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Review

Pregnancy and Thoracic Aortic Disease: Managing the Risks

Shaynah Wanga, MD,[a,b,c] Candice Silversides, MD,[d,e] Annie Dore, MD,[e] Vivian de Waard, PhD,[b] and Barbara Mulder, MD, PhD[a,c]

[a] Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands

[b] Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands

[c] Interuniversity Cardiology Institute of The Netherlands, Utrecht, The Netherlands

[d] Division of Cardiology, Department of Medicine, Mount Sinai Hospital and University Health Network, University of Toronto, Toronto, Ontario, Canada

[e] Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada

ABSTRACT

The most common aortopathies in women of childbearing age are bicuspid aortic valve, coarctation of the aorta, Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, SMAD3 aortopathy, Turner syndrome, and familial thoracic aneurysm and dissection. The hemodynamic and hormonal changes of pregnancy increase the risk of progressive dilatation or dissection of the aorta in these women. The presence of hypertension increases the risk further. Therefore, appropriate preconception counselling is advised. For women who become pregnant, serial follow-up by a specialized multidisciplinary team throughout pregnancy and postpartum period is required. In this review we discuss risk assessment and management strategies for women with aortopathies.

RÉSUMÉ

Les aortopathies les plus courantes chez les femmes en âge de procréer sont les suivantes : bicuspidie valvulaire aortique, coarctation de l'aorte, syndrome de Marfan, syndrome d'Ehlers-Danlos, syndrome de Loeys-Dietz, aortopathie associée au gène SMAD3, syndrome de Turner et formes familiales d'anévrisme et de dissection de l'aorte thoracique. Les changements hormonaux et hémodynamiques associés à une grossesse augmentent le risque d'une dilatation progressive ou d'une dissection de l'aorte chez ces femmes. Ce risque s'accroît en présence d'hypertension. Par conséquent, des conseils appropriés avant la conception sont de mise. Chez les femmes qui sont enceintes, un suivi périodique par une équipe multidisciplinaire spécialisée tout au long de la grossesse et durant la période postpartum est nécessaire. Dans cette analyse, nous discutons de l'évaluation du risque et des stratégies de prise en charge des femmes présentant une aortopathie.

Thoracic aortic disease (TAD) can present in young women of childbearing age. It is most commonly related to bicuspid aortic valve (BAV), coarctation of the aorta, Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, SMAD3 aortopathy, Turner syndrome, or familial thoracic aneurysm and dissection (FTAAD). Some women will have a thoracic aortic aneurysm (TAA) and others have normal aortic dimensions. Aortopathies are a major cause of maternal mortality in pregnancy and can be undiagnosed until the fatal event.[1] In a Dutch nationwide prospective study of cardiac mortality during pregnancy, the overall maternal mortality rate during pregnancy was 3 per 100,000 deliveries and nearly half of the deaths were caused by aortic dissection.[2]

Pregnancy causes characteristic hemodynamic changes, including an increase in blood volume, heart rate, and stroke volume.[3,4] This increased volume overload is at least partly counterbalanced by a decrease of peripheral vascular resistance, diastolic blood pressure, and aortic augmentation index. Furthermore, hormonal changes might lead to less corrugation of the aortic elastic fibres and thus to fragmentation of the aortic reticulin fibres.[5,6]

The increased hemodynamic stress and structural changes of the vascular wall might contribute to progressive aortic dilatation or dissection in pregnant women with aortopathies. The presence of (gestational) hypertension further increases the risk.[7] Appropriate preconception evaluation and serial follow-up by a specialized multidisciplinary team throughout pregnancy and postpartum period is advised. In this review we discuss risk assessment and management of TAD in pregnancy.

Complications During Pregnancy

Maternal risks

Aortic growth rate. Growth of the aortic root is a normal phenomenon in healthy women during pregnancy. The

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Corresponding author: Dr Barbara Mulder, Academic Medical Center, Meibergdreef 15, 1105AZ Amsterdam, The Netherlands. Tel.: +020-566-2193; fax: +020-697-1385.

E-mail: b.j.mulder@amc.uva.nl

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maximum diameter is reached during the third trimester; but at 6 weeks postpartum the diameter remains enlarged by an average of 1 mm.[8] In nonpregnant women with Marfan syndrome, the average aortic growth rate is higher, approximately 0.38 mm per year.[9] A recent study showed an additional increase in aortic growth rate during pregnancy to 0.3 mm per month in Marfan women. The increase in aortic dilatation rate decreased after delivery, but remained higher than the prepregnancy rate.[10] In this study, patients with an increased aortic dilatation rate during pregnancy were also at increased risk for aortic complications after long-term follow-up.[10] Two smaller studies have reported no difference in aortic growth rate between baseline and during pregnancy.[11,12] However, in Marfan women with an aortic root diameter larger than 40 mm (TAA), pregnancy did influence the long-term dilatation rate.[11] Apart from aortic growth rates in pregnant Marfan patients, the only study on other aortopathies concerns BAV patients. In a comparison of pregnant and nonpregnant BAV patients no increase in TAA risk during 216 pregnancies was found.[13]

