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Woman with Marfan syndrome in pregnancy: good maternal and fetal outcome – a case report and literature review

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Summary

Purpose: Marfan syndrome (MFS) is an autosomal dominant genetic disorder of the connective tissue associated with progressive dilation of the aorta and a potential risk for aortic dissection. Objective of this study was to review the successful management of one high-risk pregnancy to term complicated by MFS. *Material and Methods:* Authors consulted the most important scientific databases investigating the influence MFS on pregnancy, analyzing fetal and maternal complications, gestational age at the time of delivery, labor, the postpartal fetomaternal complications, and neonatal and maternal outcome. *Results:* Obstetric complications associated with MFS may also include preterm delivery, preterm prelabor rupture of the membranes, cervical incompetence, and postpartum hemorrhage. In pregnancies complicated by MFS, the most common fetal and neonatal complications are preterm birth, small for gestational age (SGA), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), fetal demise, perinatal mortality, and neonatal mortality (up to one month of life). *Conclusion:* The control of most high risk pregnancies, as this one complicated by MFS, must be multidisciplinary. The present authors' attempt was to review the important aspects of the evaluation and management of a successful outcome of a pregnancy complicated by MFS.

Key words: Marfan syndrome; Pregnancy; Delivery; Maternal outcome; Neonatal outcome.

Introduction

Marfan syndrome (MFS) is an autosomal dominant genetic disorder. It involves a mutation to the gene on chromosome 15, which makes protein fibrillin-1, resulting in an abnormal connective tissue [1]. In 1896, Dr. Antonie Bernard-Jean Marfan, a French pediatrician who had a five-year-old daughter that had elongated fingers and toes as well as limbs, was the first who described, and therefore discovered, the characteristics of the disease [2]. However, in 1986, fibrillin-1 was discovered, the major constituent of microfibrils, which are the components of the extracellular matrix as well as of the elastic fibers.

About one in 3,000 to 10,000 individuals has MFS. The occurrence of MFS is independent of gender [3], and its diagnosis is based on the revised Ghent criteria [4]. Individuals with MFS tend to be tall and thin, with long arms, legs, fingers, and toes. They also typically have flexible joints, and scoliosis is diagnosed in most of them. The most serious complications involve the heart and aorta, with an increased risk of mitral valve prolapse and aortic aneurysm**.** Other commonly affected areas include the lungs, eyes, bones, and the covering of the spinal cord [5]**.**

Normal pregnancy is associated with the dilatation of the aorta and increased aortic compliance. During the third trimester, the maximum diameter is reached, but still six weeks postpartum the diameter remains enlarged by an average of 1 mm. Donelly *et al.* was the first author who showed the significant increase in aortic growth in women with MFS during pregnancy [6]. Nollen *et al.* confirmed that hypertension and aortic regurgitation were the main etiological factors for rapid aortic growth [7]

Only two prospective studies have been performed to assess the impact of pregnancy on aortic growth and aortic complications in women with MFS [8, 9]. The European guideline (2010) recommends the avoidance of pregnancy, if the aortic root diameter exceeds 40 mm with aortic dilatation [10]. In patients who already have moderate to severe mitral regurgitation before pregnancy, the most common complications are supraventricular arrhythmias and heart failure [11]. Obstetric complications associated with MFS may also include preterm delivery, preterm prelabor rupture of the membranes, cervical incompetence, and postpartum hemorrhage. Finally, in pregnancies complicated by MFS, the most common fetal and neonatal complications are preterm birth (delivery after 24 and before 37 completed weeks of gestation), small for gestational age (SGA – birth weight less than fifth customized centile), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), fetal demise (intrauterine death after 20 weeks

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of gestation), perinatal mortality (stillbirth after 24 completed weeks of pregnancy and neonatal death up to one week after birth), and neonatal mortality (up to one month of life) [12].

Case Report

Authors consulted the most important scientific databases investigating the influence MFS on pregnancy, analyzing fetal and maternal complications, gestational age at the time of delivery, labor, the postpartal fetomaternal complications, and neonatal and maternal outcomes. Patient was enrolled in the study upon providing informed consent. Patient was informed about maternal-fetal complications in pregnancy, such as gestational hypertension, preeclampsia, intrauterine growth restriction, as well as congenital fetal heart defects, and the relation of MFS to short-term perinatal outcomes (prematurity, RDS, etc.).

