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Принципы лечения внутрипеченочного холестаза беременных

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Обоснование. Внутрипеченочный холестаз беременных занимает одно из ведущих мест в структуре гепатозов, ассоциированных с беременностью. Так же, как и при многих других заболеваниях, дебютирующих в период гестации, все симптомы внутрипеченочного холестаза беременных исчезают после родоразрешения без последствий для матери в отличие, например, от острой жировой дистрофии печени. Однако фетальный прогноз на его фоне содержит риски из-за высокой частоты преждевременных родов и токсического влияния компонентов желчи на внутриутробно развивающийся плод, приводящих к перинатальным осложнениям. Особенно опасным является сочетание внутрипеченочного холестаза беременных с внутриутробной инфекцией, плацентарной недостаточностью, тяжелой преэклампсией, сахарным диабетом или другой экстрагенитальной патологией. До недавнего времени единственным правильным решением при развитии внутрипеченочного холестаза беременных считали досрочное родоразрешение. И только в последние десятилетия предпринимаются попытки терапевтической коррекции данной патологии с целью пролонгирования беременности до доношенного срока и снижения частоты перинатальных осложнений. Ощутимых результатов удалось достичь при применении препаратов урсодезоксихолевой кислоты и внедрении в акушерскую практику эфферентных методов терапии.

Цель исследования — разработать оптимальные схемы патогенетической терапии внутрипеченочного холестаза беременных с применением гепатопротекторов из группы препаратов урсодезоксихолевой кислоты, адеметионина, эссенциальных фосфолипидов и мембранного плазмафереза.

Материалы и методы. В исследование включены 150 беременных с внутрипеченочным холестазом. В I группу (n = 50) вошли беременные, получающие терапию только препаратом урсодезоксихолевой кислоты. Во II группу (n = 50) включены беременные, получающие сочетанную медикаментозную терапию препаратами урсодезоксихолевой кислоты, адеметионина, эссенциальных фосфолипидов. В III группу (n = 50) вошли беременные, получающие эфферентные методы терапии (мембранный плазмаферез) в сочетании с препаратами урсодезоксихолевой кислоты или адеметионина. Всем беременным до начала терапии определяли уровни желчных кислот в крови, общего и прямого билирубина, активность трансаминаз (аланинаминотрансферазы, аспартатаминотрансферазы). Контроль показателей крови осуществляли с частотой 1 раз в 7 дней. Всем беременным проводили контроль за состоянием плода (фетометрию, допплерометрию, кардиотокографию).

Результаты. Применение препаратов урсодезоксихолевой кислоты без сочетания с другими гепатопротекторами (в I группе) было возможно только в случаях повышения уровня желчных кислот в крови не более чем до 40 ммоль/л. Препараты адеметионина и эссенциальных фосфолипидов в качестве монотерапии были неэффективными. При уровне желчных кислот более 40 ммоль/л и повышении активности трансаминаз в 2–3 раза и более от верхней границы нормы (во II группе) наиболее эффективным было комплексное применение препаратов урсодезоксихолевой кислоты, адеметионина и эссенциальных фосфолипидов. Наиболее значимое снижение уровней желчных кислот и показателей цитолиза (трансаминаз) отмечали при применении плазмафереза в сочетании с препаратами урсодезоксихолевой кислоты или адеметионина (в III группе).

Заключение. Выбор схемы лечения зависит от уровня повышения желчных кислот и выраженности цитолитического синдрома. При повышении уровня желчных кислот до 40 ммоль/л возможно применение только препаратов урсодезоксихолевой кислоты. При уровне желчных кислот более 40 ммоль/л необходимо комплексное применение вышеуказанных гепатопротекторов. Наиболее эффективной схемой лечения является применение мембранного плазмафереза в сочетании с препаратами урсодезоксихолевой кислоты или адеметионина.

Ключевые слова: внутрипеченочный холестаз; желчные кислоты; урсодезоксихолевая кислота; плазмаферез.

