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DIAGNOSIS AND COURSE OF PREGNANCY AND CHILDBIRTH IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

321.15 OBSTETRICS AND GYNECOLOGY

Summary of Ph.D. Thesis in Medical Sciences

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CONTENT

ABBREVIATIONS

AFD	antenatal fetal death
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
AUC	area under the curve
BA	bile acids
CrP	C-reactive protein
FIB-4	fibrosis-4 score
GGT	gamma-glutamyl transferase
ICP	intrahepatic cholestasis of pregnancy
INR	international normalized ratio
LFT	liver function test
MPV	mean platelet volume
NLR	neutrophil to lymphocyte ratio
PLR	platelet to lymphocyte ratio
RDW-CV	red cell distribution width - coefficient of variation
RDW-SD	red cell distribution width - standard deviation
ROC	receiver operating characteristics
Se	sensitivity
Sp	specificity
UDCA	ursodeoxycholic acid
VASPIS	visual analogue skin pruritus intensity scale
w.g.	weeks of gestation

CONCEPTUAL RESEARCH FRAMEWORK

Topicality and definition of research issues.

Extragenital pathologies have a major impact on maternal and fetal health and are an important issue in modern obstetrics. Liver disease is relatively common in pregnant women, which can complicate the course of pregnancy [18]. The liver shows some functional changes even during an uncomplicated pregnancy, which may increase the susceptibility to liver disease in some women.

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic liver disease in pregnancy characterized by an increase in liver function test (LFT) levels and/or bile acid (BA) values in the presence of skin pruritus that cannot be explained by other reasons [3, 8, 12, 15]. This bears various names, such as cholestasis gravidarum, cholestatic hepatosis of pregnancy, and idiopathic jaundice of pregnancy [20].

The incidence of ICP varies widely by population distribution and is influenced by genetic and environmental factors, being common among multi-ethnic populations [19]. In the general population, the incidence of ICP varies between 0.5 and 1.0% [18].

ICP can cause major maternal and fetal complications. Some authors consider that ICP may cause complications in childbirth [5, 14]. Perinatal outcomes are of clinical interest in the management of pregnancy, and childbirth in women with ICP, considering the possible risks of preterm birth, meconium staining of amniotic fluid, antenatal fetal death (AFD), and postpartum haemorrhage [4, 6, 10, 14].

The role of vitamin K in the pathogenesis of complications of cholestasis gravidarum remains questionable, given the possible steatorrhea and malabsorption of fat-soluble vitamins associated with the condition [1, 2]. Thus, hypovitaminosis K could lead to coagulopathic haemorrhages among pregnant women whose pregnancy is complicated by cholestasis gravidarum.

According to *Eriomina E. et al.*, postpartum hemorrhage rates in women with ICP can be as high as 20% [22, 23]. Perinatal losses are also increasing, reaching rates of 35-44%, according to some studies. As for preterm births in women with ICP, rates range from 25-32%, reaching up to 60%, but the data presented are the subject of controversy [2, 9, 16, 18]. However, no correlation has been shown between fetal prognosis and the severity of maternal clinical symptoms and signs, indicating the need for further research [2]. With its impact on maternal and perinatal morbidity, cholestasis gravidarum is a challenge to contemporary obstetrics and prompts the need for further research in order to determine all the issues it entails [1].

Despite the numerous tests available, an accurate and early diagnosis of ICP can be difficult given that clinical features and LFT findings may mimic other liver pathologies [23]. Performing a laboratory examination in women with ICP is crucial to diagnosing the condition. In order to elucidate the diagnostic features of ICP, it is necessary to assess the severity of cholestatic, cytolytic, and inflammatory syndromes in women with cholestasis gravidarum. At the same time, the assessment of serum BA levels remains a definite diagnostic marker of cholestasis gravidarum, as well as dynamic monitoring of the condition [18].

In the last decade, some researchers have highlighted the role of haematological inflammatory markers in ICP, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width - standard

deviation (RDW-SD), and red cell distribution width - coefficient of variation (RDW-CV). Nevertheless, the application of these markers in ICP severity assessment practice remains questionable [9].

Despite the progress achieved in identifying ICP cases, there is still no single point of view on the management of the condition, as well as on the timing of delivery in ICP patients [13, 17, 20]. The Royal College of Obstetricians and Gynaecologists suggests that there is not yet sufficient research identifying the optimal dose of ursodeoxycholic acid (UDCA) and the need for vitamin K, dexamethasone, and rifampicin in the treatment of cholestasis gravidarum [18]. However, further research is required to develop recommendations regarding the management of ICP cases.

ICP represents a challenge for modern obstetrics, considering the etiological, clinical, and diagnostic features of the condition. A comprehensive diagnosis, carried out at the appropriate time, would allow the application of appropriate management to women with ICP, which in turn would reduce clinical symptoms, improve the quality of life of the pregnant woman, reduce maternal-fetal complications related to ICP, and improve perinatal outcomes.

In order to provide an overview of the condition, it is important that all aspects related to the study of clinical and biochemical features and the assessment of ICP severity are considered to allow for the development of an individualized algorithm for managing the condition, taking into account appropriate timing for delivery. All the above-mentioned evidence argues for the initiation of this study.

The aim of the study is to evaluate diagnostic features, the clinical course of pregnancy and childbirth, and perinatal outcomes of ICP and to optimize the management of patients with ICP.

In order to achieve the proposed goal, we outlined the following **objectives of the research**:

1. To study the course of pregnancy, delivery, and perinatal outcomes in women with intrahepatic cholestasis of pregnancy;
2. To assess the diagnostic features of intrahepatic cholestasis of pregnancy;
3. To assess the vitamin K levels and haematological inflammatory markers in the development of ICP;
4. To develop a diagnostic and management algorithm for pregnant women with ICP.

Research methodology.

The paper analyzed research results through a theoretical and scientific prism, in accordance with the proposed aims and objectives. The present study was carried out on the basis of a step-by-step methodology: problem definition and development of the research plan, statistical observation and accumulation of research material, evaluation of clinical and paraclinical parameters of the women included in the study, statistical analysis and synthesis of the obtained results. The research project was approved by the Research Ethics Committee of USMF Nicolae Testemitanu (no. 46 of 28.02.2020). At the same time, the study protocol was registered in the International Standard Randomized Controlled Trial Number database with a registration number ISRCTN21187408 (https://doi.org/10.1186/ISRCTN21187408). Primary data processing was performed with IBM SPSS (Statistical Package for Social Sciences) Statistics 21, MedCalc and GraphPad software, using the functions and modules of these programs, through descriptive statistical procedures.

Novelty and scientific originality of the results obtained. The research highlighted the features of diagnosis, course of pregnancy, delivery, and perinatal outcomes in pregnant women

with ICP. Predisposing factors for the development of cholestasis gravidarum were determined. The sensitivity and specificity of liver function tests applied to women with ICP were assessed, as well as serum levels of vitamin K and haematological inflammatory markers. A visual analogue skin pruritus intensity scale (VASPIS) was also proposed. Based on the results obtained, a diagnostic and management algorithm for ICP was proposed.

The important scientific problem solved in the paper aims to elucidate the clinical and evolutionary features of pregnancy and delivery in pregnant women with cholestasis gravidarum, as well as to highlight the features of diagnosis, and management of the condition, on the basis of which the *Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy* was developed, which includes the following compartments: clinical manifestations, diagnosis, treatment and time limits of pregnancy resolution in pregnant women with ICP.

The theoretical importance of the thesis. Based on the results of the study, new features of pregnancy and childbirth evolution in women with ICP were identified. At the same time, the diagnostic features of the condition were evidenced, and major biochemical, and hematological markers in the diagnosis and management of ICP cases were described.

Applicative value of the research. The research highlights the diagnostic and evolutionary features of pregnancy and delivery in women with ICP, which has determined new aspects in the management of ICP cases. The results show increased rates of hypovitaminosis K among women with cholestasis gravidarum, as well as significant increases in some hematological inflammatory markers. On the basis of the study, the *Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy* was proposed, which can be recommended in the practical work of specialists in obstetrics and gynecology, hepatology, and family medicine at the *Nicolae Testemitanu* State University of Medicine and Pharmacy.

Implementation of scientific results:

✓ The main research results are applied in the didactic process of the Department of Obstetrics and Gynecology of the *Nicolae Testemitanu* State University of Medicine and Pharmacy.

✓ On the basis of the study, 8 Implementation Acts were registered, which were implemented in the scientific and practical processes of the two Public Medical and Health Institutions, including the Institute of Mother and Child and *Gheorghe Paladi* Municipal Clinical Hospital.

Research approval. The basic principles of the research have been reported and discussed in various national and international scientific conferences: XXI Всероссийский образовательный форум "Мать и Дитя". Москва, Российская Федерация. 28-30 сентября 2020; Congresul consacrat aniversării a 75-a de la fondarea USMF ”Nicolae Testemițanu”. Chișinău, Republica Moldova. 20-23 octombrie 2020; Zilele Medicale „Vasile Dobrovici”. Romania, Iași. 26-28 noiembrie 2020; 17th International and 59th Polish Conference Juvenes Pro Medicina 2021. Lodz, Poland. 14-16 May 2021; Twins Congress – the Joint 5th World Congress on Twin Pregnancy – a Global Perspective and the 17th Congress of the International Society on Twins Studies (ISTS). Beijing, China. 4-6 June, 2021; Congresul Național pentru Studenți și Tineri Medici KronMed. Brașov, Romania. 25-28 noiembrie 2021; Zilele Medicale „Vasile Dobrovici”. Iași, Romania. 5-7 mai 2022; International Congress For Students, Young Doctors And Pharmacists MARISIENSIS. Târgu Mureș, Romania. 4th – 8th May 2022; XXVIII European congress of perinatal medicine. Lisbona, Portugal. 22-25 June 2022; Conferința Științifică Anuală

Universitatea de Stat de Medicină și Farmacie Nicolae Testemițanu. Chișinău, Republica Moldova. 19-21 octombrie 2022; Consfatuirile comune ale medicilor Obstetricieni-ginecologi, neonatologi, pediatri. Chișinău, Republica Moldova. 28 octombrie 2022; BIRTH Congress 7-th Edition. Milan, Italy. 7-10 decembrie 2022.

Publications on thesis topic. Eleven scientific articles have been published on the thesis topic, including 6 publications in peer-reviewed journals. In addition, 11 theses, 4 posters, and 8 innovator certificates have been published, and 2 certificates of registration of copyright and related rights have been obtained.

Summary of the thesis compartments. The thesis includes a list of abbreviations, an introduction, 5 chapters, general conclusions, and practical recommendations. The bibliographic index comprises 255 sources, 10 annexes, the statement of responsibility, the author's CV, 11 tables, and 25 figures.

Key words: intrahepatic cholestasis of pregnancy, ICP, pregnancy, childbirth, perinatal outcomes, diagnosis.

