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Gestation complications in women with metabolic syndrome: pathogenesis, diagnosis and prevention (literature review)

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The article summarizes modern scientific views on the main links of pathogenesis, diagnostic criteria and methods for the prevention of gestational complications in women with metabolic syndrome.

The **aims** of study is to analyze modern domestic and foreign studies on the study of pathogenetic mechanisms of influence of metabolic components syndrome for the development of gestational complications, methods of their diagnosis and prevention in women with metabolic syndrome.

Results. It has been proven that the components of metabolic syndrome are associated with the development of pregnancy complications, such as pre-eclampsia, fetal growth retardation and macrosomia, gestational diabetes, preterm labour, fetal death, habitual early termination of pregnancy.

On the basis of joint pathogenesis, the above-mentioned complications belong to the group of «the great obstetrical syndromes». It has been shown that pregnant women with metabolic syndrome are at high risk for the occurrence of «the great obstetrical syndromes» and require timely appointment of preventive measures to reduce them.

Almost all scientific studies have demonstrated the importance of regulating metabolic processes in the body of a woman with metabolic syndrome at the stage of preconcepence period. It is reported that a lifestyle modification that aims to reduce body weight by prescribing a balanced low-calorie diet combined with exercise and the use of behavioral therapy leads to improved pregnancy outcomes for both mother and baby.

The conclusion. The problem of metabolic syndrome in women of reproductive age remains relevant in modern medicine and taking into account its social significance, requires further research in the aspect of studying pathogenesis, early diagnosis and prevention of his pathology, since it can significantly improve the condition of the pregnant woman in the future and have a positive effect on the course of pregnancy and childbirth.

Keywords: metabolic syndrome, pregnancy, gestational complications, diagnosis, pathogenesis, prevention.

Гестаційні ускладнення у жінок із метаболічним синдромом: патогенез, діагностика та профілактика (огляд літератури)

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У статті узагальнено сучасні наукові погляди на основні ланки патогенезу, критерії діагностики та методи профілактики гестаційних ускладнень у жінок із метаболічним синдромом.

Мета дослідження — проведення аналізу сучасних вітчизняних та зарубіжних досліджень щодо вивчення патогенетичних механізмів впливу компонентів метаболічного синдрому на розвиток гестаційних ускладнень, методів їх діагностики та профілактики у жінок із метаболічним синдромом.

Результати. Доведено, що компоненти метаболічного синдрому асоціюються з розвитком ускладнень вагітності, таких як прееклампсія, затримка росту плода і макросомія, гестаційний діабет, передчасні пологи, внутрішньоутробна загибель плода, звичне невиношування вагітності. За ознакою спільного патогенезу вище перелічені ускладнення відносяться до групи «великих акушерських синдромів». Показано, що вагітні із метаболічним синдромом входять до групи високого ризику по виникненню «великих акушерських синдромів» і потребують своєчасного призначення профілактичних заходів щодо їх зниження.

Майже всі наукові дослідження продемонстрували важливість регулювання метаболічних процесів в організмі жінки із метаболічним синдромом ще на етапі преконцепційного періоду. Повідомляється, що модифікація способу життя, яка спрямована на зниження маси тіла шляхом призначення збалансованої гіпокалорійної дієти в поєднанні з фізичними вправами і застосуванням поведінкової терапії призводить до поліпшення наслідків вагітності як для матері, так і для дитини.

Висновок. Проблема метаболічного синдрому у жінок репродуктивного віку залишається актуальною в сучасній медицині та, враховуючи свою соціальну значимість, вимагає подальших досліджень в аспекті вивчення патогенезу, ранньої діагностики та профілактики зазначеної патології, оскільки це може значно покращити в майбутньому стан вагітної і позитивно вплинути на перебіг вагітності та пологів.

Ключові слова: метаболічний синдром, вагітність, гестаційні ускладнення, патогенез, діагностика, профілактика.

Гестационные осложнения у женщин с метаболическим синдромом: патогенез, диагностика и профилактика (обзор литературы)

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В статье обобщены современные научные взгляды на основные звенья патогенеза, критерии диагностики и методы профилактики гестационных осложнений у женщин с метаболическим синдромом.

Цель исследования — проведение анализа современных отечественных и зарубежных исследований по изучению патогенетических механизмов влияния компонентов метаболического синдрома на развитие гестационных осложнений, методов их диагностики и профилактики у женщин с метаболическим синдромом.