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Principles of treatment of intrahepatic cholestasis in pregnant women

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BACKGROUND: Intrahepatic cholestasis of pregnancy occupies a leading place in the structure of hepatoses associated with pregnancy. As with many other diseases that debut during gestation, all the symptoms of intrahepatic cholestasis of pregnancy disappear after delivery and have no consequences for the mother, unlike, for example, acute fatty degeneration of the liver. However, the fetal prognosis remains serious due to the high incidence of preterm birth and the toxic effect of bile components on the developing fetus, which both lead to perinatal complications. Especially fatal is the situation when intrahepatic cholestasis of pregnancy is combined with intrauterine infection, placental insufficiency, severe preeclampsia, diabetes mellitus, or other extragenital pathology. Until recently, it was believed that the only correct solution for intrahepatic cholestasis of pregnancy development was early delivery. Only in recent decades, attempts have been made to therapeutic correction of this pathology in order to prolong pregnancy to full term and reduce the frequency of perinatal complications. So far, tangible results have been achieved with the use of ursodeoxycholic acid preparations and the introduction of efferent methods of therapy into obstetric practice.

AIM: The aim of this study was to develop optimal schemes for pathogenetic therapy of intrahepatic cholestasis of pregnancy using hepatoprotectors from the ursodeoxycholic acid group, as well as ademetionine, essential phospholipids, and membrane plasmapheresis.

MATERIALS AND METHODS: This study included 150 pregnant women with intrahepatic cholestasis of pregnancy. Group I (n = 50) comprised patients who were treated only with ursodeoxycholic acid. Group II (n = 50) included individuals who were given combined drug therapy with ursodeoxycholic acid, ademetionine, and essential phospholipids. Group III (n = 50) consisted of women whose treatment included efferent therapies (membrane plasmapheresis) in combination with ursodeoxycholic acid or ademetionine preparations. All pregnant women before the start of therapy were determined the blood levels of bile acids, total and direct bilirubin, and transaminases (alanine aminotransferase, aspartate aminotransferase). Blood parameters were monitored once every seven days. All the patients were also monitored for the condition of the fetus (fetometry, dopplerometry, cardiotocography).

RESULTS: The use of ursodeoxycholic acid not combined with other hepatoprotectors (group I) was possible only in cases of increased blood levels of bile acids of not more than 40 mmol/L, preparations of ademetionine and essential phospholipids as monotherapy being ineffective. With an increase in the blood levels of bile acids of more than 40 mmol/L and transaminases by two to three or more times from the upper limit of the norm (group II), the most effective was the combined use of ursodeoxycholic acid, ademetionine and essential phospholipid preparations. The most significant decrease in the blood levels of bile acids and hepatic cytolysis parameters (transaminases) was observed when plasmapheresis was used in combination with ursodeoxycholic acid or ademetionine (group III).

CONCLUSIONS: The choice of treatment regimen depends on the level of increase in bile acids and the severity of cytolytic syndrome. With an increase in the level of bile acids to 40 mmol/L, ursodeoxycholic acid preparations can be used only. With an increase in bile acid level of more than 40 mmol/L, the complex use of the above hepatoprotectors is necessary. The most effective treatment regimen is the use of membrane plasmapheresis in combination with ursodeoxycholic acid or ademetionine.

Keywords: intrahepatic cholestasis; bile acids; ursodeoxycholic acid; plasmapheresis.

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BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) requires urgent treatment. However, despite several available hepatoprotectors and choleretics, the clinical manifestations of this disease may persist in some cases [1]. Currently, the etiology and pathogenesis of ICP are not fully understood, therefore the treatment of this condition remains a challenge. Attempts have been made to treat the main symptoms and biochemical changes caused by the disease, such as skin itching due to an increase in primary bile acids in the blood [1].

Primary bile acids are toxic and can easily cross the placental barrier and accumulate in the amniotic fluid, negatively affecting the fetus. Although ICP usually has a benign course for the mother, with all symptoms completely disappearing almost immediately after delivery, the fetus may be at risk. Studies have shown that the incidence of fetal distress associated with this disorder can reach 30%, and the risk of fetal death is twice as high as in a normal pregnancy [2–4].

The negative impact of primary bile acids is due to their lipophilic and hydrophobic nature. They primarily damage hepatocyte cell membranes. Several experimental studies have also demonstrated a toxic effect of primary bile acids on fetal cardiomyocytes, resulting in arrhythmias and a vasoconstrictor effect on placental vessels, leading to intrauterine hypoxia and even fetal death [5, 6].

