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Особенности функции печени при преэклампсии

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АННОТАЦИЯ

Обоснование. Несмотря на значительное количество исследований, посвященных проблеме преэклампсии, до настоящего времени многие вопросы, связанные с этиологией, патогенезом и терапией данной патологии, далеки от окончательного решения. Именно поэтому перед акушерами-гинекологами стоит непростая задача выработки рациональной тактики ведения и родоразрешения беременных с преэклампсией с учетом всех рисков для здоровья как матери, так и ее будущего ребенка. Поиск наиболее информативных методов диагностики нарушений функции печени при нарастании тяжести преэклампсии весьма актуален. Гепатобилиарная система несет многофункциональную нагрузку в период гестации и одной из первых реагирует на нарастание тяжести преэклампсии. Чрезвычайно важен выбор приоритетных биохимических показателей крови, отражающих функциональное состояние печени при преэклампсии, способных стать дополнительными критериями для предотвращения материнских и перинатальных осложнений.

Цель исследования — изучить и проанализировать изменения функции печени при преэклампсии, определить критерии развития печеночно-клеточной недостаточности как показателя перехода к тяжелой степени преэклампсии и полиорганной недостаточности.

Материалы и методы. Включены 123 беременные. I группу (n = 40) составили пациентки с преэклампсией без изменений функции печени, II группу (n = 33) — с преэклампсией и нарушением функции печени, III группу (n = 50) — с физиологически протекающей беременностью. Всем беременным выполняли биохимический анализ крови с определением показателей цитолиза (активности аланинаминотрансферазы, аспартатаминотрансферазы и глутаматдегидрогеназы, а также коэффициента де Ритиса), холестаза (активности щелочной фосфатазы и гамма-глютамилтранспептидазы, уровней общего и прямого билирубина и желчных кислот), печеночно-клеточной недостаточности (активности холинэстеразы и лактатдегидрогеназы, уровней общего белка, альбумина и мочевины), а также клинический анализ крови и анализ показателей свертывающей системы крови. Беременных с преэклампсией наблюдали в условиях палаты интенсивной терапии, где осуществляли мониторинг витальных функций.

Результаты. Ведущим синдромокомплексом при нарастании тяжести преэклампсии был цитолитический синдром с умеренным повышением активности трансаминаз (преобладанием активности аланинаминотрансферазы над активностью аспартатаминотрансферазы). В связи с этим коэффициент де Ритиса составил менее 1,0. При развитии печеночно-клеточной недостаточности отмечали преобладание активности аспартатаминотрансферазы над активностью аланинаминотрансферазы (коэффициент де Ритиса был выше 1,33). Выявлено также повышение активности глутаматдегидрогеназы и лактатдегидрогеназы. Среди показателей холестаза отмечено повышение уровня прямого билирубина. Печеночно-клеточную недостаточность характеризовало снижение активности холинэстеразы, а также концентраций общего белка и альбумина. В группе беременных с преэклампсией выявлено статистически значимое снижение уровней гемоглобина и тромбоцитов.

Заключение. Изменение функции печени при преэклампсии отражает нарастание тяжести данного заболевания и свидетельствует о развитии полиорганной недостаточности. В ее терминальной стадии проявляются три синдромокомплекса — цитолитический, холестатический и печеночно-клеточная недостаточность.

Ключевые слова: преэклампсия; цитолиз; холестаз; печеночно-клеточная недостаточность; полиорганная недостаточность.

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Characteristics of liver function in patients with preeclampsia

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ABSTRACT

BACKGROUND: Despite a significant number of studies devoted to the problem of preeclampsia, to date, a large number of issues related to the etiology, pathogenesis, and therapy for this pathology remain far from a final solution. That is why obstetricians always face the difficult task of developing rational tactics for the management and delivery of pregnant women with preeclampsia, one has to take into account all the risks to the health of both the mother and her unborn child. Therefore, relevant is the search for the most informative methods for diagnosing liver dysfunction with an increase in the severity of preeclampsia. The hepatobiliary system is known to carry a multifunctional load during gestation and is one of the first to respond to an increase in the severity of preeclampsia. It is, therefore, crucial to choose priority biochemical parameters of blood that reflect liver function in preeclampsia, which can be used as additional criteria for making an obstetric decision in order to prevent maternal and perinatal complications.

AIM: The aim of this study was to analyze alterations in liver function in preeclampsia, in order to determine the criteria for the development of hepatic cell insufficiency as indicators of the transition to severe preeclampsia and multiple organ failure.

