Marfan Syndrome and Pregnancy-A Case Report and Review of the Literature

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Marfan syndrome is an autosomal dominant disorder characterized by abnormalities of skeletal, cardiovascular and ocular systems. Pregnant women may suffer from hemodynamic stress resulting from increased cardiac output and structural changes in the aortic wall leading dilatation and dissection of the aorta. It is usually advised to avoid pregnancy to women with Marfan Syndrome however with advances in medicine, successful pregnancies with Marfan Syndrome are reported. Therefore, the aim of this study is to review the literature over a case with a successful management during pregnancy.

Key Words: Marfan Syndrome, Pregnancy, Follow-up

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Introduction

Marfan syndrome (MFS) is an inheritable autosomal dominant disorder characterized by abnormalities of skeletal, cardiovascular and ocular systems. In 26% of the cases, the syndrome results from a new mutation.[1] Women with MFS have 50% probability of transmitting the syndrome to their offspring. During pregnancy, increased cardiac output and structural changes in the aortic wall causes hemodynamic stress.[2] This stress may lead to dilatation and dissection of the aorta which may cause maternal and fetal mortality and morbidity. Not only cardiovascular but obstetrical complications such as preterm deliveries, preterm premature rupture of membranes and fetal loss are also increased in MFS.[3] So in the past, it was usually advised against pregnancy but with advances in medicine, successful pregnancies with MFS are reported. If patient with MFS becomes pregnant, the major determinant of the outcome is the severity of cardiovascular disease. This case report is about a successful pregnancy despite worsening cardiovascular conditions.

Case Report

A 26 years old primigravid was referred to our clinic from a primary health center due to pregnancy with MFS. She was 22 weeks pregnant at the admittance. Her brother had been diagnosed as Marfan Syndrome 4 years ago after admitting to emergency department because of a dissecting aorta aneurysm. She was then diagnosed as Marfan syndrome. She did not have aortic dissection history. Before pregnancy, she had been examined in a cardiology center and aortic root diameter was found to be 44 mm. in echocardiography. At 12 week gestation, the measurement was repeated in the same center and aortic root diameter was found to be 51mm. When she presented to our institution, her physical examination revealed long stature (1 meter 76 cm) and arachnodactly. The ultrasonographic examination revealed a 22 weeks old fetus and fetal abnormality screening was normal. The patient was discussed in the perinatology council and was consultated to adult and pediatric cardiology and cardiovascular surgery departments. The possible complications, maternal and fetal morbidity and mortality risks were discussed with the patient and her family. Informed consent was taken. Fetal cardiologic examination as well as maternal ophthalmologic testing was found to be normal. In the echocardiography examination, aortic root diameter was 51mm, third degree aortic valve and first degree mitral valve insuffiency was noted. She was hospitalized and metoprolol tartarate (Beloc™) 250 mg bid was started. 1 month later at 26 gestational weeks, aortic root diameter was 54 mm. in echocardiography examination but she had no symptoms. In ultrasonographic examinations fetal growth curve was in normal limits and Doppler indices were normal. In the perinatology council, aortic valve replacement was discussed and the family was informed about the operation and possible complications but decision was close follow-up. Each week, echocardiography and fetal ultrasonography were repeated and the family was informed. She was hospital-

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ized until 34 weeks, no further dilatation was noticed in echocardiography and fetal ultrasonography revealed normal fetal growth. At 34th week, at the council, delivery options were discussed and after the informed consent was taken, cesarean delivery was decided. The family declined simultaneous aortic root replacement with cesarean delivery. Bethametasone (Celestone™) in 2 doses was applied. Cesarean delivery was done at the 34 week under general anesthesia and 2070 gram male fetus was delivered. She was followed in cardiovascular intensive care unit for 1 day and then was followed in the cardiovascular ward. The aortic root replacement was discussed with the family again and 1 month later she underwent a successful Bentall procedure. 6 months after the procedure, she was healthy and asymptomatic.