Therefore, the main aim of ICP treatment is to reduce the level of primary bile acids in the blood, which may be achieved by removing them and by preventing further accumulation.

Currently, efferent therapies, particularly membrane plasmapheresis, are widely used in obstetric practice. This procedure removes primary bile acids from the bloodstream in women with ICP [7]. Moreover, the use of ursodeoxycholic acid (UDCA) drugs, which are not cytotoxic, provides competitive displacement of primary bile acids from the bloodstream of pregnant women with ICP, preventing their further accumulation [8–10]. Membrane plasmapheresis with UDCA is the best combination of pharmaceutical and non-pharmaceutical treatment of ICP. However, efferent therapies may not always be available due to contraindications or a lack of equipment, and their high costs, in medical institutions. Therefore, there is a need for alternative therapies that include a combination of various hepatoprotectors and choleretics.

We created an experimental model of hepatopathy in pregnant Wistar rats using UDCA, ademetionine, and essential phospholipids [11–13]. The administration of the detergent tyloxapol to experimental pregnant rats resulted in cytolysis, cholestasis, and hepatic-cellular failure syndromes, confirmed by morphological and laboratory tests [14, 15]. When creating this model, the main aim was to analyze the contribution of each of the used hepatoprotectors to restoring the morphology and function of the liver and eliminating the above syndromes. UDCA and essential phospholipids restored the hepatic triad (interdollicular artery, interdollicular vein, and interdollicular bile duct) of hepatocytes in 100% of cases, whereas ademetionine was effective only in 70% of cases. The dystrophic changes in the hepatocytes were eliminated in 100% of cases by ademetionine and essential phospholipids. The biochemical blood parameters of experimental rats showed a significant decrease in the level of bile acids when using UDCA drugs, whereas a decrease in cytolysis indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was seen with ademetionine and essential phospholipids [15].

The study aimed to develop optimal schemes for the treatment of ICP using medication and other interventions.

MATERIALS AND METHODS

We enrolled 150 pregnant women with ICP for examination and treatment at the Department of Pregnancy Pathology and the Consultative and Diagnostics Department of the Research Institute of Obstetrics, Gynecology and Reproductology named after D.O. Ott. The women were divided into three groups based on the level of bile acids and the therapy received. Group I (n = 50) was treated with UDCA drugs only, Group II (n = 50) was given hepatoprotectors (UDCA drugs, ademetionine, and essential phospholipids), and Group III (n = 50) received efferent therapy (membrane plasmapheresis) with UDCA or ademetionine.

All the pregnant women underwent physical and laboratory examinations and an ultrasound scan of the liver and biliary tract. In addition, the women with ICP were assessed by a general practitioner, a gastroenterologist, a dermatologist, and an infectious disease specialist.

Physical examination included assessment of the skin for jaundice and excoriations.

Clinical and laboratory examination included assessment of the main indicators of cholestasis, such as bile acids, total and direct bilirubin, and cytolysis (ALT and AST).

A full biochemical profile (including total protein and albumin) and coagulation profile were also performed.

ICP was diagnosed according to the criteria of the 2020 Clinical Guidelines of the Russian Ministry of Health for Intrahepatic Cholestasis of Pregnancy. These include the presence of skin itching and an increase in bile acids in the blood of over 10 mmol/L. In addition, almost all women with ICP showed an increase in transaminases (ALT and AST), whereas 20% had elevated levels of bilirubin (total and direct).

Group I patients were treated with oral UDCA at a dose of 10–15 mg/kg/day (with a maximum dose of 25 mg/kg).

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The treatment regimen of Group II patients was:

1) Oral UDCA 10–15 mg/kg/day (maximum dose of 25 mg/kg)
2) Ademetionine 10–25 mg/kg/day (maximum dose of 1600 mg/day)
3) Intravenous essential phospholipids 250 mg/5 ml or 900 mg/day

The treatment regimen of Group III patients was:

1) UDCA 10–15 mg/kg/day or ademetionine 400 mg per 400 ml of saline
2) Membrane plasmapheresis (3 to 4 procedures at intervals of 1 to 2 days)

Biochemical blood parameters (bile acids, ALT, AST, and in the case of plasmapheresis, total protein) were assessed every 7 days. The treatment period ranged from 1 to 3 weeks.

