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Comparative analysis of vitamin K levels in women with intrahepatic cholestasis of pregnancy

Maria Cemortan[1*], Irina Sagaidac[1] and Olga Cernetchi[1]

Abstract

Background Intrahepatic cholestasis of pregnancy (ICP) is a liver condition that may impact both mother and fetus, including preterm birth and hemorrhage. Vitamin K, a fat-soluble vitamin essential for coagulation, may be deficient in ICP due to impaired bile flow, raising hemorrhage risk. The study aimed to analyze Vitamin K1, K2 MK4, and K2 MK7 levels in pregnant women with ICP and determine associations between Vitamin K deficiency and postpartum hemorrhage.

Methods This prospective cohort study included 44 pregnant women with ICP (L1) and 44 controls (L0). Serum Vitamin K levels, using high-performance liquid chromatography, and blood loss during delivery were assessed. Statistical analyses included t-tests and chi-square tests, with significance at $p < 0.05$. Study registration number ISRCTN21187408 https://www.isrctn.com/ISRCTN21187408 Registration date 03/06/2020.

Results Women with ICP exhibited significantly lower mean levels of Vitamin K1 (0.15 ± 0.17 µg/L in L1 vs. 0.29 ± 0.30 µg/L in L0, $p = 0.0085$) and Vitamin K2 MK7 (0.17 ± 0.13 µg/L in L1 vs. 0.26 ± 0.14 µg/L in L0, $p = 0.0024$) compared to controls. Vitamin K1 deficiency was observed in 52.3% of the ICP group vs. 2.3% in controls. Mean blood loss during vaginal delivery was higher in the ICP group (351 ± 104 mL in L1 vs. 297 ± 87 mL in L0, $p = 0.0373$).

Conclusions This study suggests that ICP contributes to significant Vitamin K1 deficiency in pregnant women, potentially increasing postpartum hemorrhage risk. Routine Vitamin K monitoring and possible supplementation with vitamin K in pregnant women with ICP may be beneficial to mitigate adverse maternal outcomes. Further research is warranted to confirm these findings.

Keywords Intrahepatic cholestasis of pregnancy, Obstetric cholestasis, ICP, Vitamin K

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Background

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder unique to pregnancy, most commonly presenting in the second and third trimesters. It is characterized by the high levels of bile acids (BA) in the blood due to impaired bile flow from the liver, resulting in clinical symptoms like intense pruritus (itching) and abnormal liver function tests (LFTs). While ICP tends to resolve shortly after delivery, it carries significant risks for both the mother and fetus, including preterm birth, stillbirth, meconium-stained amniotic fluid, and maternal hemorrhage [1]. The global incidence of ICP varies from 0.5 to 1.5%, but it can be as high as 5–15% in specific populations, such as in South America and parts of Northern Europe, where genetic and environmental factors may contribute to the increased prevalence [1, 2].

The hallmark symptom of ICP is pruritus, which affects the palms and soles and worsens at night. This symptom can appear days or even weeks before biochemical abnormalities are detected [3, 4]. In severe cases, itching can become unbearable, often leading to significant anxiety [4–6]. Elevated serum bile acids are the most reliable biochemical marker for diagnosing ICP, with levels ≥ 19 μmol/L [7]. Other commonly elevated LFTs markers include alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are often elevated in ICP cases [1–3, 8].

While the exact cause of ICP remains unknown, hormonal, genetic, and environmental factors are thought to play a role in its etiopathogenesis. Elevated estrogen and progesterone levels during pregnancy are believed to impair bile excretion, contributing to bile acid accumulation. Genetic predispositions, including mutations in ABCB4 and ABCB11 genes, which are involved in bile transport, may also increase susceptibility to ICP [2, 9]. Moreover, environmental factors, such as seasonal variations, diet, and selenium deficiency, have been hypothesized to exacerbate the condition [1, 2, 9].

Although ICP generally resolves postpartum without long-term liver damage, the condition is associated with significant maternal and fetal risks. For the mother, ICP can increase the likelihood of complications such as postpartum hemorrhage, particularly if vitamin K deficiency is present [1, 8, 10, 11]. Vitamin K is essential for the synthesis of clotting factors, and its deficiency can impair the blood's ability to clot, possibly leading to hemorrhage during delivery [1, 8, 10, 11]. For the fetus, elevated bile acid levels are strongly associated with adverse outcomes, including preterm birth, fetal distress, and stillbirth. The risk of stillbirth rises considerably when bile acid levels exceed 100 μmol/L [7].

