P R A C E K A Z U I S T Y C Z N E

położnictwo

Three pregnancies in a Marfan syndrome patient after a mitral and tricuspid valve surgery

Opis przebiegu trzech ciąż u kobiety z zespołem Marfana po kardiochirurgicznej korekcji zastawki mitralnej i trójdzielnej

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Abstract

Marfan syndrome is an autosomal dominant disorder of connective tissue with up to 25% of cases related to a spontaneous mutation. It has been associated with perinatal loss, preterm labor, and, potentially, a rupture of the maternal aortic arch. We present a case of a woman diagnosed with Marfan syndrome after a miscarriage of her first pregnancy. At the time of diagnosis she had mild aortic bulb dilation and insufficiency of the mitral and tricuspid valves. She underwent cardiosurgical correction, after which she had two uneventful pregnancies.

This case suggests that preconceptional correction of valve defects in women with Marfan syndrome may decrease the risk of cardiac decompensation during future pregnancies. Additionally, close clinical follow up and the appropriate use of beta-adrenergic blockade may decrease the risk of aortic rupture, a significant risk factor for mortality in pregnant women.

Key words: **Marfan syndrome** / **perinatal loss** / **preterm labor** /

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Streszczenie:

Zespół Marfana jest chorobą tkanki łącznej dziedziczoną w sposób autosomalny dominujący. W ok. 25 % przypadków dochodzi do spontanicznej mutacji. Zespół ten jest związany z utratami ciąż, porodem przedwczesnym oraz niesie potencjalne ryzyko pęknięcia łuku aorty u matki. W pracy opisano kobietę, u której rozpoznano zespół Marfana po poronieniu w pierwszej ciąży. W momencie rozpoznania miała łagodne poszerzenie aorty oraz niedomykalność zastawki mitralnej i trójdzielnej. Po pierwszej ciąży u pacjentki wykonano operację kardiochirurgiczną, po której przebyła bez powikłań dwie kolejne ciąże.

Przypadek ten sugeruje, iż przedkoncepcyjna korekcja kardiochirurgiczna może zmniejszyć ryzyko powikłań kardiologicznych podczas ciąży u kobiet z zespołem Marfana. Dodatkowo właściwe użycie beta blokerów może zmniejszyć ryzyko pęknięcia aorty, które jest przyczyną wysokiej śmiertelności kobiet z zespołem Marfana podczas ciąży.

Słowa kluczowe: **zespół Marfana** / **utraty ciąż** / **poród przedwczesny** /

Introduction

Marfan syndrome (arachnodactyly), described for the first time in the 19th century, is a genetic disorder of connective tissue with family occurrence of 75% [1, 2]. It is caused by mutation of a gene coding fibrillin (FBN1) - macromolecular glycoprotein 350kDa, the component of microfibrils, located at chromosome 15q21.1 [2, 3, 4, 5]. This mutation is found in 90% of patients with Marfan syndrome, and the risk of conveying the mutation to the fetus is 50% (autosomal dominant inheritance) [6, 7, 8]. The incidence of Marfan syndrome varies from 1 in 3000 to 1 in 20000 cases [9, 10], and the diagnosis is based on clinical features with genetic confirmation. On the clinical examination we can found multiorgan disturbances in the skeletal, cardiovascular, and ocular systems.[1].

McKusick described the triad of symptoms observed in this syndrome [11].

1. Slim, asthenic posture, disproportionately long extremities in comparison to the trunk, arachnodactyly, chest deformation decreasing respiratory reserve and ventilation, kyphoscoliosis, and flexibility of the joints.
2. Aortic bulb dilation and/or aortic wall dissection, aortic valve insufficiency, prolapse of the leaflet of mitral valve and mitral insufficiency [4, 12]
3. Lens ectopy and myopia [7, 13]

Physical findings include striae distensae on thighs and buttocks, recurrent inguinal, umbilical or postsurgical hernias, and they may present with spontaneous pneumothorax [9, 14]. Reported perinatal complications include: spontaneous abortion, isthmo-cervical insufficiency, preterm labor, intrauterine growth restriction (IUGR), preterm rupture of membranes and increased fetal mortality [7, 12, 15].