Результаты. Доказано, что компоненты метаболического синдрома ассоциируются с развитием осложнений беременности, таких как преэклампсия, задержка роста плода и макросомия, гестационный диабет, преждевременные роды, внутриутробная гибель плода, привычное невынашивание беременности. По признаку общего патогенеза вышеперечисленные осложнения относятся к группе «больших акушерских синдромов». Показано, что беременные с метаболическим синдромом входят в группу высокого риска по возникновению «больших акушерских синдромов» и требуют своевременного назначения профилактических мероприятий с целью их снижения.

Почти все научные исследования продемонстрировали важность регулирования метаболических процессов в организме женщины с метаболическим синдромом еще на этапе преконцепционного периода. Сообщается, что модификация образа жизни, которая направлена на снижение массы тела путем назначения сбалансированной гипокалорийной диеты в сочетании с физическими упражнениями и применением поведенческой терапии приводит к улучшению исходов беременности как для матери, так и для ребенка.

Заключение. Проблема метаболического синдрома у женщин репродуктивного возраста остается актуальной в современной медицине и, учитывая свою социальную значимость, требует дальнейших исследований в аспекте изучения патогенеза, ранней диагностики и профилактики указанной патологии, поскольку это может значительно улучшить в будущем состояние беременной и положительно повлиять на течение беременности и родов.

Ключевые слова: метаболический синдром, беременность, гестационные осложнения, патогенез, диагностика, профилактика.

The issue of gestational complications in women with various endocrinopathies remains one of the most important at present, of which metabolic syndrome (MS) is a major one.

In recent years, researchers have demonstrated more interest in studying the role of MS in the pathogenesis of obstetric and perinatal complications [1–4], which is due to several reasons. Firstly, women with MS are at high risk of developing a variety of obstetric pathologies [5–9]. Secondly, according to studies, the incidence of MS among pregnant women is steadily increasing from 12.3% to 38% [4,8,10], and among pregnant women with obesity, it reaches 85% [10].

It has been discussed that lifestyle modification plays an essential role in the MS development, which is associated with restricted physical activity, increased caloric intake of food and a steady increase in emotional stress [2,5,11,12].

Frequent complications of pregnancy and childbirth in women with MS include pre-eclampsia, pregnancy failure, placental dysfunction, thromboembolic complications, gestational diabetes, obstetric abnormalities, post-partum coagulopathy, and antenatal fetal death. Pre-eclampsia is considered the leading obstetric complication [3,6,9,11,13]. The risk of pre-eclampsia in women with a body mass index (BMI) > 30 kg/m^2 is 3–5-fold higher than in healthy pregnant women [14,15]. In addition, MS is a risk factor for both morbidly overweight and underweight children, which, in turn, increases the risk of lifetime metabolic abnormalities in this group of children [3,16].

Obstetric complications, responsible for high levels of maternal and perinatal morbidity and mortality, are listed as «major obstetric syndromes»[17,18]. The term has become widely accepted in clinical practice since the publication of G.C. Di Renzo and R. Romero in 2009 [19,20]. In terms of general pathogenesis, the «major obstetric syndromes» include pre-eclampsia, fetal growth retardation, macrosomia, premature rupture of membranes, preterm labour, premature detachment of the customarily located placenta, intrauterine fetal death and chronic pregnancy failure [17,18]. In addition, gestational diabetes has recently been published as a significant obstetric syndrome [21]. According to studies, gestational diabetes mellitus develops in 14.3% of women with MS [4].

Despite the significant number of scientific publications on the problem of obstetric and perinatal pathology in women with MS [2,8,9,12], the above data convincingly indicate the insufficient study of pathogenetic mechanisms of the influence of individual factors of MS on the development of the gestational complications, the need for further research and search for pathogenetically justified methods of their correction.

MS is a cluster of four cardiometabolic risk factors, defined by ICD-10 as obesity — E65-E68, dyslipidaemia — E78, arterial hypertension — I10-I15, impaired glucose tolerance or diabetes — E10-E14.

To date, three variants of MS identification are the most popular, namely, by WHO (1999), Adult Treatment Panel III (ATP-III, 2005) and International Diabetes Federation (IDF, 2006) [22].

The WHO recommends the following diagnostic criteria for MS (1999):

— insulin resistance (IR), which may manifest as type II diabetes mellitus (DM) or fasting hyperglycaemia > 6.1 mmol/L, or impaired glucose tolerance, in 2:00 >7.8 mmol/L together with any two or more of the following:

a) arterial hypertension (AH): an increase in blood pressure (BP) over 140/90 mm Hg;

b) plasma triglyceride (TG) levels greater than 1.7 mmol/L and/or high-density lipoprotein (HDL) levels: less than 0.9 mmol/L in men and less than 1 mmol/L in women;

c) BMI ≥30 kg/m^2 and/or waist/hip ratio: more than 0.9 in men, more than 0.85 in women.

