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Maternal vitamin D deficiency in early pregnancy and perinatal and long-term outcomes

Soo Bin Lee [a], Sang Hee Jung [a,**], Hanna Lee [a], Sae Mi Lee [a], Jae Eun Jung [a], Nari Kim [a], Ji Yeon Lee [a,*]

[a] Department of Obstetrics and Gynecology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea

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ABSTRACT

Background: Vitamin D deficiency is common in pregnant women. Some studies have linked vitamin D deficiency to obstetric complications such as gestational hypertension, gestational diabetes, and preterm birth. Therefore, the objective of this study is to investigate the potential impact of vitamin D deficiency during pregnancy on both perinatal and long-term outcomes.

Methods: In this retrospective study, conducted between 2017 and 2021, we analyzed the data of 1079 singleton pregnant women with no medical or surgical complications prior to pregnancy. We evaluated obstetric and perinatal outcomes, as well as neurodevelopmental outcomes using Bayley-III tests, Gross Motor Function Measure, or chart review.

Results: The maternal serum vitamin D level in the first trimester was 18.2 ± 9.0 ng/mL. Vitamin D deficiency (<20 ng/mL) was found in 308 (62.0%) women in the first trimester, of which 288 women (26.7%) were in the very deficient group (<10 ng/mL). There were no differences in maternal age, body mass index, and previous preterm birth between the group with vitamin D < 10 ng/mL and ≥10 ng/mL group. There were also no differences in the rates of gestational hypertension, gestational diabetes, and preterm birth between the two groups, except for the rate of preterm birth before 37 weeks of gestation, which was significantly higher in the very deficient group (adjusted odds ratios [aOR] = 7.78, 95%CI [2.23–27.12], p = 0.001). In the very deficient group, the risk of developmental delay was also higher (aOR = 4.28, 95%CI [1.40–13.05], p = 0.011).

Conclusions: This is the first study to analyze the effects of maternal vitamin D deficiency during pregnancy on both long-term developmental outcomes and perinatal prognosis. Vitamin D deficiency, defined as a level lower than 10 ng/mL in the first trimester, may increase the risk of preterm birth and developmental delay in children.

1. Introduction

Vitamin D is a well-known unique essential nutrient that is closely related to calcium and bone metabolism. Additionally, there is

* Corresponding author. Department of Obstetrics and Gynecology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam 13496, South Korea.

** Corresponding author. Department of Obstetrics and Gynecology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam 13496, South Korea.

E-mail addresses: aa2346@chamc.co.kr (S.H. Jung), lenna@hanmail.com (J.Y. Lee).

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growing evidence suggesting that vitamin D plays a role in immune regulation by decreasing pro-inflammatory mediators and increasing anti-inflammatory cytokines. Furthermore, vitamin D metabolism undergoes alterations during pregnancy to provide an optimal environment for the fetus to grow. Specifically, maternal calcitriol and vitamin D-binding protein increase two-fold during pregnancy to aid in calcium absorption, resulting in an increased requirement for vitamin D [1]. Hence, vitamin D insufficiency in pregnant women could potentially affect the fetus.

Vitamin D plays a crucial role not only during the gestational stage but also before it, given its potential influence on fertility. Colonese et al. suggest that vitamin D may have implications for the risk of polycystic ovary syndrome (PCOS), endometriosis, and ovarian reserve [2]. In addition, Lagana et al. highlight how VDR-mediated signaling pathways and vitamin D levels can impact ovarian and breast cancers, as well as women's response to menopausal status [3]. Consequently, it is becoming increasingly evident that adequate nutritional and vitamin supplementation, particularly vitamin D, significantly affects women's health [4,5].

