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Original Research

Evaluation of the Relationship Between Intrahepatic Cholestasis of Pregnancy and Serum Vitamin D, Folate, and Vitamin B12 Levels

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-related liver disease that occurs during the third trimester. Both maternal and fetal complications are common in pregnant women with cholestasis. The risk and severity of complications increase with higher serum bile acid levels. 25-hydroxycholecalciferol [25(OH)D3], folate, and vitamin B12 supplementation during pregnancy improves maternal and fetal outcomes. This study aimed to evaluate the association between serum 25(OH)D3, folate, and vitamin B12 levels in pregnant women with and without ICP. Data from 29 pregnant women diagnosed with ICP and 85 healthy pregnant women admitted to Izmir Atatürk Training and Research Hospital were compared. **Methods**: Izmir Atatürk Training and Research Hospital's electronic data record system was reviewed retrospectively, and vitamin D, folate, and vitamin B12 levels, which are routinely screened during pregnancy, were determined for both groups. **Results**: Contrary to previous studies, no significant differences were found between the serum vitamin D, folate, or vitamin B12 levels between pregnant women with ICP and healthy pregnant women. These values, except for folate, were below the reference range in both groups. **Conclusions**: Limited access to a healthy and balanced diet in our country, irregular use of vitamin supplements, and seasonal conditions may have influenced our results.

Keywords: intrahepatic cholestasis of pregnancy; folate; bile acid; pregnancy

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-associated liver disease, typically occurring in the third trimester [1]. In pregnant women with cholestasis, quality of life decreases due to symptoms such as pruritus, jaundice, and fat malabsorption. Although the maternal prognosis is generally favorable, poorly managed ICP can lead to preterm labor, meconium-stained amniotic fluid, and even fetal death [1,2]. Elevated bile acid (cholic acid and chenodeoxycholic acid) levels >10 µmol/L represent a valuable diagnostic finding and are in 90% of affected pregnant women. This may sometimes be the first and only laboratory finding. A study shows that serum bile acid levels exceeding 40 µmol/L increase the rate of fetal complications, which is defined as severe disease [3]. Alanine aminotransferase (ALT) is more sensitive than aspartate aminotransferase (AST) for detecting hepatocellular injury. However, no correlation exists between bile acid levels and ALT or AST levels [4].

Vitamin D deficiency during pregnancy may lead to adverse maternal and neonatal outcomes such as recurrent pregnancy loss, maternal infections, preeclampsia, gestational diabetes mellitus (GDM), preterm labor, and low birth weight [5]. Furthermore, maternal vitamin B12 deficiency during pregnancy or breastfeeding can cause neural tube defects (NTDs), developmental delay, failure to thrive, hypotonia, ataxia, and anemia [6–8].

A 2015 meta-analysis of randomized trials concluded that folic acid supplementation, when used alone or in combination with vitamins and minerals, had no clear effect on the frequency of congenital anomalies other than NTDs [9]. However, some anomalies, including cleft lip/palate, congenital heart defects, urinary tract anomalies, and congenital hydrocephalus, are considered folate-sensitive, based in part on the observation that the incidence of these conditions has decreased following the implementation of universal folic acid supplementation [10,11]. Folic acid supplementation does not appear to reduce the risk of most adverse pregnancy and neonatal outcomes, except congenital anomalies. However, the available data are of low quality and are insufficient to exclude the possibility of a small, dose-related benefit [12].

Aim

This study aimed to evaluate the association between serum 25-hydroxycholecalciferol [25(OH)D3], folate, and vitamin B12 levels in pregnant women with and without ICP.

2. Materials and Methods

Data from pregnant women admitted for delivery to the Department of Obstetrics and Gynecology at Izmir Katip Celebi University Ataturk Training and Research Hospital between 2019 and 2023, who were diagnosed with

Table 1. Comparison of demographic and clinical characteristics of the groups.