CONTENT OF THE THESIS

1. COURSE OF PREGNANCY AND CHILDBIRTH IN WOMEN DIAGNOSED WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

This section included a summary of the data from the literature with reference to the course of pregnancy and delivery in pregnant women with ICP, as well as the modern concept of the etiopathogenesis of the condition. ICP remains a major but overlooked medical problem. The incidence of the condition varies widely, depending on several factors. A separate section is devoted to the laboratory diagnosis of ICP. Based on local and international bibliographical sources, the specific features of the pathology are presented. ICP can be accompanied by serious complications both for the mother and fetus. 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, considering possible preterm birth, intrauterine fetal death and postpartum haemorrhage.

2. RESEARCH MATERIALS AND METHODS

The study was a prospective one, in which cases of ICP from 2020 onwards were examined. Thus, the research group (L_1) included 71 pregnant women with intrahepatic cholestasis of pregnancy. The results obtained were compared to those of the control group (L_0), consisting of 71 pregnant women without ICP.

The principle for inclusion of pregnant women in the research group was the diagnosis of ICP, skin pruritus in which other probable causes were excluded (the diagnosis was based on clinical data and biochemical test results); serum BA levels ↑ 10 μmol/l; gestation age between 22^{+0}-41^{+6} weeks; patient age ≥ 18 years; written informed consent to participate in the research.

Exclusion criteria from the study included the presence of any of the following liver diseases: acute viral hepatitis, autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis, primary biliary cirrhosis, symptomatic cholelithiasis. Women diagnosed with cytomegalovirus and Epstein-Barr virus (as they can cause liver injury with increased liver enzyme levels [11]), acute

fatty liver of pregnancy, drug-induced hepatitis, pre-eclampsia, HELLP syndrome, and congenital thrombophilia were also excluded from the study, along with those diagnosed with epilepsy to exclude the possible influence of antiepileptic medication on intestinal vitamin K absorption [1].

The research was carried out by studying medical documentation (obstetric observation record, newborn's record), clinical and instrumental examinations (questionnaire, assessment of the newborn's condition after birth), laboratory examination (general blood analysis, biochemical blood analysis, coagulogram, vitamin K, C-reactive protein (CrP), haematological inflammatory markers). At the same time, the intensity of skin pruritus in the women included in the study was assessed using two scales (Ribalta scale and visual analogue skin pruritus intensity scale (VASPIS)).

Considering that 8 cases of multiple pregnancy were detected in the research group, including 6 cases with twins and 2 cases with triplets, 81 babies born to mothers with ICP were included into the study. In the control group, 77 babies were included; 4 cases of multiple pregnancy were detected, including 2 twin pregnancies and 2 triplet pregnancies.

Data analysis was performed using IBM SPSS Statistics 21, MedCalc and GraphPad software, using the functions and modules of these programs. The results obtained were interpreted using descriptive biomedical statistics data.

3. FEATURES OF PREGNANCY, DELIVERY AND PERINATAL OUTCOMES IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

3.1. Anamnestic and clinical features of pregnancy in women with intrahepatic cholestasis of pregnancy

Given that ICP is a pathology that affects both the condition of the pregnant woman and the fetus, with the possible development of severe maternal and fetal complications, we conducted an analysis of the course of pregnancy, delivery, and perinatal outcomes in women with cholestasis gravidarum.

The study included 142 women, who were subsequently divided into two groups. L_1 (the research group) included 71 women whose pregnancies were complicated by ICP, and L_0 (the control group) comprised 71 women without ICP. The control group was randomly selected, both groups included participants according to the inclusion and exclusion criteria of the research.

The age of the study participants ranged from 18-43 years, with a mean age of 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).

An analysis of the course of previous pregnancies in multiparous women in both groups revealed the prevalence of cholestasis gravidarum is higher among women with ICP (L_1 - 14 women or 34.1% (95% CI: 17.4-51.2%) vs L_0 - 1 pregnant woman or 2.7% (95% CI: 0-5.4%), χ^2 10.438, p=0.0012; RR 12.6341, 95% CI: 1.7452-91.4614, p=0.0120).

Another important research aspect was the assessment of extragenital history in the pregnant women included in the study (*Table 1*).

Thus, the study determined a high percentage of liver pathology among women with cholestasis gravidarum: L_1 - 21 women or 29.6% (95% CI: 18.3-41.5%) vs L_0 - 8 or 11.3% (95% CI: 3.8-19.4%), χ^2 6.240, p=0.0125, presenting an increased risk of developing the condition in current pregnancy (RR 2.6250, 95% CI: 1.2463-5.5290, p=0.0111).

Table 1. **Extragenital conditions in women with intrahepatic cholestasis of pregnancy (abs.,%)**

Variable / Conditions	Research group, L_1 n_1=71 (abs., %)	Control group, L_0 n_0=71 (abs., %)	RR	95% CI	p
Hepato-biliary	21 (29.6%)	8 (11.3%)	2.625	1.2463-5.5290	0.011
Viral hepatitis A	1 (1.4%)	0	3.000	0.1243-72.426	0.498
Viral hepatitis B	6 (8.5%)	3 (4.2%)	2.000	0.5204-7.6865	0.312
Viral hepatitis C	4 (5.6%)	1 (1.4%)	4.000	0.4583-34.9112	0.209
Calculous cholecystitis	6 (8.5%)	1 (1.4%)	6.000	0.7411-48.574	0.093
Acalculous cholecystitis	4 (5.6%)	3 (4.2%)	1.333	0.3095-5.7435	0.699
Gastrointestinal	10 (14.1%)	8 (11.3%)	1.250	0.5239-2.9823	0.615
Nephrourinary	22 (31.0%)	10 (14.1%)	2.200	1.1244-4.3047	0.021
Cardiovascular	9 (12.4%)	9 (12.7%)	1.000	0.4217-2.3712	1.000
Respiratory	6 (8.5%)	7 (9.9%)	0.857	0.3031-2.4242	0.771
Endocrine	3 (4.2%)	7 (9.9%)	0.428	0.1154-1.5914	0.205
CNS disorders	1 (1.4%)	3 (4.2%)	0.333	0.0355-3.1285	0.336
Ocular	5 (7.0%)	3 (4.2%)	1.666	0.4139-6.7120	0.472
Osteoarticular	1 (1.4%)	0	3.000	0.1243-72.4260	0.498

An assessment of the current pregnancy course among women in both groups was performed. It was determined that every 4th pregnant woman in L_1 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 L_0, the difference being statistically significant (χ^2 7.471, p=0.0063). An increased frequency of iron deficiency anaemia was detected among pregnant women with ICP - 36.6% cases (95% CI: 24.7-50.2%), in comparison with the control group - 19.7% (95% CI: 8.0-27.4%), χ^2 4.211, p=0.0402. Similarly, the frequency of gestational diabetes mellitus among L_1 was 13 women, or 18.3% (95% CI: 11.3-28.2%), whereas among L_0 it was 4 women, or 5.6% (95% CI: 0-12.7%), χ^2 4.277, p=0.0386, thus representing a statistically significant difference.

3.2. Features of childbirth in women with intrahepatic cholestasis of pregnancy

In order to assess the features of childbirth and perinatal outcomes in the women, we studied and analyzed the term and mode of delivery, the incidence and structure of caesarean sections, and the condition of the newborns.

Pregnant women from both groups were included in the study at 22^{+0}-41^{+6} weeks of gestation (w.g). Thus, all pregnant women were monitored until delivery, which occurred on average at 37.6±2.0 (Me 38: 36.5; 39.2) w.g. in women with ICP. In the control group, delivery occurred on average at 39.2±1.7 (Me 39.5: 38.4; 40.3) w.g. (95% CI: -2.216 – 0.984, p<0.0001).

Comparative analysis revealed an increased frequency of preterm births among women with ICP (RR 3.8000, 95% CI: 1.5014-9.6176, p=0.0048), although in both groups at-term births most prevalent: 52 or 73.2% (95% CI: 64.3-91.9%) of women in L_1 and 66 or 92.9% (95% CI: 88.3-100%) of women in L_0 (*Table 2*).

In both study groups, the per vias naturales birth pattern was most common: 41 or 57.7% (95% CI: 47.4-70.1%) of cases in L_1 and 54 or 76.1% (95% CI: 67.2-83.1%) of cases in L_0. At the same time, an increased frequency of caesarean section in the research group was observed (χ^2 4.580, p=0.0324). In 13 or 18.3% (95% CI: 11.0-27.0%) of cases in the research group, labour was induced by amniotomy and/or Folley catheter application for cervical preparation followed by amniotomy. In 9 or 12.7% (95% CI: 5.4-21.4%) of cases in L_1, labour was induced by prostaglandin administration according to the standard clinical protocol [7]. 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 LFT values and/or BA levels in these women. Labour was induced by amniotomy or prostaglandin administration in 3 (4.2%; 95% CI: 0-7.3%) cases in L_0 and 7 (9.9%; 95% CI: 2.6-18.5%) cases in L_1; in all cases (10 women or 14.1%; 95% CI: 6.8-21.4%), induction of labour was indicated in relation to postterm pregnancy.

Table 2. **Characteristics of pregnant women in the study groups according to term and mode of delivery (%)**

Variable	Research group, L_1 n_1=71		Control group, L_0 n_0=71		χ^2	p
	Abs.	% (95% CI)	Abs.	% (95% CI)		
Term of birth:						
At term	52	73.2% (64.3-91.9%)	66	92,9% (88.3-100%)	8.474	0.0036
Premature	19	26.8% (18.1-35.7%)	5	7.1% (0-11.7%)		
Type of birth:						
Per vias naturales	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%)		

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 meconium 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).

Another important aspect related to birth complications in pregnant women with ICP is total blood loss in labour or caesarean section. Mean blood loss in natural delivery was 376.9±133.4 ml (Me 350: 300; 450) in L_1, compared to 288.5±79.6 (Me 280: 240; 320) ml in L_0 (95% CI: 44.741-132.059, p=0.0001). Mean blood loss in caesarean section was 688.3±117.9 (Me 700: 600; 800) ml in L_1 as opposed to 658.8±87.0 (Me 600: 600; 750) ml in L_0 (95% ÍÎ: -36.492 – 95.492, p=0.3727).

However, 3 cases of haemorrhage ≥500 ml after natural delivery were detected in the group of women with ICP, including 1 case of massive haemorrhage (1000 ml), which was managed conservatively. Among women in L_1 undergoing caesarean section, there was 1 case of total blood

loss ≥1000 ml. In the control group there were 2 cases of haemorrhage following natural delivery; in both cases the total volume of blood lost did not exceed 600 ml; meanwhile, among women who underwent caesarean section, no cases of haemorrhage were detected. Despite the fact that the postpartum haemorrhage rate in L_1 was 5.6% (95% CI: 1.4-12.7%) compared to 2.8% (95% CI: 0-7.3%) in L_0 (χ^2 0.174, p=0.6766), women whose pregnancies were complicated by ICP lost on average a greater volume of blood in childbirth, the difference being statistically significant.