MATERIALS AND METHODS: This study included 123 pregnant women, of which group I (n = 40) consisted of pregnant women with preeclampsia without changes in liver function, group II (n = 33) was made up of pregnant women with preeclampsia and impaired liver function, while group III (n = 50) only comprised pregnant women with normal pregnancy. All pregnant women underwent a biochemical blood test with the determination of the parameters of cytolysis (aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase, De Ritis ratio), cholestasis (alkaline phosphatase, total and direct bilirubin, gamma-glutamyl transpeptidase, bile acids), and hepatic cell insufficiency (cholinesterase, total protein, albumin, urea, lactate dehydrogenase), as well as a clinical blood test and coagulation tests. Pregnant women with preeclampsia were observed in the intensive care unit, with vital functions monitored.

RESULTS: The leading syndrome complex with increasing severity of preeclampsia was the cytolytic one, in which the levels of transaminases increased moderately with a predominance of alanine aminotransferase over aspartate aminotransferase activities (the De Ritis ratio was lesser than 1.0). With the development of hepatic cell insufficiency, aspartate aminotransferase activity dominated over alanine aminotransferase one (the De Ritis ratio was greater than 1.33). We also found an increase in glutamate dehydrogenase and lactate dehydrogenase activities and, among the cholestatic parameters, in the level of direct bilirubin. Hepatic cell insufficiency was characterized by a decrease in the activity of cholinesterase and decreased total protein and albumin concentrations. In the group of pregnant women with preeclampsia, we found a decrease in hemoglobin and platelet counts.

CONCLUSIONS: Altered liver function in preeclampsia reflects an increase in the severity of the pathology and indicates the development of multiple organ failure. In its terminal stage, all syndrome complexes manifest themselves as cytolytic, cholestatic and hepatic cell insufficiencies.

Keywords: preeclampsia; cytolysis; cholestasis; hepatic cell insufficiency; multiple organ failure.

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ECO•VECTOR

BACKGROUND

For many years, preeclampsia has been a major problem in modern obstetrics. The etiology and pathogenesis of this disease that complicates pregnancy and labor are yet unknown [1]. Severe preeclampsia is a leading cause of maternal and perinatal complications and mortality [2]. Preeclampsia is not a pathology of a single organ or system but rather a multisystem dysfunction syndrome leading to multiorgan failure.

The liver is not a specific target organ in preeclampsia. However, because of its involvement in fetal intrauterine development processes, functional stress in physiologically normal pregnancy becomes one of the first links of multisystem dysfunction in the severe course of preeclampsia.

It is believed that liver function is not altered in the early stages of preeclampsia but invariably altered as the disease progresses [3].

Generalized endothelial damage underlying preeclampsia also occurs in the liver. There is a spasm of hepatic vessels and a disturbance in hepatic blood flow under the influence of powerful vasoconstrictors, as well as local disorders of the blood coagulation system with the formation of fibrin microthrombi in sinusoids, leading to necrosis of hepatocytes and the death of endothelial and Kupffer cells. As a result, many reactive oxygen radicals and hydrogen peroxide are produced, stimulating the lipid peroxidation processes of liver lipids. Cytokines, eicosanoids, and biologically active substances are released at the same time. A so-called closed system is developed, with each element supporting the apoptosis of hepatic cells. In this case, only timely delivery can save a woman from the fatal consequences of liver failure [3, 4].

Three main laboratory syndromic complexes are used to determine the presence of one or more hepatopathies: cytolytic, cholestatic, and liver-cell failure. The cytolytic syndrome is characterized by the destruction of the hepatocyte membrane and release into the bloodstream of the primary "signal" enzymes — alanine aminotransferase (ALT), aspartate aminotransferase (AST), and, in the case of mitochondrial damage, glutamate dehydrogenase (GLDH). The "depth" of hepatic-cell damage is reflected by the so-called de Ritis coefficient, the AST/ALT ratio, which is normal at 1.3 ± 0.43. The calculation of this coefficient is believed to be more significant in determining the degree of damage and necrosis of hepatocytes than assessing the activity of these enzymes separately. Cholestatic syndrome reflects disturbance of processes of bile formation and outflow through the biliary system, and bile ducts become a target for pathological process development. The primary markers of cholestasis are alkaline phosphatase and gamma-glutamyltranspeptidase (GGTP) activity, levels of bilirubin, and bile acids. Liver-cell failure is primarily characterized by a decrease in total protein and albumin levels and blood coagulation system indicators synthesized in the liver, as well as cholinesterase activity, and may include changes indicative of cytolysis and cholestasis [5].

