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Management of aortic valve involvement with Marfan syndrome during pregnancy

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Abstract
Patients with MFS should be followed during pregnancy jointly by their obstetrician and cardiologist. For patients with normal-size aorta, antenatal visits should be scheduled every month, and an echocardiogram should be scheduled during each trimester and before the delivery. In patients with aortic diameter ≥40 mm, progressive dilation, or a history of aortic surgery for aortic dilatation or dissection, an echocardiographic examination should be performed every 4 to 6 weeks. Vaginal delivery is safe in patients with MFS who have no significant cardiovascular involvement and normal aortic diameter (<40 mm). Patients with aortic dilatation ≥40 mm, progressive dilatation of the aorta during pregnancy, or a history of aortic repair for prior dissection are at high risk for aortic dissection and should therefore have an elective cesarean section with epidural or general anesthesia to minimize hemodynamic changes associated with vaginal delivery. In case of an urgent need for surgery and to prevent unfavorable fetal outcome, an immediate cesarean section followed by cardiac surgery is recommended.

Keywords: marfan syndrome, aortic root dilatation, aortic dissection, pregnancy

1. Introduction
Marfan's syndrome (MFS) is a systemic disorder of connective tissue caused by a mutation in the gene encoding fibrillin 1 (FBN1) on chromosome 15, an extracellular matrix protein. It is transmitted as an autosomal dominant trait, even though about 25% of cases results from *de-novo* mutations. The incidence of classic Marfan's syndrome is about 2–3 per 10.000 individuals. The disease occurs worldwide, with no predilection for either sex [1]. The disease may affect different systems, in particular the cardiovascular, skeletal and ocular systems. The diagnosis of Marfan's syndrome requires a multi-disciplinary approach and it is largely based on clinical assessment, in particular on the Ghent nosology. One major criterion in an organ system and minor criteria in another organ system, if there is positivity in the family history, are necessary for the clinical diagnosis of MFS. If there is no family history, major criteria in two organ system and the involvement of a third are necessary for the diagnosis.
Important advances have been made in medical and surgical care of affected individuals. Cardiovascular complications of MFS include mitral valve prolapse, mitral valve regurgitation, left ventricular dilatation, cardiac failure, aortic dissection and pulmonary artery dilatation, but aortic root dilatation is the most common cause of morbidity and mortality. With regard to Marfan syndrome and pregnancy, the two major issues are the risk of transmission of Marfan syndrome to the fetus and the risk of cardiovascular complications in an affected mother. The risk of transmission to the offspring is at least 50%, with the possibility of a more severe clinical presentation. Thus, the management of MFS patients should require a genetic counselling before conception. Concerning cardiovascular complications, the risk of aortic dissection in pregnancy is increased compared to the general population, and may be caused by inhibition of collagen and elastin deposition in the aorta by oestrogen, and the hyperdynamic hypervolaemic circulatory state of pregnancy, which is maximal in the last trimester or within a week after delivery, when aortic complications are more frequent [2]. Recent studies have suggested an expected rate of aortic dissection of about 3%, which varies from 1% in women with aortic diameter < 40 mm to 10% in high-risk patients (aortic root diameter > 40 mm, rapid dilatation, or previous dissection of the ascending aorta) [59, 60].

2. Marfan Syndrome and Cardiovascular Risk during pregnancy
2.1 Risk for the Mother
Pregnancy is associated with increased risk of aortic dissection [3, 4], probably caused by hemodynamic changes [5] and by hormonally mediated decrease in the amount of mucopolysaccharides and loss of elastic fibers in the aortic wall [6]. Reviewing the English literature in the last decade, we found 39 cases that provide information regarding potential pregnancy-related complications in women with MFS [7-28]. The mean age of these patients was 30±4 years; 18 patients had dissection of the ascending aorta, 9 of the descending aorta, and 2 of both. In 19 patients aortic dilatation was diagnosed before pregnancy, and 4 had a history of aortic surgery. Eight women were diagnosed with MFS only after the occurrence of complications. Five patients developed acute dissection between weeks 13 and 20, 18 between weeks 24 and 40, and 6 after the delivery (between day of delivery to 3 months postpartum). In addition, 5 patients developed progressive dilatation of the ascending aorta, which required surgery during pregnancy, and 2 patients had intracranial hemorrhage postpartum (30 minutes and 6 weeks after the

