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Obstetric and cardiac outcomes in women with Marfan syndrome and an aortic root diameter ≤ 45mm☆

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ABSTRACT

Objective: To assess obstetric and aortic outcomes in women with Marfan Syndrome according to aortic root diameter, in view of recommendations for caesarean delivery when the aortic root diameter is ≥40 mm in the 2010 American guidelines versus >45 mm in the 2011 European guidelines.
Study design: In this retrospective cohort study conducted at Sainte-Justine Mother and Child Tertiary Hospital, 27 pregnancies in 20 women with Marfan Syndrome as defined by the international criteria, were followed prospectively between 1994 and 2017, after excluding women with prior aortic surgery. Obstetric and aortic outcomes were compared in 2 groups according to aortic root diameter: < 40 mm (21 pregnancies) and 40–45 mm (6 pregnancies).
Results: 21/27 women had a vaginal delivery. The caesarean section rate was 23.8% and 16.7% in women with diameter <40 mm and 40–45 mm respectively (p-value = 1), and perinatal outcome was similar across groups. Two women with a prepregnancy aortic root diameter <40 mm developed an acute type B dissection during the third trimester. Both had a family history of aortic dissection.
Conclusions: Vaginal delivery with rigorous pain control and avoidance of Valsalva maneuver may be safely considered in women with Marfan Syndrome and an aortic root diameter ≤45 mm. The risk of type B aortic dissection during pregnancy is hard to predict. Other factors such as family history of dissection and descending aorta size may play an important role, and this may modify our counselling.

Introduction

The prevalence of Marfan syndrome is about 5 cases per 10 000 persons [1]. National register-based studies have estimated a prevalence of 1.67 cases per 10,000 pregnant women in Sweden and 4.8 per 10,000 in the US [2,3]. It is caused by mutations in the *FBN1* gene on chromosome 15. Clinical diagnosis of Marfan syndrome is now based on the 2010 revised Ghent criteria [4–7]. The risk of dissection associated with pregnancy is traditionally considered to be <1% for women for an aortic root diameter <40 mm, and up to 10% for women with dilatation ≥40 mm [1,8], although new evidence seems to show that the risk might be high in either case [9]. American guidelines advise against pregnancy when the aortic root diameter is ≥40 mm, while Canadian and European guidelines contraindicate pregnancy when aortic root is dilated >44 mm and >45 mm respectively [4,5,10].

According to the American guidelines, caesarean section is the preferred mode of delivery in women with aortic root ≥40 mm. European guidelines recommend caesarean delivery when aortic root is >45 mm. Between 40–45 mm, vaginal delivery with expedited second stage may be considered [5,9–14]. Regional anesthesia is advised to prevent blood pressure peaks, and delivery can be assisted by forceps or vacuum extraction, after the fetal head is descended without maternal pushing, to avoid Valsalva manoeuvre [10].

Few studies have reported pregnancy outcome according to prepregnancy aortic root diameter, although there is no evidence that caesarean delivery protects against aortic dissection [15].

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The objective of this study was to assess obstetric and aortic outcomes according to aortic root diameter in a cohort of pregnant women with Marfan syndrome and a prior aortic root diameter ≤ 45 mm.

Materials and methods

Study design

This is a retrospective cohort study including all pregnant women with Marfan Syndrome who were followed prospectively for their pregnancy at Sainte-Justine Mother and Child University Hospital, Montreal, Quebec, Canada between 1994 and 2017. Women were considered to have Marfan syndrome if they met the 1994 or 2010 Ghent criteria [6,7], depending on the time period. Only pregnancies progressing beyond the first trimester were included. Local practice followed an established protocol and has remained constant over time. Women included were assessed prospectively before or at the start of the pregnancy to ensure that they met the Ghent criteria. All charts were reviewed at the time of this study. Women with prior aortic surgery, or not aware of their condition during pregnancy, or with features suggestive of Loeys-Dietz Syndrome or other hereditary aortopathy were excluded.

In the absence of obstetric contraindication, women with an aortic root diameter ≤45 mm were allowed to undergo a term vaginal delivery with early epidural, delayed pushing and expedited delivery with outlet forceps. Typical pregnancy follow-up included use of a beta-blocking agent and serial echocardiograms, performed at minimum once early in the second trimester and in the third trimester. All echocardiograms were performed at the Montreal Heart Institute, Quebec, Canada. Obstetric and aortic outcomes were analysed in 2 groups according to prior aortic root diameter: group 1: < 40 mm and group 2: 40–45 mm.

