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VARICOSE VEINS DURING PREGNANCY: EFFECTS ON PLACENTAL METABOLISM, ANGIOGENESIS, AND MANAGEMENT STRATEGIES

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Abstract.
Background. Varicose veins during pregnancy represent a common form of chronic venous disease and may adversely affect both maternal health and fetoplacental function.
Objective. To analyze the pathogenetic mechanisms of varicose veins during pregnancy and their impact on placental metabolism, angiogenesis, and oxidative stress.
Materials and Methods. A comprehensive review of experimental and clinical studies addressing venous hemodynamics, hormonal regulation, placental glucose metabolism, angiogenesis, and lymphangiogenesis in pregnant women with varicose veins was conducted.
Results. Varicose veins were associated with placental hypoxia, enhanced anaerobic glycolysis, lactate accumulation, impaired angiogenesis and lymphangiogenesis, and increased oxidative stress. These alterations contribute to placental dysfunction and increased risk of adverse pregnancy outcomes.
Conclusion. Varicose veins during pregnancy significantly disrupt fetoplacental exchange and require early diagnosis and a comprehensive conservative management strategy. Further research into molecular pathways may enable the development of safe surgical interventions in selected cases.
Key words: Varicose veins; pregnancy; placental dysfunction; angiogenesis; hypoxia; chronic venous disease.

ВАРИКОЗНАЯ БОЛЕЗНЬ ВО ВРЕМЯ БЕРЕМЕННОСТИ: ВЛИЯНИЕ НА ПЛАЦЕНТАРНЫЙ МЕТАБОЛИЗМ, АНГИОГЕНЕЗ И ТАКТИКУ ВЕДЕНИЯ

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Аннотация.
Актуальность. Варикозная болезнь во время беременности является распространённой формой хронической венозной недостаточности и может оказывать неблагоприятное влияние не только на состояние матери, но и на функционирование фетоплацентарного комплекса.
Цель. Проанализировать патогенетические механизмы развития варикозной болезни у беременных и её влияние на плацентарный метаболизм, ангиогенез и оксидативный стресс.
Материалы и методы. Проведён анализ современных экспериментальных и клинических исследований, посвящённых венозной гемодинамике, гормональным изменениям, метаболизму глюкозы, ангиогенезу и лимфангиогенезу плаценты при варикозной болезни.
Результаты. Установлено, что варикозная болезнь ассоциирована с гипоксией плацентарных ворсин, активацией анаэробного гликолиза, накоплением лактата,

нарушением ангио- и лимфангиогенеза, а также усилением оксидативного стресса. Эти изменения способствуют функциональной неполноценности плаценты и повышают риск осложнений беременности.
Заключение. Варикозная болезнь у беременных является значимым фактором нарушения фетоплацентарного обмена и требует ранней диагностики и комплексного консервативного лечения. Дальнейшие исследования молекулярных механизмов могут расширить возможности безопасной хирургической коррекции.
Ключевые слова: Варикозная болезнь; беременность; плацентарная недостаточность; ангиогенез; гипоксия; хроническая венозная недостаточность.

HOMILADORLIK DAVRIDA VARIKOZ KASALLIGI: PLATSENTAR METABOLIZM, ANGIOGENEZ VA DAVOLASH YONDASHUVLARI

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Annotatsiya.
Dolzarbligi. Homiladorlik davridagi varikoz kasalligi surunkali venoz yetishmovchilikning keng tarqalgan shakli bo‘lib, ona salomatligi bilan birga fetoplatsentar tizim faoliyatiga ham salbiy ta’sir ko‘rsatishi mumkin.
Maqsad. Homilador ayollarda varikoz kasalligi patogenezini va uning platsentar metabolizm, angiogenez hamda oksidlovchi stressga ta’sirini tahlil qilish.
Materiallar va usullar. Venoz gemodinamika, gormonal o‘zgarishlar, glyukoza metabolizmi, angiogenez va limfangiogenezga oid zamonaviy ilmiy tadqiqotlar tahlil qilindi.
Natijalar. Varikoz kasalligi platsentar gipoksiya, anaerob glikolizning kuchayishi, laktat to‘planishi, angiogenez va limfangiogenez buzilishi hamda oksidlovchi stressning ortishi bilan bog‘liq ekani aniqlandi.
Xulosa. Homiladorlik davridagi varikoz kasalligi fetoplatsentar almashinuvni buzuvchi muhim omil bo‘lib, erta aniqlash va kompleks konservativ davolashni talab qiladi.
Kalit so’zlar: Varikoz kasalligi; homiladorlik; platsentar yetishmovchilik; angiogenez; gipoksiya; surunkali venoz yetishmovchilik

