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ORIGINAL PAPER

ASSESSMENT OF CLINICAL SYMPTOMS IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Abstract

Introduction. Intrahepatic cholestasis of pregnancy (ICP) is a disorder characterized by pruritus and elevated liver function tests and is associated with a high incidence of adverse perinatal outcomes. Multi-disciplinary cooperation is critical for managing the condition and ensuring better pregnancy outcomes.

The objective of the study was to assess the clinical symptoms and intensity of cutaneous pruritus in women with intrahepatic cholestasis of pregnancy.

Material and methods. The study group included 71 women with ICP. The patients were asked about their symptoms and intensity of itching. The intensity of cutaneous pruritus was assessed according to two scales. SPSS 21 software was used to conduct the statistical analysis.

Results. On the onset of symptoms women had indicate the intensity of itching at 5.1±2.3 points on average, according to visual analog scale. 53.5% women indicated the symptom to be occasional or discontinuous. By the moment of the survey, 66.2% women indicated the intensity of the pruritus more or equal to 8 points, being continuous in 52.1% of cases. In the post-partum period, the intensity of the pruritus

Résumé

L'évaluation des symptômes cliniques chez les femmes atteintes de cholestase intrahépatique de la grossesse

Introduction. La cholestase intrahépatique de la grossesse est un trouble caractérisé par un prurit et des tests de fonction hépatique élevés et est associée à une incidence élevée de résultats périnatals indésirables. La coopération multidisciplinaire est essentielle pour gérer cette affection et garantir de meilleures issues de la grossesse.

L'objectif de l'étude était d'évaluer les symptômes cliniques et l'intensité du prurit cutané chez les femmes souffrant de cholestase intrahépatique de la grossesse.

Matériel et méthodes. L'étude a évalué 71 cas de cholestase intrahépatique de la grossesse. Les femmes ont été interrogées sur leurs symptômes et sur l'intensité des démangeaisons. L'intensité du prurit cutané a été évaluée selon deux échelles. Le logiciel SPSS 21 a été utilisé pour effectuer l'analyse statistique.

Résultats. Au début des symptômes, les femmes ont indiqué l'intensité des démangeaisons à 5,1±2,3 points en moyenne, selon l'échelle visuelle analogue. 53,5 % des femmes ont indiqué que le symptôme était souvent

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decreased, being assessed on the third day after delivery as less or equal with 5 points in 93.1% of cases, being occasional or discontinuous in 90.1% of cases.
Conclusions. Pruritus is the most prevalent clinical sign of ICP and it should not be ignored, being considered as a call for follow-up.

Keywords: intrahepatic cholestasis of pregnancy, liver functions tests, perinatal outcomes

occasionnel ou discontinu et se manifestait tous les jours, mais les périodes asymptomatiques prédominaient. Au moment de l'enquête, 66,2% des femmes indiquent que l'intensité du prurit est supérieure ou égale à 8 points, et qu'il est continu dans 52,1% des cas. Dans la période post-partum, l'intensité du prurit diminue, étant évaluée le troisième jour après l'accouchement comme inférieure ou égale à 5 points dans 93,1% des cas, étant occasionnelle ou discontinue dans 90,1% des cas.
Conclusions. Le prurit est le signe clinique le plus répandu de cholestase intrahépatique de la grossesse, c'est pourquoi les femmes cherchent une aide médicale supplémentaire pendant la grossesse. Par conséquent, il ne doit pas être ignoré, et doit être considéré comme un appel à un suivi.

Mots-clés cholestase intrahépatique de la grossesse, tests de fonction hépatique, résultats périnatals.

Abbreviations list
ALT = alanine aminotransferase, AST = aspartate aminotransferase, BA = bile acids, ICP = intrahepatic cholestasis of pregnancy, IVF = *in vitro* fertilization, LFTs = liver function tests, Me = median, UDCA = ursodeoxycholic acid, w.g. = weeks of gestation

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder characterized by pruritus as the main clinical symptom. Elevated liver function tests (LFTs) and/or elevated serum bile acids (BA) can be found in patients with ICP[1].

The prevalence of cholestasis gravidarum varies greatly depending on geographical region, with an estimated 0.5–1% of the global population affected[2]. At the same time, a higher incidence of ICP is exhibited in twin pregnancies (2.1%) and pregnancies conceived by *in vitro* fertilization (IVF) (2.7%)[3]. Hepatitis C virus seropositivity has been identified as a risk factor for ICP, and it may be linked to an earlier onset of the pathology[4]. Some cases of early onset ICP are described in the literature, but most commonly the disorder develops in the third trimester of pregnancy[5].

