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Original article

Severe vitamin D deficiency in the first trimester is associated with placental inflammation in high-risk singleton pregnancy

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SUMMARY

Background & aims: Vitamin D deficiency during pregnancy is a worldwide epidemic. This study aimed to identify whether vitamin D deficiency in early pregnancy is associated with placental inflammation in high-risk pregnancy.

Methods: This study comprised 23,396 women who provided serum samples in the first trimester for vitamin D analysis from January 2015 to December 2016. Among them, 2648 women with high-risk pregnancy underwent placental pathologic examination. Women were divided into placental inflammation positive (PIP) and placental inflammation negative (PIN) groups based on placental pathology. Multivariate logistic regression was used to evaluate the relationship between vitamin D levels and placental inflammation.

Results: We found that severe vitamin D deficiency in early pregnancy was associated with placental inflammation. Maternal vitamin D levels were significantly lower in the PIP group than those in the PIN group ($P = 0.025$). Compared with the highest quartile of vitamin D levels, risk for placental inflammation was significantly higher in women with extremely low vitamin D levels (<5th percentile; $P = 0.012$). The effect estimate was slightly decreased but still significant ($P = 0.027$) after adjusting for maternal age, gestational age at birth, birth weight, infant sex, and sample collection season. In addition, compared with the PIN group, the incidences of adverse neonatal outcomes, including sepsis (0.5% vs 2.4%) and fetal intrauterine infection (5.7% vs 15.6%), were significantly higher in the PIP group than that in the PIN group ($P < 0.001$).

Conclusions: Severe vitamin D deficiency in the first trimester is a risk factor for placental inflammation in high-risk pregnancy.

1. Introduction

Currently, intrauterine infection, which is frequently polymicrobial in nature [1], has become a significant problem. In pregnancy, it is linked to chorioamnionitis [2] and funisitis [3], which is associated with a range of pregnancy-related complications, including neonatal pneumonia and sepsis [4].

Vitamin D has been recognized for its key role in calcium homeostasis and bone mineralization. In recent studies, vitamin D deficiency has been found to be associated with increased risk of chronic inflammatory disorders, including allergic disorders [5], infections [6], autoimmune disorders [7], cardiovascular disease [8], and even cancer [9]. The nutritional forms of vitamin D include

Abbreviations: VDR, vitamin D receptor; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; ICP, intrahepatic cholestasis of pregnancy; PROM, premature rupture of membranes; PIP, placental inflammation positive; PIN, placental inflammation negative; LPS, lipopolysaccharide; IUGR, intrauterine growth restriction.

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ergocalciferol and cholecalciferol. Vitamin D is released into the circulation and transported by vitamin D–binding protein to the liver, where it is converted by vitamin D-25-hydroxylase (CYP2R1) into 25-hydroxyvitamin D (25[OH]D, calcidiol). The circulating 25(OH)D level is the best indicator of vitamin D nutritional status. Nevertheless, 25(OH)D requires further activation by a second hydroxylation step catalyzed by enzyme 25(OH)D-1-α-hydroxylase (CYP27B1) to generate 1,25-$(OH)_2D_3$ (calcitriol, the most active vitamin D metabolite). The placenta has been identified as a major site for the conversion of 25(OH)D to 1,25-$(OH)_2D_3$ [10,11].