Preeclampsia liver damage is primarily diagnosed by laboratory findings, such as increased ALT, AST, and uric acid levels, decreased albumin, and a relative increase in globulin concentration with unchanged bilirubin levels [6]. Even moderate changes in liver tests are believed to indicate the presence of systemic damage and characterize the course of preeclampsia as severe. hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and acute fatty liver dystrophy are two additional "dramatic" pregnancy hepatopathy variants. Both diseases are pathogenetically different but are linked by characteristic changes in hepatobiliary system function, expressed by changes in cytolysis, cholestasis, and, most importantly, liver-cell failure. The clinical diagnosis of liver damage in preeclampsia, acute fatty liver dystrophy, and HELLP syndrome is challenging due to the similarity of changes in laboratory parameters in these diseases and the lack of their specific biochemical markers [7–11]. Considering the highest risks of maternal and perinatal complications, immediate delivery has been and remains the main method of patient care. A liver biopsy is impossible and inexpedient during pregnancy. The pathological morphological picture of liver damage in severe preeclampsia is characterized by the presence of fibrin and fibrinogen deposits, thin fatty dystrophy of hepatocytes, intrahepatic and subcapsular hemorrhages, and, in especially severe cases, necrosis of hepatocytes. Fatty liver dystrophy of varying intensity occurs in all pregnant women with preeclampsia. However, its severity does not correspond with the severity and duration of preeclampsia or changes in biochemical parameters [12–14].

The study aimed to investigate and analyze the changes in liver function in preeclampsia and determine the criteria for developing hepatic-cell failure as an indicator of the transition to severe preeclampsia and multiorgan failure.

MATERIALS AND METHODS

Pregnant women were examined and treated at the Department of Pregnancy Pathology of the Research Institute of Obstetrics, Gynecology and Reproductology named after D.O. Ott. Some of the pregnant women with severe preeclampsia were monitored at other obstetric institutions in St. Petersburg and Leningrad Oblast; these patients were included in the study in case of highly unfavorable maternal or neonatal outcomes.

Pregnant women were divided into three groups: group I (n = 40) included patients with preeclampsia without changes in liver function, group II (n = 33) included patients with severe preeclampsia and liver dysfunction, and group III

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(*n* = 50) included patients with physiologically normal pregnancy.

All pregnant women underwent physical and laboratory examinations, which included extended determinations of blood biochemical parameters, blood coagulation system, and clinical blood analysis. Pregnant women in groups I and II were treated in an intensive care unit with an anesthesiologist–anesthesiologist–resuscitator, allowing for continuous monitoring of vital functions (heart rate, blood pressure, blood oxygen saturation, hourly diuresis, and proteinuria). All pregnant women with preeclampsia and patients with physiologically normal pregnancies underwent fetometry, Doppler, and cardiotocographic examinations. Pregnant women with preeclampsia underwent mandatory ultrasound examination of the abdominal cavity organs. All of the patients were given therapeutic counseling. Pregnant women with severe preeclampsia were also examined by an ophthalmologist and a neurologist.

Biochemical blood parameters included markers of cytolysis (ALT, AST, and GLDH activities), cholestasis (alkaline phosphatase and GGTP activities, total and direct bilirubin levels, and bile acids), and hepatic-cell failure (cholinesterase and lactate dehydrogenase activities and total protein, albumin, and fibrinogen levels). The most important clinical blood analysis markers were hemoglobin and platelet levels.

Severe preeclampsia was diagnosed using the criteria in the clinical recommendations of the Russian Ministry of Health "Preeclampsia. Eclampsia. Edema, proteinuria and hypertensive disorders during pregnancy, childbirth and postpartum period" 2021. Pre-eclampsia is defined as a pregnancy, childbirth, and postpartum complication characterized by a systolic blood pressure level of 140 mmHg or higher, a diastolic blood pressure of –90 mmHg or higher in combination with proteinuria, or at least one symptom of multiorgan failure. Moderate preeclampsia includes the above indicators, and proteinuria is defined as 0.3 g or more per day or 0.3 g/L or more in two portions of urine obtained at 6-h intervals. Severe preeclampsia is defined as systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of –110 mmHg or higher, and proteinuria of 5 g or higher per day or 3 g/L or higher in two portions of urine obtained at 6-h intervals.

RESULTS

Three groups of pregnant women were formed for the study, two of which comprised pregnancy-related pathology — preeclampsia, and the third is physiologically active pregnancy. Because the study aimed to assess changes in blood biochemical parameters characterizing liver function in preeclampsia, the need to compare these parameters with those in physiologically normal pregnancy was clear. Group I included pregnant women with severe preeclampsia who had not yet been complicated by multiorgan failure, one of the manifestations of which was liver dysfunction. Group II included pregnant women with severe preeclampsia and manifestation of multiorgan failure in the form of liver dysfunction. The disease first appeared in group I at 36.65 ± 2.45 weeks of gestation and in group II at 33.45 ± 3.23 weeks.

