https://doi.org/10.46389/rjd-2023-1280
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2023; volume 30, issue 2, pages 254-258

Review

Metabolic syndrome as a risk factor for the development of preeclampsia in pregnant women

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Received: 3 January 2023 / Accepted: 20 May 2023

Abstract

The main task of modern obstetrics, along with reducing maternal and perinatal mortality, is improving the health of the expectant mother, fetus and newborn. In recent decades, one of the leading topics that concern doctors all over the world, including obstetricians and gynecologists, is metabolic disorders, which in turn is the starting point for the development of complications from the second half of pregnancy. Preeclampsia is a complication of pregnancy characterized by a profound disorder of the functions of vital organs and systems of the expectant mother. Undoubtedly, preeclampsia, which from a pathogenetic point of view is one of the clinical manifestations of the "great obstetric syndrome" and is a multisystem pathological condition, continues to be an urgent problem of modern obstetrics. It is preeclampsia that makes up a significant share in the structure of maternal and perinatal morbidity and mortality. Perinatal mortality in severe forms of preeclampsia is 18–30%, and perinatal morbidity is 64–78%.

Keywords: preeclampsia, metabolic syndrome, markers, diagnosis, treatment.

Introduction

Preeclampsia, a hypertensive disorder during pregnancy, is a major cause of maternal and fetal morbidity and mortality. For a long time, preeclampsia has been considered a heterogeneous disorder with a pathogenesis that includes many factors, occupying the third place in the structure of maternal mortality. The etiology of the development of preeclampsia in scientific circles contributes to the emergence of discussions. There are many hypotheses regarding the occurrence of this pregnancy complication, in particular: maladaptation, ischemia of the placenta, hormonal, immune and toxic effects. Weight gain during pregnancy causes the occurrence of oxidant stress and the occurrence of endothelial dysfunction, which correlates with the severity of late gestosis, a combination of inhibition of cytotrophoblast invasion into the spiral arteries of the uterus and microcirculation disorders.

There are many theories of the development of preeclampsia, each of which explains only part of the symptoms. Therefore, the problem of the etiology of preeclampsia remains open. One of the reasons for the development is considered to be a violation of placentation, a pathological transformation of the muscular layer of the spiral arteries. These changes lead to a decrease in the content of oxygen in the placental perfusion, thereby stimulating trophoblast cells to produce angiogenesis and antiangiogenic factors. Their imbalance causes systemic endothelial dysfunction and vasospasm, leading to preeclampsia clinical manifestations.

Preeclampsia is a complication of pregnancy characterized by a profound disorder of the functions of vital organs and systems of the expectant mother. The most important factors affecting the course of pregnancy in patients with preeclampsia are timely and early diagnosis, as well as a full assessment of its severity, which affects further management strategies. That is why it is

important to search for new predictors of the development of preeclampsia. The issues of the course of pregnancy and childbirth in women whose pregnancy was complicated by preeclampsia against the background of metabolic syndrome remain insufficiently studied.

Weight gain during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes, independent of prepregnancy body mass index. In addition to glycemic control, weight control in women with gestational diabetes should be given special attention to prevent adverse pregnancy outcomes. Abnormal body weight measurement during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes among women [1].

The pathogenesis of preeclampsia is associated with inflammation and damage to the endothelium. Ulinastatin mainly inhibits proteolytic activity and significantly reduces the release of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) from macrophages. It also reduces vascular endothelium damage in pathological conditions [2].

Metabolic syndrome is a serious problem affecting the general condition of a person, the indicators of which are constantly increasing in all areas of medicine. Important risk factors for metabolic syndrome, such as hyperlipidemia, obesity, hypertension, and fasting hyperglycemia, are associated with stressors: smoking, unbalanced diet, and sedentary lifestyle. A large group of scientists supports the hypothesis that exposure at the perinatal stage determines the risk of developing metabolic syndrome in humans [3].

