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ANALYSIS OF RISK FACTORS FOR OBSTETRIC AND PERINATAL COMPLICATIONS PATHOGENETICALLY LINKED TO GESTATIONAL DIABETES MELLITUS

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Purpose: To analyze the prevalence of gestational diabetes mellitus among pregnant women and evaluate its impact on maternal and neonatal quality of life.

Materials and Methods. A comprehensive review of contemporary scientific literature from the past ten years was conducted using databases such as PubMed, Scopus, and Web of Science. The selection included studies examining epidemiological data, metabolic and angiogenic markers, and clinical outcomes associated with gestational diabetes mellitus. Comparative and analytical methods were applied to summarize current findings and identify key determinants influencing disease development and pregnancy outcomes.

Results. The analysis revealed a global increase in the prevalence of gestational diabetes mellitus, ranging from 2% to 38% depending on population and diagnostic criteria. GDM was shown to significantly contribute to maternal complications such as preeclampsia, hypertension, and metabolic syndrome, as well as adverse neonatal outcomes including macrosomia, hypoglycemia, and long-term metabolic disorders. Furthermore, alterations in angiogenic balance were identified as an important pathogenetic link between GDM and placental dysfunction. Early detection and preventive management strategies were found to improve pregnancy outcomes and reduce perinatal risks.

Conclusion: Gestational diabetes mellitus represents a major metabolic and vascular challenge in pregnancy, underscoring the need for early diagnostic screening and targeted interventions to improve maternal and neonatal health outcomes.

KEY WORDS: **gestational diabetes mellitus; metabolic disorders; quality of life; angiogenesis factors; placental dysfunction; maternal complications; neonatal outcomes.**

Improving maternal health and reducing child mortality are among the 17 Sustainable Development Goals adopted in 2015 at the United Nations Assembly. Ukraine, as a member of the UN, joined this landmark global initiative. Guided by international standards and recommendations aimed at improving maternal and child health, the All-Ukrainian Association of Obstetricians and Gynecologists focuses its efforts on long-term preventive and evidence-based strategies to reduce maternal and perinatal morbidity, with the overarching objective of safeguarding the health of future generations.

Within the framework of the national program for the preservation of women's reproductive health, and based on the principles of "4P medicine" (predictive, preventive, personalized, and participatory), particular attention is directed toward scientific research aimed at developing effective diagnostic models for preventing pregnancy complications and perinatal pathologies.

A fundamental component of a successful pregnancy is high-quality antenatal care provided in an outpatient setting, supported by timely antenatal screening. At this stage, the primary responsibility of the obstetrician-gynecologist lies in ensuring consistency in the promotion of a healthy lifestyle. This dimension of clinical practice encompasses several essential aspects: balanced nutrition, regular physical activity, avoidance of harmful habits, adequate sleep, and, equally importantly, the cultivation of a positive attitude in pregnant women toward their active role in monitoring physiological changes during pregnancy and in responding promptly to any pathological deviations.

In recent decades, under the influence of various external and internal factors, there has been a growing trend in the incidence of alimentary obesity, hypertension, and hyperglycemia. These conditions significantly alter the physiological parameters of the menstrual cycle and, consequently, predispose to pathological courses of pregnancy or even lead to the loss of fertility [1]. Therefore, the implementation of effective tools for the prevention and prediction of gestational complications is an essential aspect of modern pregnancy management.

According to data from The Developmental Origins of Health and Disease (DOHaD), the perinatal environment and maternal nutrition exert a persistent

conditioning or programming effect on metabolic processes, influencing long-term outcomes for both the mother and the newborn. Moreover, these factors contribute to health risks that are likely to persist across future generations [1].

The aim of the study is to analyze current scientific data on the pathogenetic mechanisms and risk factors associated with gestational diabetes mellitus and its impact on obstetric and perinatal complications.