As shown in Table 1, pregnant women in all three groups were comparable in age, with a median age of 30.50 (26.00–35.25) in group I, 31.00 (27.00–34.00) in group II, and 32.00 (28.00–35.00) years in group III. Preeclampsia was present in 65% and 81.8% of first-time mothers and 35% and

Table 1. Characteristics of the study groups
Таблица 1. Характеристики групп обследуемых беременных

Indicator	Group I (*n* = 40)	Group II (*n* = 33)	Group III (*n* = 50)
Age, Me (Q_1–Q_3), yr	30.50 (26.00–35.25)	31.00 (27.00–34.00)	32.00 (28.00–35.00)
First-born women, *n* (%)	26 (65.00)	27 (81.80)	14 (28.00)
Repeat births, *n* (%)	14 (35.00)	6 (18.20)	36 (72.00)
Delivery time, Me (Q_1–Q_3), weeks of gestation	37.00 (35.00–39.00)	34.00 (31.00–37.00)	39.00 (38.00–39.00)
Term labor, *n* (%)	21 (53.80)	9 (27.30)	50 (100.00)
Preterm labor, *n* (%)	19 (47.50)	24 (72.70)	0 (0.00)
Delayed labor, *n* (%)	0 (0.00)	0 (0.00)	0 (0.00)

Note. Me (Q_1–Q_3) — median, upper, and lower quartiles.

Table 2. Clinical manifestations of preeclampsia

Таблица 2. Клинические проявления преэклампсии

Preeclampsia index	Group I (*n* = 40)	Group II (*n* = 33)	Group III (*n* = 50)	Statistical significance of differences between indicators		
				Groups I and II	Groups I and III	Groups II and III
Edema	Generalized	Generalized	Absent	–	–	–
Proteinuria, Me (Q_1–Q_3), g/L	1.45 (0.47–2.80)	1.50 (0.50–2.82)	0.00 (0.00–0.00)	$p > 0.05$	$p < 0.001$	$p < 0.001$
Systolic blood pressure, Me (Q_1–Q_3), mmHg	150.00 (140.00–168.50)	150.00 (138.75–161.25)	110.00 (100.00–112.00)	$p > 0.05$	$p < 0.001$	$p < 0.001$
Diastolic blood pressure, Me (Q_1–Q_3), mmHg	93.50 (90.00–100.00)	90.00 (89.75–100.00)	65.00 (60.00–70.00)	$p > 0.05$	$p < 0.001$	$p < 0.001$

Note. Me (Q_1–Q_3) — median, upper, and lower quartiles.

18.2% of second-time mothers in groups I and II, respectively. It is worth noting that in group II with liver function changes in 72% of patients, the labor was preterm and the term of delivery was 34.00 (31.00–37.00) weeks of gestation, whereas in group I without liver function changes, the rate of preterm labor was 47.5% and the term of delivery was 37.00 (35.00–39.00) weeks of gestation. There were no preterm births in group III with physiologic pregnancy, and the delivery time was 39.00 (38.00–39.00) weeks. All three groups had singleton pregnancies.

The "classical triad" of clinical manifestations of preeclampsia (edema, hypertension, and proteinuria) was observed in both groups of pregnant women with preeclampsia (I and II). According to the presented data (Table 2), both groups were comparable in terms of proteinuria, blood pressure, and severity of edema syndrome, which corresponded to the severe preeclampsia criteria. There was no edema and proteinuria in Group III. Blood pressure remained within normal ranges.

The blood biochemical parameters and coagulograms in the three groups examined are described below.

Indicators of cytolysis

As shown in Table 3, the group of pregnant women with preeclampsia and liver dysfunction had the most pronounced increase in blood transaminase activity: ALT activity was 107.20 (64.00–345.40) units/L, and AST activity was 90.70 (52.10–189.00) units/L, which were statistically significantly higher than the groups with preeclampsia without liver dysfunction and with physiologically normal pregnancy. There were no statistically significant differences in transaminase levels between groups I and III. The de Ritis coefficient values were not significantly different in groups with physiologic pregnancy (III) and preeclampsia without liver dysfunction (I) and were 1.30 (1.04–1.48) and 1.48 (1.19–1.77), respectively. The group of pregnant women with preeclampsia and liver dysfunction (II) had the lowest de Ritis coefficient, 0.84 (0.64–1.02), which was statistically significantly lower ($p < 0.001$) than groups I and III.

