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CLINICAL ASPECTS OF PREGNANCY AND CHILDBIRTH IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Keywords: *intrahepatic cholestasis of pregnancy, pregnancy, childbirth.*

Introduction. *Intrahepatic cholestasis of pregnancy (ICP) is a liver pathology that has negative impact on progression of pregnancy and childbirth in affected women. This study aims to assess the clinical characteristics of pregnancy and delivery among women diagnosed with intrahepatic cholestasis of pregnancy.*

Material and methods. *The study was conducted as a prospective cohort study involving 142 clinical cases, divided into two groups according to the complication of pregnancy with cholestasis gravidarum. Evaluation of pregnancy and childbirth clinical aspects was performed alongside an examination of medical records. Statistical data were processed using IBM Statistics SPSS 21, MedCalc and GraphPad software.*

Results. *It was determined that every fourth pregnant woman diagnosed with intrahepatic cholestasis of pregnancy also presented with hyperemesis gravidarum during the current pregnancy. Additionally, an elevated prevalence of iron deficiency anemia and gestational diabetes mellitus was detected among pregnant women with this condition. Meconium staining of the amniotic fluid complicated approximately one in every four pregnancies in women with intrahepatic cholestasis gravidarum.*

Conclusions. *The study findings indicate a notable increase in hepato-biliary conditions and nephrourinary pathology among women with ICP. Hence, a high incidence of hyperemesis gravidarum, along with an elevated frequency of iron deficiency anemia and gestational diabetes mellitus, was found in women with this condition.*

Cuvinte-cheie: *colestază intra-hepatică de sarcină, sarcină, naştere.*

ASPECTELE CLINICE ALE SARCINII ŞI NAŞTERII LA FEMEILE CU COLESTAZĂ INTRAHEPATICĂ DE SARCINĂ

Introducere. *Colestaza intrahepatică de sarcină este o patologie hepatică, care are un impact negativ asupra evoluției sarcinii și nașterii la femeile cu patologie cercetată. Studiul a avut drept scop evaluarea particularităților clinice ale sarcinii și nașterii la femeile cu colestază intrahepatică de sarcină.*

Material și metode. *Premisa cercetării s-a bazat pe un studiu prospectiv de cohortă a 142 de cazuri clinice, divizate în două loturi, în funcție de complicațiile în sarcină cu afecțiunea colestaza gravidarum. Cercetarea a fost realizată prin aprecierea particularităților sarcinii și nașterii la femeile cu patologia data și analizarea documentației medicale. Datele statistice au fost prelucrate prin intermediul programului IBM Statistics SPSS 21, MedCalc și GraphPad.*

Rezultate. *S-a constatat că, fiecare a patra gravidă cu colestază intrahepatică de sarcină a fost diagnosticată cu hiperemesis gravidarum în sarcina curentă și s-a depistat o frecvență crescută a anemiei feriprive și a diabetului gestațional în rândul gravidelor cu patologie cercetată. Astfel, la femeile cu colestaza gravidarum, aproximativ fiecare a patra sarcină a prezentat complicații la nivel intrauterin, prin–colorația meconială a lichidului amniotic.*

Concluzii. *Rezultatele studiului au demostrat că ratele afecțiunilor hepato-biliare și nefrourinare au fost semnificativ mai mari la femeile cu colestaza intrahepatică de sarcină, identificându-se o rată crescută de hyperemesis gravidarum, o frecvență crescută a anemiei feriprive și a diabetului gestațional la femeile cu patologia cercetată.*

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a liver condition, that occurs in pregnancy, with an incidence of 0.5-1% worldwide (1). The incidence of the condition varies widely, depending on several factors. Despite being a significant medical concern, ICP often is overlooked. It can lead to severe complications for both the mother and fetus. However, literature data show that ICP generally follows a favorable course for mothers and yields positive outcomes. In most cases ICP develops towards the end of the second trimester or early in the third trimester, with clinical symptoms and laboratory abnormalities resolving within 2-3 weeks postpartum (2).

However, in recent years, a number of case reports have been published concerning potential fetal complications leading to adverse perinatal outcomes, related to ICP (3). One of the most dangerous complications of cholestasis gravidarum is intrauterine fetal death. At the same time, there is an increased incidence of premature births (spontaneous or iatrogenic) among women whose pregnancies are complicated by ICP (4, 5). However, the rate and nature of fetal risks associated with ICP are not fully understood (6). The authors consider that ICP may be one of the causes of birth complications. Perinatal outcomes are of clinical interest in the management of pregnancy and childbirth in women with cholestasis gravidarum, given the potential for preterm birth, intrauterine fetal death, and postpartum hemorrhage (7, 8).