The definition of vitamin D deficiency is controversial. Globally, the general consensus for deficiency is serum 25(OH)D level < 25 nM qualify [12], but the US Institute of Medicine (IOM) [13] and US Endocrine Society [14] defined serum 25(OH)D levels below 30 nM and 50 nM, respectively as vitamin D deficiency. Pregnant women with serum 25(OH)D levels ≥50.00 nM, 49.99 to 27.50 nM, and <27.50 nM are considered as vitamin D sufficient, insufficient, and deficient, respectively. These values are based on cutoff points that have been most commonly used in previous studies of pregnant women [15,16]. Vitamin D deficiency is a worldwide epidemic, with the prevalence is estimated to be 26%–84% in the general women [17] and 18%–84% in pregnant women [17], suggesting that vitamin D deficiency may begin in the womb (16). Maternal vitamin D deficiency has been linked to pregnancy complications, including preeclampsia [18,19], preterm birth [20], and intrauterine growth restriction [21], which may promote adverse neonatal outcomes, such as increased future risk of hypertension [22], enteritis [23], asthma [24], and impaired neurodevelopment [25]. Meanwhile, intrauterine/placental inflammation also has been linked to the abovementioned pregnancy-related complications [26] and adverse neonatal outcomes [27], suggesting the possibility of an association between maternal vitamin D deficiency and intrauterine/placental inflammation. Previous reports on the association between vitamin D deficiency and placental function were mostly based on animal studies and showed that vitamin D could inhibit placental inflammation by activating the vitamin D receptor (VDR)/nuclear factor kappa B pathway [28–30], but the evidence is lacking in humans [31,32]. It has been demonstrated that nutritional and environmental exposure during early pregnancy may influence fetal growth and development. Therefore, the objective of this study was to explore the association between vitamin D deficiency in early pregnancy and placental inflammation.

2. Materials and methods

2.1. Study population

In this retrospective study, pregnant women who underwent prenatal physical examination in the first trimester and delivered at the International Peace Maternity and Child Health Hospital from January 2015 to December 2016 were eligible for inclusion. The exclusion criteria were as follows: multiple pregnancy, missing values in medical records, and vitamin D level assessed after 13 weeks of gestation. We chose the first trimester level of vitamin D as the study time-point for the following reasons. First, nutrition during early pregnancy may have profound effects on both maternal and neonatal health [33]; second, the level of serum vitamin D was less likely, or to a lesser extent, to be influenced by the pregnancy itself; Third, the results, if any, may provide better evidence for early intervention during early pregnancy to reduce the risk for adverse pregnancy and neonatal outcomes.

Clinical (obstetric and neonatal) data were obtained from the medical record database. Initially, the data of 36,297 mother–infant pairs were collected; then, the following data were excluded: 894 twin pregnancies, 5595 women with incomplete medical records, 1157 women without vitamin D results, and 4895 women without first trimester vitamin D results. Ultimately, 23,396 mother–infant pairs were included. Among them, 2648 women with the following high-risk factors underwent placental pathologic examination: preterm delivery before 34 weeks of gestation, clinically suspected or confirmed chorioamnionitis, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membranes (PROM), and dystocia.

The characteristics of the study population are shown in Fig. 1. All conditions were diagnosed according to clinical protocols and defined using the International Classification of Diseases, 10th Revision, Clinical Modification.

2.2. Vitamin D level assessment and classification

Maternal fasting blood samples were collected at the first antenatal visit (9–13 weeks of gestation), transferred to hospital laboratory, which is certified by China National Accreditation Service for Conformity Assessment, then centrifuged to obtain the serum, which was stored at −20 °C until assayed. Quantitative analysis of vitamin D was performed using chemiluminescence microparticle immunoassay in an Architect I2000SR automatic analyzer (Abbott Diagnostics) with a standard curve following standard clinical procedures by two qualified inspectors. The detection range was 2.00 nM–400.00 nM. The intra- and interassay coefficients of variation were <5%.

As we mentioned above in introduction part, according to the international universal standard serum 25(OH)D levels of ≥50.00 nM, 49.99 to 27.50 nM, and <27.50 nM in pregnant women were reclassified as vitamin D sufficient, insufficient, and deficient [15,16]. Also, with consideration of the potential racial and geographical