A 38-year-old Serbian nullipara with MFS and degenerative heart diseases (aneurysmatic dilatation of the aortic root, mitral regurgitation, and prolapsus mitral valve) and Hashimoto thyroiditis was presented to the tertiary center in her eighth gestational week. She reported a family history of MFS; her father was affected. This woman was diagnosed with MFS (Ghent classification: thumb sign +, wrist sign +, aortic dilatation) and Hashimoto's thyroiditis when she was 13-years-old. The patient had regular cardiac evaluation, every three weeks beginning from her 24th week of gestation. Regarding the MFS patient data, the aortic root diameter pre-pregnancy (as measured at echocardiography), LV dimensions and function, and aortic root diameter during pregnancy (at serial echocardiographic assessments) were gathered. The aortic root diameters were measured at the four standard levels ('annulus', sinus of valsalva, sinotubular junction, and ascending aorta). The echocardiogram revealed good cardiac function with mild mitral regurgitation and slight dilatation of the aortic root from 27 mm in 12 weeks to 30 mm in 32 weeks of gestation, as well as the dilatation of aortic bulbus 44-46 mm and a. ascedens from 36 to 39 mm. Cardiac ejection fraction was above 60% in the eighth week of gestation, and decreased to 51% at the term of pregnancy. The patient was treated with beta blockers, such as Verapamyl 40 mg, orally two doses throughout her pregnancy. She had regular endocrinology evaluation of thyroid function and was treated with euthyrox 125 mg, orally two doses every 12 hours. Meticulous blood pressure control should be maintained throughout the antenatal, perinatal, and postpartum periods.

Because of her advanced maternal age of over 35 years, the patient had an evaluation of cell-free fetal DNA in the sample of venous maternal blood at 12 weeks of gestation in order to determine the fetal karyotype. The result of the cell-free fetal DNA analysis reported a normal female karyotype. The analysis of DNA is not available for MFS diagnosis in embryos in our genetics laboratory.

Ultrasound examinations were performed monthly. Detailed scannings of the fetal anatomy for associated anomalies (particularly the digits and bones) and cervical length were within normal limits. The fetal biometry was consistent with the gestational age until 36 weeks of gestation, when a difference was diagnosed between the menstrual and ultrasound age of pregnancy. Doppler examinations were performed from the 28th week of gestation twice a month until the 32nd week of gestation, and twice weekly up to delivery. The parameters of biophysical profile (BPP) did not determine fetal hypoxia, nor did the indices of umbilical circulation (pulsatility and resistance indexes). The Non-Stress test (NST) was reactive from 34 weeks of gestation up to delivery. Fetal echocardiography was performed in the 24th and 28th week of gestation. The use of 2D images to examine the chambers and blood vessels of the heart, Doppler to check the valves, and color Doppler to examine the blood flow in the heart and blood vessels did not determine any structural cardiac defect.

The echocardiography in the 36th week of gestation determined a slight decrease in cardiac ejection fraction up to 51%. Thus, it was decided to hospitalize the patient for close cardiac and fetal monitoring. In her 37th week of gestation, the patient underwent an elective cesarean section under general anesthesia. A female neonate was born, with a birth weight of 2600 grams and an Apgar score 9/9. The newborn had no characteristics of MFS. No other congenital abnormalities were detected.

The woman was transferred to a maternal intensive care unit (MICU) after the cesarean section. The duration of stay in MICU was two days. The postpartum course was normal. She was treated with antibiotic prophylaxis of bacterial endocarditis (ampicillin and gentamycin), as well as with anticoagulant prophylaxis (low molecular weight heparin, 5000 IU twice a day) for pulmonary embolism since her first inspection in the unit of intensive care.

On the seventh day after delivery she was discharged with heparinic therapy for five weeks (a total of six weeks) and antibiotic therapy (ampicillin 2 gr/24 h, intramuscular + gentamycin 120 mg/24 h intramuscular for seven days). The last echocardiogram was performed on the 21st day after delivery, indicating an unchanged dilatation of the aortic bulbus 44-46mm, and a. ascedens from 36 to 39mm. Beta-blocking agents are excreted in breast milk, and can be used in nursing mothers when required.

Discussion

In pregnancies complicated by MFS, the two major issues are: the risk of transmission of MFS to the fetus and the risk of cardiovascular complications in the 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 genetic counseling before conception. The present authors are not sure that this patient, transferred to their unit during pregnancy, had received any pre-pregnancy counseling, or whether she avoided counseling.

An echocardiogram revealed mitral valve prolapse, mitral valve regurgitation, left ventricular dilatation, decreased cardiac ejection, mild aortic root dilatation, as well as aortic root and a. ascedens dilatations in the pregnancy of this woman. Aortic root dilatation alone is the most common cause of morbidity and mortality. The growth of the aortic root is a normal phenomenon in healthy women during pregnancy. The maximum diameter is reached during the third trimester, but still six weeks postpartum the diameter remains enlarged by an average of 1 mm.