LFTs, including BA, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are essential for assessing the functional state of the liver. According to the literature, in the majority of ICP cases LFTs are significantly elevated[2,6]. The assessment of serum BA levels is considered the definitive biochemical marker for the diagnosis of ICP, as it is used for monitoring the patient's state[7]. Based on serum BA levels, ICP can be classified into mild (BA 10 – 39 μmol/L), and severe (BA ≥ 40 μmol/L)[2]. In the literature, there is a discrepancy regarding the onset of ICP and whether elevated serum BA or clinical symptoms appear first. In some studies, most patients were first diagnosed with elevated BA prior to exhibiting clinical symptoms or other changes in LFTs[8]. Nevertheless, other studies have described cases of ICP with initially normal BA and LFTs, but with the presence of clinical symptoms suggestive of the condition, which were followed by the onset of biochemical changes over 4-5 weeks later[9].

The objective of the study was to assess the clinical symptoms and intensity of cutaneous pruritus in women with ICP.

Material and methods

The prospective study was conducted during the period April 2020 – April 2022 in the Mother and Child Institute, Chisinau, Republic of Moldova. There were assessed 71pregnant women, over 22^{+0} weeks of gestation, with a confirmed diagnosis of ICP, which was established according to clinical symptoms and BA levels ≥10 μmol/L. The exclusion criteria were the diagnosis of acute viral hepatitis, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis,

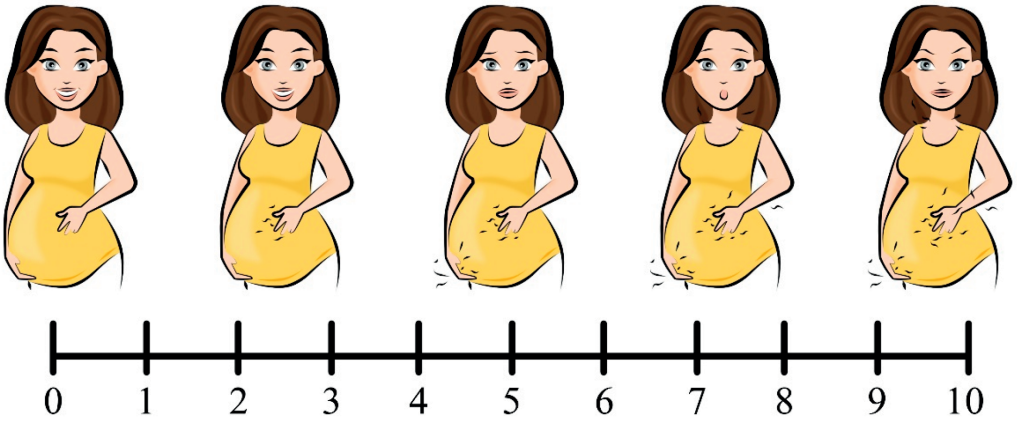

Fig. 1 Visual analogue scale for assessment of cutaneous pruritus' intensity.

primary biliary cirrhosis, symptomatic cholelithiasis, cytomegalovirus, Epstein-Barr infection, acute fatty liver of pregnancy, drug-induced hepatitis. The study obtained the ethical approval (no. 46, from 28.02.2020) from the Ethics Committee of „Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. The patients were asked to describe their symptoms and intensity of itching at the onset of the condition, at the time of the survey, and on the 3rd day after delivery. The intensity of cutaneous pruritus was assessed according to two scales. Thus, we used the scale proposed by Ribalta (Ribalta-score), which uses a score from 0 to 4 (dependent on the continuity of pruritus throughout the day):

0: absence of pruritus;
1: occasional pruritus (not every day);
2: discontinuous pruritus every day, prevailing asymptomatic lapses (i.e. pruritus is present less than 50% of time);
3: discontinuous pruritus every day, prevailing symptomatic lapses (i.e. pruritus is present more than 50% of time);
4: permanent pruritus (day and night)[10,11].

Additionally, an analog visual scale with a score range of 0 to 10 was created for the study. It is a simple method to use and allows women to describe their subjective sensation. The visual analog scale of skin pruritus intensity was developed based on a visual pain estimation scale, which is widely used to assess the level of pain sensation in patients with various conditions[12]. The women included in the study were instructed to indicate on the line their subjective assessment of the intensity of the pruritus (Figure 1), where:

- 0 points – absence of cutaneous pruritus;
- 1-2 points – mild itching, low intensity and/or occasional;
- 3-4 points – moderate cutaneous pruritus, which does not cause considerable discomfort;
- 5-6 points – pronounced cutaneous pruritus, which causes considerable discomfort;
- 7-8 points – very intense cutaneous pruritus, excruciating;
- 9-10 points – extremely intense, unbearable, or almost unbearable cutaneous pruritus.