In addition, all pregnant women with ICP underwent fetometry, a Doppler study every 2 weeks, and cardiotocography weekly.

RESULTS

The groups of pregnant women with ICP were comparable in age, ethnicity, and mode and time of delivery. The mean age in Group I was 32 (28–36) years and the time of delivery was 38 (37–39) weeks, with 70% primiparous and 30% multiparous women. The mean age in Group II was 31 (27–35) years and the time of delivery was 37 (35–38) weeks, with 65% primiparous and 30% multiparous women. In Group III, the mean age was 32 (29–35) years, the time of delivery was 38 (37–39) weeks, with 60% primiparous and 40% multiparous women.

In Group I, the women were treated with UDCA drugs only. An attempt to use ademetionine or essential phospholipids as monotherapy showed no similar effect.

Regarding biochemical indices, changes in ALT, AST, bile acid, total bilirubin, direct bilirubin, and cholesterol during monotherapy with one hepatoprotector and combined hepatoprotective therapy were assessed (Fig. 1). Combined therapy was found to be more effective. Statistically significant differences were found for ALT ($p = 0.015$), AST ($p = 0.011$), total bilirubin ($p = 0.015$), direct bilirubin ($p = 0.043$) and most significantly for bile acids. No differences were found in cholesterol levels before and after treatment ($p > 0.05$).

According to several studies, UDCA is a first-line drug for treating ICP [12–14]. UDCA used as monotherapy showed good efficacy when the level of bile acids in the blood was <40 mmol/L and the activity of the transaminases (ALT and AST) was up to 3 times the upper limit of normal. Based on these data, Group I was treated with UDCA drugs only. When assessing the level of bile acids and ALT and AST among the patients who took UDCA, significant differences ($p < 0.05$) were observed for all three indices (Fig. 2).

In Group I, 60% of cases showed a decrease to normal values in bile acids, 30% showed a 1.5–2-fold decrease, and 10% showed no changes or a slight increase in bile acids. In this group, 90% of pregnancies reached full-term, and 10 were premature deliveries. There were no perinatal complications (fetal hypoxia and asphyxia of the newborn). Remarkably, with a maximum increase in bile acids not exceeding 3–4 times normal, the ICP had a milder course.

In cases where the bile acid level increased over 5 times the upper limit of normal (≥40 mmol/L), two schemes of complex therapy for ICP were developed:

1) Use of UDCA, ademetionine, and essential phospholipids in the doses indicated above (Group II)
2) Efferent methods (membrane plasmapheresis) with a hepatoprotector (UDCA or ademetionine, Group III)