	Control group (n = 85)	Case group (n = 29)	*p*-value
Age (years), median (IQR)	30 (9)	33 (10)	0.477
Gravida, n, median (IQR)	2 (2)	2 (1)	0.874
Parity, n, median (IQR)	1 (2)	1 (2)	0.962
Additional diseases, n (%)			0.901
None	75 (88.2)	25 (86.2)	
GDM	6 (7.1)	2 (6.9)	
HT	4 (4.7)	2 (6.9)	
C/S, n (%)	42 (49.4)	18 (62.1)	0.238
BMI (kg/m^2), median (IQR)	25.7 (3.4)	27.2 (3.4)	0.180

IQR, interquartile range; n, number; GDM, gestational diabetes mellitus; HT, hypertension; C/S, cesarean section; BMI, body mass index.

ICP, as well as those selected for the control group, were reviewed retrospectively hrough the electronic data recording system and included in the study. Our hospital's electronic data record system was reviewed retrospectively, and vitamin D, folate, and vitamin B12 levels, which are routinely screened upon hospital admission for delivery, were determined for both groups. Serum 25(OH)D3, folate, and vitamin B12 concentrations (ng/mL), measured by a chemiluminescent immuno-enzymatic method, were analyzed using the Beckman Coulter DxI 800 (Beckman Coulter, Inc., Brea, CA, USA) device. The reference ranges for analytes measured in our hospital laboratory are as follows: 20–70 ng/mL for 25(OH)D3, >5 ng/mL for folate, and 200–900 ng/L (pg/mL) for vitamin B12. Although our hospital is a tertiary care center, the number of pregnant women diagnosed with ICP who deliver at our hospital is low. This has resulted in a limited sample size for our study. Data from both groups were compared statistically. Information obtained through anamnesis, such as age, gestational age, pregnancy history, type of previous birth (if any), and history of additional illnesses, was recorded in the case form. Patients younger than 18 years, those diagnosed before pregnancy, those with diseases that could alter liver enzyme levels (e.g., hepatitis B, cirrhosis), and those with anomalous fetuses were excluded from the study.

Serum bile acid levels have been categorized as follows: <10 µmol/L indicates no disease, 10–40 µmol/L indicates moderate disease, and >40 µmol/L indicates severe disease [1]. The case group was classified based on this categorization.

Prior to the study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Katip Celebi University on March 21, 2024 Approval No. 0110).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM® SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software package. Descriptive statistics were used, and quantitative variables were characterized using median (interquartile range [IQR]), and qualitative variables were expressed as percentages. Pearson's chi-square test was used for comparative analysis of qualitative variables; however, when the sample size was small (≤40), Fisher's exact test was applied. The Kolmogorov-Smirnov test was used to assess data normality. None of the variables in the study showed a normal distribution. Non-parametric continuous variables that were not normally distributed were expressed as medians and compared using the Mann-Whitney U test.

Spearman correlation analysis was performed to examine the individual correlations between bile acids and vitamin D3, folate, and vitamin B12, and the correlation coefficient (rho) was calculated. The reference ranges for analytes measured in our hospital laboratory are as follows: 20–70 ng/mL for 25(OH)D3, >5 ng/mL for folate, and 200–900 ng/L (pg/mL) for vitamin B12. A positive coefficient indicated a positive correlation (i.e., an increase in one variable corresponded to an increase in the other), whereas a negative coefficient indicates a negative correlation (i.e., an increase in one variable corresponded to a decrease in the other). A coefficient of <0.4 was considered a weak correlation; a coefficient between 0.4 and 0.7 was considered a moderate correlation; and a coefficient of >0.8 was considered a strong correlation.

A *p*-value of <0.05 was considered statistically significant for all analyses.

3. Results

The mean age of the 114 pregnant women included in the study was 29.5 years (min = 18 years, max = 42 years, median = 30 years). The mean body mass index (BMI) was 26.4 kg/m^2 (min = 16.4 kg/m^2, max = 43.1 kg/m^2, median = 25.8 kg/m^2). ICP was not detected in 85 participants (control group) but was present in 29 (case group). Among thosewith ICP, 20 had moderate cholestasis and nine had severe disease.

The comparison of the control group and the case group in terms of demographic and clinical characteristics is presented in Table 1. No significant differences were ob-

Table 2. Comparison of routine blood parameters between groups.

