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HYPERTENSIVE DISORDERS IN PREGNANCY: PROBLEMS OF CLASSIFICATION, DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

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ГИПЕРТЕНЗИВНЫЕ РАССТРОЙСТВА ПРИ БЕРЕМЕННОСТИ: ПРОБЛЕМЫ КЛАССИФИКАЦИИ, ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ И ТАКТИКИ ВЕДЕНИЯ

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Objective. To study the features of hypertensive disorders formation in pregnancy depending on the period and clinical form on the example of the population of Sverdlovsk region.
Materials and methods. The outcomes of 217 pregnant women with moderate and severe preeclampsia and gestational hypertension were analyzed (41, 74, and 102 cases, respectively).
Results. The severe preeclampsia group had the highest rate of fetal growth restriction (14.6 %), low birth weight -2045 g (1640–2650), preterm delivery (63.4 %), and cesarean delivery (87.8 %). A detailed analysis of 28 cases of gestational hypertension lasting up to 34 weeks was performed. The analysis revealed significant challenges in the differential diagnosis of this pregnancy complication, not only in terms of clinical manifestations, but also in terms of timely diagnosis in general.
Conclusions. The findings of this study spark a debate over the use of severity-based classification in clinical practice, which lessens the doctor's vigilance in milder forms that, however, result in equally se-

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rious complications. This raises the question of whether unified tactical approaches should be used in this pathology.
Keywords. Preeclampsia, hypertensive disorders in pregnancy, gestational hypertension, HELLP syndrome.

Цель. Изучение особенностей формирования гипертензивных расстройств при беременности в зависимости от срока и клинической формы на примере популяции Свердловской области.
Материалы и методы. Проведен анализ исходов у 217 беременных среди следующих клинических форм: умеренной и тяжелой преэклампсии, гестационной артериальной гипертензии, что составило 41, 74 и 102 случая соответственно.
Результаты. В группе с тяжелой преэклампсией наблюдался самый высокий процент реализации задержки роста плода (14,6 %) и дети с более низкой массой тела при рождении – 2045 (1640–2650) г. преждевременных родов (63,4 %) и частоты родоразрешения способом операции кесарева сечения (87,8 %). Проведен детальный разбор 28 случаев из категории «гестационная артериальная гипертензия» с манифестацией до 34 недель, который продемонстрировал большие сложности в подходах дифференциальной диагностики данного осложнения беременности не только согласно клиническим формам, но и своевременной постановки диагноза в целом.
Выводы. По результатам сравнительной характеристики не выявлено различий по большинству перечисленных выше показателей между группами с умеренной преэклампсией и гестационной артериальной гипертензией, что лишний раз доказывает необходимость пересмотра существующей клинической классификации и усовершенствования алгоритмов ведения беременности.
Ключевые слова. Преэклампсия, гипертензивные расстройства при беременности, гестационная артериальная гипертензия, HELLP-синдром.

INTRODUCTION

Preeclampsia (PE) is a pathological condition characterized by multisystem damage to the body of a pregnant woman and fetoplacental complex. The classic presentation of PE occurs in late pregnancy, less often in the postpartum period, and is manifested by elevated blood pressure in previously normotensive patients in combination with or without significant proteinuria. Preeclampsia is the leading cause of maternal mortality, increasing the risks of adverse perinatal complications, and induce long-term consequences in both the woman and child in the future [1–5].

It is customary to distinguish two degrees of PE severity: moderate and severe. Blood pressure (BP) level, the severity of proteinuria, and the presence or absence of clinical and/or laboratory manifestations of multiple-organ failure are used as diagnostic criteria to distinguish between these forms. The latter is a clinical variant of severe preeclampsia in the form of hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. According to the literature, the overall prevalence of this pathological condition during pregnancy ranges from 0.2 % to 0.9 %, and as a symptom complex that complements the clinical presentation of preeclampsia, it ranges from 4 % to 24 % [6; 7]. This variability in statistical data is probably due to different classification approaches of hypertensive disorders during pregnancy in different countries and considering (or underestimating) incomplete variants of HELLP syndrome. Moreover, this pathology can progress to eclampsia in about 1 % of pregnant women

with hypertensive disorders. A decrease in the incidence of seizures associated with preeclampsia was noted, especially in developed countries, which can be associated with the use of clinical protocols that indicate basic therapy with the use of magnesium sulfate, which is known as a first-line anticonvulsant drug [8].

