

MARFAN SYNDROME IN PREGNANCY: A CASE REPORT

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Marfan syndrome, which was originally described in the 19th century, is an autosomal dominant connective tissue disease associated with the mutation in the fibrillin-1 gene located on chromosome 15 (locus 15q, 21,1).¹ It is a multi-systemic disorder which primarily involves the musculo-skeletal, cardiovascular and ocular systems, but usually not together simultaneously. It carries high risks in pregnant women due to its probable complications. In this report, although the complications related to Marfan syndrome did not develop in the mother or the fetus, probable associated problems are reviewed in the light of the relevant literature.

Case Report

A 36-year-old gravida 2, parity 1 woman, who was unsure of the date of her last menstruation but was 22 weeks pregnant by ultrasonography (US) measurements, was referred to the High-Risk Pregnancy Clinic of Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey, with the diagnosis of Marfan syndrome with pregnancy. The patient had been diagnosed with Marfan syndrome at the age of 15 years, and was married to a third-degree relative. Marfan syndrome had been diagnosed in her first child as well. According to family history, there was no one else with Marfan syndrome. In addition to typical bilateral lens subluxation, arachnodactyly and long and thin extremities were found in the patient.

As the patient presented to the hospital at an advanced stage of the pregnancy, it was not possible to predict whether the fetus was influenced by methods of genetic analysis, but antepartum ultrasonographic evaluations were made and no pathology was found in the fetus. Gestational diabetes was detected in the 28th week of pregnancy and since blood sugar level could not be regulated by diet, insulin treatment was instituted. Echocardiography examinations were performed twice during the pregnancy period—the first was at the time of admission and the

second at the seventh month—and were reported to be normal. The aortic root measured 31 mm at first admission, and the dimension of the aorta was the same in the 28th week of pregnancy, which was considered to be normal.

The patient delivered at term by cesarian section, a male baby weighing 3720 g with the fetal indication of cephalopelvic disproportion. Bilateral tube ligation was carried out with respect to her demand to be surgically sterilized. No complication was seen in the intra- or postoperative period. Morphological findings suggestive of Marfan syndrome were not seen in the baby on follow-up examinations at the first and third months. No pathology was observed in the cardiovascular evaluation of the mother which was made at sixth weeks postpartum.

Discussion

Marfan syndrome is an autosomal dominant connective tissue disease with a high degree of penetrance. Approximately 15%-20% of cases are sporadic.^{2,3} It occurs at equal rates in both sexes, and there is no racial preponderance. The prevalence of Marfan syndrome is 4-6 per hundred thousand.⁴ It is a rare disease and particular care should be taken in the condition of pregnant women because of two factors. First, there is the risk of aortic dissection in the mother, and second is the 50% likelihood of risk to the fetus. In the case presented here, the lack of aorta aneurysm due to cardiac involvement was a favorable sign prognostically.

In the absence of family history, at least two other systems must be involved with one major manifestation (ectopia lentis, aortic dilatation/dissection or dural ectasia) in addition to the musculoskeletal system.

Mitral valve prolapse (MVP) is present in 90% of patients with Marfan syndrome. Aortic dilatation due to the weakening of the aorta media can start as early as the first year of life. However, it may be delayed until the fifth decade of life, and usually occurs first in the coronary sinus.⁵ Because of the variation in the clinical presentation of this disease, cardiovascular system must be examined in respect of its danger in pregnancy. The involvement of the cardiovascular system (MVP, mitral regurgitation, aorta root dilatation, and aorta failure) accounts for the 90% of deaths attributed to Marfan syndrome. Expectation of life is

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low in these cases and women are predisposed to early death while in their reproductive ages. The mean age of death is early thirties, and the risk of complications is high for pregnant women. Therefore, in cases without cardiovascular involvement, pregnancy at earlier ages before involvement starts should be recommended. In women with Marfan syndrome, even though there may not be cardiovascular problems in the preconception period, the risk of aortic dissection during pregnancy is markedly increased. Aorta root dilatation may be a sign of risk, but dissection may occur without pronounced dilatation.⁶

The size of the patient's aorta at the time of pregnancy is an important risk indicator. In a study by Sutiner and Piironein, of 15 fatal aorta dissection cases among pregnant women, 13 were observed to have Marfan syndrome.⁷ Among the causes of vascular aneurysm and increase in dissection are alterations in artery wall due to the increase in circulating estrogen level, cardiac output, intravascular volume and physiological increase in blood pressure. Healthy women or women with Marfan syndrome who have little or no cardiovascular involvement prior to pregnancy may readily tolerate these changes and pregnancy is safe. It can be seen from the previous literature that the majority of maternal deaths reported in patients with Marfan syndrome, occurred in those with previous cardiac involvement.