Fortunately, vitamin D can be easily synthesized by the body with the help of ultraviolet B radiation. However, despite its easy synthesis, vitamin D deficiency is common across the globe, especially in pregnant women. According to a 2016 systematic review, maternal vitamin D deficiency was reported in 64% of America, 57% of Europe, 46% in the Eastern Mediterranean, 87% in Southeast Asia, and 83% in the Western Pacific [6]. Due to its high prevalence, there has been a recent increase in interest in the effects of vitamin D deficiency on maternal and neonatal outcomes worldwide.

A multitude of previous studies have established a strong correlation between low vitamin D levels during pregnancy and various adverse outcomes, including pre-eclampsia, fetal growth restriction, gestational diabetes mellitus (GDM), placental implantation disorders, preterm birth, small for gestational age (SGA), and an increased risk of cesarean section [7,8]. Moreover, vitamin D serves a crucial function as a neuroprotective factor in neonates and significantly influences child neurodevelopment [9]. Some studies have gone as far as to suggest potential links between maternal vitamin D deficiency and attention deficit hyperactivity disorder [10,11], as well as autism spectrum disorder [12,13]. Nevertheless, the precise pathophysiological mechanisms through which low vitamin D affects fetal brain development remain elusive, and the current body of research in this area is limited, exhibiting inconsistencies and heterogeneity among findings. These disparities and variations among studies can be attributed to factors such as small sample sizes, variations in the timing of blood collection, and differences in outcome measures.

Therefore, this study examined vitamin D levels in a substantial sample of singleton pregnant women during the first trimester, excluding those with any medical and/or surgical conditions. Subsequently, we investigated the potential association between vitamin D deficiency and obstetric, neonatal, and perinatal neurodevelopmental outcomes.

2. Materials and methods

2.1. Patients and study design

This retrospective study includes 1079 singleton pregnant women who underwent a blood test to measure 25-hydroxyvitamin D (25(OH)D), the primary circulating form of vitamin D and the most reliable indicator of an individual's vitamin D status. The blood samples were collected during the first trimester of pregnancy at CHA Bundang Medical Center, and the women subsequently gave birth at the same hospital between 2017 and 2021. To ensure a focused analysis, cases with maternal medical or surgical comorbidities before the 25(OH)D test were excluded from the study.

2.2. Ethics approval

The institutional review boards (IRB) of CHA Bundang Medical Center approved this study (IRB no.: 2020-07-076, dates of approval: Aug. 17, 2020). Informed consent was waived for this retrospective cohort study as it involved the analysis of medical records. The IRB of the research institute approved the study and determined that obtaining informed consent was not necessary. The study methods strictly adhered to the relevant guidelines and regulations set forth by the IRB at this institution.

2.3. Serum 25(OH) D levels measurement

The level of 25(OH) D was measured as follows: Blood samples were collected from the forearm vein using 5.0 mL BD Vacutainer serum tubes, followed by centrifugation at 3500*g* for 10 min at 4 °C to obtain the serum. The resulting serum samples were immediately transferred and stored in aliquots at −80 °C until biochemical and hormonal analysis could be performed. Serum 25(OH)D levels were quantified using a commercially available kit and chemiluminescence immunoassay, according to the manufacturer's protocol (LIAISON 25 OH Vitamin D TOTAL Assay REF 310600). Consistent with previous studies, we defined vitamin D deficiency as a serum 25(OH)D level less than 20 ng/mL and classified severe deficiency as a level less than 10 ng/mL [14].

2.4. Review of medical records

We reviewed maternal demographics, clinical presentations, laboratory examinations, ultrasound assessments, and obstetrical and perinatal outcomes of all included cases. To evaluate short-term birth outcomes, we investigated composite morbidities, defined as the occurrence of at least one of the following: pulmonary hypertension, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), intracranial hemorrhage (ICH), retinopathy of prematurity (ROP), meconium aspiration syndrome (MAS), and necrotizing enterocolitis (NEC). We evaluated SGA using the standard

described in a previous report [15].