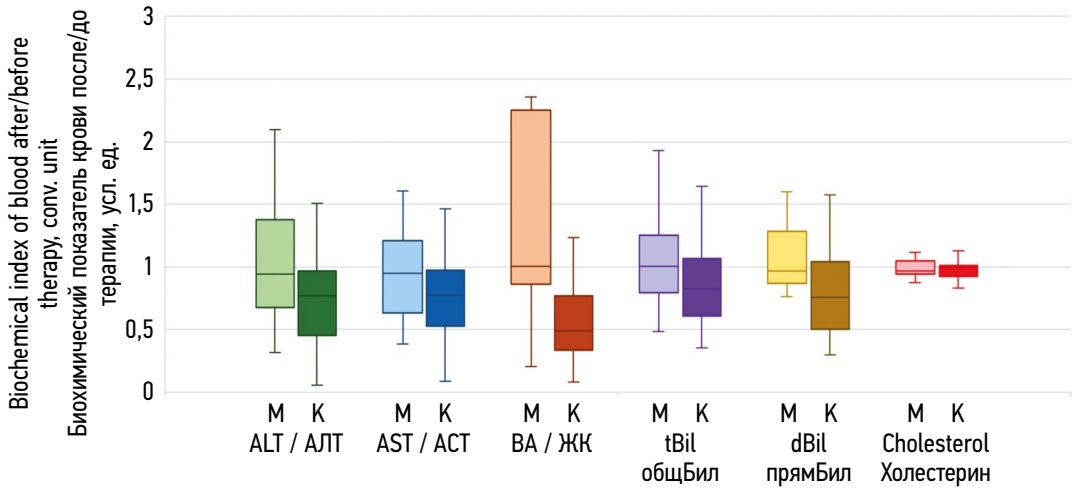

Fig. 1. Biochemical parameters of blood with the use of one hepatoprotector and with their combination: M — monotherapy; K — combination therapy. ALT — alanine aminotransferase; AST — aspartate aminotransferase; BA — bile acids; tBil — total bilirubin; dBil — direct bilirubin

Рис. 1. Биохимические показатели крови при применении одного гепатопротектора и сочетания препаратов: М — монотерапия; К — комбинированная терапия. АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; ЖК — желчные кислоты; общБил — общий билирубин; прямБил — прямой билирубин

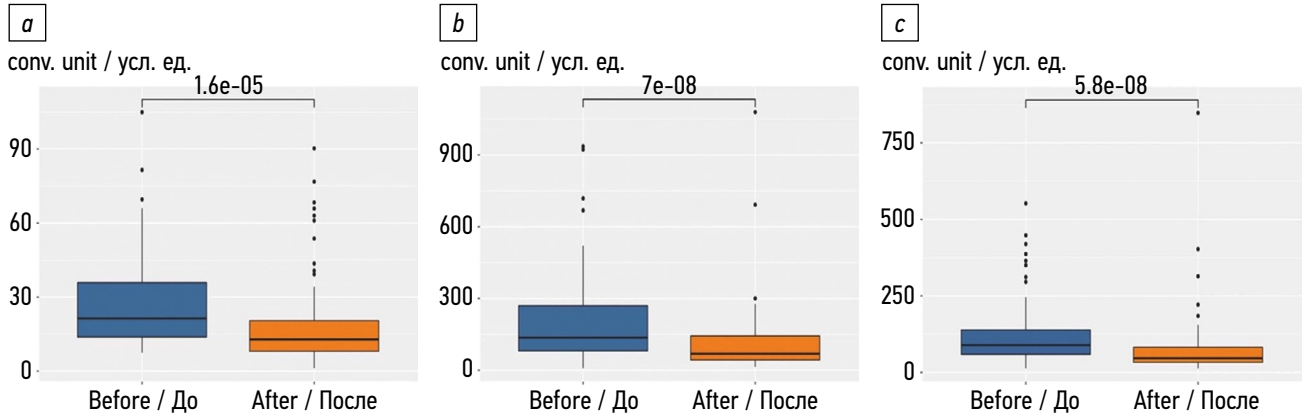

Fig. 2. Indicators of bile acids (*a*), alanine aminotransferase (*b*), and aspartate aminotransferase (*c*) in the blood before and after the use of ursodeoxycholic acid preparations

Рис. 2. Показатели желчных кислот (*a*), аланинаминотрансферазы (*b*) и аспартатаминотрансферазы (*c*) в крови до и после применения препаратов урсодезоксихолевой кислоты

The choice of treatment for ICP was frequently dictated by the severity of the clinical and laboratory parameters and the gestational age. The use of efferent therapies is inadvisable in pregnancies over 35 weeks of gestation. This is because plasmapheresis is not selective for a particular xenobiotic and it removes some plasma with all its constituent components. In this case, only hepatoprotectors should be used, and if the therapy has no effect (there is an increase in bile acids and ALT and AST), early delivery is indicated.

The efficacy of treatment was assessed weekly by measuring changes in bile acids, ALT, and AST levels and the intensity of skin itching. With positive changes in the clinical and laboratory parameters, the treatment of ICP may be continued until full-term pregnancy. The optimal delivery time for this pathology was 38 weeks of gestation. When attempting to prolong a pregnancy beyond 38 weeks, the risk of perinatal complications (intrauterine fetal hypoxia and asphyxia of the newborn) increased.