Vitamin K is a fat-soluble vitamin that plays a critical role in blood coagulation and bone metabolism. It exists in two primary forms: vitamin K1 (phylloquinone), found in green leafy vegetables, and vitamin K2 (menaquinone), which is synthesized by intestinal bacteria and found in certain animal products [12]. Vitamin K is absorbed in the small intestine via bile salts, which emulsify dietary fats and allow the absorption of fat-soluble vitamins into enterocytes. From here, vitamin K is incorporated into chylomicrons and released into the lymphatic system before entering the bloodstream [13].

Once in the liver, vitamin K acts as a coenzyme for γ-glutamyl carboxylase, an enzyme that carboxylates glutamic acid residues on vitamin K-dependent proteins, including clotting factors such as prothrombin (factor II), factor VII, factor IX, and factor X. This carboxylation process is critical for activating these clotting factors, making vitamin K indispensable for hemostasis [14]. In addition to its role in coagulation, vitamin K is also involved in bone metabolism and the regulation of vascular calcification [15].

In the context of ICP, vitamin K metabolism may be disrupted due to impaired bile flow. Bile is necessary for the absorption of fat-soluble vitamins, including vitamin K, meaning that women with ICP may experience fat malabsorption and, consequently, hypovitaminosis K [2]. Hypovitaminosis K in ICP has been linked to an increased risk of postpartum hemorrhage, as the ability to synthesize clotting factors is compromised [2, 16].

Although ICP is primarily a liver disorder, its impact on vitamin K metabolism underscores the importance of monitoring and managing vitamin K levels in pregnant women with this condition. Our previous studies have reported that 59.2% of women with ICP exhibit reduced vitamin K levels, though standard coagulation tests, such as prothrombin time, may still appear normal, possibly due to the compensatory mechanisms [11]. However, these tests are more reflective of vitamin K activity rather than its actual concentration, meaning that a deficiency could go undetected until it results in severe clinical complications like hemorrhage [11].

Given the complex interplay between impaired bile flow, fat malabsorption, and vitamin K metabolism in ICP, it is crucial to further investigate vitamin K levels in women affected by this condition. Identifying and addressing hypovitaminosis K in ICP could reduce the risk of maternal hemorrhage and improve perinatal outcomes. Additionally, comparative studies on vitamin K levels in ICP may help clinicians better understand the pathophysiology of the condition and develop more effective management protocols.

The primary objective of this study was to investigate the relationship between intrahepatic cholestasis of pregnancy and vitamin K levels, with a focus on its potential implications for postpartum hemorrhage risk. Specifically, the study aimed to:

1. Evaluate and compare the serum levels of vitamin K1, K2 MK4, and K2 MK7 in pregnant women diagnosed with ICP and in healthy pregnant controls.
2. Assess the prevalence of vitamin K deficiency in ICP patients and its association with impaired coagulation profiles.
3. Determine whether lower vitamin K levels in ICP are linked to an increased risk of postpartum hemorrhage, based on measured blood loss during delivery.

Materials and methods

Study design and population

This study was conducted between January 2020 – December 2022, as a prospective cohort analysis involving 44 pregnant women diagnosed with intrahepatic cholestasis of pregnancy (L1). The control group involved 44 pregnant women without ICP (L0).

The representative research sample was calculated using *EpiInfo 7.2.2.6 in the StatCalc Sample Size and Power* section based on the following parameters: Confidence interval for 95.0% significance of results; statistical power – 80.0%; the difference in the course and outcome of pregnancy in pregnant women with intrahepatic cholestasis of pregnancy compared to pregnant women without ICP constitutes on average up to 20.0% [17]; ratio between the investigated groups = 1:1; result: for the 95.0% CI the calculated value is 44.

Eligible participants were women with gestational ages beyond 22^{+0} weeks, who had confirmed ICP diagnoses based on clinical symptoms, such as pruritus, and laboratory results indicating serum BA levels of ≥ 19 μmol/L [7]. Participants were followed up at their postnatal check-ups, during which serum BA, LFTs, and clinical symptoms were reassessed, confirming the resolution of the condition. Exclusion criteria for the study included women with known coagulopathy, preeclampsia, HELLP syndrome, acute hepatitis, drug-induced liver injury, and epilepsy (to exclude the influence of anti-epileptic drugs on vitamin K absorption).

