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Vitamin D Levels in Women with Intrahepatic Cholestasis of Pregnancy

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Abstract

Objective: To evaluate the relationship between plasma 25-hydroxyvitamin D (25(OH)D) levels in Intrahepatic Cholestasis of Pregnancy (ICP) patients.

Method: Thirty-one ICP patients and 31 healthy controls took part in the study. At the time of diagnosis, a venous blood sample was drawn from each of the participants for the measurement of plasma analytes including 25(OH)D.

Results: Maternal plasma 25(OH)D levels in the ICP group (46 ng/ml) trended to be lower than those in the control group (52 ng/ml, p = 0.09). Patients in the ICP group with plasma ALT levels > 200 U/l had significantly lower levels of 25(OH)D (38 ng/ml) than patients with plasma ALT levels < 200 U/l (54 ng/ml, p = 0.032) and healthy controls (52 ng/ml, p = 0.041).

Conclusion: ICP patients have significantly lower levels of plasma 25(OH)D when their ALT levels are elevated (> 200 U/l).

Keywords

Vitamin D levels, Intrahepatic cholestasis of pregnancy, 25(OH)D

Introduction

Intrahepatic Cholestasis of Pregnancy (ICP) is a reversible state of cholestasis unique to pregnancy. This condition manifests mainly during the third trimester, with generalized itching and elevated plasma levels of bile acids and Alanine Transaminase (ALT), and resolves spontaneously in the early postpartum period [1]. In the absence of laboratory tests, itching can be the only presenting symptom and tends to recur in 40-60% of subsequent pregnancies [2].

Elevation of bile acids and aminotransferases are the main biochemical alterations in ICP. Total Bile Acid (TBA) concentrations vary widely depending on the method of measurement, fasting status, population studied, and gestational age at diagnosis [3]. The suggested TBA cut-off value for the diagnosis of ICP is 10-14 mmol/l. When the TBA level exceeds 40 mmol/l, fetal mortality and morbidity rates increase [4]. ICP severity can be staged based on TBA levels, with mild disease in women with TBA levels < 40 mmol/l and severe disease in women with TBA levels > 40 mmol/l [5].

Since many factors including genetic variations, diet, hormonal changes and the environment influence the development of ICP, the etiology of the disease is still unclear. Elevated steroid hormone levels may trigger the disorder, as the incidence of ICP is increased in twin pregnancies and in women with a history of ICP who used oral contraceptives. Alterations in the reductive metabolism of progesterone have been suggested as the main etiologic factor for ICP [6].

Although ICP is a relatively benign condition for the mother, the condition is associated with a higher frequency of adverse perinatal outcomes such as preterm

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labor and delivery, unexplained fetal demise, fetal distress, and meconium staining [7]. Although the pathogenesis of the fetal complications in ICP is not clear, bile acids or their toxic metabolites may play a major role [8].

Currently, the hydrophilic bile acid Ursodeoxycholic Acid (UDCA) is the most effective treatment option for ICP. Both maternal and fetal outcomes are improved with UDCA treatment [9].

Vitamin D is a fat-soluble steroid hormone responsible for calcium homeostasis and skeletal mineralization [10]. Vitamin D may also play a role in pregnancy, given the high prevalence of pregnancy complications in women with aberrant vitamin D levels [11].

As a result of Ultraviolet B (UVB) irradiation of the skin, vitamin D is generated from its precursor 7-dehydrocholesterol. Vitamin D is then converted in the liver to 25-hydroxyvitamin D (25(OH)D), the main circulating and storage form of the vitamin. 25(OH)D readily crosses the placenta and constitutes the vitamin D pool of the fetus. 25(OH)D is further hydroxylated to its active form, calcitriol ($1,25\text{-}(OH)_2D_3$) in the maternal and fetal kidneys [12]. Recent data indicates that conversion of vitamin D has been also shown to occur in the brain, immune system, the gut and blood vessels [13].

Recently, it was shown that vitamin D regulates critical steps in bile acid detoxification and transportation by the way of nuclear receptor FXR inhibition [14,15]. Hence, we postulated that maternal blood 25(OH)D levels could be of major importance in the diagnosis of ICP. To test this hypothesis, we investigated maternal plasma 25(OH)D levels in women with ICP and healthy pregnant controls.