In Group II, the complex use of hepatoprotectors did not decrease bile acids to normal levels. In 55% of the cases, bile acids and ALT and AST showed a 1.5–2-fold decrease; in 35% of cases, the levels remained unchanged or the decrease was short-term; in 10% of cases, the parameters increased. In this group, 10% of patients needed early delivery due to an increase in cholestasis and cytolysis, and spontaneous preterm deliveries occurred in 10% of cases. Perinatal complications in this group accounted for 20% of the total, with fetal intrauterine hypoxia as the leading cause.

However, complex treatment with hepatoprotectors had only a short-term effect. After 7–14 days, bile acid levels and transaminase (ALT and AST) activity increased steadily. In this case, early delivery was advisable to avoid perinatal complications.

Notably, the women with ICP receiving efferent therapies experienced the most pronounced decrease in cholestasis compared with the group receiving only hepatoprotectors. For the women treated with plasmapheresis, significant

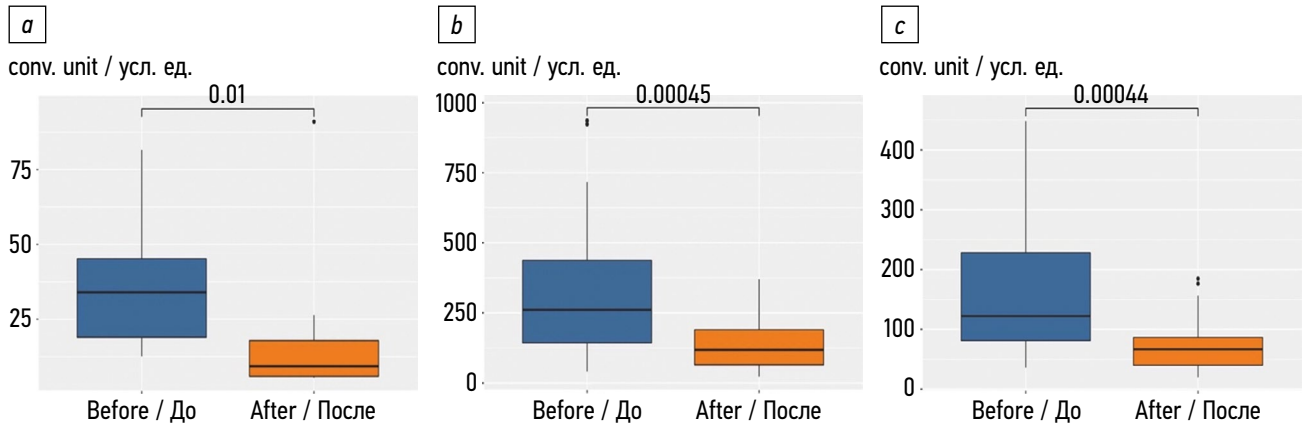

Fig. 3. Indicators of bile acids (*a*), alanine aminotransferase (*b*), and aspartate aminotransferase (*c*) in the blood before and after plasmapheresis

Рис. 3. Показатели желчных кислот (*a*), аланинаминотрансферазы (*b*) и аспартатаминотрансферазы (*c*) в крови до и после плазмафереза

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differences ($p < 0.05$) in bile acids, ALT, and AST were observed (Fig. 3).

In Group III, the use of plasmapheresis in 70% of cases produced a 2-fold decrease in the level of bile acids and transaminase activity; in 25% of cases, indices decreased to normal values and in 5% of cases, cholestasis and cytolysis indicators remained at the same level. The incidence of miscarriage and perinatal complications was 5% and 10%, respectively. Membrane plasmapheresis resulted in a pronounced and persistent decrease in bile acids, and the use of UDCA drugs prevented their accumulation, which allowed the prolongation of pregnancy to maturity.

The analysis of pregnancy outcomes in ICP showed that the disease was accompanied by various obstetric and extragenital pathologies. Therefore, the direct effect of hepatoprotectors and efferent therapies on the outcome of pregnancy in this pathology could not be fully assessed. However, in the group of pregnant women receiving hepatoprotectors with plasmapheresis, respiratory distress syndrome and cerebral ischemia in newborns were twice as common. The priority goal of the ICP therapy was to eliminate the negative effect of toxic bile acids on the developing fetus and the hepatobiliary system of the mother.