3.3 Perinatal outcomes in women with intrahepatic cholestasis of pregnancy

The question surrounding the impact of ICP on perinatal outcomes remains complex. Therefore, it was of interest to evaluate the characteristics of babies born to mothers included in the study. The analysis of preterm infants according to gestational term revealed that in the current study there were no cases of extreme prematurity; thus, the majority of preterm infants were born at 34^{+0}-36^{+6} weeks gestational term: 22 infants, or 27.2% (95% CI: 14.9-38.1%) in L_1, compared to 6 infants, or 7.8% (95% CI: 3.8-14.3%) in L_0 (χ^2 8.871, p=0.0029). At the next stage, some important parameters in the assessment of the newborn's condition at birth were considered. On the basis of the data obtained, it was found that in most cases, the general condition of newborns was satisfactory. In spite of this, an increased incidence of different pathological conditions was observed in the newborns of the research group (χ^2 4.777, p=0.0288); the data are presented in Table 3.

Table 3. **Frequency of neonatal pathology in newborns in the study groups (abs., %)**

Variable	Research group, L_1 n_1=81 (abs., %)	Control group, L_0 n_0=77 (abs., %)	χ^2	p
Presence of morbidities	23 (28.3%)	10 (12.9%)	4.777	0.0288
Neonatal respiratory distress syndrome	7 (86.4%)	7 (90.9%)	0.010	0.9209
Congenital pneumonia	16 (19.7%)	6 (7.7%)	3.767	0.0523
Intrauterine infections	2 (2.4%)	2 (2.5%)	0.003	0.9591
Neonatal jaundice	12 (14.8%)	3 (3.8%)	4.280	0.0386
Need for stage II perinatal care	18 (22.2%)	7 (9.1%)	4.172	0.0411

Among the conditions found in newborns from mothers with ICP, congenital pneumonia was observed much more frequently; there were 16 (19.8%; 95% CI: 12.4-27.2%) cases in the research group vs 6 (7.8%; 95% CI: 1.2-15.6%) cases in the control group (RR 2.5350; 95% CI: 1.0463-6.1416; p=0.0394). At the same time, there was an increased incidence of neonatal jaundice in the group of children born to mothers with cholestasis gravidarum: 12 (14.8%; 95% CI: 7.4-24.6%) cases compared to 3 (3.9%; 95% CI: 0-9.1%) cases in the control group (RR 3.8025; 95% CI: 1.1158-12.9586; p=0.0328).

4. DIAGNOSTIC FEATURES OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

4.1 Assessment of biochemical and liver function tests in patients with intrahepatic cholestasis of pregnancy

Laboratory examination in women with ICP is crucial in the diagnosis of this condition. A complex clinical and paraclinical examination helps elucidate the features of evolution and identify

the degree of cholestasis gravidarum, which facilitates the choice of management tactics and treatment for women with the condition. In view of the above, the aim of our research was to study the features of the diagnosis and management of ICP.

The key diagnostic criterion for ICP is the serum BA level. In the current study, BA values in the research group ranged from 10-211.3 μmol/l, with the mean value constituting 34.7±37.7 (Me 18.9: 11.1; 44.0) μmol/l. In the control group, the mean BA value was 3.3±1.6 (Me 3.1: 2.1; 4.4) μmol/l, ranging from 1.0 to 7.8 (95% CI: 22.546-40.254; p<0.0001) μmol/l, the data are shown in Figure 1.

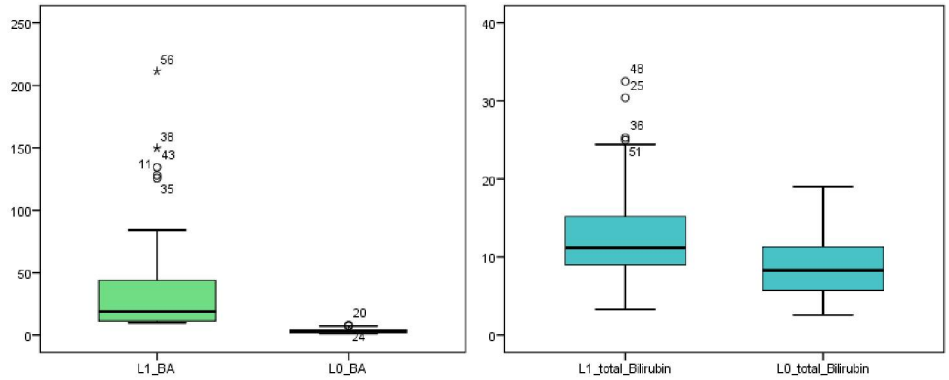

Figure 1. **Serum BA and total bilirubin levels in women included in the study (μmol/l)**

Total bilirubin values were elevated in 21 (29.6%; 95% CI: 16.5-43.7%) pregnant women in the research group, while the mean level was 12.9±6.1 (Me 11.2: 9; 15.5) μmol/l, ranging from 3.3-32.5 μmol/l (*Figure 1*). In the control group, total bilirubin values averaged 8.5±3.7 (Me 8.2: 5.7; 11.6) μmol/l, ranging from 2.6 to 19.0 (95% CI: 2.726-6.074; p<0.0001) μmol/l. Hence, in L_0 total bilirubin values in 65 or 91.5% (95% CI: 85.7-97.4%) of cases were within the normal range (χ^2 8.964, p=0.0028).

Alanine aminotransferase (ALT) values ranged from 6-1121 U/l in L_1 and 5.3-138.8 U/l in L_0. Increased ALT levels were detected in 49 (69.0%; 95% CI: 56.6-78.9%) cases in the research group compared to 7 (9.9%; 95% CI: 4.0-18.3%) cases in the control group (χ^2 49.564; p=0.0001). Mean ALT values in L_1 were 141.9±178.4 (Me 76: 22; 181) U/l vs 19.2±22.0 (Me 13: 9; 17) U/l in L_0 (95% CI: 80.524-164.876; p<0.0001); the data are shown in *Figure 2*. Increased aspartate aminotransferase (AST) levels were detected in 53 (74.6%; 95% CI: 62.3-83.5%) cases in the research group compared to 9 (12.7%; 95% CI: 4.2-18.8%) cases in the control group (χ^2 52.935; p=0.0001). Mean AST values in L_1 were 87.1±93.2 (Me 57.8: 28; 128) U/l vs 20.6±10.5 (Me 17: 14; 22) U/l in L_0 (95% ÍÎ: 44.494-88.506; p<0.0001).

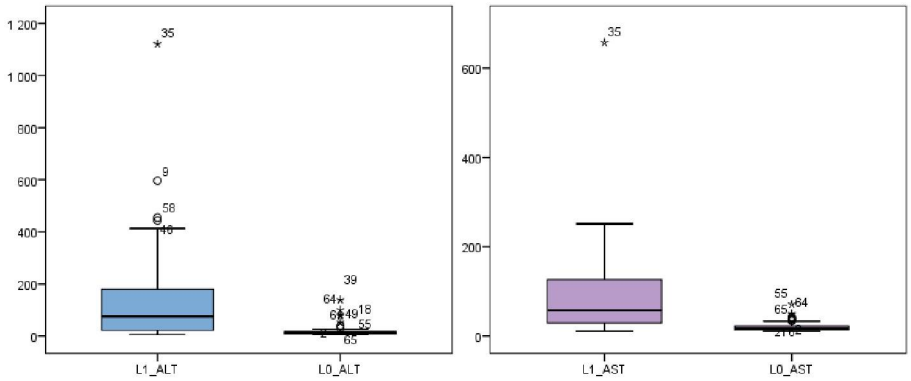

Figure 2. **ALT and AST levels in women included in the study (U/l)**

Another important point of the study is to assess the level of de Ritis coefficient in the pregnant women included in the research (*Figure 3*). A significant decrease in de Ritis coefficient was observed among women with ICP - 0.95±0.49 (Me 0.80: 0.52; 1.40), compared to the control group - 1.40±0.60 (Me 1.39: 0.98; 1.72), 95% CI: -0.6318 – -0.2682; p<0.0001.

In the next step of the research, the values of the aspartate aminotransferase to platelet ratio index (APRI) were analysed. The mean value of APRI in L_1 was 1.2±1.2 (Me 0.73: 0.38; 1.74), compared to L_0 - 0.3±0.1 (Me 0.25: 0.18; 0.34), the difference being statistically significant - p<0.0001 (*Figure 3*). Analyzing the data, we discovered a negative correlation between APRI and the term when birth occurred (r=-0.457**, p=0.01) and with the duration of birth (r=-0.218**, p=0.01). At the same time, a positive correlation was determined with the meconium staining amniotic liquid (r= 0.260**, p=0.01), with the rate of caesarean section (r= 0.257**, p=0.01) and total haemorrhage in the women included in the study (r=0.254**, p=0.01).

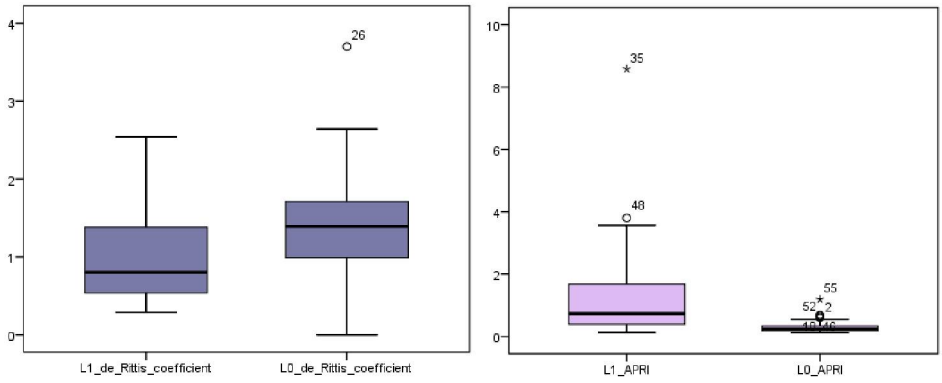

Figure 3. **De Ritis coefficient and APRI values in women included in the study**

Another indicator assessed in research is the Fibrosis-4 (FIB-4) score. The mean value of FIB-4 in L_1 was 0.97±0.59 (Me 0.81: 0.53; 1.2), and in L_0 - 0.61±0.25 (Me 0.55: 0.42; 0.7), representing a statistically significant difference (95% CI: 0.2097-0.5103; p<0.0001); the results are shown in *Figure 4*. Analyzing the data, we discovered a positive correlation between FIB-4 and the BA level (r=0.397**, p=0.01) and with the intensity of skin pruritus at the time of inclusion of women in the study (VASPIS, r=0.363**, p=0.01; Ribalta scale, r=0.360**, p=0.01). At the same time, a negative correlation was found with the term of delivery (r=-0.452**, p=0.01).