	Control group (n = 85)	Case group (n = 29)	*p*-value
AST (U/L), median (IQR)	17 (8)	40 (74)	<**0.001**
ALT (U/L), median (IQR)	12 (9)	32 (69)	<**0.001**
GGT (U/L), median (IQR)	24 (48)	42 (31.2)	0.547
LDH (U/L), median (IQR)	112 (53)	153 (60)	**0.003**
Bile acid (μmol/L), median (IQR)	5.8 (1.5)	17.0 (29.0)	<**0.001**
Total bilirubin (mg/dL), median (IQR)	0.37 (0.24)	0.41 (0.27)	0.827
Direct bilirubin (mg/dL), median (IQR)	0.10 (0.12)	0.12 (0.13)	0.158
Indirect bilirubin (mg/dL), median (IQR)	0.28 (0.23)	0.30 (0.26)	0.889
25(OH)D3 (ng/mL), median (IQR)	10.0 (10.5)	11.0 (11.0)	0.547
Folate (ng/mL), median (IQR)	9.0 (5.8)	8.0 (5.8)	0.747
VitB12 (pg/mL), median (IQR)	147 (104)	153 (79)	0.349

Bold *p*-values indicate statistical significance.

n, number; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transaminase; LDH, lactate dehydrogenase; 25(OH)D3, 25-hydroxycholecalciferol; VitB12, vitamin B12.

Table 3. Comparison of birth and newborn data between groups.

	Control group (n = 85)	Case group (n = 29)	*p*-value
Type of delivery, n (%)			0.220
SVD	21 (24.7)	4 (13.8)	
C/S	64 (75.3)	25 (86.2)	
Birth weight (g), median (IQR)	3235 (420)	3080 (845)	0.149
Sex of newborn, n (%)			0.314
Female	53 (62.4)	15 (51.7)	
Male	32 (37.6)	14 (48.3)	
APGAR 1 m, median (IQR)	9 (1)	9 (1)	0.723
APGAR 5 m, median (IQR)	10 (1)	10 (1)	0.900
NICU, n (%)	0 (0)	5 (17.2)	<**0.001**
IUGR, n (%)	2 (2.4)	5 (17.2)	**0.004**

Bold *p*-values indicate statistical significance.

SVD, spontaneous vaginal delivery; NICU, neonatal intensive care unit; IUGR, intrauterine growth restriction.

served between the two groups in terms of age ($p = 0.477$), gravida ($p = 0.874$), parity ($p = 0.962$), comorbidity status ($p = 0.901$), history of previous cesarean section ($p = 0.238$), or BMI ($p = 0.180$).

The comparison of the two groups with respect to routine blood tests is shown in Table 2. AST, ALT, lactate dehydrogenase (LDH), and bile acid levels were statistically higher in the case group compared to the control group ($p < 0.001$, $p < 0.001$, $p = 0.003$, and $p < 0.001$, respectively). No significant differences were observed for the other variables ($p > 0.05$).

A comparison of the two groups in terms of birth and neonatal outcomes is presented in Table 3. No statistically significant differences were found between the two groups in mode of delivery, birth weight, gender, and APGAR scores at 1 and 5 minutes. None of the neonates born to mothers without cholestasis required admission to the neonatal intensive care unit (NICU), whereas 17.2% (n = 5) of those born to mothers with cholestasis required NICU admission, this difference being statistically significant ($p < 0.001$). The intrauterine growth restriction (IUGR) rate in neonates born to mothers with cholestasis was 17.2% (n = 5), whereas the rate was only 2.4% (n = 2) in those born to mothers without cholestasis, and this difference was statistically significant ($p = 0.004$).

No correlation was observed between bile acid and vitamin D3 (Fig. 1), bile acid and folate (Fig. 2), or bile acid and vitamin B12 (Fig. 3).

A comparison of the demographic and clinical characteristics of pregnant women with moderate cholestasis (n = 20) and those with severe cholestasis is shown in Table 4. No significant differences were found between these two groups for age ($p = 1.000$), gravida ($p = 0.945$), parity ($p = 0.908$), comorbidity ($p = 0.536$), history of previous cesarean section ($p = 0.412$), or BMI ($p = 0.799$).

