pregnant women (2000–2013) with hereditary vascular disease (HVD: BAV, COA), heritable fibrillinopathies (HF: MFS, EDS, LDS, FTAAS), and CTD with aortic dilatation (TOF, d-TGA, DORV). MAMCRE included: aortic dissection/surgery, therapeutic abortion, change in mode of delivery, and aortic growth >0.5 cm within 1 year.

We identified 73 patients/97 pregnancies (39/50 HVD, 15/20 HF, and 19/27 CTD). There were 14 MAMCRE (14%); 85% (n = 12) occurred in HV and HF patients and was associated with higher baseline cross-sectional-to-height (CSA/Ht) ratio (6.6 ± 2.5 vs. 5.1 ± 1.3, p = 0.005). There was more aortic surgery in the HF (vs. HV) (RR 3.9, p = 0.12). Only 2 MAMCRE (aortic growth) occurred in CTD. Overall and emergent C-section was higher than the general population (52% vs. 29%, p < 0.001 and 16% vs. 3%, p < 0.001) as was postpartum hemorrhage (PPH) (6% vs. 1.5%, p < 0.001).

We describe the largest series of pregnant women with aortopathy and found a substantial incidence of MAMCRE, which was associated with higher pre-pregnancy CSA/Ht ratio. Rates of C-section and PPH were higher than the general population. Our data suggest that larger, multi-center studies are needed to define risks that predict MAMCRE/obstetric events in women with aortopathies, allowing optimal medical care during pregnancy.

1. Background

Pregnancy is associated with increased cardiovascular demand that peaks in the late second to early third trimester, and lasts up to 12 weeks postpartum [1]. Whether related to increased cardiovascular demand, the hormonal milieu of pregnancy, or a combination of both, aortic dissection is also more common in pregnancy [2]. This becomes most important when considering the safety of pregnancy in women with predisposition to aortopathy, such as heritable vascular disease (bicuspid aortic valve (BAV) and coarctation of the aorta (COA)), hereditary fibrillinopathies (Marfan syndrome (MFS), Ehlers–Danlos syndrome (EDS), Loeys–Dietz syndrome (LDS), and familial thoracic aortic aneurysm syndrome (FTAAS)), and patients with conotruncal defects where aortic enlargement is not uncommon (tetralogy of Fallot (TOF), double outlet right ventricle (DORV), and d-transposition of the great arteries (d-TGA)). Pregnancy poses an even higher risk for patients with aortopathy, and aortic pathology is reported as one of the leading causes of maternal mortality in the United Kingdom Confidential Enquiry into Maternal and Child Health [3].

A number of retrospective [4–11] and prospective [12–15] studies have evaluated the effects of pregnancy in MFS patients, with fewer studies in BAV patients [16,17]. No group has evaluated the incidence of maternal, fetal, and obstetric events in a comprehensive single-center group of women with predisposition to all types of aortopathy. Therefore, the primary aim of this study was to assess for major adverse maternal cardiovascular-related events (MAMCRE), and secondarily to report fetal/obstetric complications in a cohort of pregnant patients with either predisposition to aortopathy (heritable vascular disease, hereditary fibrillinopathy), or known aortic enlargement in the setting of conotruncal defects, and determine if there are differences between aortopathy groups.

Abbreviations: MAMCRE, major adverse maternal cardiovascular events; CSA/Ht, cross-sectional area to height ratio.

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2. Methods

We conducted a single-center retrospective review of consecutive pregnant women from 2000–2013 with hereditary vascular disease (BAV and COA), heritable fibrillinopathies (MFS, EDS, LDS, and FTAA), and conotruncal defects with aortic dilatation (TOF, d-TGA, and DORV). Maternal, obstetric, and fetal outcome data were collected in addition to serial echocardiographic and cardiac magnetic resonance imaging. When comparing pre-pregnancy/early-pregnancy imaging with postpartum imaging, MRI data, when available, was used in preference over echocardiographic measurements. Cross-sectional area of the aorta to height ratio (CSA/Ht) was calculated by the following formula: Ratio = r^2 π (cm^2) / height (m). When echo was used, aortic measurements were taken from standard long-axis views as recommended by the American Society of Echocardiography guideline statement [18]. When MRI data was used, the cusp-to-commissure method was used to measure the aortic root [19]. MAMCRE included direct and indirect cardiovascular events and were defined as: aortic dissection or aortic surgery within 1 year of delivery, therapeutic abortion, change in plan for mode of delivery for maternal reasons, and aortic diameter growth >0.5 cm within 1 year of delivery [20].

In order to identify surgeries performed specifically for aortopathy, aortic valve surgery solely for stenosis or insufficiency was not defined as MAMCRE. In assessing for aortic growth during pregnancy, pre-pregnancy aortic root dimensions were reported if they were within 1 year before and 1 year after pregnancy. Cross-sectional to height ratios were reported from the most recent imaging study prior to pregnancy up to 5 years prior to conception.

Population estimates of the prevalence of obstetric and fetal outcomes were obtained from a recent detailed publication by The Consortium on Safe Labor [21]. The following definitions were used to assess for obstetric and neonatal outcomes: antepartum hemorrhage: bleeding >24 weeks gestation, pregnancy induced hypertension: blood pressure >140/90 after 20 weeks gestation, pre-eclampsia: proteinuria with >300 mg/L/24 h or persistently ++ dipstick in the presence of hypertension, eclampsia: pre-eclampsia in the presence of seizures, preterm labor: labor <37 weeks gestation, post-partum hemorrhage: >500 mL for vaginal and 1000 mL for cesarean section delivery, preterm birth: birth between 24 to 37 weeks, fetal demise: fetal death >20 weeks gestation, perinatal mortality: still birth over 24 weeks gestation up to 1 week post-birth, and neonatal mortality: infant death up to 1 month of age.