The main cause of increased mortality in pregnant women with Marfan syndrome is the development of an aortic aneurysm of Stanford type A, its dissection and rupture [16, 17, 18, 19, 20]. An increased cardiac contractility, heart rate, and vasorelaxing action of gender hormones are the predisposing factors for these complications [12, 18, 21, 22, 23, 24].

We describe a woman who was diagnosed with Marfan syndrome after her first pregnancy resulted in a miscarriage. At the time of diagnosis she had mild aortic bulb dilation and insufficiency of the mitral and tricuspid valves. She underwent cardiosurgical correction, after which she had two uneventful pregnancies.

Case report

We admitted to the Clinic a woman in her mid 20s, at 22 weeks gestation, because of spontaneous abortion *in tractu* due to isthmo-cervical insufficiency. During the miscarriage a brief, self-limited episode of atrial fibrillation was observed but without any symptoms of respiratory or cardiac decompensation. We suspected the patient had been suffering from Marfan syndrome since childhood, however no disorders were found during annual medical check-ups at school. She had never undergone electrocardiography and echocardiography before. Slim body structure (weight 70kg, height 184cm, BMI 21.0kg/m^2, funnel-shaped chest and disproportionally long lower extremities with elongated fingers and toes) drew our attention. Striae distensae of the skin were present on the abdomen, buttocks and thighs. The echocardiogram revealed mild mitral regurgitation with parasystolic prolapse of anterior leaflet and mild aortic regurgitation with dilation of the aortic bulb. In 1996 the diagnostic criteria of Marfan syndrome were established and the diagnosis can be made in patients who have four of the eight major criteria [25].

Our patient had five major criteria: 1) decreased ratio of higher to lower half of the body, 2) scoliosis >20^o, 3) arachnoid toes, 4) the medial ankle being pushed out due to platypodia, and 5) dilation of the ascending aorta. Her minor criteria were: prolapse of mitral leaflets, striae distensae not connected with fluctuation of body weight or the pregnancy.

After the miscarriage, we referred the patient to the Department of Cardiosurgery. Reconstruction of the mitral valve was not possible due to the atrophy of chordae tendinae, so it was replaced with an artificial Carbomedix 31 valve, and similar chordae atrophy of the tricuspid valve was corrected by the De Vega method. After the operation she was started on nadroparin (a low molecular weight heparin) and later acenocoumarol was administered. The postoperative left ventricular dimensions were 45mm in contraction and 55mm in dilation (N: 22-40mm and 35-57mm, respectively). The left ventricle was thickened with the interventricular septum measuring 15mm in dilation (N:6-11mm). The ejection fraction was <50%. The mean gradient measured at the artificial mitral valve was 5mmHg and the estimated valve areas was 2.9cm^2. The regurgitant wave at the tricuspid valve was small (+). The aorta was normal.

An ultrasound performed two years later showed concentrically thickened muscle of the left ventricle (11/19mm)

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with normal size and contractility. The peak gradient across the artificial mitral valve was 8.3mmHg with a mean of 4.1mmHg. The aortic diameter was 33mm.

Three years after the surgery the patient became pregnant. Acenocoumarol was changed to nadroparin, 3800 IU subcutaneously/day. At 23 weeks gestation we applied a cervical suture using the Mc Donald technique because of isthmo-cervical insufficiency. The patient did not develop any hemodynamic disturbances during the pregnancy. Upon recommendation, she underwent multiple check-ups. Blood pressure and heart rate were normal. The measurement of the aortic bulb showed dilation up to 40mm. At 37 weeks gestation she delivered a male newborn (weight 2550g, length 49cm, 5-minute Apgar score of 8) by Cesarean section (patient preference). The follow up of the baby revealed frequent upper respiratory tract infections and a heart murmur. Prolapse of the mitral and tricuspid valves was diagnosed in the second year of his life, and Marfan syndrome was diagnosed when the child was 6 years old.