delivery). Two other patients with distal dissection diagnosed at initial evaluations remained stable during pregnancy. Fetal loss was reported in 4 cases with aortic dissection, 2 as a result of maternal death. The majority of patients who developed dissection during pregnancy (n=23) delivered by cesarean section. Timing of surgery (28 cases) was before delivery in 6 women, after delivery in 15, and immediately after cesarean section in 7. Although the majority of patients who were evaluated before or early in pregnancy had dilated aortic root, aortic dissection also occurred in 2 patients with aortic diameter <40 mm.

What is the expected rate of complications in unselected women with MFS during pregnancy? A number of recent studies [8, 9, 16, 28] have provided information on >350 unselected pregnancies in patients with MFS and suggested an expected rate of aortic dissection of ≈3% with an estimated 1% in women with aortic diameter <40 mm and 10% in high-risk patients (aortic root diameter >40 mm, rapid dilatation, or previous dissection of the ascending aorta) [29]. It should be noted, however, that although uncommon, aortic dissections have been reported in women with normal-size aorta [8, 30], and therefore an event-free pregnancy cannot be guaranteed to women with MFS even in the presence of normal aortic diameter [8, 9, 18].

2.2 Risk for the Fetus

The risk of transmission of MFS to the offspring is at least 50% [16]. Because of the variability in the clinical presentation, severe expression of the syndrome can occur in an offspring of a mother with a relatively mild presentation. It should also be noted that development of aortic dissection in the mother carries a substantial risk to the fetus [4, 8, 11, 15, 30]. In addition, MFS is associated with a high rate (40%) of obstetric complications such as premature delivery mainly due to premature rupture of membranes and increased mortality in the offspring [28].

2.3 Prenatal Diagnosis

Mutation or linkage analysis can be used for prenatal diagnosis [35, 36], which can also be accomplished by chorionic villus sampling or amniocentesis (cell culture) in informative families [36, 37]. Because >500 mutations have been reported in FBN1, almost every patient has a unique mutation, and no efficient diagnostic test yet exists [38]. Recently, mutation detection has become available with thorough screening methods, but ≈10% of mutations that cause MFS can still be missed [38]. Moreover, as indicated above, molecular diagnosis cannot predict the clinical severity of the disease [37]. In addition to the genetic linkage that can be done in early gestation, echocardiography may be used in the third trimester for the diagnosis of cardiac manifestations of MFS in the fetus such as atrioventricular valve regurgitation and dilatation of aortic root and pulmonary artery [39].

2.4 Preconception Evaluation and Counseling

The management of patients with MFS ideally should start before conception. The patient should undergo a careful cardiovascular evaluation, including assessment of proximal and distal aortic diameter as well as valvular and cardiac function by echocardiogram, computed tomography, or magnetic resonance imaging. Holter monitoring should be performed in patients with ventricular dilatation for detection of ventricular arrhythmias [40]. Patients should be informed about potential pregnancy-related maternal complications and the high risk of transmitting the syndrome to the offspring with the possibility of more severe expression of the disease [35]. The woman and her family should also be informed of the need for close follow-up during pregnancy as well as the use of β-blockers and possibly other cardiac medications and the potential side effects to the fetus. Women with a history of aortic valve replacement with a mechanical prosthesis should be informed of the complexity and risk of anticoagulation in pregnancy [41]. The possibility and limitations of prenatal diagnosis with the use of both genetic linkage and fetal echocardiography [39] should be explained. In addition, the patient should be informed about the likelihood of morbidity and possibly reduced longevity [31] even after successful pregnancy.