Given the retrospective nature of this study comprised of data from the previous 13 years, consent waiver was obtained, and the local institutional review board approved this study. Descriptive data was generated for maternal, obstetric, and fetal outcomes. Outcomes between hereditary vascular disease, heritable fibrillinopathies, and conotruncal defect groups were evaluated with 1-way analysis of variance for continuous variables and with Fisher's exact tests for categorical and ordinal variables. When comparing categorical variables between more than 2 groups, chi-square analysis was performed. All significance tests were evaluated with type I error rate of 5% ($\alpha = 0.05$). All data are presented as means with SD. The data were analyzed using SPSS (IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY).

3. Results

We identified 73 patients with 97 pregnancies who met inclusion criteria (patients/pregnancies: 39/50 hereditary vascular disease, 15/20 heritable fibrillinopathy, and 19/27 conotruncal defects).

Of those in the heritable vascular group 29 had a BAV alone, 8 had a BAV with COA, and 2 had a unicuspid aortic valve. The fibrillinopathy group was comprised of 12 patients with MFS, 2 with EDS, and 1 with LDS. No patients with FTAAS were identified in our cohort. The conotruncal defect group included 15 women with TOF, 3 with DORV, and 1 patient with d-TGA (arterial switch operation). A total of 20 patients with 28 pregnancies had prior aortic surgeries which were comprised of: aortic valve replacement (n = 2), aortic valve and root replacement (n = 6), prior coarctation of the aorta repair (n = 4), descending aorta repair (n = 2), Norwood procedure (n = 1), and unknown (n = 5). Baseline descriptive characteristics of the total population and individual aortopathy groups showed expected differences in some baseline characteristics which reflected the cardiovascular diagnosis of origin, not necessarily related to differences in the subgroup population itself (Table 1).

There were a total of 14 MAMCRE (14%) comprised of 5 aortic dissections/surgeries, 1 therapeutic abortion, 4 with change in mode of delivery, and 4 with aortic growth >0.5 cm. The majority (n = 12, 85%) of MAMCRE occurred in hereditary vascular disease and heritable fibrillinopathy patients. There was no difference in overall MAMCRE (p = 0.14), between these two groups, however the need for aortic surgery in the fibrillinopathy group was higher (RR 3.9, p = 0.12). The only 2 events that occurred in pregnancies with conotruncal defects had significant aortic growth without other MAMCRE. Details of individual MAMCRE are outlined in Table 2. Outside of the pre-determined MAMCRE, from conception to 1 year postpartum, 7 patients (18% of patients with BAV or unicuspid aortic valve) required aortic valve replacement or valvuloplasty for severe aortic stenosis.

The pre-conception size of the ascending aorta in the total population was 3.3 ± 0.5 cm with a CSA/Ht ratio of 5.3 ± 1.6 and average postpartum ascending aortic size was 3.4 ± 0.5 cm with a CSA/Ht ratio of 5.8 ± 3.1. Patients who had MAMCRE were more likely to have a higher baseline CSA/Ht ratio (6.6 ± 2.5 vs. 5.1 ± 1.3, p = 0.005). (Fig. 1)

Table 1
Descriptive characteristics in all pregnancies.

Variable	Total (n = 97) Mean ± SD[h] or frequency (%)	Heritable vascular (n = 50) Mean ± SD[h] or frequency (%)	Hereditary fibrillinopathy (n = 20) Mean ± SD[h] or frequency (%)	Conotruncal defects (n = 27) Mean ± SD[h] or Frequency (%)	p value
Age (years)	27 ± 7	29 ± 6	26 ± 6	26 ± 10	0.09
Gravida (# pregnancies)	2 ± 1.3	2.3 ± 1.2	2.2 ± 1.3	2.0 ± 1.4	0.71
Pre-pregnancy BMI (kg/m^2)[a]	27 ± 8	29 ± 6	27 ± 12	27 ± 5	0.71
History of tobacco use	13 (13%)	5 (10%)	3 (15%)	5 (19%)	0.49
Hypertension	18 (19%)	7 (14%)	4 (20%)	7 (26%)	0.34
Prior cardiac event[b]	10 (10%)	7 (14%)	1 (5%)	2 (7%)	0.47
NYHA[c] functional class >2	11 (11%)	3 (6%)	1 (5%)	7 (26%)	0.01
Left heart obstruction[d]	15 (15%)	11 (22%)	1 (5%)	3 (11%)	0.19
EF[e] <40%	1 (1%)	0 (0%)	1 (5%)	0 (0%)	0.14
CARPREG[f] score	0.4 + 0.7	0.6 + 0.7	0.3 + 0.3	0.4 + 0.7	0.30
History of dilated aorta	59 (60%)	22 (44%)	11 (55%)	26 (96%)	<0.0001
Prior aorta surgery	28 (29%)	21 (42%)	4 (20%)	3 (11%)	0.02
Taking a BB[g] before pregnancy	22 (23%)	14 (28%)	7 (35%)	1 (4%)	0.02
BB[g] started during pregnancy	4 (4%)	2 (4%)	0 (0%)	2 (7%)	0.42
Other antihypertensive therapy	9 (9%)	2 (4%)	4 (20%)	3 (11%)	0.09

[a] BMI: body mass index.
[b] Prior cardiac event defined as: heart failure, transient ischemic attack, cerebrovascular accident, or arrhythmia.
[c] NYHA: New York Heart Association.
[d] Left heart obstruction = mitral valve area <2 cm, aortic valve area <1.5 cm, peak left ventricular outflow gradient >30 mm Hg.
[e] EF: Ejection fraction.
[f] CARPREG: cardiac disease in pregnancy score.
[g] BB: beta blocker.
[h] SD: standard deviation.