Twelve years after the surgery we again admitted the patient to the High-risk Pregnancy Department at 37 weeks gestation. She was receiving metoprolol (50 mg per day) and alpha-methyldopa (750 mg per day) because of gestational hypertension, diagnosed at 20 weeks gestation. The administration of 3800 IU of nadroparin was also continued. Until the time of hospitalization, the patient was followed in the outpatient clinic without any perinatal or cardiac complications.

Antenatal ultrasounds revealed normal body weight (40-50 percentile of growth at 30 and 34 gestational weeks), biophysical profile and Doppler parameters of placental flow. Fetal echocardiography showed normal structure and pressures. Physical examination and echocardiography of the mother detected only persistent mild dilation of the aortic bulb up to 42mm. The results of the laboratory tests performed at 37 weeks of gestation were as follows: Hb 13.3 g/dl, WBC 5.7 K/ul, PLT 184 K/ul, creatinine 0.54mg/dl, urea 17 mg/dl, total protein 5.84 g/dl, total bilirubin 0.86 mg/dl, Na^+ 138 mmol/l, K^+ 4.31 mmol/l, INR 0.9.

She delivered at 38 weeks by Cesarean section (patient preference) a male newborn (weight 3450g, length 57cm, 5-minute Apgar score of 9). ECG performed after the Cesarean section revealed a few ectopic ventricular beats. The patient was discharged on the 5th postpartum day in good general condition. Outpatient check-ups showed normal post-operative recovery. Pediatric evaluation of the baby revealed normal undisturbed development consistent with age. No clinical symptoms of Marfan syndrome were apparent. A postpartum echocardiographic evaluation revealed "lazy" function of the left ventricle with EF 55%, characteristic for treatment with beta-blockers. The diameter of the aortic bulb was 40mm with preserved function of the artificial valve.

Comment

Pregnant women with cardiac diseases are at risk of pregnancy loss, IUGR and serious circulatory insufficiency leading even to maternal death. [21,26,27,28]. Presbitero et al., [6] are of the opinion that female patients with severe ostial aortic stenosis, Eisenmenger syndrome and Marfan syndrome with dilation of the aortic bulb should not become pregnant. Marfan syndrome may be associated with considerable mortality for pregnant women, especially in rare cases of aortic arch dissection or aortic rupture [13, 22, 27, 29]. Even with the lack of cardio-circulatory problems before conception, the pregnancy increases the risk of aortic root dilation [2]. The preconceptual diameter of the aorta of >45mm is regarded as an important prognostic factor and, together with other cardiac abnormalities, may be a contraindication to pregnancy. [2,4]. Clinicians should consider obtaining cardiac magnetic resonance (MR) angiography before pregnancy to evaluate the aorta, and, once the patient is pregnant, they should either repeat the MR study or obtain serial echocardiograms to monitor the progression of the aortic root dilation [12]. Various reason for the frequent occurrence of aortic dissection during pregnancy include the hyperkinetic and hypervolemic circulation [7], suppressed collagen and elastin accumulation in the aorta, along with progesterone-mediated acceleration of non-collagen protein accumulation [30]. Another reasons may be increased relaxin concentration during the pregnancy which is responsible for aortic wall remodeling [12]. Finally, a theoretical cause for additional stress on the proximal aorta is the pressure exerted by the gravid uterus on the distal aorta causing resistance to the flow of blood from the proximal aorta. A single case report of a Marfan patient suggested that after delivery, the decrease in the uterine size could favor rapid flow acceleration in the abdominal segment of the aorta and could be the cause of the development of abdominal aortic aneurism. However, it is likely that the severity of her Marfan syndrome explains her aortic disorders as she later developed proximal aortic dilation unrelated to pregnancy. [4] Medical treatment of an acute aortic dissection in non-pregnant patients includes intravenous administration of sodium nitroprusside and beta-adrenergic blocking agents in order to control blood pressure, decrease left ventricular contractility, and decrease shear forces on the aorta [14]. However, during pregnancy the use of sodium nitroprusside is contraindicated as it may cause fetal intoxication with thiocyanate, therefore beta-adrenergic blocking agents or hydralazine should be used. [7, 14]. [2]. Beta-blockers are not teratogenic and they reduce stroke volume and heart rate [4] that may decrease the percentage of aortic aneurysms and dissection [31]. Side effects of their usage may include a decrease of newborn birth weight, but this has been observed to be a risk of Marfan syndrome without medication exposure [12]. Aortic dilation is connected with extremely high mortality, so early diagnosis and surgical treatment of aortic dilation is crucial for the survival of both, the mother and the fetus [27]. Mortality can even reach 25% during the first 24 hours up to 75% in two-weeks [17]. In 1986 Gott et al., [29] demonstrated 85% 5-year survival in a population of 50 women with Marfan syndrome after ascending aorta graft. While those authors recommended surgery when the aortic bulb diameter was > 60mm, later studies by Murgatroyd et al., [32] revealed that aortic dissection can develop with the diameter of only 51±13mm. Bearing that in mind, current recommendations are to perform corrective surgery for Marfan patients with an aortic root >45mm, or if serial echocardiographic evaluations detect rapid progression of the aortic root enlargement, particularly in patients with positive family history of aorta dissection or in those who are planning pregnancy [8, 15, 21, 33]. In the absence of obstetric indications, there is no data to suggest that in cases without aortic dilation vaginal labor is contraindicated [34]. Even with aortic dilation, similarly to patients with severe mitral stenosis, it is