Materials and methods. This study is a narrative literature review based on the analysis of scientific publications from the last ten years (2015–2024). The search was conducted using electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar. Keywords included *gestational diabetes mellitus, metabolic disorders, angiogenesis factors, placental dysfunction, pregnancy complications*. Preference was given to original research articles, systematic reviews, and clinical guidelines from recognized professional associations, including the American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG). The selected sources were analyzed to identify key pathogenetic mechanisms, diagnostic criteria, and prognostic biomarkers related to gestational diabetes mellitus and its obstetric and perinatal consequences.

Research results and their discussion. One of the common physiological changes that may occur during pregnancy is the development of impaired glucose tolerance, which leads to hyperglycemia. This condition during pregnancy is defined as gestational diabetes mellitus (GDM) [2].

The American Diabetes Association (ADA) formally classifies GDM as “diabetes first diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes (type 1 or type 2) prior to gestation.” [3] The American College of Obstetricians and Gynecologists (ACOG) continues to define GDM as “a condition in which carbohydrate intolerance develops during pregnancy.” [4]

GDM is the fastest-growing type of diabetes worldwide. It is estimated that approximately one in ten pregnant women globally experiences some form of hyperglycemia during pregnancy, 84% of which are classified as GDM [1]. Statistical analyses indicate a heterogeneous global prevalence of GDM, with incidence rates ranging from 2% to 38% of pregnancies. The estimated prevalence varies considerably depending on the diagnostic criteria applied and the characteristics of the studied population.

The pathophysiology of GDM is not yet fully understood. It is characterized by impaired glucose tolerance resulting from dysfunction of the maternal pancreatic β-cells, leading to insufficient insulin production to maintain glucose homeostasis during pregnancy [2].

During normal physiological pregnancy, the mother develops a state of progressive insulin resistance induced by placental hormones such as growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone [2]. This adaptive mechanism ensures that the fetus receives an adequate supply of nutrients for healthy growth and development. To maintain glucose homeostasis despite the presence of insulin resistance, maternal β-cells compensate by increasing their overall number and by enhancing insulin synthesis and secretion.

According to The American Diabetes Association (ADA) Standards of Care in Diabetes, insulin resistance begins to increase at approximately the 16th week of gestation, and total daily insulin requirements rise linearly by about 5% per week until the 36th week [3]. Insulin resistance is a condition in which a normal concentration of insulin fails to elicit an adequate biological response due to decreased cellular receptor sensitivity. As a result, β-cells secrete higher-than-normal amounts of insulin to regulate maternal blood glucose levels. However, in the absence of adequate adaptation of maternal β-cells to the metabolic changes associated with pregnancy, hyperglycemia develops–manifesting as gestational diabetes mellitus (GDM).

Maternal hyperglycemia influences the enhanced expression of antiangiogenic factors, which, upon entering the uteroplacental circulation, lead to its disruption and result in secondary placental dysfunction [5].

The stratification of GDM risk factors has made it possible to identify specific high-risk groups, including: overweight and obesity (BMI ≥ 25 kg/m²), maternal age ≥ 35 years, a family history of diabetes mellitus in first-degree relatives, belonging to ethnic groups with a high prevalence of diabetes (such as Indigenous populations, Hispanics, South Asians, East Asians, and Africans), polycystic ovary syndrome, acanthosis nigricans, a history of GDM, and a history of fetal macrosomia [4].

Recent data on GDM indicate an increased risk of both short-term and long-term complications for the mother and the fetus. Adverse obstetric outcomes include a higher incidence of macrosomia or large-for-gestational-age fetuses (>90th percentile), neonatal hypoglycemia, jaundice, respiratory distress syndrome, stillbirth, preeclampsia, preterm delivery, instrumental or operative deliveries, and birth trauma [1; 6]. In the long term, children born to mothers with GDM have an elevated risk of developing obesity, type 2 diabetes mellitus, and cardiovascular diseases during childhood, adolescence, and adulthood [2; 6].

