

# Intrahepatic cholestasis of pregnancy: new pathogenetic links

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The article describes the features of pro- and antioxidant system in women with intrahepatic cholestasis of pregnancy. The changes in pro- and antioxidant systems in women with intrahepatic cholestasis of pregnancy is detected. The dynamics of primary lipid peroxidation products – diene conjugates, malondialdehyde, and biologically active substances that make up the antioxidant system (superoxide dismutase and  $\alpha$ -tocopherol) in serum influenced by traditional drug and adjuvant therapy. The effectiveness of efferent therapy normalization of prooxidant and antioxidant systems in women with intrahepatic cholestasis of pregnancy is shown.

**Key words:** *intrahepatic cholestasis of pregnancy, lipid peroxidation, anti-oxidant system.*

Intrahepatic cholestasis of pregnancy (ICP), also known as «obstetric» cholestasis, characterized by a significant increase in the concentration of bile acids in the mother organism and characterized by pruritus predominantly of the palms and soles in the second half of pregnancy. It is typically a reversible cholestatic disease with spontaneous relief of laboratory abnormalities and symptoms promptly after delivery but no later than one month postpartum [1–3].

The incidence of ICP varies, according to different sources, from 1 in 150 to 1 in 7000 pregnant women [1, 2]. ICP is most common in Scandinavia and South America (Chile ICP level is 15–28%) [2]. Prevalence in Europe, USA, Canada and Australia ranges from 0.1% to 1.5% [2]. ICP common among members of one family and can recur in subsequent pregnancies [1–4].

Incidence of preterm delivery is increased in women with ICP. In severe forms of ICP disseminated intravascular coagulation syndrome, acute renal failure and hepatic hypertensive syndrome may develop [2–4]. Perinatal prognosis even more serious, as the frequency of fetal distress during labor in women with ICP increases to 22% and the risk of death is 4 times higher than in the physiological pregnancy [2, 5].

It is believed that a significant role in the development of ICP play hormonal and genetic factors [1, 3, 4, 6]. According to some authors, the state of pregnancy is contributes to pregnancy cholestasis syndrome due to thickening and increased viscosity of bile, lowering the tone of bile ducts and bile increased permeability of capillaries, excessive accumulation of progesterone, estrogen and testosterone metabolism disturbances [1, 3]. These changes taking place in the II and III trimester of pregnancy physiologically, are favorable factors for ICP. Also, today proved defective gene MDR3 (ABCB4) and the development of ICP [4, 6].

One of the damaging mechanisms in ICP is the activation of lipid peroxidation (LPO) and reduced antiradical activity of enzymes. Excessive production of reactive oxygen species (ROS) and/or their inadequate neutralization by antioxidants, defined as oxidative stress, leads to damage in cell membrane, vessel wall, proteins, lipids, and even the nucleic acids in the cell. Toxic products of lipid peroxidation is one of the reasons for the regulation of homeostasis imbalance, which leads to serious metabolic disturbances, changes in immune status of the functional state of different systems. In normal conditions, to control

the flux of ROS (diene conjugates, malondialdehyde, lipid hydroperoxides), aerobic cells have developed their own defense system, the antioxidant system (AOS, system with antiradical activity) that includes nonenzymatic (such as glutathione, A, C, and E vitamins, selenium derivatives) and enzymatic components (such as superoxide dismutase, glutathione peroxidase, and catalase). AOS provides neutralize free radicals cells and maintenance of cellular homeostasis [7, 8].

Characteristic features unidirectional operation AOS is adjusting its actions (neutralization of all types of free radicals) and severity of the consequences of even a brief failure that causes damage to cell membranes and biopolymers. However, under the influence of various endogenous and exogenous factors balance between AOS and LPO in cells may be disrupted due to low or antioxidants or as a result of overproduction of free radicals. This condition is called oxidative stress [7, 8].

Combined therapy of ICP using hepatoprotectors, choleretic and antihistamines in a number of cases does not provide correction of oxidative stress, which necessitates the search for new therapeutic areas and treatment [8].

**Objective:** to study pro- and anti-oxidative activity in the blood of women with ICP and evaluate the impact of efferent therapy on the dynamics of these indicators.