This study included both singleton and multiple pregnancies in both groups. In the ICP group (L1), there were 3 twin pregnancies, while in the control group (L0), there were 2 twin pregnancies and 1 triplet pregnancy.

Assessment parameters

Vitamin K levels (including vitamin K1, vitamin K2 MK4, and vitamin K2 MK7), coagulation profiles (Prothrombin by Quick (%), Fibrinogen (g/L), International Normalized Ratio (INR)), and blood loss during delivery were evaluated. Vitamin K concentrations were measured once between 28 and 36 weeks, using high-performance liquid chromatography (HPLC). Total blood loss during delivery and cesarean section was assessed in accordance with international guidelines [18]. Blood was collected using graduated containers, and the sterile materials used during delivery were weighed to accurately quantify blood loss.

Serum bile acid levels were measured using spectrophotometry method. In this study, women were not started on UDCA before their serum bile acid levels were measured. To avoid potential false-negative or altered results, BA and vitamin K testing was conducted before initiating any pharmacological treatment for the condition, including UDCA or antibiotic drugs.

Dietary and nutritional assessment

A food frequency questionnaire was used to assess the dietary habits of participants. It included questions regarding the consumption of major food groups, such as cereals, fruits, vegetables, dairy products, meat, fish, nuts, seeds, fats, sweets, and fast food. It also collected information about vitamin and supplement intake during pregnancy. Additionally, participants' body mass index (BMI) before pregnancy was recorded, along with their weight gain during pregnancy, to evaluate their overall nutritional status and rule out the possibility of malnutrition contributing to low dietary intake of vitamin K.

Ethical considerations

The study was approved by the Ethics Committee Review Board of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova. Informed consent was obtained from all participants prior to their inclusion in the study, and all personal data were kept confidential in compliance with ethical standards.

Data collection and statistical analysis

Data collection involved coding and entering participant information into IBM SPSS Statistics version 21. The analysis was conducted using both SPSS and GraphPad software for statistical computation. Descriptive statistics, such as arithmetic means and standard deviations (M ± SD), were calculated for normally distributed variables. For non-normally distributed data, the median (Me) and interquartile range (Q1, Q3) were reported. The chi-square (χ^2) test with Yates' correction was employed to compare categorical variables between groups. For the evaluation of the statistical difference between two means, the t-test was applied. A p-value of <0.05 was considered statistically significant, and 95% confidence interval (CI) was calculated.

Results

The average age of women in L1 was 30.1 ± 6.1 years (Me 30 (25.2; 34.7)), (ranged between 18 and 43 years), comparative to average age of 28.1 ± 5.2 years (Me 27 (24; 32)) in L0 (ranged between 20 and 39 years) (95%CI:

-0.402 to 4.402, $p = 0.0989$). Biliary acids levels in women were assessed in order to determine the severity of ICP. Hence, average level of BA in L1 was 49.7 ± 41.3 μmol/L (Me 36.9 (22.6; 56.7)), (ranged between 19 and 211.3 μmol/L), comparative to average level of BA of 3.2 ± 1.4 μmol/L (Me 3.1 (2.2; 4.3)) in L0 (ranged between 1.3 and 7.7 μmol/L) (95%CI: 34.116 to 58.884, $p < 0.0001$). A mild condition (BA levels 19–39 μmol/L) was diagnosed in 24 (54.5%, 95%CI: 40.9–74.3%) cases from L1, moderate ICP (BA levels 40–99 μmol/L) in 15 (34.1%, 95%CI: 18.5–49.6%) cases in L1, and a severe condition (BA levels 100 μmol/L or more) in 5 (11.4%, 95%CI: 2.6–20.5%) cases in L1.