Methods

The study is organized as a case-control study. The study population included 31 women with ICP and 31 healthy pregnant controls who were admitted to the perinatology department of Ege University Hospital between December 2011 and March 2012, December 2012 and March 2013, or December 2013 and March 2014. Women in the control group are selected from healthy and normal weight pregnant women between 18-40 ages without any known disease, especially no liver disease trait. The study protocol was approved by the Ethics Committee of Ege University. After obtaining informed written consent from each of the participants, obstetric and general health data were collected. Having any additional disease or high liver enzyme levels were exclusion criteria for selecting healthy pregnant women. All of the participants in the study group were between the ages of 18-40 and were in the third trimester of a singleton pregnancy. Diagnoses of ICP were made based on elevated bile acids (> 10 mmol/l) and pruritus that spontaneously normalized after delivery and an absence of other diseases impairing liver function. Other problems with the liver that occur in pregnancy should be considered by the treating clinician. These include preeclampsia, the HELLP syndrome, and acute fatty liver of pregnancy. Furthermore, other causes of hepatitis, like hepatitis viruses, cancer and certain medications, should also be considered. All of the participants between 25-34 gestational weeks were treated with betamethazon, and all women with ICP were treated with 1 g/day of UDCA until delivery. Multivitamin supplements including 500 IU vitamin D were prescribed for all of the participants during routine pregnancy exams.

A blood sample was drawn from each participant at the time of enrollment in the study. Following centrifugation at 4000 rpm for 10 min, the plasma was stored at -80 °C. Plasma 25(OH)D levels were measured by High Performance Liquid Chromatography (HPLC) at the biochemistry department of Ege University.

Statistical analysis was performed using the Statistical Package for Social Sciences version 14.0 (SPSS Software, Chicago, IL, USA). Because continuous variables were well-distributed, comparisons of quantitative data were performed using Student's t-test. The confidence interval was 95%, and statistical significance was set at $p < 0.05$.

Results

There were no significant differences between the two groups according to maternal age, gravida, parity, number of alive children and gestational week at diagnosis.

Thrombocyte counts and ALT (Alanine Amino-

Table 1: Biochemical and blood count results of groups.

	Women with ICP (mean ± SD)	Healthy controls (mean ± SD)	p value
Hemoglobin (g/dl)	12.06 ± 1.09	12.02 ± 1.13	0.88
Hematocrit (%)	36.10 ± 3.43	35.29 ± 2.94	0.36
Leukocyte (K/ul)	9.97 ± 3.23	10.17 ± 2.20	0.78
Thrombocyte count (fL 10^9/L)	268.9 ± 85.8	226.5 ± 59.7	0.037
ALT (U/L)	227.9 ± 221.8	18.7 ± 8.5	< 0.001
AST (U/L)	136.8 ± 123.4	27.4 ± 12.3	< 0.001
Bilirubine total (mg/dl)	1.38 ± 1.29	0.43 ± 0.22	0.003
LDH (IU/L)	381.6 ± 185.7	263.1 ± 54.7	0.004

transferase) (227.9 ± 221.8 to 18.7 ± 8.5), AST (Aspartate Aminotransferase) (136.8 ± 123.4 to 27.4 ± 12.3), LDH (Lactate Dehydrogenase) (381.6 ± 185.7 to 263.1 ± 54.7) and bilirubin levels (1.38 ± 1.29 to 0.43 ± 0.22) were significantly higher in women with ICP than normal controls. Table 1 summarizes the blood count results of groups.

Participants were assigned to 3 strata based on their plasma 25(OH)D levels: severe deficiency: < 10 ng/ml; insufficiency: 11-32 ng/ml; adequate: > 32 ng/ml [16]. Table 2 and Table 3 summarize the differences in vitamin D status between the groups.

Although the average 25(OH)D level was lower in the ICP group (46 ng/ml) than the control group, the difference was not statistically significant (p = 0.09). In the ICP group, women with elevated ALT levels (> 200 U/l, indicative of liver damage) had significantly lower levels (38.5 ng/ml) of 25(OH)D than women with normal ALT levels (p = 0.032).

In the ICP group, the incidence of women high ALT levels (> 200 U/l) was 45% (14 of 31). Vitamin D insufficiency in ICP group was evident in patients (30%) and severe deficiency in only 1 patient. Six of these 9 patients and 1 patient with severe vitamin D deficiency were in the highly elevated ALT group as well (> 200 U/l). The incidence of vitamin insufficiency in patients with ICP and elevated ALT levels (> 200 U/l) was 43% (6 of 14) where as incidence of severe deficiency in this group was 7% (1 of 14).