We investigated the long-term neurodevelopmental outcomes after one year of corrected age. Developmental delay was diagnosed when babies did not reach their developmental milestones at the expected times. We evaluated this using Bayley-III tests and/or Gross Motor Function Measure in our study. Test scores indicating a deviation below the normal development reference were classified as developmental delay. If a developmental screening test was not performed, we checked the medical records to describe the child's developmental status. For instance, the medical staff performed brief developmental screening and administered age-appropriate questionnaires related to language, thinking, behavior, and movement. Any variations or concerns were carefully recorded. We considered a child's development to be within the normal range if they reported no difficulties in meeting their academic obligations.

2.5. Statistical analysis

Statistical analysis was conducted using SPSS software (version 23.0; SPSS Institute, Chicago, IL, USA). Categorical variables were analyzed using the Chi-square test, and continuous variables were analyzed using the Student t-test. Additionally, a multivariable analysis was performed, incorporating maternal age, body mass index (BMI), and method of conception as covariates while analyzing neonatal morbidity and mortality. Statistical significance was set at a p-value of less than 0.05.

3. Results

A total of 1079 healthy singleton pregnant women were enrolled in this study. The mean maternal serum 25(OH)D level during the first trimester was 18.2 ± 9.0 ng/mL. In the first trimester, 308 women (28.6%) were found to have vitamin D deficiency (<20 ng/mL). Among them, 288 women (26.7%) were categorized in the severely deficient group, with a 25(OH)D level of less than 10 ng/mL in the first trimester.

Table 1 shows the clinical characteristics of the study population. There were no significant differences in maternal age, BMI, and history of preterm birth between the group with vitamin D levels less than 10 ng/mL and the group with levels greater than or equal to 10 ng/mL.

Table 2 presents a comparison of the obstetric outcomes between the two groups. Compared with the vitamin D ≥ 10 ng/mL group, there were no significant differences in the rates of gestational hypertension, GDM, placenta previa, and cesarean delivery. However, the rate of preterm birth before 37 weeks of gestation (adjusted odds ratio [aOR] = 7.78, 95%CI [2.23–27.12], p = 0.001) was significantly higher in the group with vitamin D < 10 ng/mL, even after adjusting for maternal age, BMI, prior preterm birth, nulliparity, method of delivery, and method of conception.

One case of fetal death was reported in the vitamin D < 10 ng/mL group. However, no significant differences were observed in birth weight (3140 ± 490 vs. 3159 ± 456 g), small for gestational age (2.1 vs. 2.1%), Apgar score at 5 min < 7 (0.7 vs. 0.3%), or NICU admission (10.8 vs. 18.7%) between the group with vitamin D < 10 ng/mL and ≥10 ng/mL group (Table 3). Moreover, there was no evidence of a difference in the incidence of ICH, ROP, MAS, neonatal jaundice, TTN, RDS, BPD, pulmonary hypertension, and NEC between the two groups.

We assessed the risk of developmental delay and cerebral palsy in 1049 babies. In some cases, two diagnostic methods were used to diagnose developmental delay, but there was no discrepancy between the results of the two tests. The risk of developmental delay (aOR = 4.28, 95%CI [1.40–13.05], p = 0.011) was higher in the vitamin D < 10 ng/mL group after adjusting for maternal age, BMI, prior preterm birth, nulliparity, method of delivery, and method of conception.

3.1. Comment

3.1.1. Principal findings

Our study concludes that vitamin D deficiency in the first trimester, defined as a level lower than 10 ng/mL, may increase the risk of

Table 1
Clinical characteristics of the study population.