2.5 Long-Term Outcome after Pregnancy

Information regarding expected morbidity and mortality after pregnancy should be provided to a woman with MFS who is considering pregnancy. A study [31] of 125 patients with mean age of 21±15 years who did not present with aortic root dissection as a first sign of the disease reported 5- and 10-year survival after diagnosis of 95% and 88% and complication-free survival of 78% and 66%, respectively. Ten percent of the patients developed dissection, and 24% underwent prophylactic repair. Similar results were reported by Svensson *et al.* [32] and Gott *et al.* [33] in a total of 393 patients who underwent aortic surgery for aortic root replacement. The rate of death was higher in patients who had urgent or emergency operation. Major complications included arrhythmias, dissection or rupture of residual aorta, heart failure due to mitral valve disease, endocarditis, and intercerebral or spinal hemorrhage. These data clearly indicate that despite effective medical and surgical therapy, MFS is associated with increased likelihood of major morbidity and even premature death in women after successful delivery. The likelihood of complications is especially high in patients with a history of acute type A dissection, but unexpected fatal complications may also occur after prophylactic aortic root surgery [28] or mitral valve surgery [34].

2.6 Risk of Arrhythmias and Sudden Death

Yetman *et al.* [40] reported sudden arrhythmic death despite β-blocker therapy in 3 of 70 patients with MFS who had mitral valve prolapse and left ventricular dilatation as well as ventricular couplets or tachycardia on routine 24-hour Holter monitoring. Because of the increased incidence of arrhythmias during pregnancy [42], implantation of an internal defibrillator should be considered in high-risk patients before conception.

3. Surgical Treatment and Pregnancy

Current recommendations call for prophylactic surgery in cases of ascending aortic dilatation >50 mm for patients with MFS [43, 44]. In patients with aortic diameter <50 mm, surgical intervention can be considered in cases with rapid growth, a family history of premature aortic dissection, and the presence of more than mild aortic regurgitation. Because of the

increased risk associated with urgent surgery for dissection during gestation, a prophylactic elective repair is preferred in women who contemplate pregnancy. Recent guidelines have suggested an elective surgery before pregnancy for women with aortic root >47 mm [29]. Valve-sparing aortic root replacement has been advocated in young patients with MFS to prevent the need for anticoagulation associated with valve replacement [44–47]. Although excellent long-term survival and a low rate of complications have been described [45, 46], the durability of this procedure may be somewhat limited.[47] Because the risk associated with emergency operation for aortic dissection or rupture is high [48], a progressive, >10-mm dilation of the aorta during pregnancy requires an elective surgery either after a therapeutic abortion (up to 20 weeks) or during pregnancy.

Successful surgeries during gestation or shortly after delivery [4, 5, 10, 21, 30, 33] have been reported in a number of women with MFS. A review of 40 pregnant women with surgery due to type A dissection prepartum reported 15% maternal death rate; however, death rates decreased from 30% in 1990–1994 to 0% in 2002–2004, and fetal death rates decreased from 50% to 10%, respectively [30]. Because cardiac surgery continues to be associated with increased fetal loss [18, 30, 48], cesarean section should be performed before or concomitantly with thoracic surgery if fetal maturity can be confirmed [12, 13, 18].

4. Medical Therapy

β-Blockers have been shown in nonpregnant patients to slow the growth of the aortic root and significantly reduce rate of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death [49–51].β-Blockers have been used extensively during pregnancy for various medical conditions with overall favorable results [52]. Anecdotal reports of side effects include fetal growth retardation, bradycardia, hypoglycemia, hyperbilirubinemia, and apnea at birth in the newborn. Such side effects should therefore be anticipated by the clinician.

The use of propranolol, a nonselective β_1 receptor blocker that was successfully used in nonpregnant patients [50], is not ideal in pregnancy because it blocks the inhibitory effects of epinephrine on myometrial activity and may therefore facilitate uterine activity. The use of selective β_1 receptor blockers may therefore be preferred during pregnancy [52]. Because lower birth weight with atenolol during gestation has been reported [53, 54], metoprolol may be preferred. It is recommended in the nonpregnant patient that dosage be titrated to a resting heart rate of <60 bpm [49]. Because of increased sympathetic output during pregnancy, heart rate is increased, and a higher dose of β-blockers may be needed to achieve adequate heart rate control [55, 56]. When initiated during pregnancy, the dose of β-blockers should be titrated to reduce resting heart rate by ≥20%. β-Blocking agents are excreted in breast milk [57], and nursing infants should therefore be monitored for adverse effects. A recent study [58] has reported a favorable effect of angiotensin receptor blockers on the rate of progressive aortic root dilation. The use of angiotensin receptor blockers in pregnancy, however, is contraindicated because of potential toxicity to the fetus [59].