## MATERIALS AND METHODS

A comprehensive survey of 129 pregnant women with ICP and 50 healthy pregnant women with physiological pregnancy and childbirth (control group) aged 18 to 42 years. Pregnant with ICP divided into two groups – basic and comparison group, comparable for age, severity and duration of ICP. The basic group consisted of 40 pregnant women with ICP who underwent treatment with complex drug and efferent therapy (plasmapheresis). The comparison group consisted of 89 pregnant women with ICP treated exclusively with medication: hepatoprotector (ademetionin) 400 mg in capsules, twice daily, orally, between food intake, 14 days; choleretic (ursodeoxycholic acid) capsules 250 mg twice daily, orally, 14–21 days (depending on severity); antioxidants (vitamin E) 100 mg in capsules, twice daily, with meals, orally, 14–21 days and enterosorbent (silicii dioxidum) 2 gram twice a day, orally for 14 days. Comprehensive survey of pregnant women with ICP was performed before and after treatment. Efferent therapy in basic group was performed at the Obstetrics and gynecology department number 3 of the Bogomolets National Medical University in Kyiv Maternity house number 3. The membrane plasmapheresis was performed on the «Hemofeniks» using plasmafilter «Rosa». The course includes 4 procedures of plasmapheresis with 1–2 days intervals.

The study excluded pregnant women with chronic liver disease, viral hepatitis, skin diseases.

The analysis of anamnesis, clinical and biochemical screening of pregnant women with ICP was performed. Levels of Diene conjugates (DC) in serum (mcmol/l), malondialdehyde in serum (nmol/ml), superoxide dismutase (U/mg protein),  $\alpha$ -tocopherol, (mkg/ml) were determined using spectrophotometer DU-65 Beckman (USA).

Features indices of lipid peroxidation and anti-oxidant activity

Parameters	Control group, n=50	Basic group, n=40		Comparison group, n=89	
		Before therapy	After therapy	Before therapy	After therapy
diene conjugates, mcmol/l	3,6±0,2	6,5±0,7^	4,2±0,2*	6,4±0,3^	7,4±0,3*
Malon dialdehyde, nmol/ml	2,23±0,12	4,56±0,2^	3,4±0,3*	4,6±0,3^	4,8±0,1
SOD, U/mg protein	13,2±1,2	9,4±0,3^	11,8±0,5*	9,6±0,3^	9,9±0,8
α-tocopherol, mkg/ml	21,8±0,5	16,6±0,4^	20,1±0,1*	16,8±0,2^	17,1±0,1

Note: The difference relative to the control group likely ^ – p < 0.05; the difference relative to before treatment \* – p < 0.05.

Statistical processing of the results was performed using a software system STATISTICA for Windows (version 6.0). The difference between the compared values considered reliable at the level of p<0.05.

## RESULTS AND DISCUSSION

As a result, the study found that in a basic group, women with upcoming first delivery amounted to 73.6% (95), multiparous women – 26.4% (34). 25% multiparous women with ICP had cholestatic hepatosis in previous pregnancies and family history of ICP. The average pre-pregnancy BMI was calculated to be 23.4.

Analysis extragenital pathology of pregnant women with ICP showed a high frequency, diseases of the digestive tract – in 116 (89.9%) patients. Among them, in 35 (27.1%) women with ICP chronic gastritis was observed, in 38 (29.4%) – biliary dyskinesia. Gynecological anamnesis showed most frequent background diseases of the cervix – 67 (51.9%), chronic salpingo-oophoritis – 26 (20.1%), polycystic ovary syndrome – 32 (24.8%), external genital endometriosis 27 (20.9%). Obstetric history in 99 (77%) pregnant with ICP was weighed with miscarriage: in 48 (37%) cases – premature birth has happened (in 36 (28%) patients – in II trimester).

Contraceptives with estrogen used about half of pregnant women with ICP for 2 years or more, which could lead to the development of cholestasis during pregnancy.

Evaluation of complaints of pregnant women with ICP showed that the clinical manifestations characterized mainly by pruritus (100%) of undulating course; its intensity gradually increased. Jaundice was noted only in 10 cases in which the development of cholestatic liver characterized by early onset (II trimester) and severe course.

During examining a group of pregnant women with ICP revealed significant changes in rates of lipid peroxidation and antioxidation activity levels. The intensity of these changes is increasing, depending on the severity of cholestatic hepatosis. Features of lipid peroxidation and antioxidation activity and its dynamics after treatment are demonstrated in the table.

As can be seen from the table, after efferent therapy pregnant women in basic group noted a 1.5 times decrease in diene conjugates and malondialdehyde. The level of SOD and α-tocopherol increased at the end of treatment.

Against the background of drug therapy in the comparison group observed a negative trend, significantly 1.2 times increased the level of diene conjugates slightly increased level of malonic dialdehyde. After treatment was maintained suppression of antioxidant system.