SPSS 21 Software was used to conduct the statistical analysis. The arithmetic means and standard deviation (M±SD) were calculated to describe the numerical indicators. The median (Me) as well as the interquartile range (Q1; Q3) were estimated for distributions that were not normal. To compare categorical variables in groups, it was used the χ^2 test, with Yates' correction, a p-value <0.05 was considered statistically significant.

Results

The average age of the women in the study was 29.5±6.3 years (Me 30 (25;34)). According to our data, a peak of number of cases of ICP was observed in autumn (28/71 cases, 39.4%) and winter (23/71 cases, 32.3%). The onset of symptoms on average had occurred at 31.3±4.5 weeks of gestation (w.g.). However, the patients were recruited in the study at 35.3±3.9 w.g. on average, mostly being primarily diagnosed with the condition. During this period of ~4 weeks between the onset of the symptoms and the moment of recruitment most women didn't call for consult. Thus, we analysed the type of complaints at the onset of the condition and in the moment of recruitment in the study (Table 1).

The study revealed that, on the onset of cutaneous pruritus, women have indicated the intensity

Table 1. The symptoms present in women with ICP (abs., %)

#	*Symptoms*	*Number of cases at the onset of the condition n=71 (abs., %)*	*Number of cases at the moment of recruitment in the study n=71 (abs., %)*
	Skin itching		
1	Skin itching with localization on palms	35 (49.3±5.1%)	25 (35.2±5.5%)
2	Skin itching with localization on legs	36 (50.7±4.9%)	23 (32.4±6.2%)
3	Skin itching with localization on abdomen	18 (25.4±5.3%)	18 (25.4±5.3%)
4	Generalized skin itching	18 (25.4±5.3%)	37 (52.1±7.1%)
	Constitutional symptoms		
1	Fatigue	6 (8.6±3.5%)	40 (56.3±6.9%)
2	Lack of appetite	4 (5.6±2.3%)	10 (14.1±4.0%)
3	Insomnia	11 (15.5±4.5%)	38 (53.5±6.0%)
	Other symptoms		
1	Jaundice	1 (1.4±1.4%)	3 (4.2±2.3%)
2	Brown colour of urine	9 (12.7±3.8%)	31 (43.7±6.1%)
3	Pale stool	1 (1.4±1.4%)	3 (4.2±2.7%)
4	Abdominal pain	7 (9.9±3.1%)	21 (29.6±5.2%)
5	Nausea, vomiting	1 (1.4±1.4%)	6 (8.6±3.5%)

Note: the overall percentage exceeds 100% as some women complained of several symptoms at the same time.

of itching at 5.1±2.3 (Me 5.0 (3;7)) points, according to visual analog scale. Most women (38/71, 53.5%) indicate the symptom to be commonly occasional or discontinuous occurring every day, but asymptomatic periods predominate (1-2 points according to Ribalta score). At the same time, by the moment of the survey most women (47/71, 66.2%) indicate the intensity of the pruritus more or equal with 8 points (mean 7.7±2.2, Me 8.0 (6;10)), being continuous in 52.1% (4 points according to Ribalta score). In the post-partum period, the intensity of the pruritus decreases, being assessed on the third day after delivery as less or equal with 5 points in 93.1%, being occasional or discontinuous in 90.1% cases (0-2 points according to Ribalta score).

At this point we were interested in the correlation between the intensity of cutaneous pruritus (according to visual analogue scale) and the form of the disease (mild or severe). Referring to the fact that we were testing BA levels at the moment of recruitment, the females were divided into 2 groups: mild ICP (50/71 cases, 70.4%), and severe ICP (21/71 cases, 29.6%). Therefore, 16/50 females with mild ICP reported the intensity of cutaneous pruritus less or equal with 5 points, vs. 1/21 female with severe ICP (χ^2 4.622, p=0.0316).

Discussion

Considering ICP's impact on the pregnant women's health and the various perinatal outcomes associated with the disorder, the assessment of BA levels is extremely important for ICP patients. A study conducted by Glantz et al. showed an increased rate of adverse perinatal outcomes in pregnant women with serum BA levels of >40 μmol/L[13]. These conclusions were later confirmed by other researchers[12]. The same study reported a 1-2% increase in the risk of spontaneous premature birth, fetal asphyxia, and the presence of meconium in the amniotic fluid with each subsequent 1 μmol/L increase in maternal serum BA levels[14].