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reasonable to attempt a vaginal delivery and avoid the increased risks of infection, thromboembolism, and postoperative cardiac stresses associated with the Cesarean section [12, 14, 34].

Due to retrospective reports and high mortality reported among pregnant Marfan patients with aortic root dilation >45 mm, many authors state that high-risk patients with more significant cardiac/aortic structural abnormalities, such as dilation of the aortic bulb beyond 45mm, aortic dissection or significant valve abnormalities, should be delivered by Cesarean section. The theory is that by avoiding the pushing during labor we can diminish hemodynamic changes and stresses. However, it is important to understand that the postoperative fluid shifts and stresses to the heart are greater after a Cesarean section than after vaginal delivery [2, 6]. This is a controversial topic, but it seems reasonable to consider vaginal delivery, as discussed above, with aggressive control of pain, blood pressure, and heart rate. Antibiotic prophylaxis has to be implemented for prevention of endocarditis according to the recommendation of the European Society of Cardiology. Because of the low risk of bacteremia with organisms likely to cause endovascular infection, the recent guidelines from the American College of Cardiology no longer recommend bacterial endocarditis for vaginal delivery or Cesarean section [35]. Attention should be drawn to the fact that our patient had only slight aortic bulb dilation without symptoms of dissection or aortic valve defect. Similarly, her elder son was diagnosed with prolapse of mitral and tricuspid leaflets. In 1989, Glesby and Pyeritz suggested the use of an acronym MASS phenotype (**m**itral valve, **a**orta, **s**keleton, **s**kin) for patients with small criteria of Marfan Syndrome: moderate dilation of aortic bulb, mitral insufficiency, alterations in osteoarticular system and skin disorders [36].

It is worth noting that although she had severe mitral and tricuspid abnormalities during the first pregnancy, she did not present with any cardiac symptoms. In fact, the cardiac abnormalities we detected after the miscarriage when her clinical team initiated an evaluation after noting a typical Marfan body habitus. While one can postulate that cardiac abnormalities contributed to her miscarriage, in the absence of objective signs of cardiac decompensation, cervical insufficiency seems to have been a more likely cause. Cardio surgical correction most probably allowed her to tolerate her two subsequent pregnancies without further cardiac decompensation or damage. The presented case is evidence that preconceptual hemodynamically effective correction of the valve defects in women with Marfan syndrome, together with the appropriate use of beta-adrenergic blockade for concomitant aortic dilation, make conception and term delivery of consecutive pregnancies possible.

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