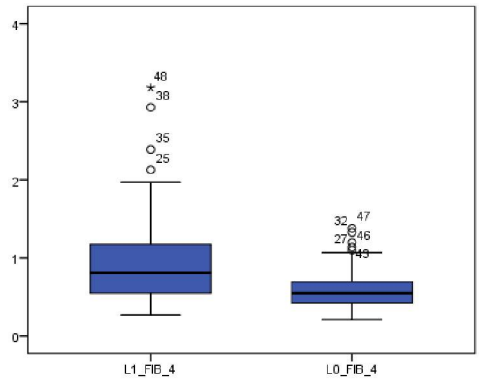

Figure 4. **FIB-4 index in women included in the study**

The biochemical marker analyzed in the current study was alkaline phosphatase (ALP); the data are shown in *Figure 5*. Thus, the mean ALP level was 264.2±141.2 U/l (Me 226: 164.4; 337) in L_1 vs 179.1±63.9 (Me 170: 137; 218) U/l in the control group (95% CI: 8.735-121.465; p<0.0001). ALP levels were elevated in 8 (11.3%; 95% CI: 5.0-21.4%) cases in the research group. In the control group, no cases of increased ALP levels were detected (χ^2 6.491; p=0.0108). The gamma-glutamyl transferase (GGT) values assessed in the study showed the following mean values: 22.4±16.9 (Me 17: 12; 29) U/l in the research group, compared to 12.7±10.4 (Me 10: 8; 15) U/l in the control group (95% CI: 5.044-14.356; p<0.0001). It should be noted that an increased level of GGT was shown by 8 (11.3%; 95% IÎ: 4.0-18.3%) women from L_1 and 3 (4.2%; 95% IÎ: 0-8.7%) pregnant women from L_0, the difference being statistically insignificant (χ^2 1.577; p=0.2092).

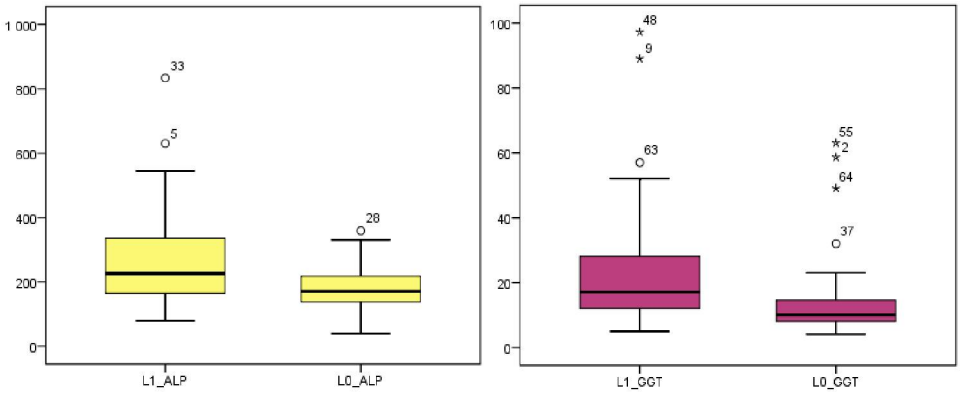

Figure 5. **ALP and GGT levels in women included in the study (U/l)**

In the next step of the research, we were interested in assessing the sensitivity and specificity of the LFTs applied in the study. Therefore, we analyzed the Receiver Operating Characteristics (ROC) curves for each indicator studied; the data are presented in *Table 4.*

When evaluating the informative value of the tests applied in ICP diagnosis based on ROC curves, the informative value of the BA level assessment is considered excellent (area under the curve (AUC) values = 1.0). When evaluating the informative value of ALT, AST and APRI in ICP diagnosis based on ROC, the informative value of the given tests is considered very good, with AUC values in the range of 0.81-0.9. The informative value of bilirubin, GGT, and de Ritis

coefficient tests is considered good according to ROC curves (AUC values = 0.71-0.8). The informative value of ALP, and FIB-4 in ICP diagnosis based on ROC is considered satisfactory (AUC values = 0.61-0.7).

Table 4. **Sensitivity (Se) and specificity (Sp) of liver function tests applied to women with intrahepatic cholestasis of pregnancy**

Index	AUC ROC	95% CI	p	Youden index	Cut off values	Se (%)	Sp (%)
BA	1.0	1.0-1.0	<0.0001	1.0	>7.8 µmol/l	100	100
ALT	0.85	0.79-0.92	<0.0001	0.6338	>18.8 U/l	81.7	81.7
AST	0.87	0.81-0.93	<0.0001	0.6197	>26.8 U/l	80.3	81.7
De Ritis coefficient	0.72	0.64-0.80	<0.0001	0.3944	≤0.88	57.7	81.7
APRI	0.86	0.79-0.91	<0.0001	0.5915	>0.55	66.2	92.9
FIB-4	0.70	0.62-0.78	<0.0001	0.3662	>0.72	57.7	78.8
Bilirubin	0.72	0.64-0.80	<0.0001	0.3662	>6.9 µmol/l	92.9	43.7
GGT	0.74	0.66-0.82	<0.0001	0.4085	>11.3 U/l	76.1	64.8
ALP	0.68	0.60-0.76	<0.0001	0.2958	>268 U/l	38.0	91.5

A coagulogram was performed, including the assessment of prothrombin by Quick Time, fibrinogen, and the international normalized ratio (INR). The study did not reveal a statistically significant difference in coagulogram indicators among women in the two groups.

4.2. Assessment of vitamin K levels in women with intrahepatic cholestasis of pregnancy

Vitamin K levels in the women included in the study were analyzed. The mean value of vitamin K1 was 0.17±0.21 (Me 0.13: 0; 0.24) µg/L in the group of women with ICP and 0.22±0.27 (Me 0.17: 0.1; 0.29) µg/L in the control group (95% CI: -0.1303-0.0303; p=0.2201); the data are presented in *Figure 6*. Studying the levels of vitamin K2 revealed the following mean values: vitamin K2 MK4 - 0.25±0.23 (Me 0.19: 0.15; 0.30) µg/L in L_1 versus 0.28±0.14 (Me 0.24: 0; 20.35) µg/L in L_0 (95% CI: -0.0932-0.0332; p=0.3494). At the same time, the mean value of vitamin K2 MK7 was 0.19±0.13 (Me 0.19: 0.11; 0.30) µg/L in L_1 compared to0.26±0.14 (Me 0.24: 0.17; 0.36) µg/L in L_0 (95% CI: -0.1148 – -0.0252; p=0.0024), the difference being statistically significant.

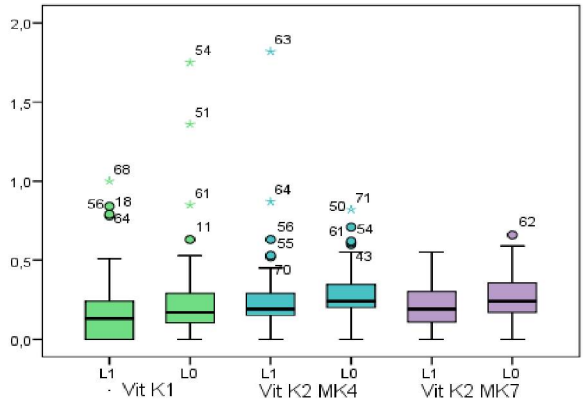

Figure 6. **Mean levels of vitamin K fractions in women included in the study (µg/L)**

The study found K1 hypovitaminosis in 35 (49.3%; 95% ÍÎ: 34.8-59.4%) women with ICP compared to 22 (31.0%; 95% CI: 18.3-41.7%) women in the control group (χ^2 4.220; p=0.0399); K2 MK4 hypovitaminosis was observed in 3 (4.2%; 95% CI: 0-8.7%) women in L_1 and 1 (1.4%; 95% CI: 0-5.6%) woman in L_0 (χ^2 0.257; p=0.6120); while hypovitaminosis K2 MK7 was identified in 13 (18.3%; 95% CI: 9.2-28.8%) cases in L_1 and 5 (7.0%; 95% CI: 1.2-12.9%) cases in L_0 (χ^2 3.117; p=0.0775); the data are presented in *Table 5*. Normal levels of all vitamin K fractions were detected in 28 women (39.4%; 95% CI: 28.2-53.7%) in L_1, compared to 46 (64.8%; 95% CI: 53.3-77.9%) in L_0 (χ^2 8.155; p=0.0043).

Table 5. **Hypovitaminosis rate of the studied fractions of vitamin K in women included in the study**

	Research group, L_1 n_1=71	**Control group, L_0 n_0=71**	**p**
	Abs., %		
Hypovitaminosis K – all fractions	43 (60.6%) 95% CI: 43.8 - 81.5%	25 (35.2%) 95% CI: 22.7 – 51.9%	0.004
Hypovitaminosis K1	35 (49.3%) 95% CI: 34.8 - 59.4%	22 (31.0%) 95% CI: 18.3 - 41.7%	0.039
Hypovitaminosis K2 MK4	3 (4.2%) 95% CI: 0 – 8.7%	1 (1.4%) 95% CI: 0 – 5.6%)	0.612
Hypovitaminosis K2 MK7	13 (18.3%) 95% CI: 9.2 – 28.8%	5 (7.0%) 95% CI: 1.2 – 12.9%	0.077

The assessment of the correlation between the severity of the condition and vitamin K levels in women with ICP was of interest. The study did not find a statistically significant difference between the rate of hypovitaminosis K (all fractions) among women with cholestasis gravidarum with BA values 10-39 μmol/l and BA values ≥40 μmol/l. However, the mean values of vitamin K2 MK7 were lower in the group of women with ICP and BA values ≥40 μmol/L - 0.16±0.11 (Me 0.15: 0.10; 0.22) μg/L, compared to women with ICP and BA values 10-39 μmol/L - 0.21±0.14 (Me 0.21: 0.11; 0.31) μg/L (95% CI: 0.0082-0.0918; p=0.0193), the difference being statistically significant.

4.3. Role of haematological markers of inflammation in intrahepatic cholestasis of pregnancy

The women in the study underwent a general blood test, which included an assessment of hematological inflammatory markers. The following markers were examined: neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width - standard deviation (RDW-SD) and red cell distribution width - coefficient of variation (RDW-CV). Besides that, in the current study, to assess the severity of the inflammatory syndrome in pregnant women with ICP, the values of leukocytes in the general blood test and the level of C-reactive protein were determined.

The mean NLR was 5.9±3.3 (Me 5.1: 3.7; 7.2) in L_1 compared to L_0, which had a mean NLR of 4.0±1.6 (Me 3.9: 3.0; 4.7), 95% CI: 1.040-2.760; p<0.0001 (*Figure 7*). Mean PLR was

149.6±59.2 (Me 135.1: 110.5; 184.3) in the group of women with ICP versus 111.2±35.0 (Me 104.4: 83.7; 132.9) in the control group (95% CI: 22.264-54.536; p<0.0001).