The purpose of the study was to assess clinical aspects of pregnancy, and childbirth in women with intrahepatic cholestasis of pregnancy.

MATERIAL AND METHODS

The prospective cohort study was conducted at the Department of Obstetrics and Gynaecology, within *Nicolae Testemitanu* State University of Medicine and Pharmacy, during the period 2020-2022.

The representative research sample was calculated using the EpiInfo 7.2.2.6 program, specifically the StatCalc - Sample Size and Power section, for the observational analytical cohort study, based on the following parameters:

- Confidence interval (CI) for a 95.0% level of significance:
- Statistical power - 80.0%;
- The average difference in pregnancy outcomes between women with intrahepatic cholestasis of pregnancy (ICP) and those without is 20.0% (9);
- Group ratio - 1:1.

Result: The calculated value for a 95.0% CI is 44, with a 10.0% non-response rate, yielding n=48.

Thus, according to the obtained data, the recommended sample size for a representative research group should be no fewer than 48 patients.

For the prospective research two groups were created:

- Group A - 71 pregnant women whose pregnancy was complicated by ICP (research group, L1);
- Group B - 71 pregnant women whose pregnancies were not complicated by ICP (control group, L0).

The inclusion criteria for the research group were as follows: pregnant women diagnosed with ICP, with the exclusion of other potential causes of skin pruritus (ICP diagnosis was established based on clinical data and biochemical test results); serum bile acids level ↑ 10 μmol/L; gestational age between 22^{+0}-41^{+6} weeks; patient age ≥18 years; informed consent, in written form, for research participation.

Exclusion criteria included women with known liver diseases such as acute viral hepatitis, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis, primary biliary cirrhosis, and symptomatic cholelithiasis. Additionally, individuals diagnosed with cytomegalovirus and Epstein-Barr virus were excluded due to their potential to induce liver injury with elevated liver enzyme levels. Other exclusion criteria comprised drug-induced hepatitis, acute fatty liver of pregnancy, pre-eclampsia, HELLP syndrome, congenital thrombophilia, and women diagnosed with epilepsy to exclude the possible influence of antiepileptic medication on intestinal vitamin K absorption.

The diagnosis of ICP was based on anamnestic, clinical and biochemical data, medical documentation (obstetric and medical observation - form no. 96/e).

Statistical data were processed using *IBM Statistics SPSS 21, MedCalc* and *QuickCalcs* section of *GraphPad*. Statistical processing of data obtained by applying specific statistical operations: systematization of the material, statistical grouping according to parameters and levels, obtaining primary indicators and statistical data series; calculation of absolute (numbers) and/or relative (percentages) frequencies for nominal or categorical variables, and 95% CI for proportion. For continuous variables, mean values and standard deviations (SD) were calculated, while the median (Me) and interquartile range (Q1; Q3) were determined for characteristics exhibiting non-normal distributions. To compare categorical variables, the χ^2 test with Yates' continuity correction was employed, while the t-test was used to assess statistical differences between the two means.

RESULTS

The age of the pregnant women included in the study ranged from 18-43 years, while 37 women (52.1%; 95% CI: 36.6-71.8%) in L1, compared to the control group - 22 women (30.9%; 95% CI: 19.4-46.9%), were over 30 years of age (χ^2 5.683, p=0.0171). The mean age of the study participants was 29.5±6.3 years [Me 30 (25; 34)] in the research group and 27.3±5.4 years [Me 27 (23; 31)] in the control group (p=0.029).

In order to assess the clinical course of pregnancy in women with ICP, it was important to consider their extragenital history. There were assessed 9 indicators, and 21 women were determined with hepato-biliary conditions viz. 29.6% (95% CI: 18.3-41.5%) in the L1 vs L0 - 8 or 11.3% (95% CI: 3.8-19.4%), indicating a significantly higher risk of developing this condition during the current pregnancy (RR 2.6250, 95% CI: 1.2463-5.5290, p=0.0111). Similarly, gastrointestinal conditions were present in 10 women (14.1%, 95% CI: 18.3-41.5%) in the L 1 vs L0 – 8 women (11.3%, 95% CI: 3.8-19.4%), RR 1.250, 95% CI: 0.5239-2.9823, p=0.615. However, nephrourinary conditions were determined in 22 women (31.0%, 95% CI: 21.1-43.9%) in the L1 vs L0 – 10 women (14.1%, 95% CI: 5.2-24.6%), RR 2.2000, 95% CI: 1.1244-4.3047, p=0.0213. However, no statistically significant difference was found when assessing other indicators of complicated extragenital history between the pregnancies with ICP and those in the control group (Figure 1).