	Vit D ≥ 10 ng/mL (N = 791)	Vit D < 10 ng/mL (N = 288)	p-value
Maternal age (y)	34.9 ± 4.1	34.5 ± 4.1	0.088
Height (cm)	161.8 ± 5.3	161.3 ± 4.8	0.459
BMI			
BMI in pre-Pregnancy	22.7 ± 4.0	22.9 ± 3.7	0.739
BMI in term	27.0 ± 3.9	27.0 ± 3.6	0.981
Nulliparity	567 (71.8)	186 (64.6)	0.023[a]
Prior preterm birth	27 (3.4)	13 (4.5)	0.397
Method of conception			0.003[a]
Spontaneous	217 (60.1)	62 (77.5)	
Ovarian stimulation	10 (2.8)	2 (2.5)	
In vitro fertilization	134 (37.1)	16 (20.0)	

Data are presented in mean ± SD or number of cases (percentage).
Vit D, vitamin D; BMI, body mass index; GA, gestational age.
[a] statistically significant difference (p < 0.05).

Table 2
Obstetric outcomes.

	Vit D <10 ng/mL (N = 288)	Vit D ≥10 ng/mL (N = 791)	p-value	Adjusted odds ratio (95% CI)[a]	p-value
GA at delivery (wk)	38.7 ± 1.9	38.7 ± 1.6	0.908		
Cesarean delivery	137 (47.6)	406 (51.3)	0.275		
Preterm birth					
23–27 + 6 week	2 (0.7)	2 (0.3)	0.290		
23–31 + 6 week	4 (1.4)	10 (1.3)	1.000	6.73 (1.03–43.98)	0.047
23–33 + 6 week	7 (2.4)	13 (1.6)	0.396	4.16 (0.76–22.75)	0.100
23–36 + 6 week	21 (7.3)	35 (4.4)	0.060	7.78 (2.23–27.12)	0.001 [b]
Pregnancies with					
Preeclampsia	3 (3.3)	10 (2.6)	0.722	2.98 (0.69–12.84)	0.142
GDM	9 (9.8)	44 (11.4)	0.652	0.65 (0.24–1.73)	0.384
Placenta previa	1 (1.1)	2 (0.5)	0.475	11.34 (0.46–278.82)	0.137
Cerclage	3 (3.3)	15 (3.9)	1.000	1.26 (0.25–6.31)	0.778
Antenatal admission due to preterm labor	8 (8.7)	27 (7.0)	0.578	1.85 (0.67–5.10)	0.236

Data are presented in mean ± SD or number of cases (percentage).
Vit D, vitamin D; GA, gestational age; GDM, gestational diabetes mellitus; [a] All outcomes were adjusted for maternal age, body mass index, prior preterm birth, nulliparity, method of delivery and method of conception.
[b] statistically significant difference ($p < 0.05$).

Table 3
The effect of vitamin D deficiency on perinatal outcomes and postnatal morbidities.

	Vit D <10 ng/mL (N = 288)	Vit D ≥10 ng/mL (N = 791)	p-value	Adjusted odds ratio (95% CI)[a]	p-value
Birth weight (gram)	3140 ± 490	3159 ± 456	0.595		
SGA	6 (2.1)	17 (2.1)	0.947		
Apgar score at 5min < 7	2 (0.7)	2 (0.3)	0.290		
NICU admission	27/251 (10.8)	127/680 (18.7)	0.004[c]	0.57 (0.25–1.32)	0.190
Fetal death	1 (0.4)	0 (0.0)	0.270		
Morbidity during hospitalization	(N = 286)	(N = 788)			
Intracerebral hemorrhage	0 (0.0)	2 (0.3)	1.000		
Retinopathy of prematurity	2 (0.7)	8 (1.0)	1.000	2.46 (0.18–33.73)	0.501
Meconium aspiration syndrome	4 (1.4)	3 (0.4)	0.086		
Neonatal jaundice	42 (14.7)	120 (15.2)	0.826	0.44 (0.17–1.20)	0.108
Transient tachypnea of newborn	12 (4.2)	44 (5.6)	0.366	0.34 (0.04–2.69)	0.306
Respiratory distress syndrome	6 (2.1)	17 (2.2)	0.953	2.82 (0.45–17.61)	0.268
Bronchopulmonary dysplasia	1 (0.3)	1 (0.1)	0.462		
Pulmonary hypertension	0 (0.0)	4 (0.5)	0.579		
Necrotizing enterocolitis	4 (1.4)	5 (0.6)	0.258	7.33 (0.33–164.0)	0.209
Composite morbidity [b]	56 (19.6)	182 (23.1)	0.220	0.56 (0.26–1.20)	0.139
Morbidity at present	(N = 274)	(N = 775)			
Developmental delay	21 (7.7)	33 (4.3)	0.028[c]	4.28 (1.40–13.05)	0.011[c]
Bayley-III tests	7/14 (50)	6/37 (16.2)	0.027[c]		
GMFM	6/11 (54.5)	16/38 (42.1)	0.510		
Chart review	9/273 (3.3)	20/772 (2.6)	0.542		

