Vitamin D and intrauterine growth restriction: a cross-sectional study

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ABSTRACT

Vitamin D plays a critical role in maintaining bone health, regulating calcium homeostasis, and modulating immune responses. During pregnancy, it supports fetal bone mineralization and proper placental function. Deficiency in vitamin D can impair calcium absorption, disrupt placental function, and lead to adverse outcomes like intrauterine growth restriction (IUGR). Despite abundant sunlight, vitamin D deficiency is highly prevalent in countries like Indonesia. This study evaluates the relationship between maternal vitamin D levels and IUGR risk while considering additional factors like placental function and calcium metabolism. In this cross-sectional study, 60 patients, 30 with IUGR and 30 without, were included. Vitamin D levels were measured using the enzyme-linked immunosorbent assay, and statistical analysis compared the IUGR and non-IUGR groups. Baseline data [age, body mass index (BMI), placental inflammation, preeclampsia status] were analyzed using Chi-square and Mann-Whitney tests. Statistical significance was set at $p<0.05$, using IBM SPSS 24 (IL, USA). A significant association between maternal factors and IUGR was found. Higher BMI (≥25 kg/m²) and placental inflammation were more prevalent in the IUGR group. Vitamin D deficiency was strongly linked to IUGR, with 90% of IUGR cases showing deficient levels. The IUGR group had significantly lower vitamin D levels (13.84 ng/mL *versus* 25.93 ng/mL), with a strong inverse correlation (r=-0.86, p=0.00). This study shows a strong link between maternal vitamin D deficiency and increased IUGR risk, emphasizing its role in placental function and fetal development.

Introduction

Vitamin D plays a pivotal role in maintaining bone health, regulating calcium homeostasis, and acting as an immunomodulator that influences immune responses, including vaccine efficacy, through antigen-presenting cells such as dendritic cells.[1,2] Vitamin D is essential for calcium metabolism during pregnancy to support fetal bone mineralization.[3] Vitamin D deficiency in pregnant women can impair calcium absorption, affect placental function, and hinder fetal bone development.[4,5] This issue remains significant even in tropical countries like Indonesia, where sun exposure is abundant, yet the prevalence of vitamin D deficiency remains alarmingly high.[6]

Intrauterine growth restriction (IUGR) occurs when the fetus fails to reach its growth potential, influenced by various maternal, fetal, and placental factors.[7,8] Vitamin D deficiency during pregnancy can trigger IUGR by disrupting calcium metabolism, impairing placental function, and restricting fetal bone growth. Fetuses affected by IUGR are at higher risk for

low birth weight (LBW), compromised immune function, and long-term health complications.[9] Although several studies have demonstrated a link between vitamin D deficiency and IUGR, the findings have been inconsistent across different populations.[10,11]

This study aims to evaluate the relationship between maternal vitamin D status and the risk of IUGR while also examining other risk factors associated with it, such as placental function and calcium metabolism.

Materials and Methods

Subjects and data collections

This study is a cross-sectional study involving 60 patients, 30 patients with IUGR, and 30 patients without IUGR. Vitamin D levels were measured using the enzyme-linked immunosorbent assay method. Statistical analysis was conducted to assess the differences in vitamin D levels between the IUGR group and the non-IUGR group. All statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS 24, IL, USA). This study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 773/UN4.6.4.5.31/PP36/2023).

Statistical analysis

Baseline data [age, body mass index (BMI), placenta inflammation, preeclampsia status, IUGR status, and vitamin D] were descriptively summarized and analyzed with Chi-square. Bivariate analysis between vitamin D level and IUGR status was analyzed using the Mann-Whitney test. Significant values were determined at $p<0.05$. All statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS 24, IL, USA).

Results

This study demonstrates a significant association between maternal factors and IUGR. Higher BMI (≥25 kg/m²) and placental inflammation were significantly more prevalent in the IUGR group, with 73.30% and 93.30% of cases, respectively (Table 1). Vitamin D deficiency was notably linked to IUGR, as 90% of those with IUGR had deficient vitamin D levels (<20 ng/mL), while none of the non-IUGR group had deficiencies (Table 2).

The mean vitamin D levels were significantly lower in the IUGR group (13.84 ng/mL) compared to the non-IUGR group (25.93 ng/mL), p=0.00, indicating a strong connection between low vitamin D and IUGR (Table 3). Additionally, a strong inverse correlation (rho=-0.86, p=0.00) between vitamin D levels and IUGR occurrence further supports this finding (Table 4).

In conclusion, maternal obesity, placental inflammation, and vitamin D deficiency are key risk factors for IUGR, emphasizing the importance of adequate vitamin D levels during pregnancy to reduce IUGR risk.