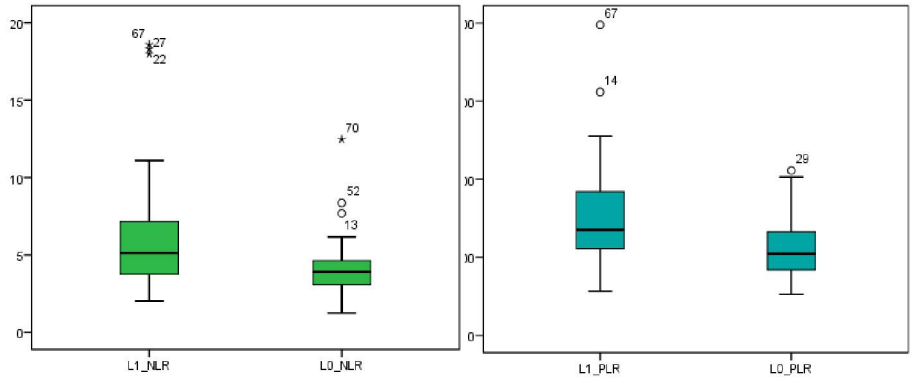

Figure 7. **NLR and PLR levels in women included in the study**

The mean values of erythrocyte distribution indices were: RDW-SD 45,9±7,8 fl (Me 45,4: 41,4; 49,5) and RDW-CV 14,6±4,7% (Me 13,4: 12,8; 14,6) in L_1 compared to RDW-SD 49,0±6,3 fl (Me 48,8: 44,9; 53,1) and RDW-CV 14,7±1,6% (Me 14,5: 13,6; 15,3) in L_0 (RDW-SD: 95% IÎ: -5,453 – -0,747; p=0,0102; RDW-CV: 95% CI: -1,265–1,065; p=0,8655).

The mean MPV in L_1 was 11.6±1.3 fl (Me 11.8: 11.0; 12.6) and in L_0 - 11.6±1.1 fl (Me 11.6: 10.9; 12.3), 95% CI: -0.400-0.400; p=1.0000. At the same time, the mean leukocyte level was 12.1±3.3 x103/μL (Me 11.8: 9.6; 14.5) in L_1, compared to L_0, which had a mean leukocyte level of 10.0±2.7 x103/μL (Me 9.3: 8.2; 11.4), 95% CI: 1.100-3.100; p=0.0001.

A comparative analysis of the mean values of hematological inflammatory markers relative to the severity of ICP did not detect a statistically significant difference.

Of interest was the study of C-reactive protein levels in the women included in the study. In the comparative analysis of the mean value of CrP in patients from the research group and the control group we found that in women with ICP this indicator was 8.1±16.9 (Me 4.1: 2.2; 8.2) mg/L, compared to 5.2±5.2 (Me 4.3: 1.8; 6.3) mg/L in the control group (95% CI: -1.249-7.049; p=0.1692). Increased CrP levels were detected in 19 (26.8%; 95% CI: 16.9-34.7%) cases in L_1 and 14 (19.7%; 95% CI: 11.0-31.2%) cases in L_0, the difference being statistically insignificant (χ^2 0.632; p=0.4268).

4.4. Dynamics of maternal clinical symptoms in women with cholestasis gravidarum

Considering that the main symptom of intrahepatic cholestasis of pregnancy is cutaneous pruritus, we were interested in assessing the intensity and location of this symptom among the women included in the study.

Cutaneous pruritus of different localization and intensity was experienced by all pregnant women in L_1 (*Figure 8*). Hence, 29 (40.8%; 95% CI: 32.2-50.9%) women in the research group reported concomitant cutaneous pruritus in several regions of the body. At the same time, 53 (74.6%; 95% CI: 66.2-84.7%) women with ICP reported increased skin pruritus during the night, while 16 (22.5%; 95% CI: 12.2-32.6%) mentioned that the intensity of skin pruritus remained the same during the day and at night.

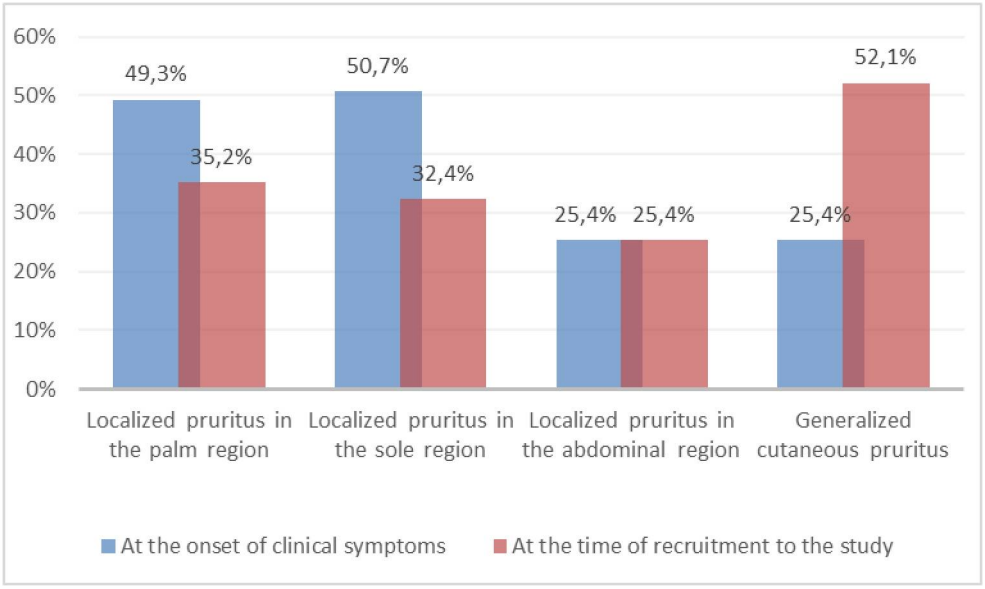

Figure 8. **Localization of cutaneous pruritus at onset of clinical symptoms and at the time of study inclusion in women with ICP (%)**

At the onset of symptoms, itchy skin localized in the region of the palms was experienced by 35 (49.3%; 95% CI: 39.2-60.8%) women in L_1, while itchy skin in the region of the soles was experienced by 36 (50.7%; 95% CI: 41.4-63.6%) women with ICP. Localization of cutaneous pruritus in the abdomen region was observed in 18 (25.4%; 95% CI: 13.9-36.1%) women whose pregnancy was complicated by cholestasis gravidarum. Generalized cutaneous pruritus at the onset of clinical symptoms was reported by 18 (25.4%; 95% CI: 15.5-35.4%)) women in L_1.

Generalized cutaneous pruritus at the time of study inclusion was experienced by 37 (52.1%; 95% CI: 33.8-65.0%) pregnant women in L_1 (χ^2 9.615; p=0.0019). Thus, a statistically significant difference was found in generalized skin pruritus at the time of study enrollment compared to the time of first clinical symptoms among pregnant women with ICP.

Although the literature demonstrates that the occurrence of specific skin rashes is not characteristic of ICP, the majority of study participants with the condition exhibited signs of excoriation, including severe cases (*Figure 9*).

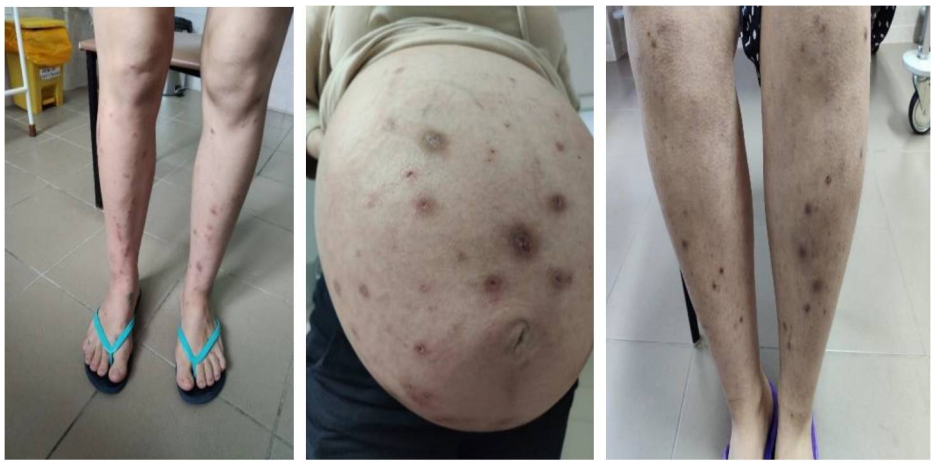

Figure 9. **Signs of excoriation present in women with ICP included in the study**

In the next stage of the research, the intensity and dynamics of skin pruritus in women with cholestasis gravidarum were assessed. Thus, participants were asked to rate the intensity of subjective skin pruritus sensation according to the two scales (Ribalta scale and VASPIS) at the onset of ICP (when the first subjective symptoms appeared), at the time of enrollment in the study, and then on the 3rd, 7th, and 10th postpartum days.

At the onset of ICP symptoms, women included in the study scored the intensity of skin pruritus on average 2.4±0.9 (Me 2: 2; 3) points according to the Ribalta scale and 5.1±2.3 (Me 5: 3; 7) points according to the visual analogue skin pruritus scale. The majority of women (38 cases, 53.5%; 95% CI: 37.8-73.4%) experienced occasional or discontinuous cutaneous pruritus (asymptomatic periods predominate) at the onset of clinical symptoms, which is equal to 1-2 points according to the Ribalta scale (*Figure 10*). At the same time, according to VASPIS, 34 (7.8%; 95% CI: 33.1-66.9%) women experienced mild to moderate skin pruritus that did not cause considerable discomfort.

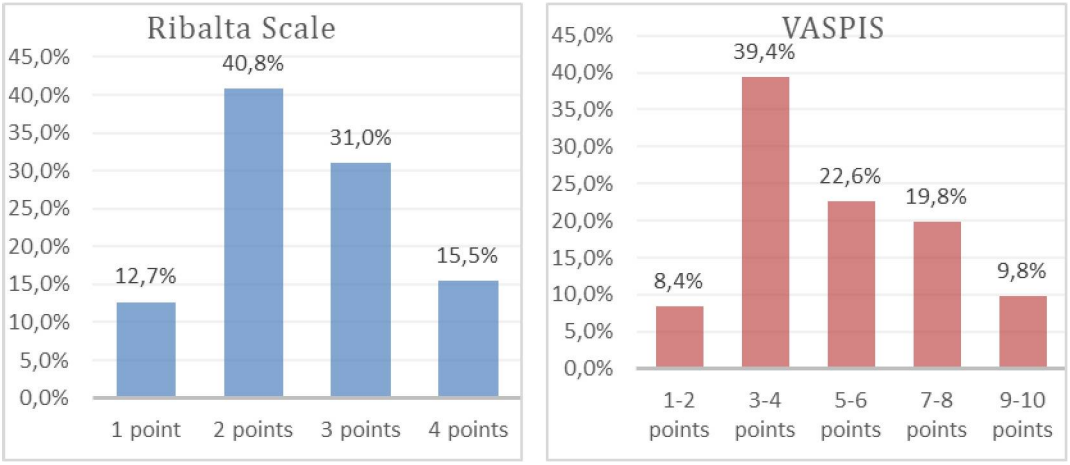

Figure 10. **Intensity of skin pruritus according to Ribalta and VASPIS scales at onset of clinical symptoms in women with ICP (%)**

Moreover, at the time of enrollment in the study, pregnant women with cholestasis gravidarum scored the intensity of skin pruritus on average 3.3±0.8 (Me 4: 3; 4) points according to the Ribalta scale (95% CI: -1.183 – -0.617; $p<0.0001$) and 7.7±2.2 (Me 8: 6; 10) points according to VASPIS (95% CI: -3.347 – -1.853; $p<0.0001$). Thus, an increase in the intensity of cutaneous pruritus was experienced by women with cholestasis gravidarum at the time of their inclusion in the study compared to the onset of clinical symptoms of the condition, the difference being statistically significant.