Regarding the possible nutritional component of vitamin intake, the participants were asked if they considered their diet balanced. Thus, 38 (86.4%, 95%CI:73.5–95.5%) women from the L1, and 37 (84.1%, 95%CI:73.1–99.3%) women from the L0 reported their diet to be well equilibrated ($\chi^2$0.090, $p = 0.7639$). However, the authors recognize that this may be a moment of bias regarding the self-reported dietary habits of participants. Given the suggestions that the possibility of vitamin K deficiency in pregnant women with a low body mass index, in order to exclude potential bias, it was of interest to study the anthropometric data of the women included in the study, pre-pregnancy BMI, as well as weight gain during the current pregnancy. Hence, according to the BMI, underweight before pregnancy was one participant (2.3%, 95%CI: 0-6.8%) from L1 ($\chi^2$1.011, $p = 0.3145$), normal BMI had 35 (79.5%, 95%CI: 68.2–94.7%) women from L1, and 28 (63.6%, 95%CI: 45.5–79.2%) women from L0 ($\chi^2$2.011, $p = 0.1561$). According to the BMI, overweight before pregnancy were 7 (15.9%, 95%CI: 2.6–27.3%) women from L1, and 11 (25%, 95%CI: 9.5–40.2%) women from L0 ($\chi^2$0.629, $p = 0.4279$). Obesity class I before pregnancy had one (2.3%, 95%CI: 0-6.8%) woman from L1, and 4 (9.1%, 95%CI: 2.3–18.2%) women from L0 ($\chi^2$0.848, $p = 0.3571$), and obesity class II before pregnancy had one woman (2.3%, 95%CI: 0-6.8%) from L0 ($\chi^2$1.011, $p = 0.3145$). During the current pregnancy, participants in both groups gained between 1 and 30 kg, with an average weight gain of 10.6 ± 5.9 kg (Me 10 (7; 13)) in the L1 and 11.4 ± 4.6 kg (Me 10 (8; 13)) in the L0 ($p = 0.3691$).

Hence, Vitamin K1(reference values: 0.13–1.19 μg/L), vitamin K2 MK4 (reference values: 0.1–0.86 μg/L) and vitamin K2 MK7 (reference values: 0.1–0.82 μg/L) levels were assessed, Fig. 1. The mean level of vitamin K1 was 0.15 ± 0.17 μg/L (Me 0.11 (0;0.24) in L1 and 0.29 ± 0.30 μg/L (Me 0.23 (0.15;0.30)) in L0 (95%CI: -0.2433 to -0.0367, $p = 0.0085$). Vitamin K2 MK4 level was 0.24 ± 0.27 μg/L (Me 0.19 (0.14;0.25)) in L1 and 0.29 ± 0.14 μg/L (Me 0.25 (0.20;0.37)) in L0 (95%CI: -0.1411 to 0.0411, $p = 0.2785$), and vitamin K2 MK7 level was 0.17 ± 0.13 μg/L (Me 0.15 (0.10;0.25)) in L1 and 0.26 ± 0.14 μg/L (Me 0.25 (0.16;0.36)) in L0 (95%CI: -0.1473 to -0.0327, $p = 0.0024$).

Whereas there were normal average levels of the studied vitamin K fractions, it was found that levels of vitamin K1, and vitamin K2 MK7 were statistically significant lower in the group of women with ICP (L1) than in the control group (L0). According to our findings, vitamin K1 deficiency was found in 23 (52.3%; 95%CI: 34.1–65.9%) women whose pregnancies were complicated by ICP, compared to 1 (2.3%; 95%CI: 0-6.8%) women in the control group; vitamin K2 MK4 deficiency in 3 (6.8%; 95%CI: 0-20.1%) women from the L1 and 3 (6.8%; 95%CI: 0-20.5%) from the L0; vitamin K2 MK7 deficiency in 10 (22.7%; 95% CI: 14.0–36.0%) cases in the L1 and 9 (20.5%; 95%CI: 11.7–39.8%) cases in the L0, as shown in Table 1.

Normal levels of all vitamin K fractions were found in 17 women (38.6%; 95%CI: 19.3–60.3%) from the research group, compared to 35 (79.5%; 95% CI: 60.2–88.3%) in the control group (χ^2 13.585; $p = 0.0002$).

Additionally, coagulation profiles were assessed in women, included in the study, presented in the Table 2. Besides the fact, that it was found a statistically significant difference in mean INR levels between two groups, the authors want to emphases, that there was one case of abnormal coagulation profile in ICP group (Prothrombin by Quick – 65.6%, Fibrinogen – 5.3 g/L, INR – 1.53), and one case in the control group (Prothrombin by Quick – 65.4%, Fibrinogen – 4.46 g/L, INR – 1.52).

