Marfan's syndrome and pregnancy: a good maternal and fetal outcome

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Summary

Introduction: **this case report highlights the important role of a multidisciplinary team's task in the care of pregnant women with Marfan's syndrome (MFS), a systemic disorder of connective tissue that is transmitted as an autosomal dominant trait.**
Case: **a 42 year-old italian pregnant woman with Marfan's syndrome and degenerative heart disease (aneurysmatic dilatation of the aortic root, mitral regurgitation and prosthetic mitralic valve) was clinically assessed jointly by an obstetrician and a cardiologist, 'the obstetric team specialised in management of high risk pregnancy', every 2-3 weeks from the 21th week of gestation.**
The first ambulatory monitoring echocardiography revelead aneurysmatic dilatation of the aortic root (41 mm), good function of the previously replaced mitral valve, cardiac ejection fraction 51% and telediastolic volume 116 ml. The echocardiographies showed no changes up to 32 weeks gestation. At the 34th week of gestation she had a slight decrease in cardiac ejection fraction and minimal increase of left ventricular diastolic volume. Therefore she underwent elective cesarean section under general anesthesia at 35 weeks' gestation. The post-partum course was uneventfull for the patient and the baby.
Conclusion: **pregnant women with heart disease benefit from an appropriate antenatal management, which may result in a favourable outcome.**

Key words: Marfan's syndrome, high-risk pregnancy, systemic disorder.

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 multidisciplinary approach and it is largely based on clinical assessment, in particular on the Ghent nosology (Tab. 1). 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.
The penetrance of some features is age dependent, therefore the Ghent nosology must be used with caution in children, in whom molecular testing can be useful.
Recently it has been demonstrated that many features (like bone overgrowth, myxomatous changes of the mitral valve, craniofacial abnormalities, muscle or fat hypoplasia) of the disease are caused by a disregulation of the transforming growth factor β (TGFβ) activity and signalling (1).
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.

Table 1. Ghent criteria.

System	Major Criteria	Minor Criteria
Skeletal:	At least 4 features of the following Pectus Carinatum Pectus excavatum requiring surgery Upper-to-lower segment ratio <0.86 or span:height>1.05 wrist and thumb signs Scoliosis >20° or spondylolisthesis Reduced elbow extension (<170°) Pes planus Acetabular protusion	Pectus excavatum Joint hypermobility High palate with dental crowding Characteristic face(dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
The involvement of the Skeletal system consists in at least 2 features contributing to the major criteria, or one of the list of the major criteria and 2 features of the minor criteria.		
Cardiovascular:	Either of the following Dilatation of aortic root, involving at least the sinuses of valsalva Dissection of the ascendining aorta	Mitral valve prolapse Dilatation of the pulmonary artery, aged <40 years Calcified mitral annulus, aged <40 years Other dilatation or dissetion of the aorta
The involvement of the Cardiovascular system consists in only one feature of the minor criteria.		
Pulmonary:	None	Spontaneous pneumothorax Apical blebs
The involvement of the Pulmonary system consists in only one feature of the minor criteria.		
Ocular:	Ectopia lentis	Flat cornea Increased axial lenght of globe Hypoplastic iris or ciliary muscle
The involvement of the Ocular system consists in at least two features of the minor criteria.		
Dura:	Lumbosacral dural ectasia	None
Skin/integuments:	None	Striae atrophicae Recurrent or incisional hernia
The involvement of the skin and integuments consists in only one feature of the minor criteria.		
Genetic findings:	Parent, child, or sibling meets these criteria independently Fibrillin 1 mutation known to cause MFS Inheritance of DNA marker haplotype linked to MFS in the family	None

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) (3, 4).

The Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease recommends that women with an aortic diameter above 44 mm should be strongly discouraged from becoming pregnant without repair and that an aortic diameter below 40 mm rarely is associated with complications, although no diameter is considered completely safe.

Table 2. Echocardiographies.