Serum GLDH levels increased in both groups with preeclampsia (I and II), 11.45 (7.12–15.79) and 17.88 (15.28–44.97), respectively, with no statistically significant differences.

Table 3. Cytolytic parameters

Таблица 3. Показатели цитолиза

Cytolysis index	Group I (*n* = 40)	Group II (*n* = 33)	Group III (*n* = 50)	Statistical significance of differences between indicators		
				Groups I and II	Groups I and III	Groups II and III
Alanine aminotransferase (normal, 5–30), units/L	14.75 (12.60–20.55)	107.20 (64.00–345.40)	16.70 (13.80–22.45)	$p < 0.001$	$p > 0.05$	$p < 0.001$
Aspartate aminotransferase (normal, 5–35), units/L	22.10 (18.00–26.48)	90.70 (52.10–189.00)	21.10 (18.45–25.03)	$p < 0.001$	$p > 0.05$	$p < 0.001$
de Ritis coefficient (normal, 0.8–1.3), units/L	1.48 (1.19–1.77)	0.84 (0.64–1.02)	1.30 (1.04–1.48)	$p < 0.001$	$p < 0.05$	$p < 0.001$
Glutamate dehydrogenase (normal, less than 5), units/L	11.45 (7.12–15.79)	17.88 (15.28–44.97)	2.79 (2.36–3.25)	$p > 0.05$	$p > 0.05$	$p < 0.001$

Note. Data are presented as median, upper, and lower quartiles.

However, there were statistically significant differences between preeclampsia and hepatic dysfunction groups and physiologic pregnancy groups [2.79 (2.36–3.25)]. The highest GLDH level was observed in the group of pregnant women with preeclampsia and liver dysfunction.

Indicators of cholestasis

Table 4 presents data on the cholestasis syndrome. In all examined groups, total bilirubin values did not exceed the reference values. Total bilirubin levels were higher in the group with preeclampsia and liver dysfunction, where this index was 12.38 (8.71–26.30) mmol/L, which was higher ($p < 0.001$) than in the preeclampsia group without liver dysfunction [8.00 (5.62–10.10) mmol/L] and in the group with physiologically normal pregnancy [8.50 (6.77–11.82) mmol/L]. Direct bilirubin levels differed similarly, with the highest level in the preeclampsia and liver dysfunction group [4.36 (1.71–13.70)], which was statistically significantly higher than the other two groups [1.75 (0.88–2.28) mmol/L in the preeclampsia group without liver dysfunction and 2.29 (1.45–2.96) mmol/L in the group with physiologic pregnancy, $p < 0.05$].

In terms of alkaline phosphatase activity, the groups with preeclampsia and liver dysfunction [135.60 (118.00–194.70)] and without hepatopathy [138.15 (82.30–169.77)] ($p < 0.05$) were not significantly different ($p < 0.05$), but there was a trend toward an increase in this activity when compared with the data in the group with physiologic pregnancy [111.80 (94.25–137.95)]. GGTP values did not differ between the groups of preeclampsia without hepatic dysfunction [13.55 (9.30–19.68) mmol/L] and physiologic pregnancy [10.75 (7.80–13.30) mmol/L], but this index was significantly higher in the group of preeclampsia with hepatic dysfunction than in the group with physiologic pregnancy 29.45 (23.72–35.95) mmol/L ($p < 0.001$). Bile acid levels did not exceed reference values in all study groups but were higher in the group of preeclampsia with hepatic dysfunction [4.30 (2.33–8.67) mmol/L] than in the groups of preeclampsia without hepatic dysfunction [3.83 (3.83–3.83) mmol/L] and physiologic pregnancy [3.08 (2.28–5.28) mmol/L] ($p < 0.05$).

Indicators of hepatic-cell failure

Table 5 shows the data for hepatic cellular insufficiency. Total protein in both groups of patients with preeclampsia (I and II) did not differ significantly 54.28 (49.09–56.81) and 52.21 (47.30–55.74) g/L, respectively, but this index was significantly lower in both groups than in the group of physiologic pregnancy [59.98 (58.96–62.02) g/L] ($p < 0.001$). Similarly, albumin levels did not differ across groups of patients with preeclampsia [25.20 (22.40–27.49) g/L in group I and 25.07 (21.53–28.41) g/L in group II; $p > 0.05$], but were lower than in the physiologically pregnant group [30.77 (29.22–31.86) g/L) ($p < 0.001$)]. The cholinesterase activity levels in groups I and III were not significantly different. They were 6.04 (5.60–6.38) and 6.12 (5.56–6.42) kEd/L, respectively ($p > 0.05$); however, these values were significantly higher than in patients with preeclampsia and hepatic dysfunction [5.11 (2.78–5.84) kEd/L] ($p < 0.001$). Blood urea levels did not exceed the reference values in the study groups. It was lowest in the group with physiologic pregnancy (2.94 [2.55–3.43] mmol/L. It was 3.88 (2.63–4.48) mmol/L in patients with preeclampsia without hepatic dysfunction, whereas it was 4.98 (3.83–8.06) mmol/L in the group of preeclampsia with hepatic dysfunction.