Discussion

In comparison to healthy controls, women with ICP had a lower average plasma level of 25(OH)D; however, the difference was not statistically significant (p = 0.09). When the ICP study group was divided into two subgroups based on plasma ALT levels (cut-off at 200 U/l), a statistically-significant difference occurred both between the subgroups and between the high ALT subgroup and the healthy controls.

Table 2: Comparison of 25-hydroxyvitamin D levels between groups.

	Women with ICP	Healthy controls	p value
25(OH) vit D (ng/ml), mean ± s.d.	48 ± 4.56	52 ± 3.26	0.09

Table 3: Comparison of 25-hydroxyvitamin D between subgroups of ICP.

	Women with ICP and higher ALT levels (> 200 U/l)	Women with ICP and lower ALT levels (< 200 U/l)	p value
25(OH) vit D (ng/ml), mean ± s.d.	38 ± 2.4	54 ± 3.26	0.032

Vitamin D has cellular and metabolic functions apart from its classical functions in bone and calcium homeostasis. Fat soluble vitamins such as vitamin A and D repress their intestinal absorption in order to protect from possible toxicity [17]. Based on the rate-limiting function of vitamin D in bile acid metabolism, we postulated that vitamin D levels in patients with ICP could be a critical parameter in prenatal diagnosis and follow-up.

There are only a few studies on this topic. The first study was published in 1986 by Kuoppala and colleagues. This study found no significant differences between the ICP group and control group with respect to the plasma levels of 24,25-$(OH)_2D_3$, 1,25-$(OH)_2D_3$ and their metabolites. However, 25(OH)D levels were significantly higher at the beginning of the study and decreased at delivery [18]. The limitations of this study are the size of the study groups (10 ICP patients and 12 healthy controls), the heterogeneity of the participants, and lack of attention to seasonal variation.

The other study evaluating vitamin D levels in women with ICP was published by Wikstrom Shemer and colleagues in 2010 [19]. This study included 22 women with ICP and 11 healthy controls. The authors evaluated vitamin D levels by measuring 1,25-$(OH)_2D_3$ in order to avoid seasonal variation. Significantly lower serum 1,25-$(OH)_2D_3$ levels were found in the women with ICP compared to the healthy controls. The authors emphasized that the mean levels of 1,25-$(OH)_2D_3$ in women with ICP, ~75 ng/l, might not impress in routine clinical practice as normal values for adults range around 10-50 ng/l. The main limitation of this study is the use of 1,25-$(OH)_2D_3$ as a surrogate for vitamin D; because of its tight metabolic regulation and short half-life, 1,25-$(OH)_2D_3$ is not considered to be a valid indicator of vitamin D status. Due to its dependence on parathormone levels, 1,25-$(OH)_2D_3$ levels can be low, normal, or high in cases of vitamin D deficiency. Instead, 25(OH)D is the most reliable surrogate for vitamin D, valid as an indicator for both endogenously-produced vitamin D and ingested vitamin D [20]. The one caveat is that the seasonal variation in 25(OH)D levels makes this metabolite unreliable for studies with continuous blood sampling over 3 months.

Because of this seasonal variation, we performed our study only during the winter for three successive years. The difference in mean 25(OH)D levels which we observed between the ICP patients and healthy controls may have reached statistical significance if we have used larger group sizes. However, there was a remarkable subgroup in our study. The ICP patients with remarkably elevated ALT levels had significantly lower levels of 25(OH)D than the ICP patients with mildly elevated ALT levels and the normal controls. Although this sub-

group was not the target of our study, the implications are clear: insufficient vitamin D levels coupled with liver damage could negatively impact fetal wellbeing.

Could administration of oral vitamin D drugs and increasing contact with sunlight especially in middle-east countries reduce the incidence of ICP? This is an interesting question and needs further studies to be answered.

Intrahepatic cholestasis of pregnancy is an unfortunate disease that cannot be well predicted. Vitamin D levels may play a role in determining the well being of the fetus in these patients. With statistically-insignificant differences in 25(OH)D levels between ICP patients and healthy controls, it is impossible to conclude whether vitamin D plays a role in the pathogenesis of ICP. Our findings may show the importance of vitamin D on early determination of fetal distress, especially in women with elevated ALT levels. Maternal serum 25(OH)D levels can be used as a fetal distress indicator in cholestatic pregnancies if this issue is supported by larger numbers of studies with postnatal outcomes of the babies.

Disclosure

The authors have nothing to disclose.

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