Aortic dissection and rupture. The potential life-threatening consequence of aortopathies is aortic dissection and rupture. In the general population, the incidence of aortic dissection outside of pregnancy is 6 per 100,000 individuals per year,[14] and pregnancy increases the incidence of dissection in the normal population 100-fold, to approximately 0.6%.[15]

The incidence of aortic dissection in women with aortopathies is already increased when women are not pregnant, to 31 per 100,000 in those with BAV,[16] at least 36 per 100,000[17] in those with Turner syndrome,[17,18] and 170 per 100,000 in those with Marfan syndrome.[19] In Marfan patients, the probability of aortic dissection, when not pregnant, largely depends on aortic diameter, with an incidence of 0.3% at 45-49 mm (95% confidence interval, 0.00-0.71) and 1.33% at 50-54 mm (95% confidence interval, 0.00-3.93).[19] Aortic diameter is also a predictor for aortic dissection in patients with BAV,[20] but is less predictive for Loeys-Dietz[21] and vascular Ehlers-Danlos syndrome.[22] Other risk factors for aortic dissection are the site of dilatation, the rate of aortic progression, previous aortic dissection, associated lesions, the specific vascular syndrome, and familial history of dissection or sudden death.[10,19,23-25] Although data on aortic complications during pregnancy in the different aortopathies are limited, several studies suggest that pregnancy further increases the incidence of aortic dissection in these disorders (Table 1). Notably, most of the TAD patients with aortic dissection during pregnancy were either not receiving preventative measures[12,26,27] or had a contraindication for pregnancy such as a previous dissection.[11,12]

One of the most extensive studies on this topic was performed in BAV patients, in whom no aortic complications were observed in 82 patients during 216 pregnancies. However, in this study only 8% of the women had an aortic diameter $>$ 40 mm.[13] We could identify 11 case reports on aortic dissection in pregnant BAV women. Of the 11 cases, 3 patients had Turner and 1 had Marfan syndrome.[43]

Several studies have reported the occurrence of aortic dissection in pregnant Marfan patients (Table 1). These studies reported different incidence rates, but overall results of these studies suggest that pregnancy increases the risk of aortic dissection in Marfan women.

There are also a number of reports on pregnancy in other, less prevalent, aortopathies. Two studies on Loeys-Dietz syndrome reported a high incidence of aortic dissection during pregnancy.[34,35] These pregnancy cohorts were small in size and it is not clear whether preventative measures were taken. In a study on pregnancy in patients with SMAD3 aortopathy, often seen as a subtype of the Loeys-Dietz syndrome, there were no cases of aortic complications.[36]

In vascular Ehlers-Danlos syndrome,[22] also a rare and severe connective tissue disorder characterized by frail vascular tissue, vascular rupture during pregnancy has been reported as high as 50%,[37] with mortality rates between 5%[38,39] and 50%.[37] In a recent study on 256 vascular Ehlers-Danlos patients who experienced 565 pregnancies, a high mortality rate of 6.5% was reported during pregnancy, without an increase in the long-term mortality risk of this patient group.[39]

In one of the least prevalent aortopathies, namely Turner syndrome, a retrospective study reported an incidence of 2% for aortic dissection during pregnancy.[40] BAV, aortic coarctation, and hypertension in the Turner population[44] are believed to further increase the risk of aortic complications during pregnancy. In a study of pregnant women with aortic coarctation,[41] the only aortic dissection occurred in a woman with Turner syndrome and BAV. However, there are also case reports on aortic complications in pregnant women with aortic coarctation who do not have Turner syndrome.[45]

A heterogeneous group of aortopathies, collectively called FTAAD, are caused by mutations in different genes. It is known that patients with a mutation in the α-actin 2 gene are at substantial risk of aortic dissection during pregnancy.[42] Further research is needed to determine the risk of aortic complications in FTAAD patients with other known or unknown mutations.

Next to aortic dissection or rupture, the different aortopathies might also lead to additional complications, such as aortic insufficiency and dissection and/or rupture of smaller arteries such as the carotid artery. In that light, the opposite is seen in fibromuscular dysplasia (FMD), a disorder that causes carotid or renal artery stenosis or dilatation, and occasionally aortic dissection is observed.[46,47] Although there are case reports on pregnant patients with FMD who have experienced complications because of either renal or carotid artery stenosis,[48,49] there are no reports of aortic dissection or rupture during pregnancy in FMD patients.

Aortic dissection might occur at any time during gestation, but is more frequent in the third trimester and postpartum.[42,50] Nicely reviewed, dissections occur for approximately 5% in the first trimester, 10% in the second trimester, 50% in the third trimester, and 20% postpartum.[50] The high incidence of aortic dissection in the third trimester might be because of the increase in cardiac output, which peaks toward the end of pregnancy.[4] Most dissections originate in the ascending aorta (type A dissection), but dissections in the descending part of the thoracic aorta (type B) might also occur.[51]

Obviously, aortic dissection during pregnancy can have devastating consequences. Overall, maternal mortality from