Clinically pregnant women in the basic group after the first session of plasmapheresis, noted subjective reduce itching, improve the quality of nighttime sleep, mood, increase efficiency, reduce irritability. After four plasmapheresis procedures in 36 (90%) of pregnant subjective manifestations of ICP disappeared completely. In 4 (10%) women with severe ICP after adjuvant therapy, which included plasmapheresis, were itching episodes, mostly at night, but they did not break the night's sleep.

Pregnant women in the comparison group of sustained decrease in the severity of itching and psycho-emotional symptoms were not observed. The intensity of itching, and therefore emotional lability, decreased during treatment, but no pregnant not marked complete clinical comfort.

## CONCLUSION

Intrahepatic cholestasis of pregnancy is characterized by increased activation of lipid peroxidation and a reduction in antioxidant activity. Only drug therapy of ICP can not effectively correct oxidative stress – increasing of lipid peroxidation, reducing antiradical activity is shown. In the context of a comprehensive treatment, including the use of plasmapheresis there is a significant reduction of reactive oxygen species and increasing of antioxidant activity.

Thus, complex treatment of ICP, including drug and efferent therapy enables to adjust effectively condition of oxidative stress and as a result to carry out prevention of possible negative consequences.

## Холестатичний гепатоз вагітних: нові ланки патогенезу

**С.В. Бенюк, Т.В. Ковалюк**

У статті розглянуті особливості про- та антиоксидантної систем при холестатичному гепатозі вагітних. Визначені зміни про- та антиоксидантної системи у вагітних з холестатичним гепатозом. Показана динаміка первинних продуктів перекисного окиснення ліпідів – дієнових кон'югатів, малонового діальдегіду, а також біологічно активних речовин, що входять до складу антиоксидантної системи (супероксиддисмутази та α-токоферолу) в сироватці крові під впливом традиційної медикаментозної та комплексної терапії. Продемонстрована ефективність еферентної терапії в нормалізації показників прооксидантної та антиоксидантної систем у жінок з холестатичним гепатозом вагітних.

**Ключові слова:** холестатичний гепатоз вагітних, перекисне окиснення ліпідів, антирадикальна активність.

## Холестатический гепатоз беременных: новые звенья патогенеза

**С.В. Бенюк, Т.В. Ковалюк**

В статье рассмотрены особенности про- и антиоксидантной систем при холестатическом гепатозе беременных. Определены изменения про- и антиоксидантной системы у беременных с холестатическим гепатозом. Показана динамика первичных продуктов перекисного окисления липидов – диеновых конъюгатов, малонового диальдегида, а также биологически активных веществ, входящих в состав антиоксидантной системы (супероксиддисмутаза и α-токоферол) в сыворотке крови под влиянием традиционной медикаментозной и комплексной терапии. Продемонстрирована эффективность эферентной терапии в нормализации показателей прооксидантной и антиоксидантной систем у женщин с холестатическим гепатозом беременных.

**Ключевые слова:** холестатический гепатоз беременных, перекисное окисление липидов, антирадикальная активность.

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Н О В О С Т И М Е Д И Ц И Н Ы

У ДЕТЕЙ ПРЕИМУЩЕСТВЕННО СОХРАНЯЮТСЯ  
ХОРОШИЕ ВОСПОМИНАНИЯ

Родители, которые проводят время, играя и разговаривая с их пятимесячным ребенком, могут задать вопросом, помнит ли их ребенок что либо из этого на следующий день.

Согласно новому исследованию, проведенному в Университете Бригама Янга, дети, с большей вероятностью что-то запоминают, если есть положительная эмоция.

Исследователи контролировали движение глаз грудных детей и то, как долго они смотрят на тестовое изображение. Дети были размещены перед плоскими панелями мониторов в закрытом помещении, а

затем человек на экране говорит им либо приветливым, нейтральным или злым голосом. Сразу после эмоционального воздействия, малышам были показаны геометрической фигуры.

Для тестирования их памяти, последующий тест был сделан через 5 минут и еще раз на следующий день. В последующем испытании, младенцам были параллельно показаны две геометрические фигуры: совершенно новая и одна из прошлого исследования. Затем исследователи смогли записать, сколько раз ребенок переходил от одного изображения к другому и как долго

он затрачивал на просмотр каждого изображения. Воспоминания младенцев были хуже, если форма была в паре с отрицательным голосом, но реакция детей была значительно лучше в ответ на фигуры, ассоциировавшиеся у них с ласковыми, приветливыми голосами.

Возможно, что сказалось положительное влияние системы повышенного внимания и возбуждения детей. По мере увеличения этих систем, способность детей обрабатывать и, вероятно, запоминать геометрический рисунок была лучше.

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