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The role of ursodeoxycholic acid in the treatment of intrahepatic cholestasis in pregnant women after ART

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Abstract
Intrahepatic cholestasis of pregnancy (IHCP) is of significant practical interest as this pathology is a borderline case between obstetric, infectious and hepatic pathology. The issues of etiology, pathogenesis, risk factors triggering intrahepatic cholestasis, the principles of its treatment and prevention are still an object of debate. At present, ursodeoxycholic acid (UDCA) is considered to be the medicine of choice for the treatment of intrahepatic cholestasis of pregnancy. The peculiarity of this medicine lies in its 4 mechanisms of action: replacement of toxic endogenous bile acids, cytoprotective action for hepatocytes and cholangiocytes, immunomodulation and choleretic action [3].
To test the efficiency of the suggested drug, we selected 71 women who got pregnant owing to ART and who presented a high risk of IHCP at the first prognostication stage. By way of randomization, they were divided into 2 groups: the basic group – 29 patients, who were treated with the recommended complex of therapy and prophylaxis, and the comparison group – 42 pregnant women, whose pregnancy was managed in accordance with the WHO guidelines.
The recommended ursodeoxycholic acid has enabled a more effective normalization of biochemical indicators associated with IHCP (reduction of the levels of total bilirubin, bile acids, ALT, AP and total cholesterol in terms of the low-density and the very-low-density lipoprotein fraction) and a significant decrease in the incidence of complications of pregnancy.

Keywords: intrahepatic cholestasis of pregnancy, infertility, assisted reproductive technologies, treatment

Introduction
The etiology of IHCP is not quite clear but, most probably, implies the combination of genetic susceptibility, hormonal and environmental factors [1, 2]. The diagnosis of IHCP is set on the basis of clinical data (itching, first local, then generalized, from light to unbearable, more intense at night, causing sleep disorders, with jaundice in 10-15% of cases) observed before the actual laboratory signs appear (increased concentration of bile acids, transaminases and bilirubin) [3, 4]. Ursodeoxycholic acid (UDCA) is currently considered to be the medicine of choice for the treatment of IHCP [5, 6].
In the 60 years of use of UDCA drugs, there have been no sufficient data proving any significant side effect or toxicity. Taking this into consideration and in view of the proved efficiency, the US Food and Drug Administration authorized the use of UDCA in pregnant women as a Category B drug (animal reproduction studies failed to demonstrate serious risks or side effects in the first trimester of pregnancy), which implies the authorization to use the drug in any trimester of pregnancy in case of indications. UDCA is also included in the guidelines of the American Gastroenterological Association for the treatment of cholestasis of pregnancy. In 2014, the Ministry of Health of Ukraine issued a bulletin called 'The Treatment of Obstetric Cholestasis', where it recommended the use of UDCA in the management of pregnancies of women with IHCP [7, 8].
Many studies show that the use of UDCA in women with IHCP effectively relieves the itching of skin, normalizes the biochemical hepatic indicators, significantly reduces the risk of preterm labor and is absolutely safe for both the mother and the fetus [9, 10]. UDCA therapy improves the prognosis for the fetus due to a decreased incidence of preterm labor, fetal distress and other neonatal disorders. Many studies of UDCA safety and efficiency in pregnant women established that the drug decreased the serum concentrations of bile acids in the mother, caused no increase in the level of toxic bile acids, and had no teratogenicity or toxic effect on the fetus [11-13].

Hydrophilic UDCA protects hepatocytes and cholangiocytes from necrosis and apoptosis caused by hydrophobic bile acids in cases of cholestasis. UDCA has the capacity for activating glucocorticoid receptors as well as a direct immunosuppressive action due to its effect on the production of immunoglobulins and cytokines by the immunocompetent cells. From the clinical point of view, UDCA therapy reduces the levels of IgM, antimitochondrial antibodies and anti-pyruvate kinase antibodies [14-16]. When used for the treatment of cholestatic liver diseases, UDCA shows the following important mechanisms of action: influence on the general pool of bile acids, immunomodulation, anti-inflammatory action, protection of liver cells and bile duct epithelium as well as action against apoptosis.

UDCA is prescribed at a ratio of 10-15 mg per 1 kg of body weight if IHCP is diagnosed before labor (the dose is divided into 2 or 3 administrations). Itch relief is usually observed after 1 or 2 weeks and the improvement of biochemical indicators after 3 or 4 weeks. If the drug does not relieve itch to a tolerable level after 2 weeks, the dose is increased to a maximum of 20 mg per 1 kg of body weight a day [17- 19].

To test the efficiency of the suggested drug, we selected 71 women who got pregnant owing to ART and who presented a high risk of IHCP at the first prognostication stage. By way of randomization, they were divided into 2 groups: the basic group – 29 patients, who were treated with the recommended complex of therapy and prophylaxis, and the comparison group – 42 pregnant women, whose pregnancy was managed in accordance with the WHO guidelines.

In the preconception period and in the first trimester of pregnancy, 12 (28.6%) out of 42 women from the comparison group and none from the basic group were diagnosed with IHCP in the period of up to 24 weeks of pregnancy (Table 6.1), whereas in the period of up to 30 weeks of pregnancy, the disease was found in 3 (10.3%) out of 29 women from the basic group vs. 15 (35.7%) out of 42 women from the comparison group (p<0.05).