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 estrogen, and also by the hyperdynamic hypervolemic cir-

culatory state of pregnancy, which is maximal in the last trimester or within a week after delivery. It was confirmed by the study of Donnelly *et al.* [6], the first prospective study that showed a significant increase in aortic growth in women with MFS during pregnancy compared with the baseline.

Pregnancy complicated by MFS remains a controversial subject. The 2010 thoracic aortic disease guidelines advocate the avoidance of pregnancy, if the aortic root diameter exceeds 40 mm, and recommend prophylactic aortic root replacement in those who desire pregnancy [11]. However, there is no agreement between the European and Canadian societies on cardiology guidelines, which report an aortic root diameter of < 45 mm to be considered safe [13]. Beta-blockers were administered throughout the pregnancy, as confirmed protection against long-term dilatation of the aortic root.

The non-invasive method of karyotyping from free fractions of fetal DNA in a sample of maternal venous blood was performed in the present patient. Normal fetal female karyotype did not confirm the absence of MFS in the fetus. In 1996, the first preimplantation genetic testing therapy for MFS was conducted on early-stage IVF embryo cells, and those embryos affected by the Marfan mutation [14] were discarded. Because > 500 mutations have been reported in FBN1, almost every patient has a unique mutation. There is still no efficient diagnostic test, and the present patient had no genetic testing for fetal MFS. Moreover, as indicated above, molecular diagnosis cannot predict the clinical severity of the disease [15].

Fetal echocardiography used from 24th to 32th week of gestation for diagnosing cardiac manifestations of MFS in the fetus, such as atrioventricular valve regurgitation, and the dilatation of the aortic root and pulmonary artery. Sonogram confirmed that the lengths of the humerus, radius/ulna, femur, and tibia/fibula are similar and increase linearly with gestation.

In the present case, beta-blockers were administered throughout pregnancy. The balance between safeguarding the prognosis for the mother and the avoidance of fetal growth restriction would require long-term follow-up in order to fully investigate this. Fetal hypoxia and acidosis, as well as intrauterine growth retardation were the most frequent fetal complications in pregnancies complicated by MFS. Doppler velocimetry of the umbilical and cerebral arteries provides a non-invasive measure of the fetoplacental hemodynamic state. The abnormality of the Doppler index in the umbilical artery correlates to fetal hypoxia, acidosis, and adverse perinatal outcome. Fetal biophysical profile testing is indicated in pregnancies at risk of fetal compromise, as in pregnancies complicated by MFS. Testing should be performed one or more times per week, depending on the clinical situation. This emphasizes the importance of prospective multicentric registries for rare conditions, such as MFS, for determining optimal management policies [12].

In pregnancies complicated by MFS, the most common fetal and neonatal complications are preterm birth, but the present patient delivered at term at 37.2 weeks of gestation. Regarding delivery, a woman with an aortic diameter < 40 mm can have a vaginal delivery. If vaginal delivery is planned, forceps or vacuum delivery is often utilized to decrease maternal expulsive efforts during the second stage of labor. MFS patients with an aortic diameter > 40 mm or progressive dilatation should have an elective cesarean section with epidural or general anesthesia, because they are at high risk of aortic dissection secondary to the hemodynamic changes associated with vaginal delivery (an increase in both systolic and diastolic blood pressure) [16]. Planned cesarean delivery rather than vaginal delivery is advised, if there is a history of previous dissection, or if there is evidence of progressive dilation of the aorta during pregnancy, as it was the case with the present patient. There is no definitive recommendation for either general or regional anesthesia. Regardless of anesthetic technique, care should be taken to prevent sudden increase in myocardial contractility, producing an increase in aortic wall tension, which could lead to aortic dissection.

The endocarditis prophylaxis at the time of labor and postpartum is not recommended in women with MFS. However, some experts continue to administer antibiotics because they believe that the risks of adverse reactions to antibiotics are smaller than the risk of developing endocarditis, which would have major health consequences. The present authors continued with antibiotics prophylaxis after cardiological recommendation.

The risk of aortic dilatation and dissection extends into the postpartum period. Pregnancy-related cardiovascular changes do not fully return to baseline until about six months postpartum. Serial echocardiography was offered for patients with MFS. In the present patient, the first postpartum echocardiogram did not report significant changes when compared with the last prepartal echocardiogram.

Conclusion

The control of most high risk pregnancies was multidisciplinary. What does this entail? Multidisciplinary care, involving specialists familiar with MFS, should be emphasized before, during, and after pregnancy with the involvement of maternal fetal medicine, genetics, cardiology, cardiothoracic surgery, anesthesia, and other specialties on a case-by-case basis. The present authors' attempt was to review the important aspects of the evaluation and management of a successful outcome of a pregnancy complicated by MFS.

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