Moreover, several studies have demonstrated that women with GDM have a sevenfold higher risk of developing type 2 diabetes mellitus, as well as an increased likelihood of developing arterial hypertension, dyslipidemia, and metabolic syndrome

compared with women without this condition [1]. GDM serves as an important determinant of type 2 diabetes mellitus development in both mothers and their offspring. Consequently, achieving optimal glycemic control during pregnancy may provide a critical window of opportunity for preventing the onset and reducing the incidence of type 2 diabetes mellitus across multiple generations [2].

According to the sectoral standard of medical care "Normal Pregnancy" (Order of the Ministry of Health of Ukraine No. 1437, dated August 9, 2022), screening for GDM is typically performed using a 2-hour oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation [8; 12]. Existing diagnostic methods for GDM identify women only after the diagnosis has already manifested and pancreatic β-cell insufficiency has occurred. Such late diagnosis exposes both the pregnant woman and the fetus to the risks associated with early and prolonged maternal hyperglycemia.

However, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) also recommends screening for overt diabetes at the first prenatal visit [3]. There is no clear consensus regarding which method should be used for this purpose – whether fasting plasma glucose, random plasma glucose, or HbA1c assessment – nor on whether such screening should be applied universally or only to high-risk subgroups of the population. Consequently, the diagnosis of "early GDM" remains controversial, and the methods employed for its detection vary considerably.

Given the established association between GDM and adverse pregnancy outcomes, there remains a pressing need to investigate novel early diagnostic and prognostic biomarkers of GDM [2]. Such research aims to prevent the development of future diabetes-related complications during pregnancy and to ensure favorable neonatal outcomes.

The process of placental angiogenesis is based on the anatomical and morphological transformations of chorionic villi throughout placentogenesis. Feto-placental angiogenesis and vascular development are tightly regulated by the interaction between pro-angiogenic and anti-angiogenic factors.

A well-developed vascular network is essential for proper placental formation and function and depends on a balance between pro-angiogenic and anti-angiogenic regulators, including vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), soluble endoglin (sEng), endothelin-1 (ET-1), and granulocyte colony-stimulating factor (G-CSF) [8; 9; 11].

An abnormal placental vascular system is considered one of the most common placental pathologies, observed in numerous pregnancy complications, including gestational diabetes mellitus (GDM) and preeclampsia (PE) [9; 10; 13]. The expression of these angiogenic biomarkers–particularly in the early stages of pregnancy–promotes vascular development and angiogenesis and is regarded as one of the most significant factors in the regulation of pregnancy progression.

VEGF promotes angiogenesis during embryonic development, and any disruption in its expression may lead to fatal outcomes as a result of abnormal blood vessel formation during embryogenesis [9; 14].

Angiopoietin-2 (Ang-2) may exert either pro-angiogenic or anti-angiogenic effects depending on the presence of VEGF. In the absence of VEGF, Ang-2 promotes endothelial cell apoptosis, vascular regression, and inhibition of angiogenesis. However, in the presence of VEGF, Ang-2 acts as an antagonist of Ang-1, destabilizing the interaction between endothelial and supporting cells, inducing vascular instability, and promoting the formation of disorganized and immature new blood vessels [8; 9; 15].

Endoglin, by contrast, is an anti-angiogenic molecule that plays a significant role in pregnancy complications. Stimulation of the endothelin-1A receptor (ET-1A) through endothelin-1 (ET-1) induces vasoconstriction, whereas activation of the endothelin-1B receptor (ET-1B) results in vasodilation. Therefore, increased stimulation or dysregulation of the ET system in pregnant women leads to hypertension, contributing to the development of preeclampsia (PE) [9; 12].

In 2017, Rizov M. et al. reported that alterations in paracrine angiogenic biomarkers affect the fetoplacental endothelium and may contribute to the development of GDM and subsequent maternal and neonatal complications [8; 11]. These include an increased risk of preeclampsia (PE), recurrent miscarriage, retinopathy, and elevated birth weight in newborns.