Since the introduction of clinical protocols to routine medical practice, the diagnostics of the above conditions has reached a higher level. Clinical recommendations include all generally accepted aspects of pregnancy management, treatment, and patient routing, including diagrams and algorithms, which enables doctors to navigate and make decisions quickly. Currently, during the first trimester of pregnancy, the risk of preeclampsia and other pregnancy complications from the group of "major obstetric syndromes" is assessed using the analysis of risk factors, biochemical indicators of prenatal screening in the first trimester, and Doppler ultrasound of the uterine arteries [9; 10]. If a high risk of preeclampsia is determined, according to modern clinical guidelines, drug prophylaxis with acetylsalicylic acid (ASA) and calcium supplements (in case of low calcium intake by the pregnant woman) are prescribed to pregnant women [9]. These measures have been proven to reduce the risk of developing PE for up to 34 weeks of pregnancy. Moreover, in several cases, the prescription of ASA is ineffective or the high risk of PE is not determined, and its prevention is not prescribed [11]. Therefore, scientific research aimed at developing alternative preventive measures [12] and new ways to predict PE and other hypertensive disorders during pregnancy continues [10; 13; 14].

Most classifications of hypertensive disorders during pregnancy include not only preeclampsia as such and the above-mentioned aspects of its clinical course (eclampsia, HELLP syndrome) but also such nosologies as chronic, preexisting arterial hypertension (AH) and gestational (pregnancy-related) AH which occurred after week 20 of pregnancy [9]. Moreover, these pathological conditions can be challenging to combine, aggravating the clinical manifestations of the main nosology, namely, preeclampsia. In clinical practice, white coat hypertension and transient hypertension caused by the emotional state of the pregnant woman are not rare; their differential diagnostics is of fundamental importance and seems to be a difficult task.

This study aimed to analyze the features of the formation of hypertensive disorders during pregnancy depending on the term and clinical form using the example of the Sverdlovsk region population.

MATERIALS AND METHODS

As part of a study on risk stratification for predicting hypertensive disorders in pregnancy (HDP), 217 patients were identified among 1089 pregnant women who had various forms of HDP, namely, severe and moderate PE, and gestational AH. Outcomes

were assessed retrospectively based on an analysis of the pregnant woman's electronic record of the Regional Obstetric Monitoring of the Sverdlovsk Region. The study received approval from the local ethics committee at the Ural State Medical University of the Russian Ministry of Health.

The working hypothesis regarding HDP implies the following. The earlier HDP occurs, the more severe is the form and the higher the risk of complications and adverse perinatal outcomes [1; 9]. In this regard, the patients were distributed into three groups, according to the available forms: severe preeclampsia (SPE), 41 cases; moderate preeclampsia (MPE), 74 cases, and gestational arterial hypertension (GAH), 102 cases, which accounted for 3.76 %, 6.79 %, and 9.36 %, respectively, of the total number of pregnant women who participated in the study.

Statistical processing of the results obtained was performed using Excel 2016 (Microsoft, USA) and StatTech 3.1.6 (Stattech, Russia).

Quantitative indicators were assessed for compliance with normal distribution using the Kolmogorov–Smirnov test. In case quantitative data were not normally distributed, they were described using the median (*Me*) and lower and upper quartiles (Q_1–Q_3). Categorical data were determined using absolute values and percentages. Comparison of three groups for quantitative indicators, which distribution differed from normal, was performed using the Kruskal–Wallis test, and post hoc comparisons were conducted using Dunn's test with Holm's correction. Comparison of percentages in the analysis of four-field contingency tables was performed using the Pearson chi-square test (χ^2).

Results and discussion

The parameters characterizing the course of pregnancy and perinatal outcomes were analyzed, including the frequency of fetal growth restriction (FGR), preterm delivery (PD), cesarean section (CS), and the average weight of the newborn. The results are presented in Fig. 1.

The presented graph shows that the lowest average newborn weight (*Me* (Q_1–Q_3)) was recorded in the group with severe preeclampsia (2045 g (1640–2650)) and the highest weight in the GAH group (3300 g (2992–3668)), which is an expected result confirmed by a statistically significant difference when comparing three groups ($p < 0.001$).

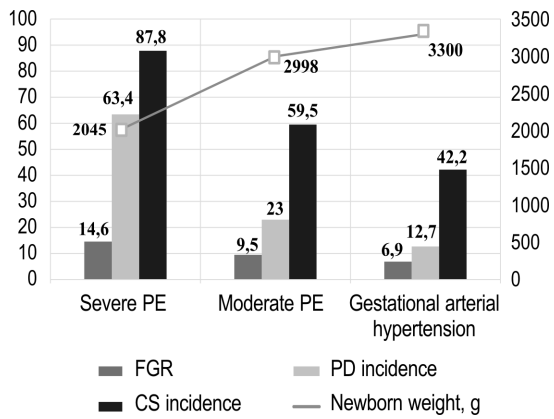

Fig. 1. Characteristics of the assessed indicators in the HDP groups

Notably, the incidence of FGR was highest in pregnant women with SPE, and the lowest FGR was in the group with GAH; however, the differences were not statistically significant. When comparing severe and moderate PE $p = 0.540$ (OR = 0.609; 95 %: 0.190–1.953), MPE and GAH $p = 0.580$ (OR = 0.705; 95 %: 0.236–2.105), SPE and GAH $p = 0.196$ (OR = 0.430; 95 %: 0.135–1.367).