It is reported that rate of dissecting or ruptured aneurysm increases in pregnancy and that this fatal complication occurs predominantly in the third trimester of pregnancy due to increasing stress on the aorta, it may also be seen during any stage of pregnancy, labor or puerperium.³ Pyeritz investigated 74 pregnancies of 32 pregnant women with Marfan syndrome and reported death or aorta dissection in 20 patients during pregnancy or puerperium.⁸ Women with minimal involvement may tolerate pregnancy without serious problems. It has been reported by Elkayam et al. that cardiac complications developed in 10 of 15 pregnant women with Marfan syndrome. In eight, aorta dissection developed, with two deaths.⁹ In the follow-up of 91 pregnancies of 36 women with Marfan syndrome who did not undergo any echocardiographic examination and who did not have any symptoms related to cardiovascular disorder, aortic events occurred in six women, aorta dissection and progressive aorta root dilatation developed in four and two women respectively, and eight women showed cardiovascular involvement during the 10 years following their last pregnancies.²

Aortic dilatation larger than 40 mm in diameter, or cardiovascular complications in patients with mitral valve dysfunction may lead to life-threatening risks, and pregnancy is contraindicated in these patients. If pregnancy occurs, transthoracic echocardiography evaluation should be carried out monthly for the first six months and twice monthly thereafter, and the diameter of the aortic root and cardiac valve functions should be evaluated. If aortic

dilatation has reached 5.5 cm., surgery is indicated and it can be performed even in pregnancy. For the ideal treatment of hypertension, which is a risk factor for aortic dissection in pregnancy, β -blockers should be prescribed and in those with findings of dilatation, prophylactic β -blocker treatment should be considered after the mid-trimester in order to decrease the rate of aortic dilatation and prevent rupture.¹⁰ In the case reported here, hypertension did not develop and no treatment was required.

Therapeutic abortion should be recommended to pregnant women with Marfan syndrome having moderate or severe cardiovascular disease. If surgical intervention is indicated due to cardiovascular disease, the first line of treatment is termination of pregnancy with cesarian section and then cardiovascular surgery should be performed.

Marfan syndrome may be responsible for cervical incompetence, abnormal placentation and postpartum hemorrhage. There are risks of increased spontaneous abortion, premature rupture of membranes and preterm labor. Of 106 pregnancies of women with Marfan syndrome, spontaneous abortion and premature labor has been reported at the rates of 21% and 12%, respectively.¹¹ In another study of 91 pregnancies of 36 women with Marfan syndrome, 75 resulted in live births, 2 in first trimester abortion, 6 in second trimester abortion, 1 in stillbirth and 1 in intrauterine exitus. Seven pregnancies were terminated, and postpartum hemorrhage occurred in 7 patients. In another study, spontaneous abortion rate was reported at 16%.¹²

Prenatal Diagnosis

If gene mutation is present, prenatal diagnosis of Marfan syndrome is possible with chorion villus sampling and amniocentesis, using genetic linkage analysis with fibrillin specific marker. Godfrey et al. has reported successful results in the prenatal diagnosis of the patients with Marfan syndrome.¹³ Although it is not possible to detect mutation in all cases, blood and skin may be sampled for the investigation of gene mutation in lymphocytes and skin fibroblasts. Prenatal screening with ultrasound of cardiovascular and joint abnormalities may be possible in the second half of pregnancy. In routine ultrasound at week 34, oligohydramnios and cardiomegaly may be demonstrated. Fetal echocardiography has typical features especially in those with family history of Marfan syndrome, regurgitation of atrioventricular valve, and dilatation of aortic root are findings that are suggestive of the condition.⁴

In patients with aorta diameter larger than 4 cm, vaginal delivery is recommended with epidural anesthesia. Epidural anesthesia helps to restrict the increase in systolic and diastolic blood pressure due to pain and anxiety during uterine contractions. Though Marfan syndrome does not constitute an indication for cesarian section by itself, elective section with epidural anesthesia is recommended in those with aortic involvement and aorta diameter >4cm. In

cases without aortic involvement, obstetrical indications are valid for cesarian section. If surgery is indicated due to cardiovascular disease, delivery with section is recommended. If general anesthesia is to be used, agents stimulating hypertension should be avoided in induction. Although the incidence of bacteremia is reported to be very low (0% -5%) in uncomplicated vaginal deliveries, many centers give prophylactic antibiotic treatment to women with Marfan syndrome associated with MVP and mitral regurgitation.⁴

In differential diagnosis, especially homocystinurea, congenital contractural arachnodactyly, cutis laxa syndrome should be considered. Patients with Marfan syndrome should undergo cardiologic and genetic examination preconceptionally and should be informed of the obstetrical and cardiological risks, and the possibility that 50% of their children may suffer from Marfan syndrome.

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