Table 1: Clinical manifestations of IHCP in pregnant women after ART, depending on the applied complex of therapy and prophylaxis

Clinical manifestations of IHCP	Basic group, n = 29		Comparison group, n = 42	
	absolute number	%	absolute number	%
Onset in the period of up to 30 weeks of pregnancy	3	10.3*	15	35.7
Clinical manifestations of IHCP in the period of up to 24 weeks of pregnancy	-	-	12	28.6
Itching of skin: light, local (anterior abdominal wall, forearms, shins)	16	55.2*	13	31.0
intense, local, without sleep disorders	12	41.4	23	54.8
generalized, with sleep disorders and emotional disorders	1	3.4*	6	14.3
Condition of skin: no excoriation	6	20.7*	2	4.8
isolated excoriations	21	72.4	31	73.8
multiple excoriations	2	6.9*	9	21.4
Jaundice: none	5	17.2	4	9.5
subicteric	23	79.3	31	73.8
apparent jaundice	1	3.4	5	11.9
Manifestations in terms of gastrointestinal tract: none	25	86.2*	18	42.9
nausea	2	6.9*	17	40.5
vomiting	-	-	2	4.8
steatosis	-	-	2	4.8
decreased appetite	1	3.4*	6	14.3
Severe course	2	6.9	8	19.0

Note: * - the difference is significant with regard to the indicator in women from the comparison group (p<0.05).

The women from the basic group present a significantly lower rate of apparent manifestations of IHCP (generalized itching of skin, with sleep disorders and emotional disorders, multiple excoriations). As for manifestations in terms of the gastrointestinal tract, only 2 (6.9%) women had nausea (vs. 40.5% of women in the comparison group) and 1 (3.6%) woman complained of decreased appetite (vs. 14.3% respectively) (p<0.05). Generally speaking, a severe course of IHCP was observed in 2 (6.9%) patients from the basic group and 8 (19.0%) patients from the comparison group (p<0.05).

Women who had got pregnant after ART and were diagnosed with IHCP, presented characteristic changes in the respective indicators. Although the latter were slightly less apparent in the basic group, we found no significant difference between the two groups before the beginning of treatment (Table 6.2).

Table 2: Biochemical signs of IHCP in pregnant women after ART, depending on the applied complex of therapy and prophylaxis

Indicator	Basic group, n = 29				Comparison group, n = 42			
	Before treatment		After treatment		Before treatment		After treatment	
Total bilirubin, µmol/l	16.7±	2.21	8.9±	2.43^	20.4±	2.57	15.3±	2.62
Direct bilirubin, µmol/l	3.12±	0.52	2.54±	0.37	3.94±	0.45	3.16±	0.48
Bile acids, µmol/l	31.3±	4.18	14.8±	3.38^*	41.3±	3.61	28.3±	4.16^
ALT, U/l	52.1±	3.89	28.4±	3.91*^	59.5±	4.28	43.7±	4.37^
AST, U/l	41.3±	3.59	30.6±	4.15	44.5±	3.74	40.1±	4.22
GGT, U/l	38.5±	5.3	24.7±	5.1	41.6±	4.97	34.8±	5.1
AP, U/l	208.4±	17.3	121.4±	21.5*^	235.2±	24.1	189.6±	20.3
Cholesterol, mmol/l	7.38±	0.42	6.1±	0.44^	7.95±	0.51	7.32±	0.46
HDL cholesterol, mmol/l	1.16±	0.14	1.43±	0.17	1.02±	0.18	1.26±	0.15
LDL cholesterol, mmol/l	4.68±	0.28	3.75±	0.26^	4.95±	0.32	4.39±	0.31
VLDL cholesterol, mmol/l	1.64±	0.25	0.92±	0.25^	1.83±	0.24	1.62±	0.31

TG, mmol/l	2.3±	0.21	1.6±	0.32	2.5±	0.20	2.1±	0.30

Notes: * - the difference is significant with regard to the indicator in women from the comparison group (p<0.05).
^ - the difference is significant with regard to the indicator before treatment (p<0.05)

The applied recommended treatment has enabled the normalization of the majority of biochemical indicators: significantly decreased levels of total bilirubin (from 16.7±2.21 to 8.9±2.43 µmol/l, p<0.05), bile acids (from 31.3±4.18 to 14.8±3.38 µmol/l, p<0.05), ALT (from 52.1±3.89 to 28.4±3.91 U/l, p<0.05), AP, total cholesterol in terms of the low-density and the very-low-density lipoprotein fraction. The patients from the comparison group also showed some improvement in the indicators, yet it was significant only for the concentration of bile acids in blood (from 41.3±3.61 to 28.3±4.16 µmol/l, p<0.05) and ALT (from 59.5±4.28 to 43.7±4.37 U/l, p<0.05). However, the average level remained significantly higher in comparison to the patients from the basic group. Thus, the recommended complex of treatment has enabled a more effective normalization of the biochemical indicators associated with IHCP.

Conclusion The proved efficiency of ursodeoxycholic acid for women who got pregnant after ART and show manifestations of IHCP makes it possible to recommend it for wide use in complex treatment. With a positive effect of the applied therapy (absence or relief of itch, decreased or stabilized level of bile acids), labor was induced after 37 or 38 weeks of pregnancy. IHCP implies no contraindication to breast feeding. Treatment with ursodeoxycholic acid ends with the beginning of labor, its content in breast milk is very low and has no adverse effect on the newborn.

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