In the USA, new, much simpler criteria for the diagnosis of MS have been proposed (ATP-III, 2005). According to these criteria, to establish the

diagnosis of MS, a patient must have three or more of the following signs:

— abdominal obesity is characterised by a waist circumference of more than 92 cm in men and more than 88 cm in women;

— increased plasma TG content of more than 1.69 mmol/L;

— decreased HDL-C: less than 1.0 mmol/L in men and less than 1.29 mmol/L in women;

— AH or a history of high blood pressure over 130/85 mm Hg or antihypertensive therapy;

— a history of fasting hyperglycaemia of more than 6.1 mmol/L.

According to the consensus (IDF, 2006), to diagnose the MS following abdominal obesity requires a waist circumference of over 94 cm in males and 80 cm in females in Caucasians; also, any two features described in the guidelines (ATP-III, 2005) have to be detected. Consequently, this consensus does not require a diagnosis of IR, but it does exclude the possibility of diagnosing MS in non-obese individuals.

Based on contemporary studies, the key to the formation of MS is IR, the development of which is associated with both genetic factors and abdominal obesity [16,23]. Furthermore, markers of MS have been found to affect female reproductive function, severely limit the adaptive capacity of the maternal body, provoke the development of many obstetric complications and worsen pregnancy [1,24,25].

It has been proved that maternal insulin does not penetrate the placenta; by contrast, it is destroyed by the enzyme insulinase. Therefore, in conditions of chronic hyperglycaemia, the fetal pancreas produces excessive amounts of insulin. Excess carbohydrates are converted into fat by fetal insulin. The combination of maternal hyperglycaemia and excess fetal insulin production is one of the causes of macrosomia, which occurs in one in three pregnant women with MS [1]. In addition, hyperglycaemia activates peroxidation processes, the products of which inhibit endothelial production of nitric oxide, which is a potent vasodilator and has an antiaggregant effect. The activation of peroxidation in endothelial cells in MS leads to increased production of vasoconstrictor, prothrombotic, proliferative and pro-inflammatory substances, eventually leading to severe tissue hypoxia and, consequently, to the development of major obstetric syndromes [11,25].

Lipid metabolism disorders in pregnant women with MS are expressed in the accumulation of TG by endothelial cells with the formation of systemic endotoxemia, endothelial dysfunction, and, consequently, the development of the clinical picture of pre-eclampsia [26]. This leads to an increased incidence of operative caesarean delivery [6,8,13]. In addition, hyperlipidemia causes acute spiral atherosclerosis, which impairs uteroplacental blood flow and increases the risk of stillbirth by 2.1–4.6 times in women with multiple sclerosis. [14].

According to epidemiological studies, hypertriglyceridaemia is often combined with a state of hypercoagulability and impaired fibrinolytic activity [1,25]. Hypercoagulation in MS occurs due to increased activity of plasma hemostasis, decreased fibrinolysis, the occurrence of endothelial dysfunction and increased platelet activity [16,27]. Disorders in the coagulation and fibrinolysis system are additional factors that worsen the course of pregnancy and increase the risk of thrombotic complications in women with MS [3,9,28]. Given the thrombophilic component of MS, the assessment of hemorheological parameters is at the forefront of current research [7,10,24,29]. The risk of pulmonary embolism in pregnant women with MS is more than doubled [14].

Increasing attention is being paid to the study of the effect of MS on the course of pregnancy as a recognised predictor of endotheliopathy and thrombophilia, factors contributing to the impaired vascular tone of the uteroplacental complex [8,13,29]. Reduced placental blood flow leads to placental ischaemia, which involves compensatory mechanisms aimed at restoring its perfusion. Additionally, vasopressor factors released by the placenta exacerbate endothelial dysfunction, which leads to BP progression and pre-eclampsia, closing a «vicious circle» [13,30]. To compensate for these impairments, in order to block TG in fat cells and prevent hyperglycemia, the insular apparatus of the pancreas has to increase insulin production, resulting in hyperinsulinemia [25]. Influenced by hyperinsulinemia, reabsorption of sodium in the tubules of the kidneys increases. Increased sodium levels in the blood lead to hypervolemia, circulating blood volume, and elevated BP, which constitute a significant pre-eclampsia feature [7,14,25]. In addition, hyperinsulinemia boosts sympathoadrenal activity, increases vascular tone and peripheral vascular resistance, and leads to higher BP [14,25]. Hyperinsulinemia increases leptin concentrations in women with MS during pregnancy, also considered a pathogenetic mechanism of pre-eclampsia and placental dysfunction [31].

