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§9.2 HYPERTENSIVE DISORDERS DURING PREGNANCY: DIAGNOSTIC AND PROGNOSTIC VALUE OF ANGIOGENESIS REGULATION MARKERS

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Introduction. Nowadays, the issue of predicting the development and severity of hypertensive disorders in pregnant women, like preeclampsia remains of current importance. Originating from the Greek for «flash», eclampsia was first named by Celsus, a philosopher from ancient Greece, as a sudden, severe convulsion disorder exclusive to pregnant women, known for its rapid onset and severe impacts on both mother and fetus. The early signs, such as swelling and the presence of protein in urine, were only linked to the condition in the XIX century, leading to the recognition of an initial stage termed «preeclampsia», indicating the phase occurring before eclampsia manifests. This condition is considered one of the most threatening complications during pregnancy. According to the World Health Organization, severe preeclampsia complicates 2% to 8% of all pregnancies worldwide, and it ranks second in the structure of causes of maternal mortality, accounting for about 14% [1, 2, 3]. Annually, complications associated with hypertensive disorders result in the deaths of over 50,000 pregnant women globally. In developed countries, they are the second direct cause of antenatal and postnatal mortality in 12-18% of cases and affect perinatal mortality in 20-25% of cases.

It should be noted that the International Federation of Gynecology and Obstetrics defines the causes of maternal mortality related to hypertensive

disorders during pregnancy, including preeclampsia, as preventable. Most deaths caused by hypertensive disturbances could be avoided provided that women suffering from such complications are given timely and effective medical assistance. This makes the search for effective and accurate methods of predicting the occurrence and development of this pathology in pregnant women one of the priority tasks of modern obstetrics [4, 5, 6].

Presentation of the Main Material. Preeclampsia in pregnant women is a multisystem disorder specific to the human species, developing in women during the second half of pregnancy. It represents a clinical form of gestational endotheliopathy and is associated with maternal symptoms of hypertension and proteinuria. It manifests through heterogeneous disorders of organs and organ systems, adversely affecting the condition of both the mother and the fetus. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), preeclampsia is a condition characterized by a combination of high blood pressure (systolic/diastolic BP over 140/90 mmHg) and significant proteinuria (over 300 mg/day) manifesting after the 20th week of pregnancy [7]. The diagnosis, screening, and assistance in preeclampsia, as well as the classification of the severity of this disorder, remain subjects of controversy. Despite numerous fundamental clinical studies, the pathogenesis of preeclampsia has not been fully elucidated to date, and the only pathogenetically substantiated method of treatment remains premature delivery. The only definitive solution for preeclampsia involves the birth of the placenta. Deciding when to deliver balances extending the pregnancy for fetal development against the risk of maternal health issues. However, specific treatments to safely delay delivery are largely unavailable. Treatment primarily aims at managing the mother's blood pressure to reduce risks. [8, 9].

According to current clinical protocols in Ukraine, pregnant women are classified into risk groups for the development of preeclampsia based on the

analysis of clinical and anamnestic data [10]. Literary sources recommend differentiating identified factors into two categories – high and moderate risk, as a basis for the prescription of prophylaxis depending on specific conditions [11]. Unfortunately, it has been established that the method based on the analysis of the pregnant woman's anamnestic data allows predicting only 37% of cases with a later early manifestation of preeclampsia and 29% with a late manifestation, with a false positive rate of 5% [12].

Similarly, the National Institute for Health and Care Excellence (NICE) in the UK and the American College of Obstetricians and Gynecologists consider the analysis of anamnestic data as the only recommended method of preeclampsia screening [13, 14]. The effectiveness of screening according to NICE is 41% for cases of preeclampsia identified up to 32 weeks, 39% up to 37 weeks, and 34% after 37 weeks. Using the screening recommended by ACOG, preeclampsia is detected in 94% of cases up to 32 weeks, in 90% up to 37 weeks, and in 89% at terms beyond 37 weeks. However, the false positive results amount to 64.2% [15].

According to current understanding, preeclampsia is a multifactorial disease with endothelial dysfunction being one of the key mechanisms in its pathogenesis [16, 17]. There are several potential serological markers for predicting the development of preeclampsia. Most of them are produced by trophoblast cells and ensure its invasion and adequate remodeling of the uterine vascular bed. Under physiological pregnancy conditions in the first trimester, the transition of trophoblast from proliferative to invasive depends on the concentration of oxygen, which decreases towards the placenta from the decidua. An oxygen-depleted environment induces trophoblast proliferation, protects the trophoblast from oxidative stress, and increases angiogenic factors involved in the development of the placental vascular network and endothelial function support.