During a normal pregnancy, the concentration of the anti-angiogenic factor sFlt-1 (soluble fms-like tyrosine kinase-1) remains low, allowing for proper signaling mediated by the pro-angiogenic factors VEGF and PlGF (placental growth factor). This balance is crucial for maintaining physiological vasodilation. Under conditions of placental hypoperfusion, the placenta increases sFlt-1 synthesis, thereby elevating maternal blood pressure and improving placental perfusion. Consequently, this process contributes to GDM-associated alterations in placental angiogenesis: circulating levels of pro-angiogenic factors decrease, vascular homeostasis becomes disrupted, and endothelial dysfunction develops – ultimately leading to hypertension, proteinuria, and other multi-organ manifestations in the mother.

The sFlt-1/PlGF ratio has been extensively studied since 2004 as a diagnostic and prognostic marker of preeclampsia (PE) and other manifestations of placental dysfunction. To date, the large prospective

clinical study “PROGNOSIS” has clearly demonstrated that an sFlt-1/PlGF ratio of 38 or lower can be used to reliably exclude PE within one week, regardless of gestational age [10; 15].

Conclusions. Thus, the presence of gestational diabetes mellitus (GDM) in a pregnant woman represents a significant risk factor for the development of placental dysfunction, the underlying mechanism of which is an imbalance of angiogenic biomarkers and disruption of compensatory adaptive mechanisms. These alterations may lead to pregnancy and delivery complications, as well as to maternal and neonatal morbidity.

Prospects for further research involve identifying and validating novel early biomarkers of gestational diabetes mellitus to improve prediction, prevention, and management of pregnancy and perinatal complications.

Conflicts of Interest. The authors declare no conflict of interest.

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АНАЛІЗ ФАКТОРІВ РИЗИКУ АКУШЕРСЬКИХ ТА ПЕРИНАТАЛЬНИХ УСКЛАДНЕНЬ, ПАТОГЕНЕТИЧНО ПОВ'ЯЗАНИХ З ГЕСТАЦІЙНИМ ЦУКРОВИМ ДІАБЕТОМ

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Мета: проаналізувати поширеність гестаційного цукрового діабету серед вагітних жінок та оцінити його вплив на якість життя матері й новонародженого.

Матеріали та методи. Проведено комплексний огляд сучасної наукової літератури за останні десять років із використанням баз даних PubMed, Scopus та Web of Science. Відбір передбачав дослідження, що аналізували епідеміологічні дані, метаболічні та ангіогенні маркери, а також клінічні наслідки, пов'язані з гестаційним діабетом. Для узагальнення результатів і визначення основних чинників, що впливають на розвиток захворювання та перебіг вагітності, застосовано порівняльно-аналітичні методи.

Результати. Аналіз показав глобальне зростання поширеності гестаційного цукрового діабету – від 2 % до 38 % залежно від популяції та діагностичних критеріїв. Установлено, що ГЦД значно підвищує ризик ускладнень у матері, як-от прееклампсія, гіпертензія та метаболічний синдром, а також негативно впливає на стан новонародженого, спричинюючи макросомію, гіпоглікемію та довготривалі метаболічні порушення. Крім того, порушення ангіогенного балансу визначено як важливу патогенетичну ланку між ГЦД і плацентарною дисфункцією. Раннє виявлення та профілактичне лікування дають змогу покращити результати вагітності й знизити перинатальні ризики.

Висновок. Гестаційний цукровий діабет є суттєвою метаболічною та судинною проблемою вагітності, що підкреслює необхідність раннього скринінгу й цілеспрямованих профілактичних заходів для покращення стану здоров'я матері та новонародженого.

КЛЮЧОВІ СЛОВА: **гестаційний цукровий діабет; метаболічні порушення; якість життя; фактори ангіогенезу; плацентарна дисфункція; материнські ускладнення; неонатальні результати.**

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