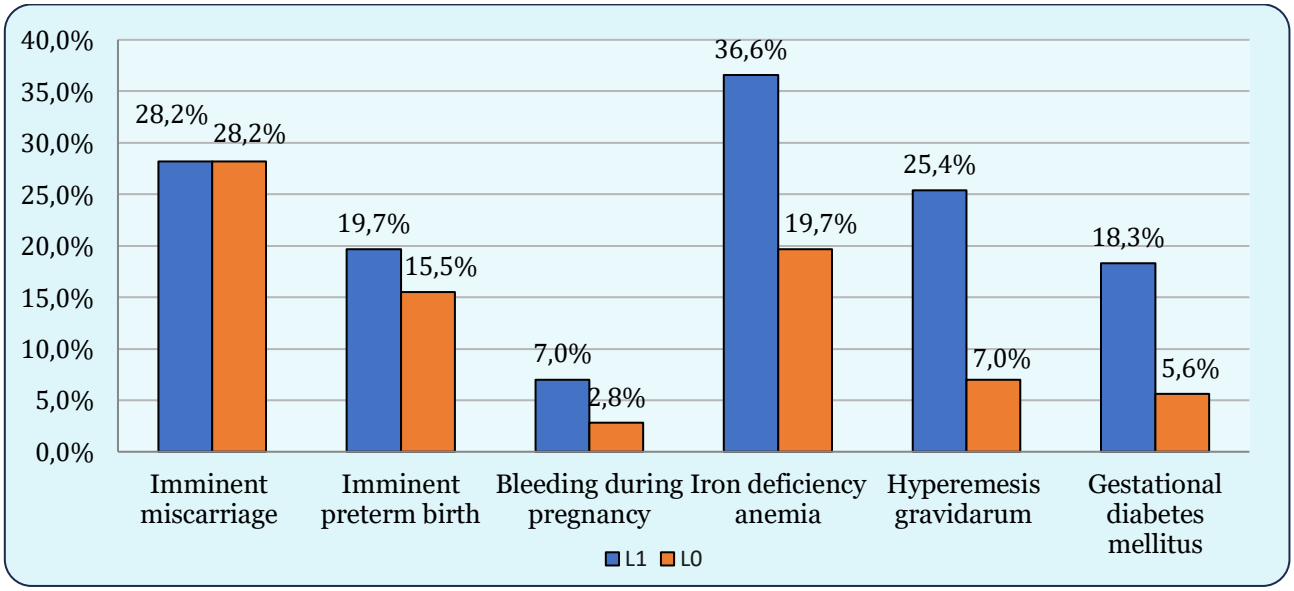

Fig. 1. Pregnancy outcome of pregnant women included in the study (%).

The study found no statistical difference in the number of complicated cases with imminent miscarriages [L1 - 20 women or 28.2% (95% CI: 18.3-38.5%) vs L0 - 20 or 28.2% (95% CI: 18.3-38.5%), χ^2 0.000, p=1.0000], imminent preterm birth [L1 - 14 women or 19.7% (95% CI: 9.9-32.8%) vs L0 - 11 or 15.5% (95% CI: 5.2-27.2%), χ^2 0.194, p=0.6595], bleeding during pregnancy [L1 - 5 cases or 7.0% (95% CI: 1.2-13.1%) vs L0 - 2 or 2.8% (95% CI: 0-8.5%), χ^2 0.601, p=0.4382].