	Aortic root	Ascending aorta	Ejection fraction	Telediastolic volume
25th weeks' gestation	4.1 cm	4 cm	51%	116 ml
29th weeks' gestation	4.1 cm	4 cm	55%	118 ml
32nd weeks' gestation	4.2 cm	4 cm	49%	142 ml
34th weeks' gestation	4.2 cm	4 cm	46%	149 ml
7th day post-delivery	4.2 cm	4 cm	47%	140 ml
4th month of puerperium	4.2 cm	4 cm	52%	145 ml

Case report

A 42 year-old italian woman, 0 para, at 21 week's gestation came to our observation with the diagnosis of Marfan's syndrome and degenerative heart disease, following previous counseling suggesting pregnancy termination pregnancy.
The patient reported a family history of Marfan's syndrome (sister and nephews affected).
Her condition had gone undiagnosed until 2002, when she underwent prosthetic valve replacement surgery (St. Jude prothesis) subsequently to investigations for febrile episodes with evidence of severe heart failure associated with mitralic valve insufficiency.
During her pregnancy the patient was clinically assessed jointly by an obstetrician and a cardiologist, "the obstetric team specialised in management of high risk pregnancy", every 2-3 weeks.
She was treated with a beta-blocker (metoprolol 100 mg/die; the patient was already taking it before pregnancy) and low molecular weight heparin (LMWH 6000 UI/die) starting from the first inspection in maternity unit.
The first echocardiography revelead aneurysmatic dilatation of the aortic root (41 mm), good function of the previously replaced mitral valve, cardiac ejection fraction 51% and telediastolic volume 116 ml.
The echocardiographies showed no changes up to the 32nd week of gestation (telediastolic volume 142 ml, cardiac ejection fraction 49%, aneurysmatic dilatation of the aortic root 42 mm) (Tab. 2).
The fetal biometry was always consistent with the gestational age. Renal function and blood pressure have always been normal.
The echocardiography at the 34th week of gestation showed slight decrease in cardiac ejection fraction and minimal increase of left ventricular diastolic volume. Therefore it was decided to hospitalize the patient for close monitoring and she underwent elective cesarean section under general anesthesia at 35 weeks' gestation. A female baby was born, weighing 2590 grams, with an Apgar score 3/9. After the cesarean section the woman was transferred to the intensive care unit for high-level surveillance just for one day.
The post-partum course was marked by a suspected prostetic valve endocarditis despite antibiotic prophylaxis with ampicillin and gentamicin.
On the 7th day post-partum an echocardiography was performed because of persistent fever despite antibiotic therapy, that showed a normo functioning mitralic prosthetic valve, sligth decrease in cardiac ejection fraction and in left ventricular diastolic volume.
On the 28th day after delivery the mother was discharged with heparinic terapy for four weeks (low molecular weight heparine 5000 IU for two times a day) and antibiotic therapy for six weeks (amoxicillin 1 g for three times a day, ciprofloxacin 500 mg for two times a day). The post-delivery course was uneventfull for the baby. Actually, regarding the suspicion of endocarditis, this was not confirmed by blood cultures and transesophageal ultrasonography. The ultrasound images would be compatible with the presence of floating sutures of the prosthetic valve. The last echocardiography, performed at the fourth month of puerperium, showed that valvular vegetations were unchanged in size. Moreover, the same echocardiography showed the improvement of ejection fraction and the reduction of telediastolic volume.

Discussion

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 (5).
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 (5).
Regarding delivery, women with aortic diameter <40 mm can have a vaginal delivery (5), 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).

Conclusion

In conclusion, as recommended by the Heart Disease and Pregnancy Study Group Statement (2006), all women with heart disease should be assessed as soon as possible by a multidisciplinary team ("the obstetric team specialised in management of high risk pregnancy") of obstetricians, cardiologists and anaesthetists, but also neonatologists and intensivists, because some women will deliver preterm infants and some women will need intensive care.
The multidisciplinary team's task are to determine the frequency and content of antenatal care, by the risk stratification of the pregnant women with hearth disease, and the timing, place and mode of delivery to obtain the best result in terms of health for the woman and her baby.

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