Discussion

Marfan syndrome is an autosomal dominant condition and the incidence is approximately 1/5000. [4] Marfan syndrome is caused by mutations in the fibrillin-1 gene (FBN1) which is located on chromosome 15q21. More than 400 mutations have been described and 25% of cases are due to de novo mutations. [5] The syndrome encompasses a wide variety of symptoms[6] and in some cases the diagnosis may be delayed until aortic dissection occurs. The cardinal clinical features of the syndrome are the results of the involvement of ocular, cardiovascular and musculoskeletal systems. The diagnostic criteria accepted for Marfan syndrome is known as Ghent nosology and clinical features of organ systems are used for diagnosis. [7] It is postulated that direct hormonal effect on the aortic wall, increase in cardiac output which causes increased shear stress on the aorta are the causes for increased risks. The cardiovascular complications of Marfan syndrome include mitral valve prolapse and regurgitation, pulmonary artery dilatation, left ventricular dilatation and cardiac failure. Aortic dissection, rupture, chronic regurgitation and congestive heart failure are primarily responsible for a reduction in expected lifespan by as much as 40% in these individuals with a mean age at death of 32 years.[8,9] However, life-span of Marfan patients is now comparable to normal individuals with the usage of ß-blockers and preventive aortic surgery.[10] In some patients, ß-blockers reduce the rate of aortic dilatation and prophylactic aortic root surgery is superior to emergency surgery for dissecting aneurysm.[11] Cerebral vascular accidents are also more likely in Marfan syndrome patients.[12]

The most life threatening complication of MFS is thoracic aortic aneurysms leading to aortic dissection, rupture, or both. These fatal complications may occur at any time during pregnancy but third trimester has the highest risk. Maternal mortality may be as high as 50% in case rupture occurs.[13] Aortic valve incompetence usually arises in context of dilated aortic root and risk of aortic rupture increases substantially when diameter of sinus of Valsalva is >5.5 cm.[14-15] Risk factors for aortic dissection in Marfan syndrome include aortic diameter >5 cm, aortic dilatation extending beyond the sinus of Valsalva, rapid rate of aortic dilatation (>5% per year, or 2 mm/year in adults), and family history of aortic dissection.[11]

Pregnancies in women with Marfan syndrome have a 4.5% risk of aortic dissection.[16] But this is not the mere complication. Preterm delivery, preterm premature rupture of membranes, perinatal mortality[3] and postpartum hemorrhage[13] are also increased in pregnant Marfan syndrome patients. The rate of aortic dilatation is greater in women who have been pregnant with an aortic root diameter of more than 4 cm, than in women who have remained childless, or women with children whose aortic root is less than 4 cm.[3] Pregnancy increases the risk of aortic dissection in general population but when there is accompanying Marfan syndrome, the risk is further increased. This further increase is normalized after delivery so pregnancy is not associated with an increased life-long risk for aortic dissection.[17,18] Rossiter et al.[19] observed no apparent worsening of cardiovascular status of Marfan syndrome patients after pregnancy as well. Women with pre-existing cardiac disease are most vulnerable to complications.[11]

For pregnant patients with Marfan syndrome, the risk for dissection is low when there is minimal cardiac involvement and aortic root diameter is smaller than 40 mm.[20-22] Normal values for aortic root diameter in an adult pregnant or non-pregnant women range from 2.0 cm - 3.7 cm.[8] In the study by Meijboom LJ et al,[18] pregnant Marfan syndrome patients were prospectively followed and aortic dissection did not occur when there was no previous aortic dissection and aortic root diameter ≤45mm. During pregnancy, when aortic root diameter dilates to 5 cm or more, as the risk of dissection is high immediate aortic replacement, early delivery or termination of pregnancy are proposed.[23] In our patient, in prepregnancy period the aortic root diameter was 44 mm, at 12 gestational weeks it was 51 mm and during the follow-up it gradually reached to 54 mm. Despite a gradual increase in the diameter, the patient was not symptomatic. In aortic replacement surgery during pregnancy, although successful results are reported,[7,24] cardiopulmonary bypass and deep hypothermia may result in fetal death[25] so it bears its own serious risks. We are in a point of view that aortic valve replacement may be an option when the aortic root diameter is >50 mm but it is not a "must"; close follow-up may be an additional option for suitable patients for who all facilities are always available so the decision should be tailored for the patient.

Labor analgesia and anesthesia for the parturient with Marfan syndrome should be tailored to the patient. In an asymptomatic patient with no cardiovascular complications and echocardiography findings, epidural analgesia may be advantageous for vaginal delivery as stress of the labor is re-

duced.[26] Spinal malalignment should be kept in mind during epidural catheterization. When cardiovascular complications are present (enlarged aorta, progressive enlargement of the aorta, aortic regurgitation), cesarean delivery is usually considered.[27,28] Meijboom LJ et al.[3] recommend vaginal delivery for pregnant Marfan syndrome patients due to increased complication risk of bleeding, infection and thromboembolism in cesarean deliveries even if they have aortic root dilatation. The choice of anesthesia depends on the status of the patient. Attention should be paid for hemodynamic alterations during endotracheal intubation and possible interaction of inhalational agents and prophylactic ß-blockers with myocardial contractility.[26]

