

CONDITION OF FETURES AND NEWBORNS FROM WOMEN WITH INFERTILITY TREATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES AND WITH CONCOMITANT INTRAHEPATIC CHOLESTASIS

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ABSTRACT

The aim: Improving the effects of pregnancy on the fetus and newborn through early diagnosis and timely comprehensive therapy of pregnant women with intrahepatic cholestasis.

Materials and methods: We have conducted a complex examination of 60 women who got pregnant owing to assisted reproductive technologies, with concomitant intrahepatic cholestasis, and 20 practically healthy women with a physiological course of pregnancy and labor (reference group), aged between 18 and 42. The research did not involve pregnant women with chronic liver diseases, viral hepatitis, skin diseases. Women who underwent the suggested complex drug therapy with Ursofalc, L-arginine and Omega 3, with peroral administration for 14 days according to the following scheme: Ursofalc – 250 mg once a day, L-arginine – 5 ml 3 times a day, Omega 3 – 1 capsule a day. The complex examination of pregnant women with IHC was conducted before and after treatment. We analyzed the data of anamnesis, carried out anthropometric measurements, clinical biochemical examinations of the women with IHC, including the measurement of the levels of alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, total and placental alkaline phosphatase, leucine aminopeptidase, 5'-nucleotidase, cholic, deoxycholic and chenodeoxycholic acids as well as their total level.

Results: Almost 40% of women with intrahepatic cholestasis gave birth to babies with asphyxia, including severe one in 11.1% of cases, 1/3 of the newborns were premature, 40% had signs of hypotrophy, and 66.7% experienced a disturbed course of early neonatal adaptation. There was also a higher level of perinatal mortality. The newborns from women who had undergone the suggested complex therapy presented no cases of hypotrophy, prenatal infection or cerebral circulation disorder.

Conclusions: Thus, functional hepatic disorders in women with infertility play a certain role in the carrying of pregnancy after ART, in the development of pregnancy complications and adverse consequences for women and their newborns. The conducted research shows that early diagnosis and timely complex therapy of pregnant women with intrahepatic cholestasis makes it possible to influence the pathogenesis of perinatal complications and improve the consequences of pregnancy for the fetus and the newborn.

KEY WORDS: intrahepatic cholestasis; perinatal complications; infertility

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INTRODUCTION

The interrelation between the reproductive and the hepatobiliary system is generally known [1–5]. On the one hand, patients with infertility often present diseases of liver and the biliary tract, which contribute to estrogen metabolism disorders [6–11], on the other hand, a surplus of certain sex steroids in blood negatively influences various liver functions [12–15].

In the majority of patients with reproductive pathology, functional hepatic disorders develop in the absence of clinical signs of diseases of the hepatobiliary system [16–19].

The most important issue of the contemporary obstetrics is prevention of severe complications of pregnancy and labor, stillbirths, neonatal morbidity and mortality [20–24]. Obstetric and perinatal pathology may be caused by liver diseases that developed long before pregnancy. At the same time, pregnancy achieved as a result of assisted reproductive technologies may

lead to severe liver lesions as this extremely vital organ undergoes significant functional strain in the gestational period. Intrahepatic cholestasis (IHC) is a liver dysfunction characterized by the most benign clinical course among the liver diseases that occur only during pregnancy [25–30].

In women, symptoms disappear immediately or within one month after labor but they imply serious consequences for the fetus. According to the literature, IHC is related to an increased risk of preterm labor, meconium-stained amniotic fluid, embryonal bradycardia, fetal distress and fetal death [31–36]. The basic mechanisms of development of adverse consequences for the fetus are not sufficiently researched. A number of studies revealed a connection between an increased level of bile acids (>40 micromole/l) in the mother's blood serum during pregnancy and the incidence of preterm labor and neonatal asphyxia [37–40]. Although the issue of liver diseases and pregnancy is

Table 1. Fetal biophysical profile score in the women involved in the research.

Parameter	Group of women		
	Basic group, n= 50	Comparison group, n= 50	Reference group, n = 50
Non-stress test	(1.46±0.13)*	1.85±0.18	1.92±0.05
Fetal respiratory movements	(1.27±0.09)*^	(1.74±0.15)*	1.91±0.06
Fetal movements	(1.35±0.08)*^	(1.73±0.12)*	1.95±0.03
Fetal tone	(1.61±0.12)* ^	1.89±0.11	1.96±0.04
Volume of amniotic fluid	(1.79±0.11)*	1.89±0.17	1.97±0.03
Total BPP score	(7.77±0.43)* ^	9.21±0.35	9.92±0.17

* – the difference is significant with regard to the score in women from the reference group ($p < 0.05$);

^ – the difference is significant with regard to the score in women from the comparison group ($p < 0.05$).

Table 2. Indices of uterine-placental and fetal blood circulation in the women involved in the research.