5. Follow-Up during Pregnancy

Patients with MFS should be followed during pregnancy jointly by their obstetrician and cardiologist. For patients with normal-size aorta, antenatal visits should be scheduled every month, and an echocardiogram should be scheduled during each trimester and before the delivery. In patients with aortic diameter ≥40 mm, progressive dilation, or a history of aortic surgery for aortic dilatation or dissection, an echocardiographic examination should be performed every 4 to 6 weeks.

6. Labor and Delivery

Vaginal delivery is safe in patients with MFS who have no significant cardiovascular involvement and normal aortic diameter (<40 mm) [6, 32]. To minimize the stress of labor, epidural anesthesia should be used to reduce pain, and forceps or vacuum should be used to shorten the second stage of labor. Because ≈70% of patients with MFS present with lumbosacral dural ectasia, an anesthetist should be consulted before delivery [4]. Both systolic and diastolic blood pressures increase markedly during uterine contractions and pain [5].These changes should be anticipated and prevented with epidural anesthesia, β-blockers, and vasodilator agents. Patients with aortic dilatation ≥40 mm, progressive dilatation of the aorta during pregnancy, or a history of aortic repair for prior dissection are at high risk for aortic dissection and should therefore have an elective cesarean section with epidural or general anesthesia to minimize hemodynamic changes associated with vaginal delivery. Postpartum hemorrhage of the uterine vasculature 3 days after cesarean section secondary to MFS has been reported [11] and should be anticipated. If elective aortic repair is indicated in the later stage of pregnancy, surgery should be performed after delivery, if possible. In case of an urgent need for surgery and to prevent unfavorable fetal outcome, an immediate cesarean section followed by cardiac surgery is recommended [11, 13, 18, 19, 30].

7. Case presentation

A 29-year-old Indian woman with Marfan syndrome (MFS) was referred for cardiac evaluation in the 22nd week of her first pregnancy. Although she was diagnosed with MFS at the age of 9 years, the patient did not have cardiac evaluations before her pregnancy. 2D Echocardiography revealed mildly dilated left ventricle with normal systolic function, moderately dilated left atrium, severe dilation of the aortic root with maximum diameter of 62 mm, and moderate aortic regurgitation. Magnetic resonance imaging showed a 60×52-mm aortic root aneurysm with no evidence of aortic dissection. The patient was started on metoprolol 25 mg BID, which was increased to 50 mg BID, and she was advised to have an elective surgical aortic repair. She decided to delay her surgery to allow fetal maturity. The patient was hospitalized for 2 weeks for close monitoring and underwent a successful cesarean section at 28 weeks' gestation followed by a successful Bentall procedure to repair her aortic aneurysm and replace her aortic valve.

The optimal management of pregnant Marfan patients should

therefore require a multidisciplinary approach, consisting not only of obstetric and cardiologic controls, but also of an anaesthesiology visit before delivery, because about 70% of patients with MFS have lumbusacral dural ectasia. Women with a normal aortic diameter should be submitted to prenatal visits every month and to echocardiogram each trimester and before the delivery, while women with an aortic diameter >40 mm or a progressive dilatation should be submitted to echocardiogram every month. Regarding delivery, women with aortic diameter <40 mm can have a vaginal delivery, while patients with aortic diameter >40 mm or progressive dilatation should have an elective cesarean section with epidural or general anesthesia, because they are at high risk for aortic dissection secondary to the hemodynamic changes associated with vaginal delivery (increase in both systolic and diastolic blood pressure).

8. Conclusion

Our case scenario presents some of the challenges faced by the pregnant patient with MFS and her physicians. Although diagnosed at a young age, she was not treated with β-blockers and did not have a preconception evaluation and thus was exposed to a high risk of acute aortic dissection during pregnancy. A finding of a dilated aorta before pregnancy would have mandated surgery before conception. The case also demonstrates the dilemma faced by the patient of having surgery during pregnancy, which is associated with high rate of fetal loss and other fetal complications. Because of concern for her fetus, the patient preferred to assume the risk herself and delayed the surgery to allow fetal maturity and delivery of the baby before the operation. Because of an increased risk of aortic dissection due to the hemodynamic strain involved with vaginal delivery, the delivery was done by cesarean section.

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