In general, when the aortic root diameter is < 40 or 45 mm and the patient tolerates well, the patient may be followed-up in a general hospital but in our opinion all pregnant Marfan syndrome patients should be followed-up in special centers where emergency cardiac surgery facilities are available. In the best practice, the patient should be seen in the prepregnancy period and evaluated. Preconceptional counseling is very important and should be available to all Marfan syndrome patients. The problems which may be encountered and future plans of the family should be freely talked, and the risk of transmission of the condition to the offspring should be clearly explained to the family. Prenatal diagnosis of neonatal Marfan syndrome is possible by ultrasonography[28] but it's value is limited.[23] Chorionic villous sampling (CVS) or amniocentesis may be offered to the family for prenatal diagnosis. Preimplantation genetics is becoming an alternative option.[29] The patient should be consultated with a cardiologist and a cardiovascular surgeon. The aortic root dimension should be measured throughout the pregnancy on every 4-6 weeks[28] and the first measurement should be done in the prepregnancy period. Before pregnancy, all women should undergo a magnetic resonance angiogram to investigate if there is dilatation in the aortic root or in other parts of the aorta.[3] Beta-blockers should be continued throughout the pregnancy. [30] If the aortic diameter is <40-45 mm, blood pressure measurements are in normal limits, she has no symptoms and the fetal surveillance is good, the patient may be followed-up on outpatient basis but she must be aware of the potential risks and the hospital facilities should be ready available for her all the time. In cases where the diameter is > 40-45 mm, there is rapid increase in the measurements of the diameter, cardiac decompansation symptoms occur, fetal status is not suitable and she is not well cooperated for close follow-up and then the patient should be hospitalized. The family should be well informed about the possible fetomaternal complications and the consent should be taken and they should be encouraged to attend the decision taking steps.

Advances in medicine caused improved longevity and quality of life for these patients and because of this, obstetricians may encounter more pregnant Marfan syndrome patients than ever. Some guidelines discourage pregnancy when aortic root diameter is >44 mm[31] or 40 mm[32] We are in a point of view that if there are centers, where good maternal-fetal surveillance and cardiac surgical facilities are available, the pregnancy decision should be left to the patient and advices should not be very strict.

Marfan Sendromu ve Gebelik Olgu Sunumu ve Güncel Derleme

Marfan Sendromu iskelet, kardiyovasküler oküler system anomalileri ile seyreden otozomal dominant geçişli kalıtsal bir hastalıktır. Gebelikte kardiyak yükün artması ve aort duvarında olan genişleme hemodinamik strese neden olup aorta dilatasyonuna ve hatta diseksiyonuna neden olabilir. Marfan Sendromu olan kadınlara genelde gebelikten kaçınılması önerilse de tıpta olan gelişmeler sayesinde Marfan sendromu ile birlikte başarılı olarak sonuçlanan gebelikler de bildirilmiştir. Bu çalışmanın amacı, Marfan Sendromu olan bir gebeliğin başarılı bir şekilde yönetimi üzerinden litertürdeki son durumun derlenmesidir.

Anahtar Kelimeler: Marfan Sendromu, Gebelik, İzlem

References

1. Gray JR, Bridges AB, West RR, et al. Life expectancy in British Marfan syndrome populations. Clin Genet 1998; 54:124-8.
2. Anderson RA, Fineron PW. Aortic dissection in pregnancy: importance of pregnancy-induced changes in the vessel wall and bicuspid aortic valve in pathogenesis. Br J Obstet Gynaecol. 1994;101(12):1085-8.
3. Meijboom LJ, Drenthen W, Pieper PG, Groenink M, van der Post JA, Timmermans J, Voors AA, Roos-Hesselink JW, van Veldhuisen DJ, Mulder BJ; On behalf of ZAHARA investigators. Obstetric complications in Marfan syndrome. Int J Cardiol. 2006; 110(1):53-9.
4. De Paepe A, Devereux RB, Dietz HC, Hannekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996; 62:417-26.
5. Robinson P, Booms P, Katzke S, Ladewig M, Neumann L, Palz M, et al. Mutations of FBN1 and genotype-phenotype correlations in Marfan syndrome and related fibrillinopathies. Hum Mutat 2002; 20:153-61.
6. McKusick VA. Heritable disorders of connective tissue. St Louis:CV Mosby, 1972.
7. Buffolo E, Palma JH, Gomes WJ, Vega H, Born D, Moron AF, Carvalho AC. Succesful use of deep hypothermic circulatory arrest in pregnancy. Ann Thorac Surg. 1994; 58(5):1532-4.