The odds of PD in the MPE group were 5.8 times lower compared to those in the SPE group, which was a statistically significant indicator ($p < 0.001$, OR = 0.172; 95 %: 0.075–0.397), and expectedly lower in the GAH group by 11.8 times ($p < 0.001$, OR = 0.084; 95 %: 0.036–0.199). Despite the fact that the odds of PD in the GAH group were two times lower compared to those in the MPE group, no significant differences were revealed between the groups ($p = 0.075$, OR = 0.490; 95 %: 0.221–1.085).

When assessing the method of delivery, CS ranked first, which frequency in the SPE group was 36 (87.8 %), and a slightly smaller number was noted in the MPE group (44 cases; 59.5 %), whereas in GAH patients, it was 43 (42.2 %). No significant differences were found in the mode of delivery between the last two groups ($p = 0.101$).

For most of the parameters assessed, no significant difference was noted between GAH and MPE. Whether this indicates the difficulties of differential diagnostics and overdiagnosis in obstetrics or, conversely, underestimation of the existing status is unclear. Because proteinuria is not an obligatory component of the preeclampsia symptom complex, differential diagnostics of these two conditions seems impractical, as GAH is naturally included in the concept of "preeclampsia".

Citing as an example the criteria for gestational AH, the authors of the clinical protocol for the management of patients with hypertensive disorders during pregnancy, published in 2020, under the auspices of the American College of Obstetricians and Gynecologists, emphasize its similarity with preeclampsia without complications and do not note significant differences in monitoring such patients. Additionally, it highlights the serious impact of GAH on perinatal outcomes and cites statistics that demonstrate that approximately half of GAH patients will eventually develop proteinuria and other manifestations of organ dysfunction. It should be further noted that patients with GAH not accompanied by proteinuria are more probable to experience changes in clinical and laboratory parameters that characterize HELLP syndrome, and, generally, according to cohort studies, pregnancy more often ends in premature delivery [15; 16].

The International Society for the Study of Hypertension in Pregnancy classification divides preeclampsia into premature, birth before week 37; full-term, delivery after week 37; and postpartum preeclampsia. Among modern classifications, preeclampsia was characterized as early onset (delivery at a term less than 34 weeks) and late

onset (delivery at a term more than 37 weeks). However, how such a classification is applicable in clinical practice and, at the same time, a classification reflecting the timing of HDP manifestation is extremely useful for development of laboratory diagnostic tests, taking into account the different pathogenesis of early and late forms of preeclampsia, remains debatable [17; 18].

The next stage of the study was dividing the patients with HDP according to the period of manifestation, based on which the following data were obtained: 53 cases before week 34, 50 cases before week 37, and 114 cases after week 37, which amounted to 23.3 %, 22 %, and 50.2 %, respectively, among all pregnant women with HDP included in the study. Indicators considering the ranking by forms of HDP are presented in Fig. 2.

Based on the data obtained, the focus of attention of the attending physicians shifted to the group of patients in whom the manifestation of GAH occurred before week 34, which amounted to 28 cases (27.5 %), higher than with moderate PE where there were only 10.8 % of such patients. A detailed study of 28 records of patients with AH manifestations before week 34 and a final diagnosis of GAH yielded the following data. Twelve patients (42.8 %) had an outpatient record of elevated BP at a term earlier than 20 weeks or an indication of a periodic increase in BP before pregnancy. This group of pregnant women should most probably be specified as having pre-pregnancy chronic AH perhaps with superimposed gestational hypertension or preeclampsia; however, such a diagnosis has not been made in these and other cases of HDP. Meanwhile, 47 (21.7 %) of 217 patients had indications of chronic diseases of the cardiovascular system in the form of chronic AH or hypertensive disease.