The spread of obesity is associated with non-infectious diseases – the occurrence of type II diabetes and non-alcoholic fatty liver disease. Only 29.3% of the population of our country has a normal body weight, and 70.7% are overweight. Signs of obesity in children are increasing every year; now, it is 10 times higher than in previous years. In adulthood, obesity reveals correlations with metabolic disorders [4, 5].

The problem of preeclampsia is one of the serious complications in modern obstetrics and remains a formidable disease of the second half of pregnancy, despite significant advances in diagnosis, prevention and treatment. Despite researchers' great interest in this problem, the question of etiology and pathogenesis remains debatable. To date, there is no unified classification, diagnostic and prognostic methods, as well as an algorithm for managing pregnant women with preeclampsia against the background of metabolic syndrome. Timely diagnosis and treatment of this pregnancy complication is one of the most urgent problems of obstetrics and is important in prevention. The high frequency of preeclampsia requires the improvement of diagnostic and treatment methods to rethink scientific experience. Also, there is not enough information in the modern literature about the markers of diagnosis and treatment of preeclampsia against the background of metabolic syndrome; therefore, the problem of diagnosis and choosing the optimal treatment tactics for data management of women remains relevant in the future. All this causes increased interest in the pathogenesis of this problem.

A high risk of complications characterizes the course of pregnancy in women with metabolic syndrome. In this regard, issues of early diagnosis and assessment of severity are key for preventing maternal and perinatal mortality. Thus, the choice of diagnosis, determination of predictors of the development of this complication, prevention, and treatment of preeclampsia against the background of metabolic syndrome is an important and relevant issue today.

When choosing management tactics, that is, in clinical situations that do not pose a threat to the life of the mother and the fetus at this particular stage, stationary observation with monitoring of indicators that informatively reflect the dynamics of the condition of both patients is indicated. It is necessary to understand that drug therapy during pregnancy complicated by preeclampsia has only a symptomatic effect without stopping the development of the pathological process in the vascular system. The development of disseminated intravascular coagulation syndrome inevitably accompanies endothelial dysfunction and vasospasm. Micro coagulants scattered in small-caliber vessels are one of the leading inducers of the development of organ dysfunction, which accompanies this process and leads to the deterioration of hemostatic potential (consumptive coagulopathy). Activation of the hemostasis system begins from the moment of pregnancy complications with preeclampsia [6, 7].

Pregnancy complications in patients with metabolic syndrome occur more often than in pregnant women with normal weight, namely, miscarriage, and preeclampsia, due to which perinatal losses increase. Pregnancy and childbirth against the background of obesity often take on a pathological course (84.8%): placental dysfunction and fetal growth retardation syndrome are diagnosed almost twice as often, and fetal distress is diagnosed 9 times more often. There is a relationship between the number of components of metabolic syndrome, the degree of obesity, and the frequency of pregnancy complications [8].

The influence of metabolic syndrome on the occurrence of moderate preeclampsia was investigated histologically. In the placenta, there were signs of non-compliance of the structure of chorionic villi with the histological norm for a full-term pregnancy. A percentage of 7.5 more often than in healthy women, avascular villi were visualized, 8.75% – the one-two-layer structure of villous epithelium, 7.5% more frequently Kashchenko-Hofbauer cells. The following criteria characterized the morphofunctional state of the epithelium of chorionic villi. Peeling of epithelial structures in the second group was observed 26.25% more often than in the comparison group. At the same time, in the first group, the difference from the control values was minimal – 1.25%. Different vector dynamics were observed in the proliferative activity of the epithelium: the number of such cells in the second group decreased by 22.5%, and in the first group, it increased by 20% [9].

Previous studies have shown that pregnant women do not know about preeclampsia and the impact of metabolic syndrome on the course of pregnancy, which is an important cause of maternal morbidity and mortality. This lack of knowledge can affect their ability to report symptoms, follow recommendations, and receive appropriate follow-up care. Pregnant people commonly seek information from sources outside their treating clinician, including pregnancy books and online sources. The researchers examined commonly used sources of information about preeclampsia to determine whether pregnant people were receiving up-to-date information based on guidelines [10].