The analysis of the method of delivery revealed that the majority of women from both groups gave birth naturally. However, vaginal births took place statistically significant more common control the group: 25 cases (56.8%; 95%CI: 45.5–76.5%) in L1 vs. 32 cases (72.7%; 95%CI: 64.0-88.3%) in L0 (χ^2 8.208; $p = 0.0042$).

Hence, we compared the total blood loss in women who gave birth naturally in both groups, whereas the total blood loss in those women who had a c-section was compared as well, as shown in Table 3. Therefore, blood loss in vaginal delivery ranged between 200 and 680 mL in L1, and 200–600 mL in L0. According to our findings, in each group there were 2 (8%: 95%CI: 0-22.7%) cases the total blood loss during vaginal delivery was greater than 500 mL. However, it should be noted that the total blood loss in vaginal delivery was statistically significant higher in group of women with ICP. Blood loss in women who had a cesarean section ranged between 500 and 800 mL in L1, and 600–800 mL in L0.

Discussions

The findings of our study demonstrate an association between intrahepatic cholestasis of pregnancy and Vitamin K1 deficiency, reinforcing the hypothesis that bile acid malabsorption in ICP disrupts the absorption of fat-soluble vitamins, including Vitamin K. Our results align

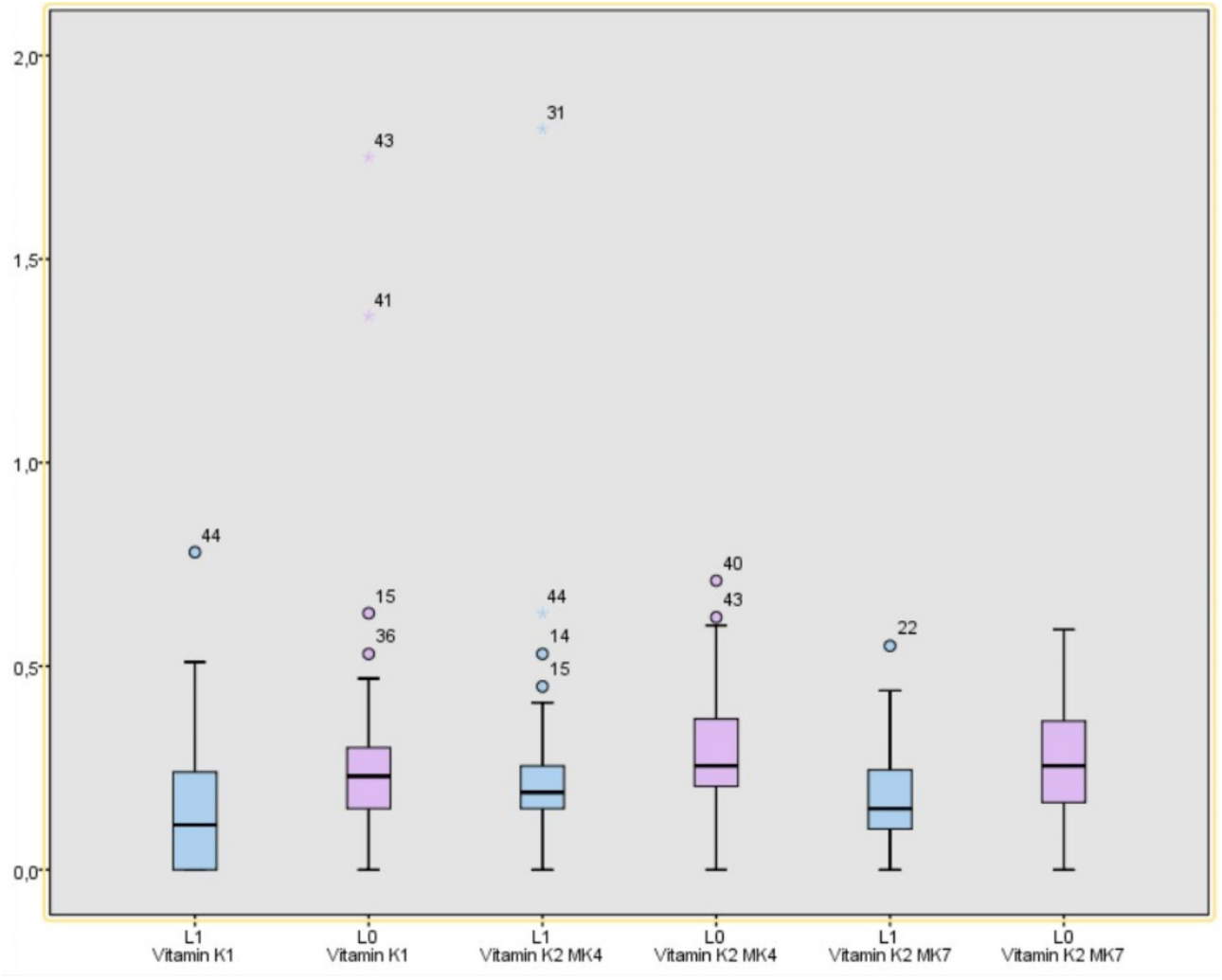

Fig. 1 The mean levels of vitamin K1, vitamin K2 MK4, and vitamin K2 MK7 in the women included in the study. Stars (*) represent extreme outliers, defined as values exceeding 3 times the interquartile range. Circles (○) represent mild outliers, defined as values exceeding 1.5 times the interquartile range but within 3 times the interquartile range. The box represents the interquartile range, with the whiskers extending to the minimum and maximum values within 1.5 times the interquartile range. The horizontal line within the box represents the median value

Table 1 Rate of hypovitaminosis K in the women included in the study

	L1 ***n*** **= 44**	**L0** ***n*** **= 44**	χ^2	***p***
	Abs. (%)			
Hypovitaminosis K1	23 (52.3%) 95% CI: 34.1–65.9%	1 (2.3%) 95%CI: 0-6.8%	25.266	< 0.0001
Hypovitaminosis K2 MK4	3 (6.8%) 95%CI: 0-20.1%	3 (6.8%) 95%CI: 0-20.5%	0.000	1.0000
Hypovitaminosis K2 MK7	10 (22.7%) 95% CI: 14.0–36.0%	9 (20.5%) 95%CI: 11.7–39.8%	0.067	0.7956