8. Kalu G, Toplis P. Marfan syndrome and pregnancy-a district hospital perspective. J Obstet Gynaec 1999;19 (6):594-7
9. Murdoch JL,Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. N Engl J Med 1972; 286:804-8.
10. Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. Am J Cardiol 1995; 75:157-60.
11. Dean JCS. Management of Marfan syndrome. Heart 2002; 88:97-103.
12. Lind J, Wallenburg HCS. The Marfan syndrome and pregnancy: a retrospective study in a dutch population. Eur J Obstet Rep Bio 1998;2001:28-35
13. Lalchandani S, Wingfield M. Pregnancy in women with Marfan's syndrome. Eur J. Obstet Gynecol Reprod Bio 2003;110:125-30.
14. Groenink M, Lohuis TA, Tijssen JG et al. 1999. Survival and complication free survival in Marfan's syndrome: implications of current guidelines. Heart 82:499-504
15. Roman MJ, Rosen SE, Kramer-Fox R et al. 1993. Prognostic significance of the pattern of aortic root dilatation in Marfan syndrome. J Am Col Cardio 22:1470-6.
16. Chow SL: Acute aortic dissection in a patient with Marfan's syndrome complicated by gestational hypertension. Med J Aust 1993;159:760-2.
17. Pacini L, Digne F, Boumendil A, Muti C, Detaint D, Boileau C, Jondeau G. Maternal complication of pregnancy in Marfan syndrome. Int J Cardiol. 2008 Jul 14. [Epub ahead of print]
18. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJM. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study European Heart Journal 2005;26:914-20.
19. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. Am J Obstet Gynecol 1995; 173:1599-1606.
20. Pyeritz RE. Maternal and foetal complications of pregnancy in the Marfan syndrome. Am J Med.1981; 71(5): 784-90.
21. Pyeritz RE. Marfan syndrome and other disorders of fibrillin. In: Principles and practice of medical genetics, edited by Emery and Rimoins, chapter X, 1030-1158. London, Churchill Livingstone.
22. Simpson LL, Athanassious AM, D'Alton ME, Marfan syndrome in pregnancy. Curr Opin Obstet Gynecol 1997; 9(5):337-41.
23. Dean JCS. Marfan syndrome: clinical diagnosis and management. European Journal of Human Genetics 2007; 15:724-33.
24. Matsuda H, Ogino H, Neki R, Kitamura S. Hemiarch replacement during pregnancy (19 weeks) utilizing normothermic selective cerebral prefusion. Eur J Cardiothorac Surg. 2006; 29(6):1061-3.
25. Mul TF, van Herwerden LA, Cohen-Overbeek TE, Catsman-Berrevoets CE, Lotgering FK. Hypoxic-ischemic fetal insult resulting from maternal aortic root replacement, with normal fetal heart rate at term. Am J Obstet Gynecol. 1998; 179(3 Pt 1):825-7.
26. Kuczkowski KM. Labor analgesia for the parturient with an uncommon disorder: A common dilemma in the delivery suite. Obstet and Gynecol Survey 2003; 58(12):800-3.
27. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. Circulation 2005; 111:150-7.
28. Ramaswamy P, Lytrivi ID, Nguyen K, Gelb BD. Neonatal Marfan Syndrome. In Utero Presentation with Aortic and Pulmonary Artery Dilatation and Successful Repair of an Acute Flail Mitral Valve Leaflet in Infancy Pediatr Cardiol 2006;27:763-5.
29. Spits C, DeRycke M, Verpoest W, Lissens W, Steirteghem AV, Liebaers I, Sermon K. Preimplantation genetic diagnosis for Marfan syndrome. Fertil Steril 2006;86(2):310-20.
30. Shores J, Berger KR, Murphy EA, Pyerit RE. Progression of aortic root dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. N Engl J Med 1994; 330:1384-5.
31. Therrien J, Gatzoulis M, Graham T, Bink-Boelkens M, Connelly M, Niwa K, Mulder BJM, Pyeritz RE, Perloff J, Somerville J, Webb GD. Canadian Cardiovascular Society Consensus Conference 2001 update: Recommendations for the Management of Adults with Congenital Heart Disease-Part II. Can J Cardiol 2001;17:1029-50
32. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J 2003;24:761-81.