In the analysis of pregnancy complications associated with various hypertensive conditions, 2 cases (2.8%; 95% CI: 0-7.3%) of essential hypertension were found in L1 vs L0 - 5 cases (7.0%; 95% CI: 1.2-14.3%), χ^2 0.601, p=0.4382; pregnancy-induced hypertension was detected in 6 cases (8.5%; 95% CI: 2.8-14.5%) in L1 vs L0 - 13 cases (18.3%; 95% CI: 11.0-31.0%), χ^2 2.187, p=0.1391, the difference being statistically insignificant. There was no statistically significant difference in the number of cases complicated with fetal growth restriction [L1 - 3 cases (4.2%; 95% CI: 1.2-11.7%) vs L0 - 3 cases (4.2%; 95% CI: 1.2-11.7%), χ^2 0.000, p=1.0000]; oligohydra mnios [L1 - 1 case (1.4%; 95% CI: 0-4.4%) vs L0 - 5 (7.0%; 95% CI: 2.4-12.9%), χ^2 1.566, p=0.2108]; polyhydramnios [L1 - 3 cases (4.2%; 95% CI: 1.2-11.7%) vs L0 - 3 (4.2%; 95% CI: 1.2-11.7%), χ^2 0.000, p=1.0000].

Table 1. Characteristics of pregnant women in the study groups according to term and mode of delivery (%).

Type of birth	Research group, L_1 n_1=71		Control group, L_0 n_0=71		χ^2	p
	abs.	% (95% CI)	abs.	% (95% CI)		
Vaginal birth	41	57.7% (47.4-70.1%)	54	76.1% (67.2-83.1%)	4.580	0.0324
Caesarean section	30	4.,3% (29.9-52.6%)	17	2.,9% (16.9-32.8%)		

It was determined that every fourth pregnant woman in L1 was diagnosed with hyperemesis gravidarum in the current pregnancy - 25.4% women (95% CI: 18.3-38.0%) compared to 7.0% (95% CI: 2.6-14.3%) in L0, (χ^2 7.471, p=0.0063). An increased frequency of iron deficiency anemia was detected among pregnant women in L1 - 36.6% cases (95% CI: 24.7-50.2%), vs L0 - 19.7% (95% CI: 8.0-27.4%), χ^2 4.211, p=0.0402. Thus, the frequency of gestational diabetes mellitus among L1 was 13 women, or 18.3% (95% CI: 11.3-28.2%), whereas 4 women were found among LO, or 5.6% (95% CI: 0-12.7%), χ^2 4.277, p=0.0386, thus indicating a statistically significant difference.

Hence, the features of childbirth were assessed, we studied and analyzed the term and mode of delivery. On average, delivery occurred at 37.6±2.0 (Me 38: 36.5; 39.2) w.g. in women with ICP, vs L0 - 39.2±1.7 (Me 39.5: 38.4; 40.3) w.g. (95% CI: -2.216 – 0.984, p<0.0001). A higher frequency of preterm births was determined among women in L1 – 19 cases (26.8%, 95% CI: 18.1-35.7%), vs L0 – 5 cases (7.1%, 95% CI: 0-11.7%), RR 3.8000, 95% CI: 1.5014-9.6176, p=0.0048, despite the predominance of term births both groups. Vaginal delivery was the most common mode of delivery in both study groups: 41 or 57.7% (95% CI: 47.4-70.1%) of cases in L1 and 54 or 76.1% (95% CI: 67.2-83.1%) of cases in L0 (tab. 1). At the same time, a higher frequency of cesarean sections in the research group was observed (χ^2 4.580, p=0.0324).

In 13 (18.3%, 95% CI: 11.0-27.0%) of cases in the L1, labour was induced by amniotomy and/or Folley catheter application for cervical preparation followed by amniotomy. In 9 (12.7%, 95% CI: 5.4-21.4%) of cases in L1, labour was induced by prostaglandin administration according to the standard clinical protocol (10). It should be noted that the reason for delivery by caesarean section or induction of labour in 21 (29.5%; 95% CI: 15.5-42.5%) cases in the research group was the presence of severe maternal symptoms and/or increased liver function tests values and/or bile acids levels in these women. Labour was induced by amniotomy or prostaglandin administration in 3 (4.2%; 95% CI: 0-7.3%) cases in L0 and 7 (9.9%; 95% CI: 2.6-18.5%) cases in L1; in all cases (10 women, 14.1%; 95% CI: 6.8-21.4%), induction of labour was indicated in relation to postterm pregnancy.

In the current study, no statistical difference was found regarding birth complications in both groups in terms of prenatal amniotic sac rupture, failure of contraction forces, placental and/or membranal tissue defects, or incidence of soft birth canal lacerations. Nevertheless, in women with cholestasis gravidarum, approximately every 4th pregnancy was complicated with meco-

nium staining of the amniotic liquid (L_1 - 20 cases or 28.2%; 95% CI: 18.3-38.0%, vs L_0 - 9 cases or 12.7%; 95% CI: 4.0-22.5%; χ^2 4.333, p=0.0374).

