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THE BASIC POINTS OF SAFE MANAGEMENT OF PREGNANCY AND DELIVERY IN PATIENTS WITH MARFAN SYNDROME

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Summary

Marfan syndrome is dominantly inherited connective tissue diseases, associated with microfibrillar fiber connective tissue deficiency in vascular walls, heart valves, joints, dural membrane, bones, and other organs. Diagnosis may be confirmed by clinical criteria and molecular tests. Pregnancy bears a risk of fatal complications, including aortic dissection, aortic root dilation, mitral valve insufficiency. Women must be followed and managed in a high risk pregnancy unit by a team from obstetricians, cardiologists, anesthetists, pediatricians, neonatologists and cardiac surgeons who are skilled in high risk pregnancies. This approach allows to avoid the serious maternal and fetal complications. Caesarean section should be offered for such patients, because it minimizes the hemodynamic changes, associated with vaginal delivery. Some authors recommend to perform post-cesarean hysterectomy, because of the high incidence of massive hemorrhage in postpartum.

Key words

Mesenchimal displasias, inherited connective tissue disorders, Marfan syndrome, Ehlers-Danlos syndrome, Osler-Weber-Rendu disease, pregnancy, aortic dissection in pregnancy, cesarean section, bleeding, hemorrhage.

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Conflict of interests

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ВЕДЕНИЕ БЕРЕМЕННОСТИ И РОДОРАЗРЕШЕНИЯ У БОЛЬНЫХ С СИНДРОМОМ МАРФАНА

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Резюме

Синдром Марфана является доминантно-наследуемым заболеванием соединительной ткани, связанным с дефицитом соединительной ткани микрофибриллярных волокон в стенках сосудов, клапанах сердца, суставах, оболочке мозга, костях и других органах. Диагноз может быть поставлен с помощью клинических признаков и молекулярных тестов. Беременность связана с высоким риском опасных осложнений, включая расслоение аорты, расширение корня аорты, недостаточность митрального клапана. Беременные с синдромом Марфана относятся к группе высокого риска и должны находиться под наблюдением акушеров, кардиологов, анестезиологов, педиатров, неонатологов и кардиохирургов, имеющих опыт ведения сложных беременностей. Групповой подход позволяет избежать серьезных осложнений у матери и плода. Таким пациенткам следует предлагать кесарево сечение, поскольку оно минимизирует гемодинамические нарушения, связанные с вагинальными родами. Из-за частых послеродовых массивных кровотечений некоторые авторы рекомендуют выполнять гистерэктомию сразу после кесарева сечения.

Ключевые слова

Мезенхимальные дисплазии, наследственные болезни соединительной ткани, синдром Марфана, синдром Элерса-Данлоса, болезнь Ослера-Вебера-Рендю, беременность, расслоение аорты при беременности, кесарево сечение, кровотечение, кровоизлияние.

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Introduction

Marfan syndrome is an autosomal dominant connective tissue disease associated with a mutation in the fibrillin gene, one of the main elastic components of connective tissue. In this case, the synthesis of microfibrillary fibers in the walls of vessels, heart valves, ligaments, joints, dura mater, bones and other organs is disturbed. The prevalence of the Marfan syndrome according to various sources is 1 per 5-10 thousand of the population [1-3].

What is the molecular genetic defect?

Synthesis of fibrillin type 1 is encoded by a gene located on chromosome 15q21.1. Most mutations represent missense mutations, less frequently there are nonsense mutations and mutations with a shift of the reading frame. There is no clear correlation with the species and localization of the mutation and the severity of the Marfan syndrome. Even mutations in the same codon can lead to both severe Marfan syndrome of newborns and to the classic Marfan syndrome in adults. It was also found that

mutations in the central region of the gene (exons 24-32), the so-called «neonatal site», cause a wide range of manifestations from the severe Marfan syndrome in newborns to isolated ectopia of the lens.

What are the clinical manifestations of Marfan syndrome?