The comparison of these two subgroups of pregnant women with cholestasis in terms of routine blood tests is shown in Table 5. AST, ALT, and bile acid levels were significantly higher in those with severe cholestasis than in those with moderate cholestasis ($p = 0.002$, $p = 0.04$ and

Table 4. Comparison of demographic and clinical characteristics of the cholestasis groups.

	Moderate cholestasis (n = 20)	Severe cholestasis (n = 9)	*p*-value
Age (years), median (IQR)	32.5 (15)	33 (8)	1.000
Gravida (n), median (IQR)	2 (1)	2 (2)	0.945
Parity (n), median (IQR)	1 (2)	1 (2)	0.908
Additional diseases, n (%)			0.536
None	17 (85.0)	8 (88.9)	
GDM	1 (5.0)	1 (11.1)	
HT	2 (10.0)	0 (0)	
C/S, n (%)	11 (55.0)	7 (77.8)	0.412
BMI (kg/m^2), median (IQR)	27.3 (3.7)	26.4 (4.5)	0.799

HT, hypertension; BMI, body mass index.

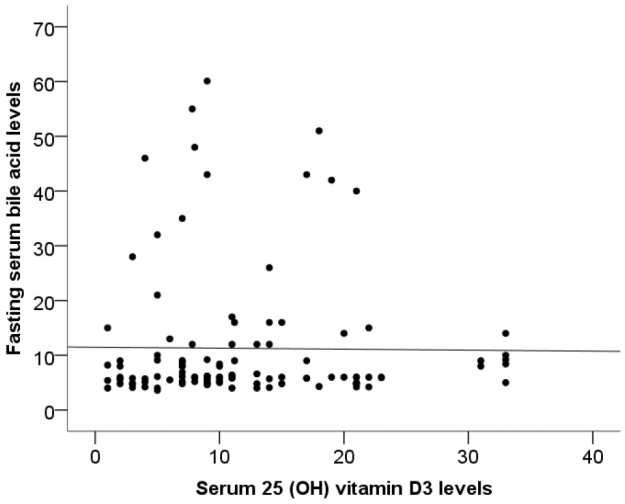

Fig. 1. Correlation between bile acid and vitamin D3 (rho = 0.058, *p* = 0.543).

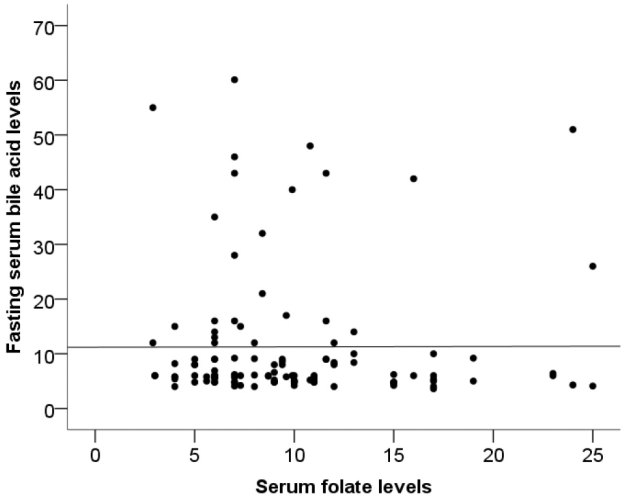

Fig. 2. Correlation between bile acid and folate (rho = –0.116, *p* = 0.218).