Vessels	Index	Group of women		
		Basic group, n= 50	Comparison group, n= 50	Reference group, n = 50
Placental artery	PI	(0.594±0.025)*	0.521±0.027	0.458±0.021
	RI	(0.415±0.021)*	0.355±0.026	0.325±0.027
Umbilical cord artery	PI	(1.102±0.031)*	0.978±0.047	0.941±0.023
	RI	(0.684±0.020)*	0.631±0.023	0.624±0.028
Fetal aorta	PI	(1.735±0.095)*	1.637±0.058	1.511±0.077
	RI	0.821±0.032	0.733±0.046	0.729±0.047
Fetal cerebral arteries	PI	1.428±0.036	1.341±0.048	1.349±0.036
	RI	0.786±0.021	0.702±0.022	0.724±0.025

* – the difference is significant with regard to the index in women from the reference group ($p < 0.05$).

most widely researched [41–43], the majority of studies is dedicated to the clinical aspects of the problem while the specific pathogenetic mechanisms of obstetric and perinatal disorders remain not completely identified. The issues of conception, preservation, course and perinatal aspects of pregnancy in women with hepatobiliary pathology and after the treatment with ART are practically unaddressed.

The topicality of this issue is accounted for by a wide spread of hepatobiliary pathology and perinatal consequences in women with infertility treated with ART [44].

The purpose is to study the perinatal consequences of intrahepatic cholestasis in women with infertility treated with assisted reproductive technologies.

THE AIM

The aim improving the effects of pregnancy on the fetus and newborn through early diagnosis and timely comprehensive therapy of pregnant women with intrahepatic cholestasis.

MATERIALS AND METHODS

We have conducted a complex examination of 60 women who got pregnant owing to assisted reproductive technologies, with concomitant intrahepatic cholestasis, and 20 practically healthy women with a physiological course of pregnancy and labor

(reference group), aged between 18 and 42. The research did not involve pregnant women with chronic liver diseases, viral hepatitis, skin diseases. Women with intrahepatic cholestasis who got pregnant as a result of ART were divided into two groups – the basic group and the comparison group – compatible in terms of age, degree and duration of IHC. The basic group consisted of 30 pregnant women with IHC, who underwent the suggested complex drug therapy with Ursofalc, L-arginine and Omega 3, with peroral administration for 14 days according to the following scheme: Ursofalc – 250 mg once a day, L-arginine – 5 ml 3 times a day, Omega 3 – 1 capsule a day. The comparison group included 30 pregnant women with IHC treated with a conventional drug therapy. The complex examination of pregnant women with IHC was conducted before and after treatment. We analyzed the data of anamnesis, carried out anthropometric measurements, clinical biochemical examinations of the women with IHC, including the measurement of the levels of alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, total and placental alkaline phosphatase, leucine aminopeptidase, 5'-nucleotidase, cholic, deoxycholic and chenodeoxycholic acids as wells as their total level.

The obtained data were processed using standard statistical methods using a personal computer HP PREMIER EXPERIENCE with MicrosoftWord 2010, the graphics were built using Microsoft Excel. Statistical processing was performed by the program Statistics 10.

Table 3. Indicators of the condition of newborns absolute number (%)

Indicator	Babies of women treated with ART		Reference group, n = 50
	Basic group, n = 51	Comparison group, n = 58	
Prematurity	20 (39.2) * [^]	13 (22.4)*	1 (2.0)
Hypotrophy	25 (49.0) * [^]	18 (31.0)*	3 (6.0)
Body weight loss by over 10%	28 (54.9)* [^]	22 (37.9)*	1 (2.0)
Suckling delay	34 (66.7) * [^]	32 (39.7)*	2 (4.0)
Neonatal adaptation disorders	38 (74.5)* [^]	28 (48.3)*	4 (8.0)

* – the difference is significant with regard to the indicator in women from the reference group ($p < 0.05$);

[^] – the difference is significant with regard to the indicator in women from the comparison group ($p < 0.05$).

RESULTS

In women treated with ART, the first half of pregnancy presented no significant peculiarities. The second half of pregnancy in women with IHC was most often characterized by placental insufficiency (72.0 % vs. 42.0 and 8.0 % of women from the comparison group and the reference group respectively, $p < 0.05$) and, consequently, fetal distress (46.0 % vs. 28.0 and 6.0 %, $p < 0.05$) and intrauterine growth retardation (38.0 % vs. 22.0 and 4.0 %, $p < 0.05$). Almost half of the women from the basic group presented risk of preterm labor, 38.0 % – preeclampsia, including severe one in 14.0 % of women (cf. 6.0 % of women from the comparison group, $p < 0.05$). Non-developing pregnancy was found in 2 women from the basic group (4.0 %) and 1 woman from the comparison group (2.0 %).