In 17 (60.7 %) patients, according to the case diaries, the diagnosis changed from 2 to 5 times or was completely absent at the next visit according to the principle of no diagnosis if there was no high BP. The well-known

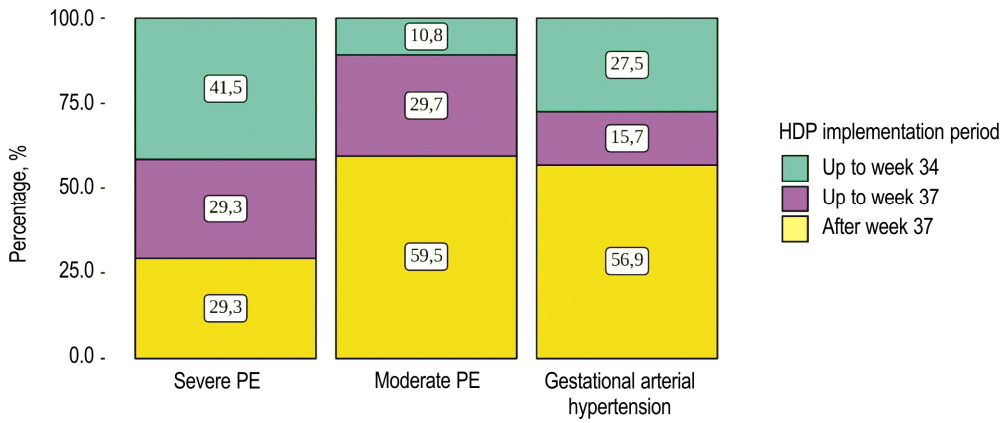

Fig. 2. Ranking of patients according to the form and timing of HDP manifestation

variants included vegetative-vascular dystonia of the hypertensive or mixed type, neurocirculatory dystonia, situational AH, and AH outside of a crisis. These conclusions should be considered incorrect owing to noncompliance with the generally accepted criteria for diagnosing AH during pregnancy, which leads to defects in treatment approach, for example, untimely prescription of hypertensive drugs. In several cases, various types of neurological diagnoses were practiced, which in most countries worldwide are not used at all. Limited appropriate treatment is another problem that arises with delayed diagnostics of preexisting chronic forms of AH, where the question of using combination antihypertensive therapy should often be raised.

In 7 of 28 patients (25 %), in parallel with AH, pregnancy complications, such as FGR and thrombocytopenia, developed; one case of antenatal fetal death was recorded, and episodes of rising systolic BP to 150–160 mmHg and diastolic BP to 90–100 mmHg were noted, which calls into question the final diagnosis of gestational AH.

Almost all the prescriptions outlined in the current clinical guidelines "Preeclampsia. Eclampsia. Edema, Proteinuria and Hypertensive Disorders during Pregnancy, Childbirth and the Postpartum Period" cover two conditions, namely, moderate and severe PE. However, as can be seen in practice and in most studies, the diagnosis of GAH raises the greatest difficulties and various questions, especially regarding differential diagnostics. It seems that in most cases, the conclusion of gestational AH shifts the focus of the doctor's vigilance towards the normal course of pregnancy, rather than towards the development of possible complications.

The existing classifications will be repeatedly reviewed. The American College of Cardiology has revised the criteria for stage 1 AH, in which figures now are 130–139/80–89 mmHg and not 140/90 mmHg [19]. Both international and Russian authors discussed the feasibility of dividing HDP by severity and time of manifestation; such an approach should improve diagnostics and ensure maximum timeliness in treatment [17; 20].

In anticipation of the revision of existing Russian clinical recommendations, the existing algorithms for the management of pregnancy in HDP should be improves. In particular, it is crucial to specify clearly the indications for consultation with a cardiologist, 24-hour BP monitoring, and subsequent collegial discussion of the results obtained, which does not seem difficult in the era of telemedicine. The American College of Cardiology guidelines regarding suspected transient AH or white coat hypertension recommend the use of "out-of-office" BP measurement to confirm the diagnosis and select therapy, with an emphasis on the possibility of telemedicine consultations [19]. However, this approach requires training patients to correct measurement of blood pressure at home; thus, it is proposed to include in the clinical recommendations a universal instruction leaflet for the patient, which

will indicate the criteria for correct BP measurement.

Ranking of patients according to the time of manifestation of HDP is significant, since most of the existing tests that can predict preeclampsia are most sensitive to earlier forms; hence, the risk groups identified as a result of calculating the combined risk in the first trimester should not be neglected.

Conclusions

1. Isolating GAH as an independent form of hypertensive disorders during pregnancy seems inappropriate owing to the lack of pathogenetic differences with preeclampsia.

2. Prognostically, GAH should be considered as preeclampsia with all the ensuing consequences regarding pregnancy management approach and preventive and therapeutic measures.

3. Maternal and perinatal outcomes with moderate preeclampsia and GAH do not differ significantly, indicating another argument in favor of the absence of the need to distinguish between these symptom complexes.

4. Preeclampsia and GAH show comparable tendencies towards worsening clinical manifestations during pregnancy up to the occurrence of multiple-organ lesions, which requires the use of uniform approaches in the formation of this pathology.

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