CONCLUSIONS

1. Bile acids are the main factor to be considered when selecting the therapy for ICP. With bile acid levels up to 40 mmol/L, UDCA may be used as monotherapy, however at higher levels, complex treatment with hepatoprotectors including UDCA, ademetionine, and essential phospholipids according to the prescribed schemes is required.
2. The most effective treatment regimen is a combination of plasmapheresis with UDCA and/or ademetionine. In the group of patients receiving this therapy, a decrease in bile acids and transaminase activity to normal values was observed in 40% of cases.
3. With the positive effects of ICP therapy, the optimal delivery time was 38 weeks of gestation.
4. A pathologic indicator for the lack of effect of ICP therapy is an increase in bile acids over 40 mmol/L which is associated with a 2-fold increase in the risk of perinatal complications.

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All authors made a significant contribution to the study and preparation of the article, read and approved the final version before its publication.

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REFERENCES

1. Lineva OI, Osadchenko EYu, Nesterenko SA, et al. Clinic and treatment of cholestatic hepatosis. *Obstetrics and Gynecology.* 2000;(2):15–17. (In Russ.)

2. Lineva OI, Romanova EYu, Zhelnova TI. Cholestatic hepatosis of pregnant women. Samara: Perspektiva; 2002. (In Russ.)

3. Maev IV, Andreev DN, Dicheva DT, et al. Intrahepatic cholestasis of pregnancy: the state-of-the-art. *Klinicheskaya meditsina.* 2015;93(6):25–30. (In Russ.)

4. Lammert F, Marschall HU, Glantz A, et al. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol.* 2000;33(6):1012–1021. DOI: 10.1016/s0168-8278(00)80139-7

5. Wong LF, Shallow H, O'Connell MP. Comparative study on the outcome of obstetric cholestasis. *J Matern Fetal Neonatal Med.* 2008;21(5):327–330. DOI: 10.1080/14767050802034446

6. Brouwers L, Koster MP, Page-Christiaens GC, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. *Am J Obstet Gynecol.* 2015;212(1):100.e1–100.e1007. DOI: 10.1016/j.ajog.2014.07.026

7. Voinov VA, Zhestkova NV, Karchevskiy KS, et al. Membrannyi plazmaferez pri kholestaticheskom gepatoze beremennykh. *Bulletin of Almazov Federal Heart, Blood and Endocrinology Centre.* (Zdorovaya zhenshchina — zdorovyi novorozhdennyi: tezisy VIII mezhdistsiplinarnoi konferentsii po akusherstvu, perinatologii, neonatologii, posvyashchenoi 200-letiyu so dnya rozhdeniya Aleksandra Aleksandrovicha Kitera (1813–1879). 15-16 november, 2013). 2013;(2):29. (In Russ.)

8. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. *Orphanet J Rare Dis.* 2007;2:26. DOI: 10.1186/1750-1172-2-26

9. Beuers U, Pusl T. Intrahepatic cholestasis of pregnancy – a heterogeneous group of pregnancy-related disorders? *Hepatology.* 2006;43(4):647–649. DOI: 10.1002/hep.21156

10. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels

and fetal complication rates. *Hepatology*. 2004;40(2):467–474. DOI: 10.1002/hep.20336
11. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology*. 2005;129(3):894–901. DOI: 10.1053/j.gastro.2005.06.019
12. Glantz A, Marschall HU, Lammert F, et al. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology*. 2005;42(6):1399–1405. DOI: 10.1002/hep.20952
13. Zapata R, Sandoval L, Palma J, et al. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience. *Liver Int*. 2005;25(3):548–554. DOI: 10.1111/j.1478-3231.2004.0996.x
14. Patent RF No. 2 610536 / 13.02.2017 Byul. No. 5. Petrosyan MA, Zhestkova NV, Balashova NN, et al. Sposob modelirovaniya ostrogo zhirovogo gepatoza beremennykh. (In Russ.) [cited 2023 Feb 12]. Available from: https://patents.s3.yandex.net/RU2610536C1_20170213.pdf.
15. Petrosyan MA, Zhestkova NV, Tumasova ZN, et al. Effects of S-adenosyl methionine and essential phospholipids on serum biochemical parameters in simulated acute liver disease in late pregnancy. *Reviews on Clinical Pharmacology and Drug Therapy.* 2021;19(1):65–70. (In Russ.) DOI: 10.17816/RCF19165-70