Introduction. Varicose veins (VV) are a chronic venous disorder characterized by dilation, elongation, and tortuosity of the veins, as well as impaired blood circulation. The primary cause of varicose veins is venous valve insufficiency, which leads to backflow of blood and increased venous pressure. According to statistics, varicose veins affect 20% to 64% of the population, and women are 1.5–2 times more likely to experience this problem than men [1]. Pregnancy is a key cause of varicose veins in women, which can lead to chronic venous insufficiency and swelling in the lower extremities. Studies show that varicose vein symptoms occur in 20–70% of pregnant women [1], with the most pronounced manifestations observed in the second and third trimesters. Women who have had multiple pregnancies face an increased risk of both developing and worsening varicose veins. Furthermore, for those who had varicose veins before pregnancy, the risk of recurrence can reach 50% in the postpartum period. Varicose veins of the superficial veins of the lower extremities most often develop in the great saphenous vein (70–85%), less often in the small saphenous vein (5–12%). With varicose veins, vein damage is usually bilateral and is observed in 50–70% of patients [2]. In late pregnancy, varicose veins of the pelvis are often observed due to the fact that the enlarged uterus creates increased pressure on adjacent organs and, along with this, on the veins, which can lead to hemorrhagic, purulent-septic, and thrombotic complications in the perinatal period [3].

Pathogenesis of varicose veins during pregnancy. The increase in uterine size during pregnancy leads to mechanical compression of the inferior vena cava and external iliac veins,

causing venous obstruction and increasing venous capacitance. This, in turn, leads to blood stagnation and increases the risk of venous hypertension. Furthermore, the physiological increase in circulating blood volume by 20–30% during pregnancy also contributes to an increase in venous pressure [3]. Excessive production of placental steroid hormones also plays a significant role in the development of degenerative-dystrophic changes in the vein walls of pregnant women. Histological studies reveal the presence of estrogen and progesterone receptors in the subcutaneous veins of the lower extremities [1]. By the end of pregnancy, vascular distensibility can increase by up to 150% due to a 250-fold increase in progesterone concentration, as well as under the influence of relaxin. Progesterone promotes relaxation of smooth muscles and myocytes in the venous wall, and restoration of normal tone occurs only 8–12 weeks after delivery. Estrogen secretion during pregnancy increases 60-fold, which increases arterial inflow to the uterus and other pelvic organs, negatively affecting venous outflow from the external iliac veins. Estrogens also promote the synthesis of vitamin K-dependent coagulation factors in the liver (II, VII, IX, X) and reduce antithrombin III levels, increasing the risk of thrombosis [2]. Thus, the combination of increased circulating blood volume, hormonal changes, mechanical compression, and increased venous pressure leads to dilation of the veins of the lower extremities and relative valve insufficiency, contributing to the development of varicose veins in pregnant women.

The influence of varicose veins on placental metabolism. It is now recognized that not only changes in the pregnant woman's body contribute to the development of varicose veins, but also that cardiovascular diseases can negatively impact fetal development. Women with varicose veins experience increased placental hypoxia, which is manifested by increased expression of hypoxia-inducible factor 1α [4], as well as increased anaerobic glycolysis and angiogenesis. These changes resemble tumor processes known as the Warburg effect, characterized by increased cell proliferation and invasiveness. However, placental hypoxia manifests itself early in pregnancy and decreases over time, unlike tumors, where it steadily increases [5,6].