with existing data that highlights the role of impaired bile flow in ICP, leading to vitamin malabsorption and increasing the risk of postpartum hemorrhage due to coagulation defects [1, 2]. The significantly lower levels of Vitamin K1 in women with ICP in our study ($p < 0.0001$) support the need for enhanced clinical monitoring and potential Vitamin K1 supplementation in this population.

Interestingly, while Vitamin K1 deficiency was prominent, the levels of Vitamin K2 subtypes (MK4 and MK7) did not show the same pattern of deficiency across groups. This difference may be attributed to the distinct metabolic pathways and dietary sources of Vitamin K2, which is synthesized by intestinal bacteria and is found in animal products and fermented foods [19].

While vitamin K deficiency is a recognized cause of prolonged prothrombin time, there is limited research specifically evaluating vitamin K levels in pregnant women with intrahepatic cholestasis of pregnancy. Our study directly measured serum vitamin K1, K2 MK4, and K2 MK7 levels using high-performance liquid chromatography, providing precise biochemical evidence of

Table 2 Comparison of coagulation profile between ICP and control groups

	L1 ***n*** **= 44**	**L0** ***n*** **= 44**	**95%CI**	***p***
	M ± SD (Me (Q1;Q3))			
Prothrombin by Quick	111.9 ± 17.5% (Me 117 (97.8;128.5))	106.6 ± 19.1% (Me 110 (93.3;123.8))	-2.463 to 13.063	0.1783
Fibrinogen	4.6 ± 1.2 g/L (Me 4.3 (4.0;5.2))	4.2 ± 0.9 g/L (Me 4.0 (3.9;4.5))	-0.050 to 0.850	0.0805
INR	0.9 ± 0.13 (Me 0.95 (0.9;1.02))	1.02 ± 0.14 (Me 0.96 (0.9;1.11))	-0.1773 to -0.0627	0.0001

Table 3 Comparison of total blood loss based on mode of delivery in the women included in the study

	L1 ***n*** **= 44**	**L0** ***n*** **= 44**	**95%CI**	***p***
	M ± SD (Me (Q1;Q3))			
Vaginal delivery	351 ± 104 mL (Me 300 (285;425))	297 ± 87 mL (Me 280 (250;335))	3.29 to 104.71	0.0373
Cesarean section	644 ± 95 mL (Me 600 (600;700))	650 ± 90 mL (Me 600 (600;750))	-76.24 to 64.24	0.8625

vitamin K deficiency in ICP patients, rather than inferring it from coagulation tests alone. Our results suggest that Vitamin K1 deficiency is more pronounced in ICP, while Vitamin K2 (MK4) remains largely unaffected, highlighting differential effects of cholestasis on fat-soluble vitamin absorption.