In 37 (52.1%; 95% CI: 42.0-66.9%) cases women indicated an intensity of cutaneous pruritus at the time of questioning equal to 4 points according to the Ribalta scale, i.e. permanent itching, present day and night (*Figure 11*). At the same time, 32 (45.1%; 95% CI: 30.8-63.6%) pregnant women reported an intensity of itching equal to 9-10 points on the visual analogue scale, the most intense being unbearable or almost unbearable.

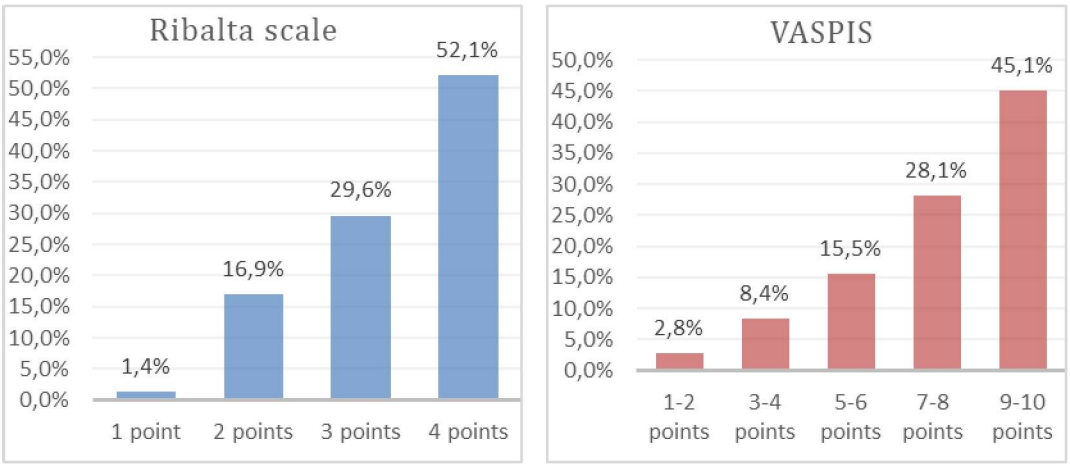

Figure 11. **Intensity of skin pruritus according to Ribalta and VASPIS scales at the time of recruitment to the study in women with ICP (%)**

It is also important to consider the intensity of cutaneous pruritus in the postnatal period in women with ICP. We found that by day 3 postpartum, 15 (21.1%; 95% CI: 12.5-33.3%) women were already free of complaints, and the pruritus had resolved on its own. Of the total 56 (78.8%; 95% CI: 59.5-100%) women in whom the main symptom of cholestasis gravidarum persisted, the intensity of cutaneous pruritus subsided slightly, averaging 1.6±0.7 (Me 2.5: 2; 7) points on the Ribalta scale and 3.1±1.7 (Me 2.5: 1; 2) points on the VASPIS at 3 days postpartum.

At day 7 after delivery, 60 (85.4%; 95% CI: 77.2-93.6%) women had no complaints, but among the 11 (15.4% (95% CI: 7.7%-27.7%)) women who had experienced occasional skin itching up to this point, they rated it at 1.0±0.0 (Me 1: 1; 1) points on the Ribalta scale and 1.3±0.5 (Me 1: 1; 2) points on the VASPIS. At day 10, 3 women (4.2%; 95% CI: 0.8-1.2%) reported persistence of skin pruritus with an intensity of 1.0±0.0 (Me 1: 1; 1) points according to the Ribalta scale and 1.0±0.0 (Me 1: 1; 1) points according to VASPIS.

Table 6. **Rare clinical symptoms of intrahepatic cholestasis of pregnancy**

Symptoms	**At the onset of clinical symptoms Abs., %**	**At the time of recruitment to the study Abs., %**	**p**
Jaundice	1 (1.4%)	3 (4.2%)	0.6120
Jaundice coloration of urine	9 (12.7%)	31 (43.7%)	<0.0001
Pale stool	1 (1.4%)	3 (4.2%)	0.6120
Abdominal pain	7 (9.9%)	21 (29.6%)	0.0061
Insomnia	11 (15.5%)	38 (53.5%)	<0.0001
Inappetence	4 (5.6%)	10 (14.1%)	0.1593
Fatigability	6 (8.5%)	40 (56.3%)	<0.0001
Nausea	1 (1.4%)	6 (8.5%)	0.1210

A particular aspect of the diagnosis of cholestasis gravidarum concerns the rare clinical symptoms of the pathology under investigation. Thus, we analyzed the presence of clinical symptoms at the onset of the condition and at the time of inclusion in the study, *Table 6.*

An increased rate of general symptoms in women with ICP, such as insomnia and fatigability, caused by intense cutaneous pruritus, was attested. Data in the literature denote that skin pruritus of any intensity affects the quality of life of pregnant women and leads to anxiety and depression [11, 14].

In view of the above, the diagnosis and management of pregnancy in women with cholestasis gravidarum require special attention from healthcare providers, considering the possible risks and complications. For this reason, we set out to develop a *Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy*, which included the results of our own research as well as data from international guidelines (Annex 1).

GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

General conclusions

1. The research determined the major risk factors that indicate an unfavorable premorbid background for the development of ICP, represented by hepatobiliary (viral hepatitis, calculous cholecystitis) (RR 2.6250, p=0.0111) and nephrourinary (chronic pyelonephritis, hydronephrosis) (RR 2.2000, p=0.0213) conditions and pre-existing pregnancy. A study of the characteristics of the course of pregnancy in women with ICP showed a high rate of iron deficiency anaemia (36.6%), hyperemesis gravidarum (25.4%) and gestational diabetes mellitus (18.3%) compared to the control group.

2. The study demonstrated that ICP has a negative influence on the newborn, which is characterized by a 3.8-fold increased incidence of prematurity (95% CI: 1.5014 - 9. 6176, p=0.0048), increased risk of developing congenital pneumonia - 2.5-fold (95% CI: 1.0463-6.1416, p=0.0394) and neonatal jaundice - 3.8-fold (95% CI: 1.1158-12.9586, p=0.0328), compared to the control group.

3. Evaluation of serum levels of LFTs: BA, ALT, AST, APRI and FIB-4 can be conclusive in predicting the risk of pregnancy progression to ICP, especially at gestation periods of 30-32 weeks, due to their high sensitivity and specificity (78.8% - 100%) in the diagnosis and prognosis of complications of ICP.

4. The research results of the study show that women with cholestasis gravidarum have a high level of hypovitaminosis K (60.6%), mainly due to K1 and K2 MK-7 fractions. At the same time, there is a negative correlation between ALT (r=-0.218, p=0.01), AST (r=-0.181, p=0.05) , APRI (r=-0.172, p=0.05) and vit. K2 MK-7, indicating malabsorption and/or metabolic disorders of the vitamin, caused by the pathological action of ICP, increasing the risk of developing coagulopathic haemorrhages.

5. The current study found significantly elevated hematological inflammatory markers: NLR (95% CI: 1.040-2.760; p<0.0001) and PLR (95% CI: 22.264-54.536; p<0.0001) in women whose pregnancies were complicated by ICP, demonstrating both the presence and the degree of activity of the inflammatory response as a result of the condition.

Practical recommendations

1. Pregnant women with a history of complicated ICP in previous pregnancies with liver disease (viral hepatitis, calculous cholecystitis) and nephrourinary disease (chronic pyelonephritis, hydronephrosis) will be included in the risk group for the development of ICP, requiring an individualized program of monitoring and antenatal care for the timely diagnosis of the condition.

2. The management of cases of ICP will be carried out according to the *Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy* proposed in the research.

3. Determination of serum bile acid levels is a crucial diagnostic criterion in assessing the severity of ICP for maternal and fetal prognosis and the differential diagnosis of the condition with other liver disorders in pregnancy.

4. Pregnant women in the risk group are recommended at 30-32 weeks of gestation to have their serum BA, ALT and AST levels assessed for early detection and diagnosis of ICP in primary health care units. It is also recommended to supplement the screening program for pregnant women with ICP with weekly assessments of BA, ALT, AST, APRI, and FIB-4 levels from the time of diagnosis until delivery.

5. For the purpose of prophylaxis of coagulopathic haemorrhages in mother and foetus, it is recommended to test vitamin K levels in pregnant women with ICP.

6. In order to dynamically monitor the main symptom of cholestasis gravidarum, pruritus, it is necessary to train ICP patients to assess the intensity of skin pruritus according to the visual analogue skin pruritus intensity scale (VASPIS).