The most frequent clinical signs of the disease are progressive dilatation of the aorta, prolapse and insufficiency of the mitral and aortic valves, hypermobility of the joints, high growth, long limbs, arachnodactyly, chest deformation, scoliosis, lens subluxation, myopia, gothic palate, striae on the skin. X-ray examination often reveals ectasia of the dura mater and protrusion of the acetabulum. In some cases, there is a history of repeated episodes of pneumothorax. Manifestations of the cardiovascular system have a particular importance because of them the high mortality is associated with this disease [4]. A major problem with Marfan's syndrome, as with other hereditary collagen diseases, is multiple cerebral aneurysms. Their incidence in patients with Marfan syndrome is about 28%, according to autopsy data.

How to diagnose Marfan syndrome?

Currently, the diagnosis of Marfan syndrome is established in accordance with the diagnostic criteria of Ghent, which were proposed in 1996 in place of the previously existing Berlin criteria of the year 1988 (**table 1**).

One basic criteria from the two different organ systems is necessary for diagnosis to be made (4 features from the skeleton form the main criterion) and 1 additional criterion from another system.

Changes in the skeleton can be assessed according to the Steinberg's symptoms (the nail phalanx of the thumb

System	The main criteria	Additional criteria
Skeletal abnormalities	At least 4 of the following symptoms: • pigeon chest (pectus carinatum) • pronounced deepening in the thoracic region, requiring surgical correction • disproportionately high growth (the ratio of the upper segment to the bottom is less than 0.86 or the ratio of the magnitude of the span of arms to growth is more than 1.05) • scoliosis > 200 or spondylolisthesis • incomplete extension in the elbow joint (< 1700) • flat feet with valgus foot deviation; • protrusion of the acetabulum	2 main criteria or 1 primary and 2 of the following symptoms: • deepening in the thorax • hypermobility of joints • high palate • specific face
Organ of vision	• subluxation of thelens	• flattening of the cornea • an increase in the long axis of the eyeball, leading to myopia • hypoplasia of the iris or ciliary muscle, leading to miosis
The cardiovascular system	• aortic root dilatation • ascending aortic dissection	• mitral valve prolapse • pulmonary artery dilation at the age of 40 years • calcification of the mitral valve at the age of 40 years • dilation and dissection of other aortic areas
Lungs	• absence	• spontaneous pneumothorax
Skin	• absence	• atrophic striae • recurrent hernia
Spinal cord	• lumbosacral ectasia of the dura mater	• absence
Genetic data	• presence of Marfan syndrome in accordance with the listed criteria among close relatives of patients, regardless of the presence of a mutation in the fibrillin gene • presence of the DNA markers of the Marfan syndrome among the relatives	• absence

Table 1. The main diagnostic criteria for the Marfan syndrome.

Таблица 1. Основные диагностические критерии синдрома Марфана.

extends beyond the inner border of the hand) and Walker-Murdoch's (with the wrist around the thumb and little finger partially overlapping each other) X-ray (to detect protrusion of the acetabulum) and MRI (For the detection of lumbosacral ectasia) are carried out only in those cases when existing criteria are not sufficient for the diagnosis.

Particularly it is necessary to single out the so-called «marfanoid phenotype». It includes not pronounced signs of the syndrome, such as high growth, arachnodactyly, hypermobility of the joints, high gothic palate and other symptoms when there are not enough criteria for diagnosis. Marfanoid phenotype is also characterized by such indicators as the ratio of the upper segment to the bottom less than 0.86 and the ratio of the magnitude of the span of arms to growth is more than 1.05. The length of the lower segment is measured from the pubic symphysis to the floor, the length of the upper segment is the difference between the height and length of the lower segment. Such patients need constant monitoring, because they have a high risk of developing more serious manifestations of Marfan syndrome.

Molecular diagnostics of the Marfan syndrome is complicated by two reasons: first, each mutation in the fibrillin-1 gene is unique and the probability of its recurrence is extremely small; secondly, mutations in the fibrillin-1 gene are detected not only in Marfan's syndrome, but also in diseases similar to it , which do not have severe manifestations of the cardiovascular system, for example, in the case of MASS syndrome (myopia, mitral valve prolapse, aortic dilatation, skin involvement, skeletal involvement), an isolated subluxation of the lens.

With what diseases can the Marfan syndrome be differentiated?