Lactate dehydrogenase activity was also higher in the group of pregnant women with preeclampsia and liver dysfunction [750.75 (492.87–1095.80)] than in

Table 4. Cholestatic parameters

Таблица 4. Показатели холестаза

Indicators of cholestasis	Group I ($n = 40$)	Group II ($n = 33$)	Group III ($n = 50$)	Statistical significance of differences between indicators		
				Groups I and II	Groups I and III	Groups II and III
Total bilirubin (normal, 3.5–20.5), mmol/L	8.00 (5.62–10.10)	12.38 (8.71–26.30)	8.50 (6.77–11.82)	$p < 0.001$	$p > 0.05$	$p < 0.05$
Direct bilirubin (normal, 0–3.4), mmol/L	1.75 (0.88–2.28)	4.36 (1.71–13.70)	2.29 (1.45–2.96)	$p < 0.05$	$p < 0.05$	$p < 0.05$
Alkaline phosphatase (normal, 80–270), units/L	138.15 (82.30–169.77)	135.60 (118.00–194.70)	111.80 (94.25–137.95)	$p > 0.05$	$p > 0.05$	$p < 0.05$
Gamma-glutamyl transpeptidase (normal, 5–50), units/L	13.55 (9.30–19.68)	29.45 (23.72–35.95)	10.75 (7.80–13.30)	$p < 0.05$	$p > 0.05$	$p < 0.001$
Bile acids (normal, 2.5–8.1), μmol/L	3.83 (3.83–3.83)	4.30 (2.33–8.67)	3.08 (2.28–5.28)	$p > 0.05$	$p > 0.05$	$p < 0.05$

Note. Data are presented as median, upper, and lower quartiles.

Table 5. Hepatic cell insufficiency parameters

Таблица 5. Показатели печеночно-клеточной недостаточности

The liver-cell failure rate	Group I (n = 40)	Group II (n = 33)	Group III (n = 50)	Statistical significance of differences between indicators		
				Groups I and II	Groups I and III	Groups II and III
Total protein (normal, 62–80), g/L	54.28 (49.09–56.81)	52.21 (47.30–55.74)	59.98 (58.96–62.02)	$p > 0.05$	$p < 0.001$	$p < 0.001$
Albumin (normal, 35–51), g/L	25.20 (22.40–27.49)	25.07 (21.53–28.41)	30.77 (29.22–31.86)	$p > 0.05$	$p < 0.001$	$p < 0.001$
Cholinesterase (normal, 4.7–10.4), kU/L	6.04 (5.60–6.38)	5.11 (2.78–5.84)	6.12 (5.56–6.42)	$p > 0.05$	$p > 0.05$	$p < 0.05$
Urea (normal, 1.7–8.2), mmol/L	3.88 (2.63–4.48)	4.98 (3.83–8.06)	2.94 (2.55–3.43)	$p < 0.05$	$p < 0.05$	$p < 0.001$
Lactate dehydrogenase (normal, 0–450), units/L	449.70 (393.00–520.10)	750.75 (492.87–1095.80)	334.40 (276.98–358.40)	$p < 0.001$	$p < 0.001$	$p < 0.001$

Note. Data are presented as median, upper, and lower quartiles.

the group with preeclampsia without liver dysfunction [449.70 (393.00–520.10)] and the group with physiologically normal pregnancy [334.40 (276.98–358.40)] ($p < 0.001$).

Table 6 shows data on the state of the blood coagulation system. Only the prothrombin index differed significantly between the group with physiologic pregnancy [114.00 (112.00–117.00)%] and the preeclampsia group without hepatic dysfunction [129.50 (116.00–145.05)%] ($p < 0.001$). The corresponding values in the preeclampsia group with hepatic dysfunction [140.00 (94.00–156.00)]%) revealed no significant differences with the data in the other groups ($p > 0.05$), with a higher median value, which may be explained by the increased variability of this characteristic in this group.