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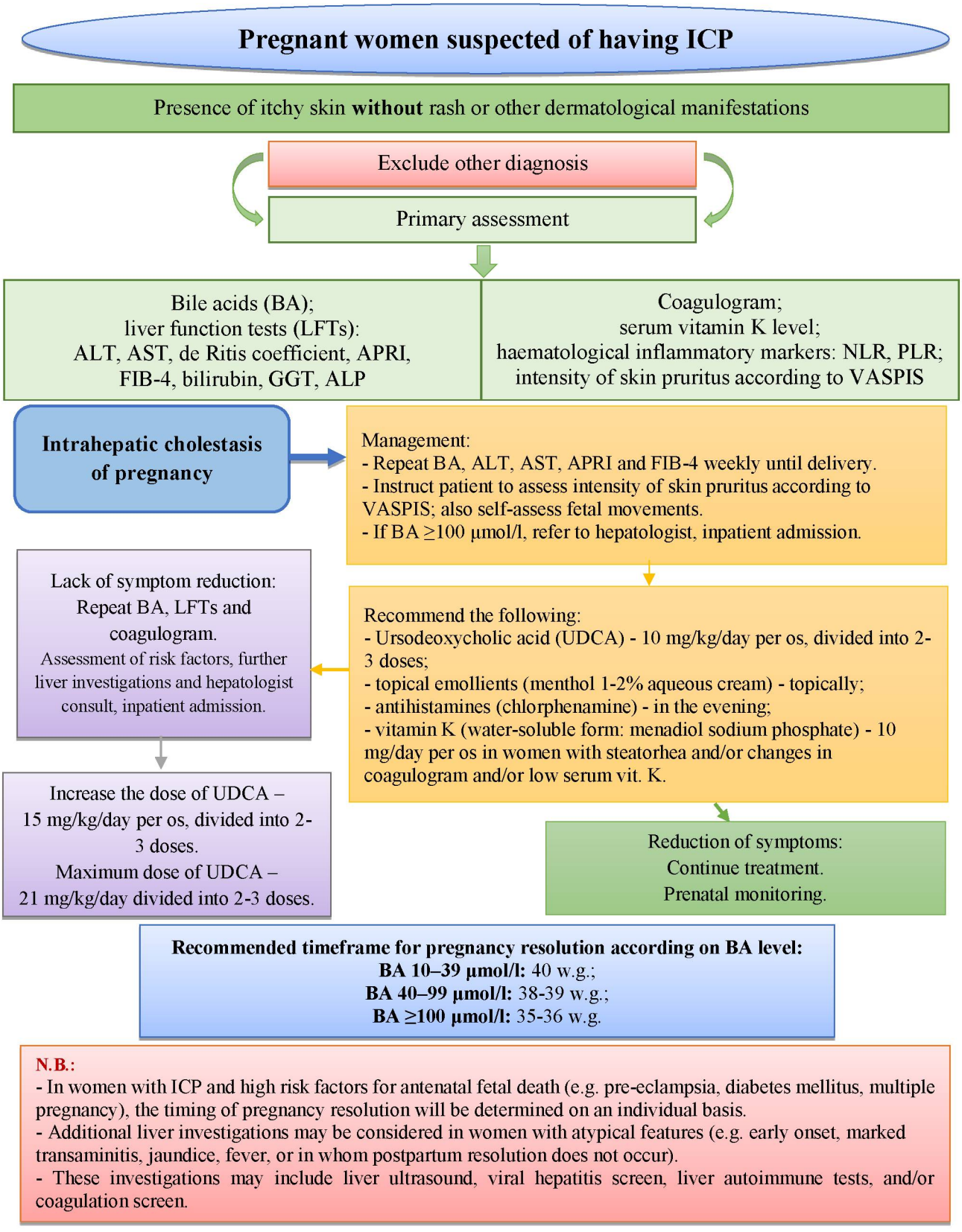
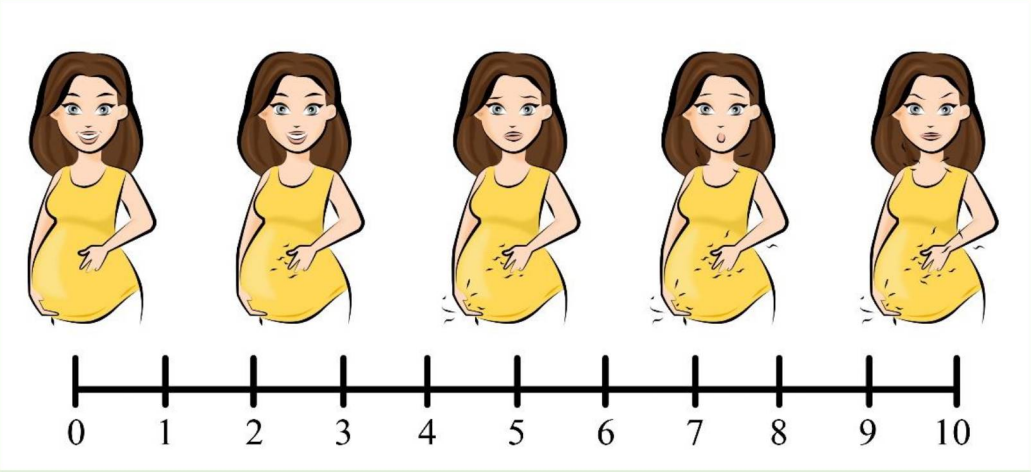
Annex 1. **Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy**



Visual analogue skin pruritis intensity scale (VASPIS)



Liver function tests

De Ritis coefficient - AST to ALT ratio index	De Ritis coefficient = AST (U/l) / ALT (U/l) =
APRI – platelet AST ratio index, calculated by calculator, available online https://www.hepatitisc.uw.edu/page/clinical-calculators/apri	APRI = (AST Level (IU/L) / AST (Upper Limit of Normal) (IU/L)) / Platelet Count (10^9/L) x 100 =
The Fibrosis-4 score is calculated by calculator, available online https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4	FIB-4 = (Age (years) x AST Level (U/L)) / (Platelet Count (10^9/L) x √ALT (U/L)) =

Hematological inflammatory markers

NLR – neutrophil to lymphocyte ratio	NLR = Absolute neutrophil count (10^3/µL) / Absolute lymphocyte count (10^3/µL) =
PLR – platelet to lymphocyte ratio	PLR = Absolute platelet count (10^3/µL) / Absolute lymphocyte count (10^3/µL) =

LIST OF PUBLICATIONS

- **Articles in scientific journals abroad:**

✓ **Articles in accredited journals abroad:**

1. **Cemortan M.;** Sagaidac I. Clinical course of pregnancy, childbirth and perinatal outcomes in women with intrahepatic cholestasis of pregnancy. In: *Акушерство и гинекология*. 2021, nr. 5, pp. 94-99. ISSN o3oo-9092. DOI: https://doi.org/10.18565/aig.2021.5.94-99
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21. **Чемортан М.** Оценка частоты появления редких симптомов у женщин с внутрипеченочным холестазом беременных. В: *Материалы XXIII Всероссийского образовательного форума "Мать и Дитя – 2022"*. Москва, Российская Федерация. 2022, сс. 110-111.

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- **Patents, registration certificates, materials at invention fairs:**

23. **Cemortan Maria,** Ostrofeț Constantin. *Aprecierea nivelului seric al vitaminei K (vitamina K1, vitamina K2 (MK-4), vitamina K2 (MK-7)) la gestantele cu colestază intrahepatică*

de sarcină. Certificat de inovator nr. 5895 din 23.03.2022 (eliberat de IP USMF *Nicolae Testemițanu*)

24. **Cemortan Maria,** Ostrofeț Constantin. *Aprecierea nivelului markerilor hematologici de inflamație (NLR, PLR, MPV, RDW-SD, RDW-CV) la gestantele cu colestază intrahepatică de sarcină.* Certificat de inovator nr. 5896 din 08.04.2022 (eliberat de IP USMF *Nicolae Testemițanu*)

25. **Cemortan Maria**. *Aprecierea nivelului indicelui raportului aspartataminotransferazei la trombocite (APRI) la gestantele cu colestază intrahepatică de sarcină.* Certificat de inovator nr. 5952 din 30.09.2022 (eliberat de IP USMF *Nicolae Testemițanu*)

26. **Cemortan Maria**. *Aprecierea intensității pruritului cutanat la femeile cu colestaza intrahepatică de sarcină cu elaborarea unei scale vizuale analogice (SVAIP).* Certificat de inovator nr. 6063 din 26.05.2023 (eliberat de IP USMF *Nicolae Testemițanu*)

27. **Cemortan Maria,** Ostrofeț Constantin. *Aprecierea nivelului seric al vitaminei K (vitamina K1, vitamina K2 (MK-4), vitamina K2 (MK-7)) la gestantele cu colestaza intrahepatică de sarcină.* Certificat de inovator nr. 499 din 13.10.2022 (eliberat de IMSP Institulul Mamei și Copilului)

28. **Cemortan Maria,** Ostrofeț Constantin. *Aprecierea nivelului markerilor hematologici de inflamație (NLR, PLR, MPV, RDW-SD, RDW-CV) la gestantele cu colestază intrahepatică de sarcină.* Certificat de inovator nr. 500 din 13.10.2022 (eliberat de IMSP Institulul Mamei și Copilului)

29. **Cemortan Maria**. *Aprecierea nivelului indicelui raportului aspartataminotransferazei la trombocite (APRI) la gestantele cu colestază intrahepatică de sarcină.* Certificat de inovator nr. 501 din 13.10.2022 (eliberat de IMSP Institulul Mamei și Copilului)

30. **Cemortan Maria**. *Aprecierea intensității pruritului cutanat la femeile cu colestaza intrahepatică de sarcină cu elaborarea unei scale vizuale analogice (SVAIP).* Certificat de inovator nr. 521 din 26.05.2023 (eliberat de IMSP Institutul Mamei și Copilului)

31. Diploma of **Silver medal** International Exhibition of Innovation and Technology Transfer *EXCELLENT IDEA* – 2022, 1-st edition. **Cemortan Maria,** Ostrofeț Constantin. For inovation *Assessment of serum vitamin K levels (vitamin K1, vitamin K2 (MK-4), vitamin K2 (MK-7)) in women with intrahepatic cholestasis of pregnancy.* 2022.

32. Diploma of **Gold medal** European Exhibition of Creativity and Innovation *EUROINVENT* – 2023, 15-th edition. **Cemortan Maria,** Ostrofeț Constantin. For inovation *Assessment of serum vitamin K levels (vitamin K1, vitamin K2 (MK-4), vitamin K2 (MK-7)) in women with intrahepatic cholestasis of pregnancy.* 2023.

33. **Cemortan Maria,** Sagaidac Irina, Cernețchi Olga. *Particularitățile de diagnostic al colestazei intrahepatice de sarcină.* Adeverință privind înscrierea obiectelor dreptului de autor și ale drepturilor conexe. Seria OȘ nr. 7553 din 28.06.23 (Eliberat de Agenția de Stat pentru Proprietatea Intelectuală).

34. **Cemortan Maria,** Sagaidac Irina, Cernețchi Olga. *Particularităţile evoluţiei sarcinii, a naşterii şi rezultatele perinatale la femeile cu colestază intrahepatică de sarcină.* Adeverință privind înscrierea obiectelor dreptului de autor și ale drepturilor conexe. Seria OȘ nr. 7555 din 28.06.23 (Eliberat de Agenția de Stat pentru Proprietatea Intelectuală).

- **Participation with communications in scientific conferences**

✓ **international:**

35. **Cemortan M.** Функциональные пробы печени и перинатальные исходы у женщин с внутрипеченочным холестазом беременных. XXI Всероссийский образовательный форум "Мать и Дитя – 2020". Москва, Российская Федерация. 28-30 сентября 2020 г.

36. **Cemortan M.** Explorarea funcțională a ficatului și evoluția nașterii la femeile cu colestază intrahepatică de sarcină. Conferința națională Zilele Medicale *Vasile Dobrovici*. Iași, România, 26-28 noiembrie 2020.

37. **Cemortan M.** Assessment of vitamin K level in women with intrahepatic cholestasis of pregnancy. 17th International and 59th Polish Conference Juvenes Pro Medicina 2021. Lodz, Poland, 14-16 May 2021.