Such diseases include Luyang-Frins syndrome (a rare X-linked disease, manifested by mental retardation and some signs similar to Marfan's syndrome), the Shprintzen-Goldberg syndrome (a disease with autosomal dominant inheritance, accompanied by craniosynostosis). In some cases, the syndrome of the Shprintzen-Goldberg reveals a mutation in the fibrillin-1 gene, so some authors refer it to the rare variants of the Marfan syndrome. In homocysteinuria, excretion of homocysteine in the urine is detected in addition to the marfanoid phenotype, and in the Bella syndrome (an autosomal dominant disease associated with a mutation in the fibrillin gene-2), the contractures in the joints and the anomalous structure of the auricles.

In some cases, a differential diagnosis with Marfan syndrome presents certain difficulties. So, the MASS syndrome can be considered as a variant of the Marfan syndrome. The name comes from the initial letters of the main symptoms of the disease: myopia, mitral valve prolapse, aortic dilatation, skin involvement, skeletal involvement. The manifestations of the MASS syndrome are similar to those in the Marfan syndrome, but they are much less pronounced. Dilation of the aorta, generally, is not expressed and does not tend to progress. Some cases of the disease are accompanied by a mutation in the fibrillin gene 1. An autosomal dominant disease with a marfanoid phenotype and ectopic lens is described, but without any cardiovascular symptoms accompanied by a mutation in the fibrillin gene 1.With mutations in genes of chromosomes 5 and 11 which are not yet identified, congenital aortic aneurysms without other signs of Marfan syndrome are associated. Many symptoms of such diseases as Ehlers-Danlo syndrome and Sticker syndrome are similar to Marfan's syndrome. However, for Ehlers-Danlo syndrome the increased skin extensibility and its damage at the slightest trauma is more typical, and for Sticker syndrome – myopia with retinal detachment, but there is no ectopia of the lens. In addition, patients with Sticker Syndrome often have hypoplasia of the facial part of the skull, cleft palate and hearing loss.

What are the main principles of safe planning and management of pregnancy in patients with Marfan syndrome?

Patients with Marfan syndrome are recommended to have a thorough examination during pregnancy planning, which necessarily includes transthoracic or transesophageal ultrasound examination of the aorta. With aortic diameter of more than 4 cm, pregnancy is contraindicated. All necessary surgical interventions on the valves and aorta should be performed before pregnancy [5].

In the management of pregnant women with Marfan syndrome, two main factors should be considered:

- pregnant women with Marfan syndrome have a high risk of developing lethal complications from the cardiovascular system (in particular aortic rupture);
- disease is inherited in children in 50% of cases.

The reasons for the high risk of aortic rupture during pregnancy in patients with Marfan syndrome are physiological increase in the volume of circulating blood and cardiac output in the background of a congenital abnormality of collagen. Hormonal changes also have a certain significance. The inhibitory effect of estrogens on the deposition of collagen and elastin in the aortic wall is shown. In experiments on rats, the stimulating effect of progesterone on the deposition of non-collagen proteins in the aortic wall was also demonstrated. Gestational hypertension and preeclampsia acutely increase the risk of dilatation, stratification and rupture of the aorta.

Approximately 70% of pregnant women have an aortic rupture in the area 2 cm above the aortic valve or in the descending thoracic aorta. Usually, aortic damage affects only half of the diameter of the aorta, the other half remains intact. When the ascending aorta ruptures, generally, the right lateral wall is involved, then the process spreads downward, capturing the arc and chest of the descending aorta, which often leads to the involvement of the right coronary, left common carotid and left subclavian arteries [6, 7].

When is it possible to diagnose the development of aortic dissection in Marfan syndrome?