Features of modern diagnostic markers

The placental growth factor is an important marker for the prognosis, diagnosis and treatment of preeclampsia. It affects fetoplacental circulation and trophoblast growth. The mechanism of PlGF expression is still under investigation but decreased PlGF has been established as a predictor of clinical disease in pregnancies complicated by preeclampsia. Further studies of PlGF are promising and may help to address the question of predicting the highest risk of adverse pregnancy outcomes [11]. Studies have shown that protein factors may play an important role in the pathogenesis of preeclampsia, and there are many proteins that still need to be studied in the diagnosis of preeclampsia. Previous studies have not evaluated plasma concentrations of LIF or flutazine in women with PE; thus, the obtained results indicate that these proteins are new factors that may play an important role in pathogenesis [12].

Endoglin, inhibin A, and PlGF were highly predictive of preeclampsia. Quantification of pro-RLX2 was not predictive of preeclampsia. However, the potential involvement of relaxin 2 in the pathophysiology of preeclampsia requires further investigation [13]. Given the high prevalence of preeclampsia, this pathology can mask the clinical picture and significantly change the course of the disease with adverse consequences for the mother and the fetus. Currently, there are no definitive tests to predict the risk of preeclampsia [14]. The simultaneous study of the concentration of inhibin A in the blood serum of the mother and the placenta according to the severity of preeclampsia became important in the diagnosis of preeclampsia, and the importance of this biomarker in diagnosis and monitoring was also established. The importance of inhibin A has been demonstrated and studies have been conducted to confirm this and provide quantitative data suggesting a direct link to the development of preeclampsia.

One of the most promising predictors of preeclampsia at present is the soluble form of the tyrosine kinase-like receptor sFlt-1. The substance acts as an antagonist of endothelial and placental growth factors. The possible contribution of its increased concentrations in the first trimester is described, and the effect on endothelial dysfunction and the development of all relevant pregnancy complications are also evaluated. When this factor was later discovered, it was proposed as a screening method to select pregnant women among individuals at high risk of developing preeclampsia [15].

Elevated plasma homocysteine concentrations in the first trimester are associated with a greater likelihood of preeclampsia and fetal growth retardation. Experiments have shown that the vascular network during pregnancy can show increased sensitivity to homocysteine. This effect of homocysteine apparently occurs due to the loss of NO-mediated vasodilation, which is characteristic of oxidative inactivation of the NO synthase cofactor. The concentration of homocysteine is negatively affected by the variety of the diet (especially the consumption of foods with a low content of folic acid and vitamin B12), which leads to an increase in the level of homocysteine and a violation of NO synthesis [16]. An increase in the synthesis of adipokine and a decrease in the production of adiponectin is observed in metabolic syndrome. Systemic concentrations of adipokines and their chronic increase are crucial for developing metabolic syndrome. It is known that TNF-α,

https://doi.org/10.46389/rjd-2023-1280

IL-6 and resistin play a key role in the development of chronic inflammation, and deficiency of angiotensin, leptin and adiponectin play a key role in the development of arterial hypertension and atherosclerosis [17]. When studying chronic systemic inflammation in patients with MS, scientists found that TNF-α (a marker of inflammation in the blood) is strongly associated with insulin resistance, and its severity is directly proportional to accompanying abdominal obesity. Patients with a history of metabolic syndrome had high levels of vasoconstrictor ET-1, indicating endothelial dysfunction [18]. An increase in the synthesis of adipokine and a decrease in the production of adiponectin is observed in metabolic syndrome. Systemic concentrations and chronic elevation of adipokines contribute decisively to the development of metabolic syndrome.