Thrombin time values in the groups of physiologic pregnancy and preeclampsia without hepatic dysfunction were not significantly different ($p > 0.05$), at 14.55 (13.90–15.25) and 15.00 (14.50–15.93) s, respectively, but were significantly lower than in the group of preeclampsia with hepatic dysfunction [16.20 (15.10–17.30) s] ($p < 0.05$). When comparing the group of preeclampsia without hepatic dysfunction [0.91 (0.88–0.95)] and the group of physiological pregnancy [0.94 (0.89–0.98)] the values of the international normalized ratio did not differ ($p > 0.05$), but there was a significant

Table 6. Coagulation test parameters, hemoglobin and platelet concentrations in the study groups

Таблица 6. Показатели свертывающей системы крови, гемоглобина, тромбоцитов

Indices of blood coagulation system, hemoglobin, and platelets	Group I (n = 40)	Group II (n = 33)	Group III (n = 50)	Statistical significance of differences between indicators		
				Groups I and II	Groups I and III	Groups II and III
Prothrombin index (normal, 70–130), %	129.50 (116.00–145.05)	140.00 (94.00–156.00)	114.00 (112.00–117.00)	$p > 0.05$	$p < 0.001$	$p > 0.05$
Thrombin time (normal, 11–17), s	15.00 (14.50–15.93)	16.20 (15.10–17.30)	14.55 (13.90–15.25)	$p < 0.05$	$p > 0.05$	$p < 0.05$
International normalized ratio (normal, 0.9–1.4)	0.91 (0.88–0.95)	0.86 (0.80–0.90)	0.94 (0.89–0.98)	$p < 0.05$	$p > 0.05$	$p < 0.001$
Activated partial thromboplastin time (normal, 0.8–1.2)	0.87 (0.84–0.94)	0.89 (0.85–0.98)	0.87 (0.85–0.89)	$p > 0.05$	$p > 0.05$	$p > 0.05$
Fibrinogen (normal, 2–4), g/L	5.00 (4.52–5.64)	4.24 (3.39–5.24)	4.42 (4.10–5.21)	$p < 0.05$	$p > 0.05$	$p > 0.05$
Hemoglobin (normal, 120–160), g/L	115.50 (106.75–123.25)	111.00 (102.00–122.00)	122.00 (117.00–127.75)	$p > 0.05$	$p > 0.05$	$p > 0.05$
Тромбоциты (normal, 140–400 $\times 10^9$/L)	194.00 (162.50–234.50)	145.00 (95.00–227.00)	201.50 (174.75–245.75)	$p < 0.05$	$p > 0.05$	$p < 0.001$

Note. Data are presented as median, upper, and lower quartiles.

decrease in this index in the group of preeclampsia with hepatic dysfunction [0.86 (0.80-0.90)] compared with the data of other groups. In pairwise comparisons of all groups, the activated partial thromboplastin time values did not differ ($p > 0.05$).

The fibrinogen level differed significantly between groups with preeclampsia: it was 5.00 (4.52–5.64) g/L in the absence of hepatic dysfunction and 4.24 (3.39–5.24) g/L in its presence ($p < 0.05$), but there were no differences when the indicators were compared in groups I and II and group III. Hemoglobin level in patients with preeclampsia was lower than in patients with physiologic pregnancy [122.00 (117.00–127.75) g/L]. When comparing the group without hepatic dysfunction [115.50 (106.75–123.25) g/L] and the group with hepatic dysfunction [111.00 (102.00–122.00) g/L] ($p > 0.05$), there was no significant difference. Platelet count was lowest in the group of patients with preeclampsia and hepatic dysfunction [145.00 (95.00–227.00) $\times 10^9$/L], which was lower than the preeclampsia group without hepatic dysfunction [194.00 (162.50–234.50) $\times 10^9$/L] and the physiologic pregnancy group [201.50 (174.75–245.75) $\times 10^9$/L], with no significant differences found when two groups were compared.

DISCUSSION

Although biochemical laboratory tests are useful in diagnosing liver diseases, they are not precisely specific and do not guarantee diagnosis accuracy. Their results; however, can be used to assess the involvement of the liver in the pathological process and the degree of its severity.

Aminotransferases are the most sensitive indicators of hepatocyte damage. According to the present studies, as the severity of preeclampsia increases, ALT and AST activity increases three to five time times from the upper limit of normal, except in cases of multiorgan failure with extremely unfavorable outcomes for the mother, and transaminase activity increases 10- to 20-fold. The predominance of ALT activity over AST activity is a characteristic feature of severe preeclampsia, and the de Ritis coefficient (AST/ALT) is less than 1.0.