Data are presented in mean ± SD or number of cases (percentage).
SGA, small for gestational age; GMFM, gross motor function measure; [a] All outcomes were adjusted for maternal age, body mass index, prior preterm birth, nulliparity, method of delivery and method of conception; [b] Composite morbidity during hospitalization includes neonatal sepsis, intracerebral hemorrhage, retinopathy of prematurity, meconium aspiration syndrome, neonatal jaundice, transient tachypnea of newborn, respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary hypertension and necrotizing enterocolitis.
[c] statistically significant difference ($p < 0.05$).

preterm birth and developmental delay in children.

3.1.2. Review in the context of what is known

This study showed that severe vitamin D deficiency is associated with a significantly increased risk of preterm birth. This aligns with a recent Cochrane review and previous studies, which have reported how vitamin D supplementation can lower the rates of preterm birth and birth weight below 2500 g [16]. Several animal studies involving rats have demonstrated the critical role of vitamin D in successful implantation and decidualization. Ashour et al. demonstrated that vitamin D supplementation in rats reduced inflammation and oxidative stress, leading to improved uterine receptivity and endometrial decidualization during implantation. Furthermore, vitamin D supplementation contributed to the reduction of uterine myometrial contraction, potentially preventing preterm labor and enhancing uterine receptivity by increasing uterine blood flow [17]. Hence, ensuring an adequate supply of vitamin D during implantation for women with vitamin D deficiency may be crucial in mitigating the risk of preterm birth.

Recent large population-based cohort studies have consistently emphasized the connection between vitamin D deficiency and chronic inflammation [18]. Consequently, a plausible hypothesis arises that vitamin D deficiency during pregnancy might play a role in chronic intrauterine inflammation, such as chorioamnionitis, which is recognized as a contributing factor to late preterm birth. Nonetheless, given the current limitations of the available evidence, further studies are imperative to validate and reinforce our hypothesis.

Our study specifically delved into the connection between low vitamin D levels and preterm birth at various stages, including very early (before 28 weeks of gestation), early (between 28 and 34 weeks of gestation), and late (between 34 and 37 weeks of gestation) preterm birth. Interestingly, our findings revealed a more robust association between vitamin D deficiency and late preterm birth (defined as birth between 34 and 37 weeks of gestation) as opposed to very early or early preterm birth. Notably, previous studies have proposed that vitamin D deficiency might influence chronic inflammation, offering a plausible explanation for this particular finding. According to Gervasi et al. late spontaneous preterm birth was associated with elevated levels of interferon gamma-inducible protein-10, which is known to be associated with chronic chorioamnionitis [19]. Furthermore, recent large population-based cohort studies have consistently emphasized the connection between vitamin D deficiency and chronic inflammation [18]. Based on these findings, we could hypothesize that vitamin D deficiency during pregnancy might lead to chronic intrauterine inflammation, such as chorioamnionitis, which is associated with late preterm birth. However, further studies are needed to support our hypothesis given the current limitations of the evidence.