Table 1. Subjects' characteristics.

Variable	Intrauterine growth restriction, n (%)		p-value
	Without	With	
Age			
<20 or >35 years	8 (26.70)	6 (20.00)	0.54
20-35 years	22 (73.30)	24 (80.00)	
Parity			
Primipara	9 (30.00)	8 (26.70)	0.12
Multipara	21 (70.00)	22 (73.30)	
Body mass index			
<25 kg/m	16 (53.30)	8 (26.70)	0.04*
≥25 kg/m	14 (46.70)	22 (73.30)	
Placental inflammation			
Without	27 (90.00)	1 (6.70)	0.00*
With	3 (10.00)	27 (93.30)	
Preeclampsia			
Without	29 (56.90)	22 (43.10)	0.01*
With	1 (11.1)	8 (88.90)	

Table 2. Vitamin D level among patients.

Vitamin D serum	Intrauterine growth restriction, n(%)		Total
	Without	With	
Deficiency (<20 ng/mL)	0 (0.00)	27 (90.00)	27 (45.00)
Insufficiency (20-29 ng/mL)	25 (83.30)	3 (10.00)	28 (46.70)
Normal (>30 ng/mL)	5 (16.70)	0 (0.00)	5 (8.30)

Table 3. Bivariate analysis of vitamin D among patients

Variable	Without IUGR Mean (SD)	IUGR Mean (SD)	p
Vitamin D (ng/mL)	25.93 (3.75)	13.84 (4.44)	0.00*

IUGR, intrauterine growth restriction; *Mann Whittney test, significant.

Table 4. Correlation between Vitamin D and intrauterine growth restriction.

Variable	rho	p
IUGR	-0.86	0.00*

*Spearmann correlation, significant.

Discussion

In this study, analysis of maternal age indicated no significant differences between groups. This suggests no difference in IUGR risk between pregnant women younger than 20 or older than 35 and those aged 20-35. This differs from findings in India, where mothers under 20 and over 35 years of age had a higher risk of IUGR. Additionally, mothers over 35 had a greater chance of delivering an IUGR baby compared to younger women.[12-14]

This study found a relationship between BMI and IUGR. Low maternal BMI is associated with impaired placental function and nutrient transfer, restricting fetal growth. Pathophysiological factors include oxidative stress, placental insufficiency, and altered hormonal environments, leading to insufficient oxygen and nutrients for fetal development.[15-18]

In this study, parity was found to have no significant difference between the groups, suggesting that the number of previous pregnancies did not impact the incidence of IUGR. This aligns with research showing that rather than parity, placental function plays a critical role in IUGR pathophysiology. Mechanistically, impaired nutrient and oxygen delivery to the fetus due to placental insufficiency, irrespective of parity, remains a key factor in IUGR development.[19-21]

A significant difference in serum vitamin D levels was observed between the two groups, with the IUGR group having significantly lower levels. The study showed a negative correlation between vitamin D levels and IUGR ($p<0.001$; $r=-0.866$), meaning lower vitamin D levels increased the risk of IUGR. This finding is consistent with the idea that pregnant women with adequate vitamin D had a reduced risk of IUGR. Women with vitamin D deficiency were more likely to have IUGR.[9,22,23]

Vitamin D deficiency has been linked to various adverse pregnancy outcomes, including IUGR, preterm birth, LBW, and neonatal hypocalcemia.[24,25] Research has also demonstrated that vitamin D deficiency increases the risk of placental inflammation, which can impair placental function and lead to poor pregnancy outcomes.[26,27] The role of vitamin D in placental development and function is crucial, influencing placental implantation, immune response, and glucose regulation for fetal growth. Vitamin D signaling components, like the vitamin D receptor and enzyme CYP27B1, further support its vital role in placental function and fetal development.[28,29]

Conclusions

This study highlights the significant association between maternal vitamin D deficiency and increased IUGR risk. The results demonstrated that 90% of IUGR cases had deficient vitamin D levels, significantly lower than the non-IUGR group, with a mean difference of 13.84 ng/mL *versus* 25.93 ng/mL. The strong negative correlation ($r=-0.86$, $p<0.001$) between vitamin D levels and IUGR risk emphasizes the critical role of adequate maternal vitamin D levels in fetal development. Furthermore, vitamin D's involvement in placental function, immune regulation, and nutrient transfer underlines its importance in reducing adverse pregnancy outcomes. Therefore, ensuring optimal vitamin D levels during pregnancy could prevent IUGR and improve overall pregnancy outcomes.

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