СПИСОК ЛИТЕРАТУРЫ

1. Линева О.И., Осадченко Е.Ю., Нестеренко С.А. и др. Клиника и лечение холестатического гепатоза // Акушерство и гинекология. 2000. № 2. С. 15–17.
2. Линева О.И., Романова Е.Ю., Желнова Т.И. Холестатический гепатоз беременных. Самара: Перспектива, 2002.
3. Маев И.В., Андреев Д.Н., Дичева Д.Т., и др. Внутрипеченочный холестаз беременных: современное состояние проблемы // Клиническая медицина. 2015. Т. 93. № 6. С. 25–30.
4. Lammert F., Marschall H.U., Glantz A., et al. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management // J. Hepatol. 2000. Vol. 33. No. 6. P. 1012–1021. DOI: 10.1016/s0168-8278(00)80139-7
5. Wong L.F., Shallow H., O'Connell M.P. Comparative study on the outcome of obstetric cholestasis // J. Matern. Fetal. Neonatal. Med. 2008. Vol. 21. No. 5. P. 327–330. DOI: 10.1080/14767050802034446
6. Brouwers L., Koster M.P., Page-Christiaens G.C., et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels // Am. J. Obstet. Gynecol. 2015. Vol. 212. No. 1. P. 100.e1–100.e1007. DOI: 10.1016/j.ajog.2014.07.026
7. Воинов В.А., Жесткова Н.В., Карчевский К.С., и др. Мембранный плазмаферез при холестатическом гепатозе беременных // Бюллетень Федерального центра сердца, крови и эндокринологии им. В.А. Алмазова. (Здоровая женщина — здоровый новорожденный: тезисы VIII междисциплинарной конференции по акушерству, перинатологии, неонатологии, посвященой 200-летию со дня рождения Александра Александровича Китера (1813–1879). 15–16 ноября 2013 г.). 2013. Прилож. № 2. С. 29.
8. Pusl T., Beuers U. Intrahepatic cholestasis of pregnancy // Orphanet. J. Rare Dis. 2007. Vol. 2. P. 26. DOI: 10.1186/1750-1172-2-26
9. Beuers U., Pusl T. Intrahepatic cholestasis of pregnancy – a heterogeneous group of pregnancy-related disorders? // Hepatology. 2006. Vol. 43. No. 4. P. 647–649. DOI: 10.1002/hep.21156
10. Glantz A., Marschall H.U., Mattsson L.A. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates // Hepatology. 2004. Vol. 40. No. 2. P. 467–474. DOI: 10.1002/hep.20336
11. Kondrackiene J., Beuers U., Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy // Gastroenterology. 2005. Vol. 129. No. 3. P. 894–901. DOI: 10.1053/j.gastro.2005.06.019
12. Glantz A., Marschall H.U., Lammert F., et al. Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid // Hepatology. 2005;42(6):1399–1405. DOI: 10.1002/hep.20952
13. Zapata R., Sandoval L., Palma J., et al. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience // Liver Int. 2005;25(3):548–554. DOI: 10.1111/j.1478-3231.2004.0996.x
14. Патент РФ на изобретение № 2 610536 / 13.02.2017 Бюл. № 5. Петросян М.А., Жесткова Н.В., Балашова Н.Н., и др. Способ моделирования острого жирового гепатоза беременных [дата обращения 12.02.2023]. Доступ по ссылке: https://patents.s3.yandex.net/RU2610536C1_20170213.pdf
15. Петросян М.А., Жесткова Н.В., Тумасова Ж.Н., и др. Влияние препаратов S-аденозилметионина и эссенциальных фосфолипидов на биохимические показатели сыворотки крови крыс в модели острого поражения печени на позднем сроке беременности // Обзоры по клинической фармакологии и лекарственной терапии. 2021. Т. 19. № 1. С. 65–70. DOI: 10.17816/RCF19165-70

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