$p < 0.001$, respectively). Total and indirect bilirubin levels were higher in pregnant women with severe cholestasis

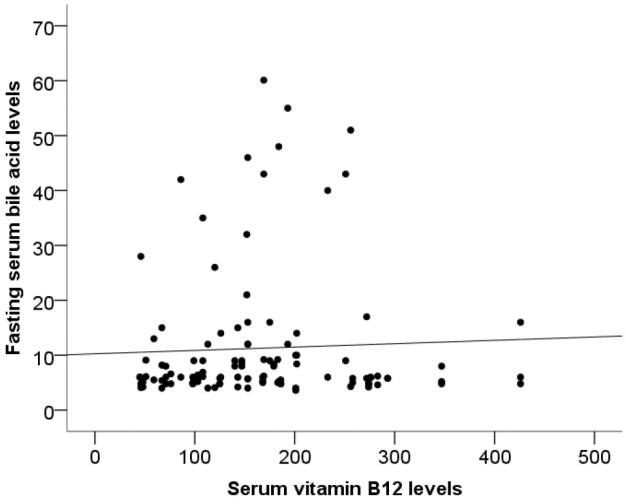

Fig. 3. Correlation between bile acid and vitamin B12 (rho = 0.039, *p* = 0.681).

than in those with moderate cholestasis ($p = 0.07$ for both). Although these values did not reach statistical significance, they approached the threshold for significance. No significant differences were observed for the other variables ($p > 0.05$).

The comparison of cholestasis subgroups with respect to birth and neonatal outcomes is presented in Table 6. No significant differences were found between the two groups in terms of mode of delivery, birth weight, gender, or APGAR scores at 1 and 5 minutes. The proportion of neonates requiring NICU admission was higher in the severe cholestasis than in the moderate group (22.2% vs. 15%), but this difference was not statistically significant ($p = 0.633$). The proportion of neonates diagnosed with IUGR was also higher in the severe cholestasis group than in the moderate cholestasis group (22.2% vs. 15%), without statistical significance ($p = 0.633$).

Table 5. Comparison of routine blood parameters between the cholestasis groups.

	Moderate cholestasis (n = 20)	Severe cholestasis (n = 9)	*p*-value
AST (U/L), median (IQR)	25.5 (34)	107.0 (71)	**0.002**
ALT (U/L), median (IQR)	20 (41)	72 (81)	**0.040**
GGT (U/L), median (IQR)	33 (39.8)	42 (28.5)	0.295
LDH (U/L), median (IQR)	136 (94)	154 (24)	0.562
Bile acid (µmol/L), median (IQR)	15 (8)	46 (10.5)	**<0.001**
Total bilirubin (mg/dL), median (IQR)	0.37 (0.26)	0.45 (0.54)	*0.070*
Direct bilirubin (mg/dL), median (IQR)	0.12 (0.13)	0.12 (0.07)	0.835
Indirect bilirubin (mg/dL), median (IQR)	0.24 (0.27)	0.33 (0.34)	*0.070*
25(OH)D3 (ng/mL), median (IQR)	11.1 (9.5)	12.5 (10.6)	0.694
Folate (ng/mL), median (IQR)	7.6 (5.9)	9.9 (6.8)	0.532
VitB12 (pg/mL), median (IQR)	152.5 (84)	184 (81)	0.127

Bold *p*-values indicate statistical significance. Italicized *p*-values indicate a trend toward statistical significance.

Table 6. Comparison of birth and newborn data between the cholestasis groups.

	Moderate cholestasis (n = 20)	Severe cholestasis (n = 9)	*p*-value
Type of delivery, n (%)			1.000
SVD	3 (15.0)	1 (11.1)	
C/S	17 (85.0)	8 (88.9)	
Birth weight (g), median (IQR)	3200 (909)	2920 (585)	0.317
Sex of newborn, n (%)			0.245
Female	12 (60.0)	3 (33.3)	
Male	8 (40.0)	6 (66.7)	
APGAR 1 m, median (IQR)	9 (1)	9 (1)	0.594
APGAR 5 m, median (IQR)	10 (1)	10 (1)	0.594
NICU, n (%)	3 (15.0)	2 (22.2)	0.633
IUGR, n (%)	3 (15.0)	2 (22.2)	0.633