Well-timed diagnosis and therapy of sudden dissection of the aorta is vital, as about 50% of patients die within 48 hours after the onset of the complication [8]. During pregnancy, this percentage is much higher [9]. The main symptoms of aortic dissection are chest pain radiating to the back, shoulders and abdomen. The most dangerous complications are extravasal bleeding in the pericardium, pleural cavity, mediastinum, retroperitoneal space, pulmonary artery wall, heart cavity. In addition, symptoms associated with partial or complete occlusion of various arteries with hematoma of the aortic middle shell are often observed. Occlusion of coronary arteries can lead to sudden death or myocardial infarction, general carotid – to syncopal conditions, stroke or coma, subclavian artery – upper limb ischemia and paraparesis, intercostal or lumbar arteries – spinal cord ischemia. Sometimes there is an occlusion of the celiac trunk, renal, mesenteric or common iliac arteries. Due to dilatation or stratification of the aorta at the level of the aortic valve, severe aortic insufficiency and pulmonary edema can develop. Obstruction of the aorta or pulmonary artery often leads to circulatory collapse. Physical examination often reveals a pulse deficit, a diastolic noise on the aorta, neurologic manifestations (cerebrovascular disorders, loss of consciousness, paraparesis or paraplegia). Chest X-ray reveals an expansion of the mediastinum. Sometimes there are signs of hemothorax (mainly left-sided with the separation of the distal aorta). However, the radiographic data are nonspecific and the absence of pathological changes on the radiographs does not allow to exclude the diagnosis. The gold standard for the diagnosis of aortic dissection is aortography. However, in connection with their non-invasiveness and the absence of a negative effect on the fetus, the methods of choice during pregnancy are contrast computer tomography, magnetic resonance imaging, transesophageal echocardiography and ultrasound. Differential diagnosis of aortic dissection in pregnant women with Marfan syndrome is performed with acute conditions such as amniotic fluid embolism, myocardial infarction and aortic regurgitation due to other causes, pneumothorax, stroke, rupture of the uterus, placental abruption, thrombosis of mesenteric vessels. Generally, the diagnosis of aortic dissection is established post mortem [10, 11].

Is it possible to reduce the risk of life-threatening complications in pregnant women with Marfan syndrome?

To prevent and well-timed correction of life-threatening complications during the whole pregnancy, patients with Marfan syndrome should be closely monitored by obstetricians and vascular surgeons. For all pregnant women with Marfan syndrome (not even previously having signs of cardiovascular damage) transthoracic ultrasound or MRI in dynamics is prescribed [12].

The effectiveness of beta-blockers to prevent progressive aortic dilatation has been proven in many studies. When the distal aortic rupture is broken, intravenous beta-blockers are used to achieve a 20% decrease in heart rate, a decrease in blood pressure and left ventricular contractility [13]. Surgical intervention in situations of ineffectiveness of drug therapy, rupture or threat of aortic rupture, progressive aortic dissection is prescribed. In situation of separation of the proximal aorta, urgent surgical intervention is necessary, because only this measure can prevent a fatal outcome [14, 15]. Urgent surgical intervention is also prescribed for pregnant women with Marfan syndrome with augmentation of aorta diameter exceeding 45 mm: in the early terms, abortion is recommended, in the late – a caesarean section with subsequent reconstructive surgery on the aorta [14, 15]. Another frequent indication for urgent surgical intervention during pregnancy in patients with Marfan syndrome is progressive aortic insufficiency. The success of surgical interventions in pregnant women with Marfan syndrome depends on the severity of the complication, the length of pregnancy, the timeliness of the intervention. Siu et al. describe the case of a favorable outcome of pregnancy after reconstructive surgery on the ascending aorta and aortic valve made at the 22nd week of pregnancy due to aortic dilatation from 5.5 to 7.7 cm. There are also cases of favorable pregnancy outcomes after surgical interventions due to aorta stratification [15, 16]. However, in most cases, surgical treatment leads to the termination of pregnancy, so if the fetus is viable, the cesarean section is performed before or at the same time as the heart and vascular surgery [15, 16].

What are the features of the delivery of patients with Marfan syndrome?

The optimal method of delivery of pregnant women with Marfan syndrome is a cesarean section, which minimizes hemodynamic changes associated with vaginal delivery. Only in a few cases with aortic diameter less than 40 mm, absence of concomitant manifestations of the disease, adequate anesthesia and good control of blood pressure, vaginal delivery is possible. In certain cases, to shorten the second period of labor, forceps delivery is prescribed. Some authors recommend at the same time with cesarean section to do a hysterectomy, because in the postpartum period, mothers with Marfan syndrome often have massive uterine bleeding. The cause of such bleeding is a violation of the contractility of the spiral arteries, which occurs in other connective tissue diseases, for example, in the Ehlers-Danlo syndrome.

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