A recent study suggests that women with ICP in whom BA values were > 40 μmol/L gave birth on average two weeks earlier than pregnant women in the control group[15]. According to recent data, in approximately 20% of cases of cholestasis gravidarum, serum BA levels exceed 40 μmol/L[16]. In a recent meta-analysis of published studies, perinatal outcomes in pregnant women with ICP were assessed. Extremely high serum BA levels (> 100 μmol/L) were found to significantly increase the risk of fetal intrauterine death[17]. There are data in the literature suggesting that in pregnancies complicated by ICP, elevated levels of total bilirubin are observed in approximately 10% of cases, although their values rarely exceed 85.5 μmol/L[4,15]. At the same time, other authors consider that total bilirubin values increase in 25% of ICP cases, often being the only laboratory anomaly[19]. Serum GGT levels are expected to decrease during an uncomplicated pregnancy, while alkaline phosphatase (AP) activity may increase in late pregnancy due to

placental isoenzyme production and increased bone isoenzyme levels. Simultaneous elevation of GGT and AP indicates liver pathology, serving as markers of bile duct alteration[20]. Moreover, it is known that ALT levels can increase by 2-10 times in ICP, compared to AST[8]. In the postpartum period it is recommended a follow-up for women with ICP and ensure that itching has resolved and LFTs and BA levels have normalized[1].

A study conducted by Browers et al. showed that treatment with natural progestins in patients with imminent preterm birth can cause cholestasis gravidarum, which was diagnosed in 11 out of 12 women included in the study[21]. These conclusions have been confirmed by other researchers[22].

The first-line pharmacological treatment in the management of ICP is ursodeoxycholic acid (UDCA), which improves LFTs and relieves maternal symptoms in the majority of cases[6]. UDCA is used to improve excretion of pruritogenic substances, such as progesterone sulfates[2]. A number of other pharmacological drugs, such as S-adenosylmethionine, rifampicin, and cholestyramine, among others, can be used in the management of ICP. However, there is conflicting medical evidence about the effectiveness of the aforementioned drugs in relieving pruritus and improving LFTs. Thus, the Cochrane review concluded that there is insufficient evidence of the drugs' effectiveness in the management of cholestasis gravidarum[23]. Nevertheless, some authors consider that in women treated with UDCA failing to exhibit improvements in LFTs and clinical symptoms, the other drugs could be recommended as a second-line treatment[24].

According to the different ICP guidelines, most management strategies recommend delivery between 37- and 38-weeks' gestation; however, obstetric anamnesis, laboratory tests data and gestational age should be considered. A study conducted in the United Kingdom revealed a stillbirth rate of 7% among women with ICP. Intrauterine death of the fetus in the case of ICP has occurred at various gestational ages. On average, intrauterine fetal demise in patients with ICP takes place within 38 weeks of gestation for singleton pregnancies. In the case of multiple pregnancies, the intrauterine fetal death rate before 37 weeks' gestation was 22%[4]. Hence, women with ICP should be informed about the inability to predict stillbirth[1].

In most cases, the maternal prognosis of ICP is benign. However, some authors suggest an increased risk of cholangitis, chronic hepatitis, fibrosis, and liver cirrhosis among women with an anamnesis of ICP, compared to women whose pregnancy was uncomplicated[4]. Reports in the literature suggest that there are currently no methods for ICP prophylaxis[17].

Conclusions

The most common clinical manifestation of ICP is pruritus, reason for which women seek further health assistance during pregnancy. As a result, even if discomfort is mild and decreases after delivery, it should not be disregarded. The symptom should be considered as a call for further investigation. According to our data, it was found a statistically significant association between BA levels and the intensity of cutaneous pruritus in women with ICP. Thus, the authors propose the use of the visual analogue scale for cutaneous pruritus' intensity in clinical practice for indirect monitoring of patient's status. However, we consider that future research is required.

Author contribution

M.C. and O.C. – the concept and design of the study; M.C, I.S and C.O. – data acquisition; I.S, O.C. and C.O. interpreted the results and analysed the data and drafted the manuscript. All the authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Ethics

The study obtained ethical approval (no. 46, from 28.02.2020) from the Ethics Committee of „Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. Written informed consent was obtained from all participants, 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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Competing interests

The authors have declared that no competing interests exist.

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