Conceptual selection of treatment

Diet therapy is the main priority of non-drug treatment of patients with a body mass index (BMI) greater than 25 kg/m^2. It is built on the principles of healthy nutrition. Considering the pathogenesis of MS, which triggers its development, is a decrease in sensitivity to insulin, an important preventive measure will be a decrease in the actual concentration of insulin in the blood. It is known that the fasting insulin level depends on many factors, primarily on nutrition and body weight. At the same time, the results of studies on the effectiveness of the use of acetylsalicylic acid in pregnant women with preeclampsia remain questionable, which may be due to the irreversible inhibition of cyclooxygenase-1 biosynthesis by acetylsalicylic acid. As is known, this enzyme is an important participant in the systemic biosynthesis of prostacyclin, which is an effective vasodilator and antagonist of thromboxane A2. Two large meta-analyses have been devoted to the assessment of the effect of aspirin, but their results need to provide convincing data in favor of prescribing these antiplatelet agents. There is an obvious need to find other means with a moderate anticoagulant effect, capable of reducing the aggregation of platelets and thus improving the conditions of micro blood flow during pregnancy complicated by preeclampsia. Such components should not have side effects that could negatively affect the mother's condition and development of the fetus. Currently, there is a long enough and extensive positive experience of using the method of systemic enzyme therapy for this purpose [19], and it is positively correlated with an increase in blood pressure, the level of total cholesterol, uric acid, C-peptide, and negatively with the level of cholesterol.

Early administration of low-dose acetylsalicylic acid in high-risk women reduces the risk of early preeclampsia. The significance of the effect of acetylsalicylic acid on the integration of trophoblasts and its effect on angiogenic and invasive pathways in preeclampsia was studied. Acetylsalicylic acid improves the integration of trophoblast cells into the endothelium by inhibiting the effect of TNF-a without significant effects on antiangiogenic, invasive, or endothelial activation markers [20, 21].

Vitamin D plays an important role in life, however, the optimal vitamin D status during pregnancy is currently unclear. Scientists investigated maternal vitamin D status and its influence on anthropometric and later child neurocognitive outcomes. Extensive research on vitamin D is needed for further study in the field of obstetrics and gynecology [22, 23]. Vitamin D deficiency may be associated with an increased risk of respiratory distress syndrome in premature infants. Recommended vitamin D supplementation during pregnancy may reduce the incidence of respiratory distress syndrome (RDS) in premature infants.

Vitamin D plays an important role in modulating the immune response and acts through the vitamin D receptor. Pregnancy is associated with significant changes in vitamin D metabolism, including increased maternal levels of the active vitamin D 1,25-dihydroxy vitamin D (1,25(OH)2D). This is probably explained by an increase in the renal activity of the enzyme 25-hydroxyvitamin D-1α-hydroxylase, which catalyzes the synthesis of 1,25(OH)2D. The precise function of placental 1,25(OH)2D synthesis remains unclear, but it likely involves localized tissue-specific responses, with both the decidual membrane and the trophoblast, which also express the vitamin D receptor for 1,25(OH)2D. Metabolism of vitamin D during pregnancy reveals striking differences compared to non-pregnant women. Calcitriol increases 2–3 times in the first weeks of pregnancy, while maternal 25-hydroxyvitamin D crosses the placental barrier and is the main pool of the vitamin in the fetus. Moreover, during pregnancy, the vitamin D receptor and regulatory metabolic enzymes expressed in the placenta and decidua indicate a potential critical point for maternal-fetal immunomodulation. Given these effects, maternal hypovitaminosis D during pregnancy may be associated with pregnancy-related disorders [24].

The effects of vitamin D with or without calcium during pregnancy reduce the risk of preeclampsia and

hypertension. The analysis showed that calcium and vitamin D can reduce the risk of preeclampsia compared to placebo. Therefore, calcium and vitamin D preparations can be used to prevent preeclampsia and endothelial dysfunction caused by placental ischemia by reducing resistance to placental soluble FMS-like tyrosine kinase-1 [25].

Conclusion

Summarizing the analysis of the literature described above, it can be established that at the moment, there is no clear opinion regarding the connection of obstetric pathology with metabolic disorders and obesity in pregnant women, there is no unanimous pathogenetic rationale for this problem, and, therefore, there are no quick, accessible screening diagnostic tests. Prospects for the development of the problem foresee further modern search and necessary studies of markers of the development of preeclampsia. The possibility of choosing a reasonable management tactic for patients whose pregnancy was complicated by preeclampsia against the background of metabolic disorders.

Conflict of interest

The authors declare no conflict of interest.

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