The assessment of the condition of fetuses in the 32–35th week of pregnancy with the use of instrumental methods has shown the following results (Table 1). According to the results of ultrasonography and the biophysical profile (BPP) score, taking into consideration the non-stress test (assessment of cardiovascular reactivity of the fetus), there is a trend towards the decrease of scores of all the BPP components in women with IHC, mainly due to the decrease of movements and tone of the fetus. Women after ART who underwent conventional treatment for IHC also presented reduced fetal movements, yet the total BPP score did not differ from that of the women from the reference group whereas the BPP score of women from the basic group is significantly lower than that of the women from the other two groups (7.77 ± 0.43 vs. 9.21 ± 0.35 and 9.92 ± 0.17 respectively, $p < 0.05$).

The analysis of the peculiarities of uterine-placental and fetal blood circulation in the pregnant women (Table 2) has shown in the women of the comparison group a trend towards a slight increase of the pulsatility index (PI) and the resistivity index (RI) in the arteries of placenta, the umbilical cord and the fetal aorta and a slight decrease of these indices in cerebral arteries. In women with IHC, there is a significant increase of PI and RI in the arteries of placenta and the umbilical cord, which is an initial sign of disorders of blood circulation and vital

support of the fetus. An increase of these indices in the fetal aorta is indicative of fetal distress, while the most dangerous sign is an increase of PI and RI in cerebral arteries, especially after their dynamic decrease, which was observed in 8 women (16.0 %) from the basic group and is indicative of progressive fetal distress and a threat to fetal vital activity.

Nowadays, pregnancy achieved as a result of ART is not an absolute indication for cesarean section, however, in view of the high incidence of placental insufficiency, preeclampsia and fetal distress, the frequency of this surgery at labor of the women after ART is significantly higher in comparison with the women from the reference group: 74.0 % in women who underwent the suggested complex therapy for IHC and 62.0 % in women under conventional treatment vs. 12.0 % in the reference group ($p < 0.05$). The women treated with ART presented a significantly bigger number of cases of preterm labor and fetal distress at labor (20.0 and 22.0 % vs. 8.0 % respectively, $p < 0.05$).

The factors determining the peculiarities of the course of pregnancy and labor also contribute to the development of a number of complications in the postnatal period in women treated with ART. We have found a significantly higher incidence of uterine involution disorders and purulent and septic complications. In contrast to the women from the reference group, the women treated with ART presented late hemorrhages, which occurred three times more often in women from the basic group in comparison with those from the comparison group (16.6 vs. 6.0 %, $p < 0.05$).

Live birth was given to 35 babies by the women from the basic group (1 stillbirth, 5 twins), to 34 babies by the women from the comparison group (4 twins) and to 20 babies by the women from the reference group.

Almost all the babies of the women from the reference group were in satisfactory condition at birth, with only 4 % of babies presenting moderate-degree asphyxia. In contrast, 49.0 % of the newborns from the basic group and 32.7 % from the comparison group presented asphyxia at birth ($p < 0.05$), with the percentage of severe asphyxia almost five times higher in the first group in comparison with the second one (9.8 vs. 1.7 %, $p < 0.05$).

DISCUSSION

The analysis of the babies' body weight at birth has shown the following results. A significantly bigger percentage of babies of the women treated with ART were born with a decreased body weight, which is accounted for by both prematurity and hypotrophy. The majority of babies of the women with IHC weighed less than 2,500 g, which significantly differs not only from the percentage of such babies in the reference group but also in the comparison group (66.7 vs. 48.3 %, $p < 0.05$).

Over 1/3 of the newborns from the basic group were premature (Table 3), which significantly exceeds not only the percentage of such babies in the reference group but also in the comparison group ($p < 0.05$). Still more babies presented signs of hypotrophy, which is accounted for by both prematurity and intrauterine growth retardation. As a result, babies of the women treated with ART started suckling later.

The majority of the newborns from the basic group (74.5 %) presented neonatal adaptation disorders (cf. 48.3 % in the comparison group, $p < 0.05$). Dysadaptation syndromes most often included neurological disorders (43.1 % vs. 25.0 % in the comparison group, $p < 0.05$) and conjugated hyperbilirubinemia (47.1 % vs. 29.3 %, $p < 0.05$) as well as respiratory disorders (35.3 % vs. 15.5 %, $p < 0.05$) and gastrointestinal disorders (37.3 % vs. 24.1 %). The incidence of hemorrhagic syndrome was two times higher in the basic group (19.6 % vs. 10.3 %). No cases of neonatal death were recorded.

CONCLUSIONS

Intrahepatic cholestasis is a pregnancy complication characterized by a cascade of pathologic processes that deteriorate the quality of life of a pregnant woman and, what is very important, lead to perinatal complications.

Fetal and neonatal complications make it necessary to search for improved methods of prevention and treatment of this dangerous complication of pregnancy and its consequences.

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The Authors declare no conflict of interest.

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