DISCUSSIONS

The data obtained are consistent with data from the literature showing that cholestasis gravidarum more often affects women over the age of 35 years (4). However, a recent study by M. Guszczynska-Losy et.al (2020) reported an average age of 30 years of pregnant women with ICP (11). The present study revealed a statistically significant difference in women's age between two groups. Hence, here exists a heterogeneity between L1 and L0 (age); thus, one of the limitations of the study is that the results may not be generalizable to larger populations.

Analyzing the extragenital anamnesis of the women included in the study, it was identified that hepato-biliary and nephrourinary conditions serve as risk factors for ICP, increasing the risk of developing cholestasis gravidarum by 2.6 (p=0.0111) and 2.2-fold (p=0.0213), respectively. These findings were also supported by other researchers, who reported hepatobiliary conditions such as gallbladder dysfunction, chronic cholecystitis, chronic viral hepatitis C and/or chronic viral hepatitis B as risk factors for ICP (12). Hepatitis C virus infection is considered by some authors as a risk factor for the development of CIS and may be associated with early onset of the pathology (13, 14). Conversely, other authors found no difference in the incidence of hepatitis C virus among pregnant women with cholestasis gravidarum compared with the control group (15). Concurrently, studies have demonstrated an increased risk for developing CIS among pregnant women infected with hepatitis B virus (16).

Hence, the data obtained were confirmed by other study, that highlighted that nephrourinary conditions may be a risk factor for the development of cholestasis gravidarum (11).

Assessing the particularities of delivery in the women included in the study, it was determined that 28.2% of cases of intrahepatic cholestasis of pregnancy were complicated by meconium staining of the amniotic fluid (p=0.0374). However, there is controversy in the literature about the rate of meconium staining of the amniotic fluid among women with ICP, ranging from 12% to 25% according to different studies (2, 17). At the same time, some studies report that in pregnancies complicated by stillbirth, meconium amniotic fluid was reported in about 100% of cases (18, 19). Some authors suggest that the frequency of occurrence of meconium staining amniotic fluid may correlate with maternal serum bile acids values, with a positive interdependence (20, 21). However, the mechanism by which bile acids cause this effect is not fully understood (22). Bile acids are thought to increase fetal colonic motility, which may explain the presence of meconium in the amniotic fluid, although this process may be a side effect of bile acids toxicity (21).

According to literature data, preterm birth accounts for approximately half of perinatal deaths (23). Therefore, the impact of preterm birth on newborn health cannot be ignored. The results of the study revealed a preterm birth rate of 26.8%. These findings can be compared with other studies, which indicate a preterm birth rate of 25-32% in pregnancies complicated by cholestasis gravidarum (1, 24). R. Reid and coauthors reported an increased incidence of preterm birth of up to 36% in women with cholestasis gravidarum. However, a more recent study by Saleh and coauthors reported a preterm birth rate of approximately 44% in women whose pregnancies were complicated by ICP (25, 26). Some authors suggest a correlation between maternal serum bile acids levels and the preterm birth rate in women with ICP. The rate of this complication was significantly higher in pregnant women with ICP and bile acids values >40 μmol/L (2). However, in patients with bile acids levels <20 μmol/L, an increase in the rate of preterm birth was not observed (27). Experimental rodent studies have shown that the myometrium of the non-pregnant rat responds to cholic acid administration by increasing contractility, and administration of this bile acid to sheep increases the incidence of spontaneous preterm birth (28). Thus, it has been hypothesized that the myometrium of ICP patients may be more sensitive to the effects of oxytocin (20).

CONCLUSIONS

1. The study results revealed a significant increase in the rates of hepato-biliary conditions and nephrourinary pathology among women with ICP.

2. A high rate of hyperemesis gravidarum in the current pregnancy, along with an increased frequency of iron deficiency anemia and gestational diabetes mellitus, was found in women with intrahepatic cholestasis of pregnancy.
3. Hence, ICP has been shown to have a negative impact on the evolution of labor, which is characterized by increased rates of meconium staining of the amniotic liquid.

CONFLICT OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

The study obtained ethical approval (nr.46, from 28.02.2020) from the Ethics Committee of the *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. Written informed consent was obtained from all participants, whereas all methods were carried out in accordance with relevant guidelines and regulations. Study registration number ISRCTN21187408 https://www.isrctn.com/ISRCTN21187408.

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