Given the pathogenetic features of obstetric complications in women with MS, the recommen-

dations of the American Diabetes Association (2015) [32] and those of the Uniform Protocol of Care for Type II DM [33], hypertension [34], preventive measures have to begin at the pre-pregnancy stage with lifestyle modification, with weight loss as the core of the treatment. Proper nutrition, increased physical activity, and psychological support are crucial to weight loss [35,36]. Although the need for weight loss in pre-conception and pregnancy is evident, how overweight women eat is widely debated [20,37–39].

Existing dietary options, limiting saturated fats and digestible carbohydrates, suggested by current studies, can reduce IHD, improve carbohydrate metabolism, improve the lipid spectrum, reduce AH and obtain positive changes in the haemostatic system [20,38].

The review [40] reported that individuals with untreated eating disorders have higher rates of comorbid psychiatric disorders and are more severely affected by cardiovascular disease compared with those without an eating disorder. In addition, obesity as a significant component of MS reduces physical health and negatively affects stress perception, mood symptoms, quality of sleep, and quality of life, leading to further weight gain [12].

A systematic review and meta-analysis [41] report that lifestyle modification aimed at weight loss also reduces symptoms of depression. In a multicentre randomised trial [39], mental wellbeing and good sleep quality are important determinants of adequate day-to-day functioning. They might increase motivation to lose weight and lead to better weight maintenance.

Reducing physical activity is the second most important environmental factor after overeating. It contributes to obesity, and hypodynamia leads to slower lipolysis and TG utilisation in muscle and adipose tissue and reduced glucose transporter translocation, leading to IR development [5,25]. A systematic review, where six databases (Pubmed, CINAHL, Psyarticle, SportDiscus, Web of Science and Proquest) were researched by independent reviewers, demonstrated knowledge of motivation, barriers and preferences for physical activity in individuals with BMI $\geq$30 kg/m^2. Based on the four available studies, walking is considered to be the best mode of physical activity [42].

However, to date, no randomised controlled trial has demonstrated an effective means of weight loss that leads to improved pregnancy outcomes for both mother and child [43].

The results of a longitudinal randomised controlled trial currently underway in the Netherlands are considered very promising [36]. It is expected that cognitive behavioural therapy delivered by a mental health professional together with a nutritionist and a physiotherapist (a three-pronged intervention) will be more effective in promoting healthy lifestyles and achieving weight loss in the long term, which in turn will improve reproductive and metabolic outcomes as well as the quality of life.

The International Federation of Gynaecology and Obstetrics (FIGO) guidelines [44], based on evidence-based interventions, set out standards for universal screening for pre-eclampsia in the first trimester and its prevention. Universal screening includes maternal risk factors, measurement of the mean value of arterial blood pressure (MBP), serum placental growth factor (PLGF) and uterine pulsatility index (UTPI).

Women with MS have to be screened for gestational diabetes. Moreover, a mandatory two-hour glucose tolerance test at 24–28 weeks is recommended [14]. On top of that, pregnant women at high risk of pre-eclampsia, including women with MS, ought to receive aspirin prophylaxis from 11–14 + 6 weeks gestation at a dose of 150 mg until 36 weeks of pregnancy (level of evidence A) [44].

In women with a low calcium intake (<800 mg/d), calcium replacement ($\leq$1 g of elemental calcium daily) or calcium supplementation(1.5–2 g of essential calcium daily) can reduce by about half the risk of pre-eclampsia, preterm delivery, death or severe morbidity [45].

If a pregnant woman has two or more additional risk factors for thromboembolic complications, prophylaxis with low molecular weight heparin, in addition to aspirin, is recommended. In women with a BMI of 40 kg/m^2, postpartum thromboprophylaxis is mandatory in MS, irrespective of the mode of delivery. Earlier mobilisation of the woman after delivery reduces the risk of thromboembolic complications [14].

Conclusions

The paper has summarised the current aspects of pathogenesis, diagnosis and prevention of gestational complications in women with MS. It has been proved that MS components play an important role in the significant obstetric complications development, which affect the further prognosis for mother and child.

Given the high prevalence of MS in women of reproductive age, the need for further study and introduction into obstetric practice of new modern methods of diagnosis and prevention of gestational complications in pregnant women

with MS is relevant. Consequently, it can significantly improve the condition of pregnant women and positively affect the course of pregnancy and childbirth.

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