Insufficient trophoblast invasion is considered one of the leading mechanisms in the pathogenesis of preeclampsia, leading to disturbed angiogenesis, endothelial dysfunction, changes in immunoreactivity, development of hypoxia, placental dysfunction, and ultimately the manifestation of the preeclampsia syndrome itself. Persistent hypoxia in the environment under preeclampsia creates a vicious cycle with high levels of factors that inhibit trophoblast invasion and lead to insufficient placentation with impaired remodeling of spiral arteries and the development of hypercoagulation [18].

Determining changes in angiogenic factor levels is not only useful as diagnostic tests for preeclampsia but also allows for assessing the risk of developing adverse pregnancy outcomes associated with preeclampsia. Angiogenic factors, in addition to early pre-clinical diagnosis of preeclampsia, can be helpful in differential diagnosis of preeclampsia with other vascular disorders of pregnancy (gestational and chronic hypertension) [19].

Moreover, an essential feature of angiogenesis markers is their ability to differentiate actual preeclampsia from chronic hypertension, which was not previously detected, and chronic kidney disease, as the pathogenesis links of these diseases and the clinical manifestations of the mentioned pathologies overlap [20].

However, this issue requires further research. In addition to anamnestic, clinical, and biochemical predictors of preeclampsia, a combination of tests including ultrasound examination with dopplermetry fetoplacental circulation and ultrasound assessment of placental structure is considered. In the second trimester of gestation, long before the appearance of clinical symptoms of preeclampsia, disturbances in uterine blood flow were registered in pregnant women. According to existing studies, ultrasound dopplermetry indices of blood flow in the uterine arteries in pregnancies that subsequently became complicated by preeclampsia were higher than similar parameters under physiological pregnancy conditions.

Thus, pregnant women with impaired uterine blood flow in the second trimester are classified as high risk for developing preeclampsia. In the third trimester, with the development of preeclampsia and increasing severity, pathological changes progress: changes in fetoplacental blood flow accompany the disturbance in uteroplacental blood flow [21].

Studying ultrasound dopplermetry indices in the «mother-placenta-fetus» complex in pregnancies complicated by preeclampsia is currently relevant and can significantly improve the accuracy of diagnosis in combination with other methods.

Sequencing the human genome, the discovery of single nucleotide polymorphism (SNP) phenomena in genes and studying the impact of the genetic code on quantitative changes in expression and protein function have opened possibilities for investigating the genetic component in the theory of preeclampsia development [22, 23]. An analysis of genetic polymorphism association conducted in a Europoid population in the PGF area revealed that two SNPs (rs2268614 and rs11850328) are associated with plasma PGF levels. The genetic variant rs2268614 is found within the third intron, while rs11850328 is situated 4.3 kilobases upstream of the gene's transcription initiation site. Given the high linkage disequilibrium between these two SNPs, two alternative hypotheses can be formulated: 1) one of the two identified SNPs plays a functional role in altering PGF levels; 2) both SNPs are in linkage disequilibrium with another unidentified causal variant.

A similar analysis for SNP rs2268614 also identified a potential binding site for the SNP: it is located in the core sequence of the binding site for GA-binding factors. Therefore, both SNPs appear to be potential candidates for causally modulating PGF levels. However, functional studies are required to demonstrate a direct link between these SNPs and PGF levels. This study also shows that the

impact of genetic and environmental factors on circulating PGF levels is independent of possible PGF-correlated pathologies [24].

Another population study found a significant association between the polymorphism rs2268613 in the PGF gene and plasma PGF levels [25]. Regarding VEGF, numerous studies indicate a convincing association between the polymorphism rs2010963 and the development of preeclampsia and the level of circulating VEGF in the serum of pregnant women from various populations [26, 27].

Conclusions. The identification of reliable screening markers can potentially predict the onset of preeclampsia long before the manifestation of its clinical symptoms. Developing combined prediction methods is a promising direction to increase the sensitivity and specificity of many screening tests. This could allow obstetric care to focus on identifying pregnancies at high risk and monitoring them in the antenatal period, which could be beneficial for future therapeutic or preventative interventions.

Currently, a large variety of options for the pharmacological prevention of this pathology have been proposed. However, the problem of choosing a treatment approach for preeclampsia remains relevant, as existing prevention schemes today are insufficiently effective.

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