4. Discussion

Serum 25(OH)D3 levels below 20 ng/mL (50 nmol/L) are defined as vitamin D deficiency, whereas levels between 21–29 ng/mL (52.5–72.5 nmol/L) are defined as vitamin D insufficiency [13]. Although there is no consensus on the optimal serum 25(OH)D3 level, it is generally accepted that levels of at least 20 ng/mL are sufficient for bone health healthy individuals [14]. In a study conducted in healthy pregnant women in Turkey, the mean serum 25(OH)D3 level was 11.5 ng/mL, which falls within the range of vitamin D deficiency [15]. Even after supplementation with either a single dose (200,000 IU) or a daily dose (800 IU) of vitamin D, only a small proportion of women achieved satisfactory levels [16]. Since our study was conducted on a socioeconomically middle-class population, malnutrition was considered a possible factor. In accordance with the guidelines of the Ministry of Health of the Republic of Turkey, each pregnant woman received supplementation starting in the second trimester: 1200 IU/day of vitamin D, 400 microgram/day folate, and 4 microgram/day vitamin B12.

Recent studies highlight significant associations between vitamin D deficiency in pregnant women and serious pregnancy complications, such as preeclampsia and GDM [17]. In our study, we investigated the relationship between vitamin D levels and ICP.

In a study of 33 pregnant women, Wikström Shemer and Marschall [18] observed lower 25(OH)D3 levels in women with ICP compared with healthy pregnant women. Kuoppala *et al*. [19] reported a decrease in 25(OH)D3 levels during the third trimester in healthy pregnant women, with even lower levels in those with ICP. In another study from Turkey, a total of 80 pregnant women were examined and 25(OH)D3 levels were also lower in pregnant women with ICP [20]. In our study, 25(OH)D3 levels were low in all pregnant women and no significant difference was found between those with ICP and healthy controls. Although adequate vitamin supplementation was provided, factors such as inadequate and imbalanced nutrition, poor adherence to supplementation, and seasonal variation may have affected our results. In addition to recent studies, Wolski *et al*. [21] in Poland reported that some mutations in vitamin D receptor genes play a role in hepatobiliary homeostasis and may be associated with ICP. The vitamin D receptor FokI polymorphism was significantly more frequent in women with ICP [21]. Folic acid and vitamin B12 are essential factors for fetal growth [22]. In a study of 11,549 women, Yuan *et al*. [23] suggested that low folic acid levels increased the risk of preeclampsia, ICP, GDM, and SGA. The same study

also reported that low vitamin B12 levels were associated with preeclampsia but did not significantly increase ICP or SGA [23]. In our study, no significant differences were observed between serum folic acid and vitamin B12 levels between groups. As such, larger randomized controlled trials are warranted.

As reported in previous studies with a larger sample sizes, vitamin D supplementation in pregnant women may help prevent ICP formation. However, in our study, despite supplementation with vitamin D, folate, and vitamin B12, levels were lower in both groups compared with the general population. These findings highlight the extent of vitamin deficiency in the study population and are relevant from a public health perspective. Cavoretto and Viganò [24] also addressed the same issue, noting the high prevalence of vitamin D deficiency in the community and recommending that vitamin D supplementation be included in routine obstetric care. National guidelines are warranted.

Limitations

Our study has several limitations, including the small sample size, its retrospective design, uncertainty regarding the exact season in which vitamin levels were measured, and the high prevalence of vitamin deficiencies in the study population. A major limitation of our study is the inability to accurately predict the season at the time of vitamin D measurement. Although standard-dose vitamin supplementation was prescribed for all pregnant women, adherence could not be confirmed. Further prospective studies with larger sample sizes are needed in this area.

5. Conclusions

Unlike previous studies, no significant differences were observed between ICP and serum 25(OH)D3, folate, and vitamin B12 levels. These values were also low in healthy pregnant women. Factors such as limited access to a healthy and balanced diet, as well as inadequate use of vitamin supplements may have contributed to these findings. The limited number of relevant studies in the literature restricted our assessment. Additional prospective studies on this topic are warranted.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

YA designed and performed the research study. YA and MS analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Prior to the study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Katip Celebi University on 21.03.2024, with decision number 0110. The study was carried out in accordance with the guidelines of the Declaration of Helsinki. All participants in the study were required to sign an informed consent form.

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Conflicts of Interest

The authors declare no conflicts of interest.

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