Hence, INR was assessed as part of the coagulation profile, we found that most ICP patients with low vitamin K levels had INR values within the normal range. This finding supports the concept of subclinical hypovitaminosis K, where vitamin K levels are reduced, but standard coagulation tests (such as INR) remain within normal limits due to compensatory mechanisms. Previous studies have suggested that routine coagulation tests may not always detect early vitamin K deficiency because INR primarily reflects the activity of vitamin K-dependent clotting factors but does not directly indicate vitamin K reserves or early-stage deficiencies.

Our results also support findings from other studies concerning the heightened risk of postpartum hemorrhage in ICP patients. The mean blood loss during vaginal deliveries in our ICP group was statistically significantly higher than in the control group ($p = 0.0373$), suggesting that the coagulation impairments related to Vitamin K deficiency may exacerbate bleeding risks. This is consistent with the work of Arthuis C et al., who demonstrated that women with ICP are at higher risk of postpartum hemorrhage, particularly in the context of suboptimal coagulation profiles [17]. However, no blood transfusions or prolonged hospital stays were required in our cohort. These findings collectively underscore the need for vigilant monitoring of coagulation parameters in ICP patients and suggest that Vitamin K supplementation could mitigate the risk of hemorrhage in those with confirmed Vitamin K deficiencies.

While the study included both singleton and multiple pregnancies, there were 6.8% of twin pregnancies in L1, and 6.8% in L0 were multiple pregnancies (2 twin pregnancies and 1 triplet pregnancy). Given the small proportion of multiple pregnancies, statistical analysis did not reveal a significant difference in blood loss between singleton and multiple gestations within each group. However, multiple pregnancies are a known risk factor for increased postpartum blood loss, and their presence in both groups was considered when analyzing the results. To minimize potential bias, subgroup comparisons between singleton and multiple pregnancies were reviewed, but due to the limited number of cases, no separate stratified analysis was performed. Future studies with larger sample sizes of multiple pregnancies may provide further insight into their influence on vitamin K levels and coagulation parameters in ICP vs. non-ICP pregnancies.

While current clinical guidelines, such as those from the Royal College of Obstetricians and Gynaecologists, recommend monitoring coagulation profiles in women with ICP, routine Vitamin K supplementation is not universally implemented [6]. Our study's results advocate for a reconsideration of this approach, particularly in light of the association between ICP and Vitamin K1 deficiency. Hence, vitamin K supplementation may be warranted in cases where hypovitaminosis K is confirmed.

Despite the findings of our study, certain limitations must be acknowledged. First, the relatively small sample size may limit the generalizability of our results. One limitation of this study is that vitamin K levels were

measured only once between 28 and 36 weeks of gestation, rather than being assessed longitudinally at multiple time points throughout pregnancy. Since vitamin K metabolism may fluctuate due to physiological changes in pregnancy, dietary variations, and disease progression, a single measurement may not fully capture the dynamic nature of vitamin K status in intrahepatic cholestasis of pregnancy. Future studies should consider multiple time-point assessments of vitamin K levels to better characterize its trajectory in ICP and to determine the most clinically relevant gestational period for potential screening and supplementation interventions. Furthermore, the self-reported nature of dietary intake assessments introduces potential bias, as participants may have overestimated or underestimated their consumption of Vitamin K-rich foods. Future studies should aim to recruit larger, more diverse cohorts and include more objective dietary intake assessments to better quantify the relationship between dietary Vitamin K intake and serum levels in women with ICP.

Conclusion

In conclusion, our study reinforces the connection between ICP and vitamin K deficiency, particularly with vitamin K1. These findings support the need for routine monitoring of vitamin K levels in ICP patients and raise the possibility of prophylactic vitamin K supplementation as a strategy to mitigate hemorrhagic complications. Further research is warranted to explore the long-term benefits of vitamin K supplementation and its impact on both maternal and fetal outcomes in ICP.

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

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participation
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, all methods were carried out in accordance with relevant guidelines and regulations. Study registration number ISRCTN21187408 https://www.isrctn.com/ISRCTN21187408.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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