Data collection

Data was retrieved from women' charts. Background and genetic characteristics were age, parity, height, weight, smoking, family history of Marfan syndrome and dissection, scoliosis, ectopia lentis, pectus excavatum, dural ectasia, *FBN1* test results. Obstetric outcomes were gestational hypertension and diabetes, induction of delivery, anesthesia, delivery mode, gestational age, birthweight, fetal growth restriction (defined as an Hadlock estimated fetal weight $<10^{th}$ percentile [16]), labor length, postpartum hemorrhage, and postpartum length of stay. Fetuses or infants' *FBN1* test results were recorded when available.

The aortic outcome of interest was occurrence of aortic dissection during pregnancy or within 1 year postpartum. The diameter of the aortic root was measured before pregnancy (defined as the last recorded measurement within 18 months prior to conception), during the course of the pregnancy (maximum measurement before delivery), and postpartum (next measurement within one year postpartum).

Aortic diameter was obtained from echocardiography reports. Sinus of Valsalva diameters were consistently reported but the recommended method of measurement varied with time. Measurements were taken in M-mode from leading edge-to-leading-edge before 2006 [17]. From 2006 to 2015, measurements from inner edge-to-inner edge were used, as accepted in echocardiography guidelines [18]. From 2015 onwards, measurements were made in 2D-mode at the largest diameter at end-diastole from leading edge-to-leading edge, reflecting the most recent American Society of Echocardiography guidelines [19].

An increase in aortic root diameter of ≥5 mm during pregnancy was defined as a progressive dilatation [20,21]. Only prepregnancy aortic root diameters were considered because they are used for pregnancy counselling. Serial aortic root diameters in this cohort are presented as an exploratory analysis.

Statistical methods

Descriptive statistics are presented as percentages for qualitative variables, mean with standard deviation for normal variables, and median with interquartile range (IQR) for non-normal variables.

Women in group 1 were compared with women in group 2, using the Student *t*-test or Mann-Whitney test for continuous variables as appropriate, and the Chi- squared and Fisher tests were used to test differences between categorical data as appropriate.

A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using the STATA software (version 10.0, College Station, Texas, USA). This study was approved by the CHU Sainte-Justine, Research Centre Ethics Committee (Reference: #3645, Year 1992, Reapproved 09/2017).

Results

Participants

Nine pregnancies were excluded (4 with genetic or clinical features suggestive of other hereditary aortopathy, 3 in women who were not aware of their condition during pregnancy, and 2 because of prior aortic surgery). Twenty-seven pregnancies in 20 women met the inclusion criteria, including 17 pregnancies in primipara. Fifteen women had a *FBN1* mutation. The other 5 women were not tested, most of them because they declined genetic testing.

Twenty-one women entered pregnancies with an aortic root diameter <40 mm (group 1), and 6 with a diameter between 40 and 45 mm (group 2).

Obstetric outcomes

Maternal characteristics are shown in Table 1. Overall, 21 pregnancies (77.8%) ended in a vaginal delivery. Indications for caesarean delivery were: breech presentation (n = 2), acute type B aortic dissection (n = 2) and Harrington rods precluding loco-regional anesthesia (n = 1) in group 1, and breech presentation in group 2 (n = 1, Table 2). Among primipara (N = 17), vaginal delivery rate was 82.4% (14/17) overall, and 78.6% (11/14) for women in group 1 and 100% (3/3) in group 2.

The preterm birth rate was 15%, with gestational age at birth ranging between 31 and 36 weeks of gestation. Causes related to preterm delivery were aortic dissection (n = 1), and preterm labor/rupture of membrane (n = 3). Two infants of women with preterm labor/preterm premature rupture of membranes were tested positive for *FBN1* mutations, the third one is asymptomatic, and *FBN1* testing was not performed.

Aortic outcomes

The prepregnancy mean aortic root diameter was 37.0 ± 3.8 mm, and the median was 35.5 mm (IQR: 34.0-39.0). In one pregnancy, the echocardiography results prior to pregnancy were not available but the diameter did not exceed 40 mm throughout pregnancy.

Eighteen women were treated with a beta-blocking agent, and 6 used their treatment inconsistently because of side-effects. Two women with a non-progressive aortic diameter < 40 mm and using beta-blocking agents (Metoprolol at a dose of 25 mg bid or 12.5 mg