Glucose metabolism. Women with cardiovascular diseases exhibit changes in the glycolytic phenotype of the placenta, which is manifested by increased expression of GLUT1, phosphofructokinase 1 (PFK1), aldolase (ALD), glyceraldehyde 3-phosphate dehydrogenase (GA3PDH), and lactate dehydrogenase A (LDHA), which are key components of glucose metabolism. GLUT1, a key glucose transporter, plays an important role in pregnancy and changes with complications. Studies have shown that in women with varicose veins, the level of its expression in the placenta is significantly higher than in the control group [5]. In addition, under hypoxic conditions, increased expression of PFK1 and ALD activity, as well as an increase in the content of GA3PDH and LDHA, are observed, which indicates the activation of metabolic processes under stressful conditions [5]. It is known that GA3PDH is responsible for the formation of nicotinamide adenine dinucleotide (NADH+H+) in glycolysis. This molecule, in turn, can be used either in aerobic respiration, facilitating ATP formation, or it can mediate the conversion of pyruvate to lactate by lactate dehydrogenase. However, since we are dealing with hypoxia in the placental villi, increased expression of GA3PDH and LDHA indicates high lactic acid production. It is impossible to say for sure whether anaerobic glycolysis is a cause or a consequence of placental damage—both are likely true. Lactate is important in early pregnancy, exerting immunomodulatory effects and promoting angiogenesis; increased production may be a protective response of the placenta. At the same time, increased lactic acid levels lead to metabolic acidosis. When comparing the pH of the umbilical veins, it was noted that the fetuses of women with varicose veins had a significant decrease in venous pH compared to the fetuses of women without cardiovascular insufficiency (pH on average = 7.20 in the experimental group versus 7.28 in the control group) [7]. Acidification of the environment has a negative effect on the placenta, promoting condensation of nuclear chromatin and further apoptosis of villous cells.

Lymphangiogenesis and angiogenesis. It has been shown that pregnant women with cardiovascular disease exhibit alterations in vascular elastogenesis in placental villi. The level of EGFL7 protein, which influences endothelial homeostasis in both the maternal and fetal vascular systems, is virtually eliminated in these villi [8]. Unlike most angiogenic molecules, such as vascular endothelial growth factor, which are primarily produced by fibroblasts, EGFL7 is unique in that it

is expressed in endothelial cells themselves and acts directly on them. One of the mechanisms of EGFL7 action is to stimulate the proliferation, migration, sprouting, and invasion of endothelial cells. Furthermore, it acts as a chemoattractant for embryonic endothelial cells and promotes their adhesion. In any case, decreased EGFL7 levels inhibit capillary sprouting in the placenta. Pregnant women with varicose veins also showed a decrease in the percentage of decidual cells expressing this protein (15.50% versus 31.00% in the control group) [8]. A number of studies have noted that pregnant women with varicose veins have elevated levels of podoplanin (D2–40), vascular endothelial growth factor (VEGF), and human placental growth factor (PIGF) in chorionic villi. Although the human placenta lacks a fully developed lymphatic system, chorionic villous stromal cells express podoplanin, performing functions similar to primitive lymphatic vessels [6]. Moreover, placental blood supply in women with cardiovascular diseases is associated with abnormal expression of human placental growth factor (PIGF) and a significant increase in the level of vascular endothelial growth factor receptor (Flt1) [6, 9]. The increased level of vascular endothelial growth factor (VEGF) in the placental villi of women with CVD is explained by a vascular compromise arising as a result of CVD during pregnancy and stimulating angiogenesis and lymphangiogenesis. Although the described processes are aimed at correcting the situation created by CVD, these vessels have an incomplete structure, manifested by the presence of various defects, gaps, or thinning of the basement membrane. It has been shown that the placentas of women with varicose veins have more villi with PAS-positive material (91.93% versus 51.92% in the control group) – a method demonstrating the presence of aldehyde groups obtained as a result of carbohydrate oxidation, the accumulation of which suggests that the chorionic villi are not fully functional [6]. Thus, in one case of pregnant patients with cardiovascular disease, hypoxia was shown to inhibit angiogenesis, while in another, it promoted increased synthesis of blood and lymphatic vessels in the placental villi, although their function was impaired due to their abnormal structure. This allows us to conclude thatthat varicose veins in the mother to one degree or another disrupt the exchange of gases and nutrients between her and the fetus [10].

Oxidative stress. Another interesting discovery is the fact that pregnant women with cardiovascular diseases have increased activity of the redox-sensitive transcription factor 2 (Nrf2) in the placenta compared to healthy patients [4]. This factor plays a key role in regulating the expression of genes such as heme oxygenase, thioredoxin, and thioredoxin reductase, which are involved in antioxidant defense and detoxification mechanisms. However, increased Nrf2 activity can, on the contrary, contribute to the development of oxidative stress. One of the main markers of cellular damage associated with this process is the level of malondialdehyde (MDA), which is formed as a result of lipid peroxidation. Studies have shown that the concentration of MDA in the blood plasma of women with varicose veins is significantly higher than that of healthy participants (14.55 μmol/L in the varicose vein group versus 8.04 μmol/L in the control group) at 32 weeks of pregnancy [7]. Furthermore, dysfunction of the Nrf2 system can lead to the development of numerous pathologies, including inflammatory processes that arise due to impaired suppression of proinflammatory cytokine production by macrophages. These circumstances adversely affect both maternal health and fetal development, and the current situation highlights the need for careful monitoring and adequate health management in pregnant women suffering from cardiovascular diseases.