When ALT activity is higher than AST activity, similar changes occur in acute viral hepatitis. AST activity may be higher than ALT activity in the fulminant course of viral hepatitis. The AST/ALT ratio is less than 1.0 in nonalcoholic fatty liver disease (in the steatosis stage), which is the hepatic component of metabolic syndrome, and the activity of the transaminases themselves exceeds the upper limit of normal no more than two to three times, which is similar to the changes in these indicators in preeclampsia. The de Ritis coefficient is thought to indicate the duration and intensity of the pathologic process. Because AST has a relatively short half-life of 18 h and ALT has a half-life of 36 h, the predominance of AST activity in serum over ALT activity reflects the progressive destruction of hepatocytes [15].

Given this, it should be noted that in severe preeclampsia, the predominance of AST activity in relation to ALT activity indicates the development of hepatic cellular failure. The same indicator enzyme characterizing hepatocyte mitochondrial damage is GLDH, whose dramatic activity increase similarly predicts hepatic cellular failure development. It should be noted that the increase in GLDH activity was also revealed in group I with preeclampsia, where transaminase activity was still within normal values, but the de Ritis coefficient increased to 1.47 (with a norm of 1.33). Complementing the "picture" of hepatic-cell necrosis is increased lactate dehydrogenase activity. This nonspecific enzyme found not only in the liver but also in the myocardium, kidneys, and skeletal muscle, is considered nonspecific and indicates the development of multiorgan tissue hypoxia. Lactate dehydrogenase activity increased in both groups with preeclampsia compared with the index in the group with physiologic pregnancy. This indicator increased the most pronounced in the group with severe preeclampsia (II), indicating the development of tissue hypoxia and hepatic-cell failure.

It is known that the manifestations of cholestasis do not result in preeclampsia. When considering hepatopathy associated with pregnancy, the cholestatic syndrome takes a higher priority in intrahepatic cholestasis of pregnant women than in preeclampsia. However, as the severity of preeclampsia increases, there is primarily an increase in the level of total bilirubin, mainly due to direct (parenchymatous) bilirubin, as well as alkaline phosphatase activity, GGTP, and bile acid levels, reflecting the "total" hepatobiliary system lesion.

The totality of all the above biochemical indicators is a criterion for developing hepatic cellular insufficiency in preeclampsia. Determining cholinesterase activity is equally important for assessing the severity of the pathological process in the liver. This enzyme belongs to the α2-globulins and is synthesized in the ribosomes of hepatocytes' endoplasmic network. A decrease in enzyme activity suggests enzyme breakdown and the development of hepatic cellular failure, indicating the severity of the pathological process. The group of pregnant women with preeclampsia and liver dysfunction (II) significantly reduced cholinesterase activity.

The protein-synthetic function of the liver is the most sensitive in the development of preeclampsia. However, due to the needs of the developing fetus in the uterus, total protein and albumin levels decrease in physiologic pregnancy. These parameters were found to be significantly lower in groups with preeclampsia. No significant differences were found in pairwise analysis of the proteins of the blood coagulation

system synthesized in the liver. This is explained by the fact that in the study, the indicators of the blood coagulation system could correspond to different "phases" of coagulopathy, from hypercoagulation to hypocoagulation, particularly in cases of severe preeclampsia with extremely unfavorable outcomes for the mother. Groups with preeclampsia also had lower hemoglobin and platelet levels than groups with physiologic pregnancies.

CONCLUSIONS

1. Changes in liver function are one of the criteria for increasing the severity of preeclampsia and indicate the development of hepatic cell and multiorgan failure.
2. The primary cause of severe preeclampsia is cytolytic syndrome, which is characterized by a moderate increase in the activity of transaminases (ALT and AST). In the early stages of the development of hepatic-cell failure, ALT activity prevails in relation to AST, and the de Ritis coefficient (AST/ALT) is less than 1.0. When there are signs of hepatic cellular insufficiency, the predominance of AST activity in relation to ALT is observed as a result of more "deep" hepatocyte damage, as well as the development of tissue hypoxia outside the hepatobiliary system (de Ritis coefficient is higher than 1.33).
3. GLDH is one of the most informative cytolysis enzymes in severe preeclampsia. Increased activity of this enzyme suggests the destruction of not only hepatocyte membranes but also mitochondria, indicating significant liver-cell damage. The increase in GLDH activity occurs before the increase in the activity of ALT and AST.
4. The development of cholestatic syndrome is not characteristic of preeclampsia, except in highly severe cases with unfavorable outcomes. An increase in the bilirubin level, mainly due to the direct fraction, is the main indicator of cholestasis.
5. The criteria for the development of hepatic cellular failure in preeclampsia include an increase in cytolysis and cholestasis and a decrease in indicators of synthetic liver function (cholinesterase activity, total protein level, albumin level, and coagulation system proteins), which is a prognostically very unfavorable factor.

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