In addition, our study observed that severe maternal vitamin D deficiency did not worsen perinatal outcomes, but it did increase the risk of long-term developmental delays in children. This finding is similar to the previous large-scale prospective study by Voltas et al. also known as the ECLIPSE study. According to this study, vitamin D deficiency during the first trimester was associated with lower scores on the BSID-III scale and poorer cognitive and language skills in children compared to those with normal vitamin D levels [20]. Other studies have even suggested a connection between low vitamin D levels and the development of schizophrenia or autism in offspring [21,22]. Vitamin D deficiency may play a crucial role, particularly during the early stages of gestation, as it coincides with fetal nervous system development, such as neurogenesis and myelination processes, which occur in the first and second trimesters [23].

Although the precise mechanism leading to developmental delay in offspring of mothers with severe vitamin D deficiency in early pregnancy remains unclear, it is possible that vitamin D's role in anti-inflammatory function is involved. Poorly controlled maternal systemic or intrauterine acute inflammation in early pregnancy or chronic maternal systemic or intrauterine inflammation that began early in pregnancy and persisted chronically may affect fetal organ development, particularly the brain. Research has shown that elevation of C-reactive protein, tumor necrosis factor (TNF)-α, interleukin (IL)-8, and intercellular adhesion molecule-1 in the first month of pregnancy was associated with lower IQs in children at 10 years of age [24]. Moreover, placental inflammation followed by elevation of TNF-α or IL-8 has been associated with adverse outcomes, such as cerebral palsy [25,26]. Additionally, maternal chronic inflammation with or without infection is usually subclinical and has been associated with various neonatal organ injuries, including the brain [27–30]. Chronic intrauterine inflammation can lead to fetal brain injury through a direct insult to astrocytes, oligodendrocytes, and neurons, or as secondary injury via microglial cell activation, subsequently resulting in the secretion of pro-inflammatory cytokines that damage surrounding cells [31,32]. The lack of vitamin D may interfere with its anti-inflammatory role, which could cause developmental delays in the offspring of mothers with severe vitamin D deficiency in early pregnancy.

Meanwhile, uterine receptivity refers to the period when the uterus has adequately differentiated and is ready to initiate implantation, requiring sufficient blood supply at this stage [33]. The active form of vitamin D is critical to the process of decidualization, which is a key step in implantation [34]. Uterine tissue responds to vitamin D through biological binding to the vitamin D receptor [35]. A review article highlighted the significance of vitamin D during implantation. The expression of components of the vitamin D system in the maternal decidua and fetal trophoblast promotes invasion of the extravillous trophoblast and establishes early pregnancy [36]. Maternal serum vitamin D levels are known to have a positive effect on the implantation rate of in vitro fertilization [37,38]. One essential mechanism through which vitamin D affects early pregnancy implantation and embryonic development is the regulation of endothelial cell function. Vitamin D influences endothelial cell function by regulating nitric oxide production, which is important for vascular dilation and blood flow [39]. Vitamin D also regulates the expression of genes involved in angiogenesis or the formation of new blood vessels. Studies have shown that vitamin D can increase the expression of pro-angiogenic factors, such as vascular endothelial growth factor, which is essential for the growth and development of placental blood vessels [40,41]. Furthermore, Vitamin D can suppress the production of reactive oxygen species (ROS), which can contribute to maternal-placental malperfusion. Vitamin D can regulate the expression of genes involved in antioxidant defense mechanisms, such as superoxide dismutase, glutathione peroxidase, and catalase. These enzymes help to neutralize ROS and prevent oxidative damage to cells [42]. Additionally, vitamin D can modulate calcium homeostasis, which is important for maintaining cellular redox balance. Calcium signaling is involved in the regulation of many antioxidant enzymes, and vitamin D can help to regulate this process [43]. It is possible that the developmental delay of offspring in mothers with severe vitamin D deficiency in early pregnancy was caused by the blockade of this positive role of vitamin D.