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40. **Cemortan M.** Perinatal outcomes in women with intrahepatic cholestasis of pregnancy. XXVIII European Congress of Perinatal Medicine. Lisbon, Portugal, 22-25 June 2022.

✓ **national:**

41. **Cemortan M.** Aspectele clinice ale sarcinii și rezultatele perinatale la femeile cu colestază intrahepatică de sarcină. Conferința Științifică Anuală, Universitatea de Stat de Medicină și Farmacie *Nicolae Testemițanu*. Chișinău, Republica Moldova, 19-21 octombrie 2022.

42. **Cemortan M.** Colestaza intrahepatică de sarcină: aspectele clinice și de tratament. Consfătuirile comune ale medicilor obstetricieni-ginecologi, neonatologi, pediatri. Chișinău, Republica Moldova, 28 octombrie 2022.

- **Participation with posters in scientific conferences**

✓ **international:**

43. **Cemortan M.;** Iliadi-Tulbure C. Perinatal outcomes in twin vs. singleton pregnancies in relation to intrahepatic cholestasis of pregnancy. Twins Congress – the Joint 5th World Congress on Twin Pregnancy – a Global Perspective and the 17th Congress of the International Society on Twins Studies (ISTS). Beijing, China, 4-6 June 2021.

44. **Cemortan M.** Assessment of the role of haematological inflammatory markers in intrahepatic cholestasis of pregnancy. Zilele Medicale *Vasile Dobrovici*. Iași, România, 5-7 mai 2022.

45. **Cemortan M.** Post-partum blood loss in women with intrahepatic cholestasis of pregnancy. BIRTH Congress, 7-th Edition. Milan, Italy, 7-10 December 2022.

✓ **national:**

46. **Cemortan M.** Rezultatele perinatale la femeile cu colestază intrahepatică de sarcină. Congresul consacrat aniversării a 75 de ani de la fondarea USMF *Nicolae Testemițanu*. Chișinău, Republica Moldova, 20-23 octombrie 2020.

ANNOTATION

Cemortan Maria

Diagnosis and course of pregnancy and childbirth in women with intrahepatic cholestasis of pregnancy

PhD thesis in Medical Sciences. Chisinau, 2023

Thesis structure. The thesis is laid out on 124 pages of main text, consisting of an introduction, 5 chapters, general conclusions, recommendations, and a bibliographic index of 255 references, 25 figures, 11 tables, and 10 annexes. The results obtained are published in 22 scientific articles.

Keywords: intrahepatic cholestasis of pregnancy, pregnancy, childbirth, perinatal outcomes, diagnosis.

Purpose of the thesis: To evaluate the diagnostic features and clinical course, perinatal outcomes, and optimize the management of pregnant women with intrahepatic cholestasis of pregnancy (ICP).

Objectives of the study: To determine the clinical course of pregnancy, delivery, and perinatal outcome in women with intrahepatic cholestasis of pregnancy; to evaluate the diagnostic features of intrahepatic cholestasis of pregnancy; to assess vitamin K levels and haematological markers of inflammation in case of intrahepatic cholestasis of pregnancy; to develop a diagnostic and management algorithm for pregnant women with intrahepatic cholestasis of pregnancy.

Scientific novelty and originality. The study elucidated the evolution peculiarities of pregnancy, delivery and perinatal outcomes in women with ICP. The diagnostic features of intrahepatic cholestasis of pregnancy were investigated, as well as the level of vitamin K and haematological markers of inflammation in this group of pregnant women.

The important scientific problem solved in the paper aims to elucidate the clinical and evolutionary features of pregnancy and delivery in pregnant women with cholestasis gravidarum, as well as to highlight the features of diagnosis and management of the condition, on the basis of which the *Diagnostic and management algorithm for intrahepatic cholestasis of pregnancy* was developed, which includes the following compartments: clinical manifestations, diagnosis, treatment, and time limits of pregnancy resolution in pregnant women with ICP.

Theoretical significance. The thesis, through the results obtained, highlights and updates data related to the particularities of gestation, delivery, maternal clinical symptoms of intrahepatic cholestasis of pregnancy, as well as the level of vitamin K and hematological markers of inflammation in the condition.

Applicative value. Diagnostic peculiarities of intrahepatic cholestasis of pregnancy were highlighted. The level of vitamin K in women with ICP and the role of haematological markers of inflammation in ICP were assessed. An algorithm for the diagnosis and management of pregnant women with intrahepatic cholestasis of pregnancy was proposed.

Implementation of scientific results. The study results were implemented in the teaching process of the Department of Obstetrics and Gynecology of *Nicolae Testemitanu* PI SUMPh, as well as in the curative activity of the Institute of Mother and Child and *Gheorghe Paladi* Municipal Clinical Hospital.

ADNOTARE

Cemortan Maria

Diagnosticul și evoluția gravidității și a nașterii la femeile cu colestază intrahepatică de sarcină

Teză de doctor în științe medicale. Chișinău, 2023

Structura tezei. Lucrarea este expusă pe 124 de pagini de text de bază; constă din introducere, 5 capitole, concluzii generale, recomandări; indice bibliografic cu 255 de referințe; include 25 de figuri, 11 tabele și 10 anexe. Rezultatele obținute sunt publicate în 22 de lucrări științifice.

Cuvinte-cheie: colestază intrahepatică de sarcină, sarcină, naștere, rezultate perinatale, diagnostic

Scopul lucrării. Evaluarea particularităților de diagnostic și de evoluție clinică, a rezultatelor perinatale și optimizarea conduitei gravidelor cu colestază intrahepatică de sarcină (CIS).

Obiectivele cercetării. Studierea evoluției sarcinii, nașterii și a rezultatelor perinatale la femeile cu colestazaă intrahepatică de sarcină; evaluarea particularităților de diagnostic al colestazei intrahepatice de sarcină; aprecierea nivelului vitaminei K și al markerilor hematologici de inflamație în evoluția colestazei intrahepatice de sarcină; elaborarea algoritmului de diagnostic și de conduită a gestantelor cu colestazaă intrahepatică de sarcină.

Noutatea și originalitatea științifică. Studiul realizat a elucidat particularitățile evoluției sarcinii, a nașterii și rezultatele perinatale la femeile cu CIS. Au fost cercetate particularitățile de diagnostic al colestazei gravidarum, a fost apreciat nivelul vitaminei K și al markerilor hematologici de inflamație în acest grup de gravide.

Problema științifică importantă soluționată în lucrare vizează elucidarea particularităților clinico-evolutive ale sarcinii și nașterii la gestantele cu colestază gravidarum, precum și evidențierea particularităților de diagnostic și de management al patologiei cercetate, în baza căreia a fost elaborat *Algoritmul de diagnostic și de conduită al colestazei intrahepatice de sarcină*, care include următoarele compartimente: manifestările clinice, diagnosticul, tratamentul și termenele de rezolvare a sarcinii la gravidele cu CIS.

Semnificația teoretică. Lucrarea, prin rezultatele obținute, scoate în evidență și actualizează datele ce țin de particularitățile gestației și nașterii, de simptomele clinice materne ale colestazei intrahepatice de sarcină, precum și de nivelul vitaminei K și al markerilor hematologici de inflamație în patologia cercetată.

Valoarea aplicativă. Au fost evidențiate particularitățile de diagnostic al colestazei intrahepatice de sarcină. A fost apreciat nivelul vitaminei K la femeile cu CIS, fiind evidențiat rolul markerilor hematologici de inflamație în colestaza gravidarum. A fost propus algoritmul de diagnostic și de conduită al gravidelor cu colestază intrahepatică de sarcină.

Implementarea rezultatelor științifice. Rezultatele studiului au fost implementate în procesul didactic la disciplina *Obstetrică și ginecologie* în IP Universitatea de Stat de Medicină și Farmacie *Nicolae Testemițanu* din Republica Moldova, precum și în activitatea curativă curentă a IMSP Institutul Mamei și Copilului și a IMSP Spitalul Clinic Municipal *Gheorghe Paladi*.

АННОТАЦИЯ

Чемортан Мария

Диагностика и течение беременности и родов у женщин с внутрипеченочным холестазом беременных

Диссертация кандидата медицинских наук. Кишинэу, 2023.

Структура диссертации. Работа представлена на 124 страницах основного текста, состоит из введения, 5 глав, общих выводов, рекомендаций и библиографии, включающей 255 источника, 25 рисунков, 11 таблиц и 10 приложений. По теме диссертации опубликовано 22 научные работы.

Ключевые слова: внутрипеченочный холестаз беременных, беременность, роды, перинатальные исходы, диагностика.

Цель исследования: Изучение особенностей диагностики, клинического течения, перинатальных исходов и оптимизация ведения женщин с внутрипеченочным холестазом беременных (ВХБ).

Задачи исследования: Определить клиническое течение беременности, родов и перинатальных исходов у женщин с внутрипеченочным холестазом беременности; изучить диагностические особенности внутрипеченочного холестаза беременности; оценить уровень витамина К и гематологических маркеров воспаления при внутрипеченочном холестазе беременности; разработать алгоритм диагностики и ведения беременных с внутрипеченочным холестазом беременности.

Научная новизна и оригинальность. В ходе исследования выявлены особенности течения беременности, родов и перинатальные исходы у женщин с внутрипеченочным холестазом беременных. Изучены особенности диагностики ВХБ, а также уровень витамина К и гематологических маркеров воспаления в данной группе беременных.

Решенная научная проблема заключается в выявлении клинических особенностей течения беременности и родов у женщин с внутрипеченочным холестазом беременных, а также на выявлении особенностей диагностики и менеджмента исследуемой патологии, на основании чего разработан *Алгоритм диагностики и менеджмента случаев внутрипеченочного холестаза беременных*, включающий следующие разделы: клинические проявления, диагностика, лечение и сроки родоразрешения у беременных с ВХБ.

Теоретическая значимость. Полученные результаты выявили и обновили данные, касающиеся особенностей беременности, родов, клинических симптомов внутрипеченочного холестаза беременных у женщин, а также касающиеся уровня витамина К и гематологических маркеров воспаления при исследуемой патологии.

Практическая значимость. Выделены диагностические особенности внутрипеченочного холестаза беременных. Оценен уровень витамина К у женщин с ВХБ и роль гематологических маркеров воспаления при исследуемой патологии. Предложен алгоритм диагностики и лечения беременных женщин с внутрипеченочным холестазом беременных.

Внедрение научных результатов. Результаты исследования были внедрены в учебный процесс дисциплины *Акушерство и гинекология* ГМФУ им. Николае Тестемицану РМ, а также в лечебную деятельность МСПУ Институт Матери и Ребенка и МСПУ Муниципальная клиническая больница им. Георге Палади.

CEMORTAN MARIA

DIAGNOSIS AND COURSE OF PREGNANCY AND CHILDBIRTH IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

321.15 OBSTETRICS AND GYNECOLOGY

Summary of Ph.D. Thesis in Medical Sciences