Treatment. All of the above-mentioned placental metabolic disorders due to varicose veins in pregnant women can lead to serious problems, including premature birth, preeclampsia, and intrauterine growth retardation. [11] Therefore, it is important to begin treatment as soon as possible. Modern surgical methods for correcting chronic venous insufficiency, such as subfascial endoscopic dissection of perforating veins, sclerotherapy, and endovasal laser coagulation, are not recommended for pregnant women due to the risk to the mother and fetus, as well as the possibility of spontaneous regression of varicose veins after childbirth. According to the recommendations of the International Union of Angiology, phlebosclerosing treatment should be avoided during pregnancy and lactation. [1] The most preferable treatments are the removal of varicose veins before pregnancy or conservative treatment. Phlebologists recommend wearing compression hosiery from the first day of pregnancy and for several months after childbirth. The first compression class (18–

22 mmHg) is suitable for pregnant women without varicose veins, and the second class (23–32 mmHg) is for those with symptoms of chronic venous disease. [1] Pregnant women using compression therapy showed a smaller increase in the diameters of the shins and ankles compared to the control group: changes in the diameters of the shins were 0.30 cm in the experimental group versus 1.95 cm in the control group, and for the ankles – 0.15 cm versus 1.73 cm. [12] Pharmacotherapy plays an important role in the treatment of chronic venous insufficiency; however, there are no clear recommendations for the use of drugs during pregnancy. In the 2nd and 3rd trimesters, it is allowed to use micronized purified flavonoid fraction and other phlebotonics for a course of 1 to 3 months with the possibility of re-prescription in case of relapse. [1] However, the use of phlebotropic drugs in the first trimester and during breastfeeding is not recommended, despite the absence of a teratogenic effect of flavonoids. Interestingly, when combining compression hosiery with phlebotonics, a bilateral decrease in calf circumference was recorded at two points (3 cm above the medial malleolus and 10 cm below the tibial tuberosity) by 0.5 cm and 1 cm, respectively, compared with baseline values. At the same time, in pregnant women from the control group, a statistically significant increase in calf circumference was observed by 0.2 cm and 2.2 cm [13]. These data emphasize the importance of a comprehensive approach to the treatment of venous insufficiency in pregnant women, including both drug and non-drug methods. Despite all the existing cautions, an experiment was conducted in which pregnant women with ineffective conservative treatment for varicose veins underwent subfascial endoscopic perforator surgery (SEPS) in the second trimester. This procedure aims to eliminate the perforator shunt with minimal tissue damage. The technique involves a 2-3 cm incision above the trophic changes.The video endoscope was inserted and small perforators were coagulated, while large ones were fixed with a metal clip and divided. The average operative time was 90 minutes, and the postoperative hospital stay was 1–2 days. Remarkably, no intraoperative or postoperative complications, such as bleeding, gas embolism, seromas, abscesses, infections, or deep vein thrombosis, were recorded. The average ulcer healing time was 7–8 weeks, and long-term follow-up of patients was at least three years, with recurrences recorded in only 11.1% of them [14]. Therefore, it can be concluded that SEPS is a promising minimally invasive and relatively safe procedure for the treatment of varicose veins in the second trimester of pregnancy with insufficiency of the perforating veins below the knee.

Conclusion. An analysis of studies conducted in recent years has revealed that women with varicose veins during pregnancy experience changes in the glycolytic phenotype of the placenta and lactate accumulation, as well as impaired angiogenesis and lymphangiogenesis, which is associated with abnormal production of growth factors and leads to functional failure of the placental villi. Increased activity of redox-sensitive factors also negatively impacts the fetoplacental system, causing inflammation and metabolic disturbances. These data highlight the need for further research into the molecular mechanisms of cardiovascular disease during pregnancy. Currently, the focus is exclusively on conservative treatment methods. Future studies of venous hemodynamics may lead to the introduction of effective surgical treatments for pregnant women with varicose veins.

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