Lastly, our study found that severe maternal vitamin D deficiency (<10 ng/mL) during the first trimester of pregnancy was not related to a higher risk of adverse pregnancy outcomes, such as pre-eclampsia and GDM. This finding contrasts with recent prior studies that emphasize the role of vitamin D in reducing pregnancy-related complications [16]. For example, Rostami et al. conducted a study on a large group of low-risk pregnant women and found that adequate vitamin D supplementation can reduce pre-eclampsia by 60% and GDM by 50% [44]. However, the exact pathophysiology of vitamin D in preventing these adverse pregnancy outcomes remains unknown, and studies have provided inconclusive results. This may be due to the lack of standardized universal guidelines for the timing of vitamin D-level tests during pregnancy, leading to variations in test timing. Furthermore, heterogeneous influencing factors of vitamin D, such as ethnicity, body mass index, latitude, and smoking, may have contributed to the inconsistent findings in

these studies.

3.1.3. Clinical applications

Vitamin D deficiency is common in pregnant women and may be linked to pregnancy complications, especially preterm birth and offspring's neurodevelopmental delay. Vitamin D supplementation should be considered before or during early pregnancy in women with severe vitamin D deficiency.

3.1.4. Strengths and limitations

This study has several strengths. First and foremost, to the best of our knowledge, this is the first study to investigate the potential link between vitamin D deficiency in pregnant women and neurodevelopmental delays in their offspring. Second, this study focused on Asian women, a population that has been relatively underrepresented in previous research. Specifically, women in East Asia regions such as Korea, Japan, and China often avoid excessive sunlight exposure, making vitamin D deficiency a significant concern. By examining this cohort, we have established a foundation for gaining a better understanding of the pathophysiology of severe maternal vitamin D deficiency during pregnancy and its potential impact on obstetric outcomes.

This study has some limitations. First, we have yet to confirm the concentration of various substances, including serum calcium, phosphorus, calcitonin, and parathyroid hormone, which are associated with vitamin D metabolism in maternal blood. Second, we could not evaluate developmental delays using an identical method for all children. Third, to support our hypothesis, it would be necessary to conduct further analysis on chronic inflammation and oxidative stress in tissues such as the amniotic fluid, placenta, and umbilical cord.

4. Conclusions

In conclusion, this is the first study to show the effects of maternal vitamin D deficiency in early pregnancy on long-term neurodevelopmental outcomes in offspring. Lower than 10 ng/mL of maternal serum Vitamin D in the first trimester may increase the risk of late preterm birth and developmental delay in children. Vitamin D supplementation should be considered before or during early pregnancy in women with severe vitamin D deficiency.

Condensation

Severe vitamin D deficiency during the first trimester of pregnancy may increase the risk of preterm birth and developmental delay in children.

Heliyon at a glance

A. Why was this study conducted?

Vitamin D deficiency is prevalent among pregnant women and has been associated with pregnancy complications. However, its precise impact on fetal brain development remains uncertain, and studies have yielded conflicting results, possibly due to limited sample sizes and variations in outcome measures. Therefore, the primary objective of this study was to explore the potential influence of vitamin D deficiency during pregnancy on both perinatal and long-term outcomes.

B. What are the key findings?

Vitamin D deficiency in the first trimester, defined as a level lower than 10 ng/mL, may increase the risk of preterm birth and developmental delay in children.

C. What does this study add to what is already known?

This study contributes valuable evidence to the existing knowledge, indicating that vitamin D deficiency during pregnancy may have adverse effects on both perinatal and long-term outcomes. Furthermore, it emphasizes the significance of closely monitoring vitamin D levels in pregnant women and considering potential vitamin D supplementation to prevent deficiencies and associated complications.

Author contribution statement

Soo Bin LEE: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Sang Hee JUNG: Conceived and designed the experiments; Analyzed and interpreted the data.

Hanna LEE; Sae Mi LEE; Jae Eun JUNG; Na Ri kim: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Ji Yeon Lee: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed

reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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