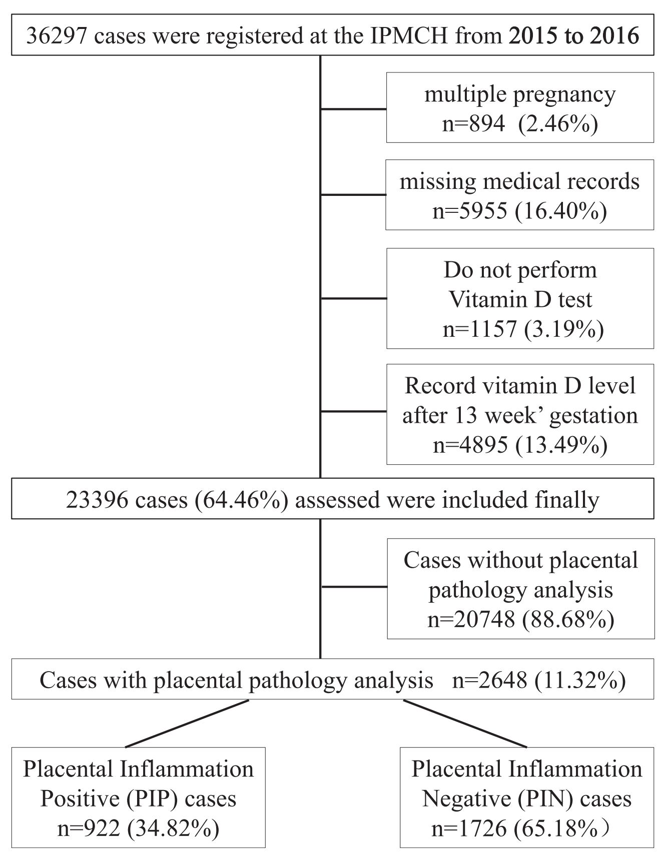

Fig. 1. Flow chart of protocol used to select the study cases.

differences between our study and studies in other countries [34,35], we also perform additional analysis by classifying all the 23,396 study woman, based on the bottom 5% ($<P_5$), middle 70% (P_5–P_{75}), and top 25% (P_{75}–P_{100}) vitamin D levels into severe deficient, relatively insufficient, and absolutely sufficient, respectively.

2.3. Placental pathologic examination

All placentas from women with high-risk pregnant factors were transferred to the pathology department for macro- and microscopic analyses, following standard protocols [36]. Briefly, placenta tissues were fixed in 4% paraformaldehyde and processed as sections that were cut to 3–5-μm thickness and hematoxylin & eosin staining. Placental inflammatory lesions were evaluated via histologic examination of 2 membrane rolls, 2 cross-sections of the cord, and 3 blocks of the placental disk. Blinded to clinical data, the placenta slides were reviewed by a single qualified pathologist. The placental inflammation positive (PIP) was defined if there was any of the following pathologic conditions: decidualitis, villositis, chorioamnionitis, chorionic plate inflammation, umbilical vasculitis, or umbilical cord inflammation. Placentas without any of these inflammatory lesions were defined as the placental inflammation negative (PIN) group.

2.4. Statistical analysis

Data were presented as median and interquartile range (IQR) for continuous variables with non-normal distribution, and as frequency and percentage for categorical variables. The normality distributions were checked through the shape of histograms and with Kolmogorov–Smirnov test. The chi-square test was used for categorical variables. The Mann–Whitney U test was used to comparing vitamin D level between PIN and PIP group, and between infant with and without placental pathology.

Multivariate logistic regression analysis was performed to assess the relationship between maternal vitamin D level and placental inflammation. We tested the confounders for each model outcome and selected or excluded covariates based on the confounding plausibility or change in effect estimate of the variable of interest, and the reduction of residual variance of the model. There was no adjustment in model 1; model 2 was adjusted for maternal age; model 3 was model 2 plus adjustment for gestational age at birth, birth weight, infant sex, and sample collection season; model 4 was model 3 plus adjustment for GDM, PIH, ICP, and PROM.

We further investigated the risk for placenta inflammation using restricted cubic splines model with seven knots at the 5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles. All statistical analyses were performed using SAS version 9.2 software (SAS Institute Inc) and R statistical software version 3.03 (package rms) with 2-sided P values of <0.05 considered to be statistically significant.

2.5. Ethical statements

This study was performed in accordance with relevant guidelines and regulations. Ethical approval for this project was granted by the Ethics Committee of the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University.

3. Results

3.1. Clinical characteristics

Compared with infants without placental pathology, infants with placental pathology had a significantly greater proportion of Apgar score <7 at 1 min (0.54% vs 3.13%), preterm birth (3.46% vs 20.84%), respiratory distress syndrome (0.06% vs 0.76%), wet lung (0.94% vs 7.25%), hyperbilirubinemia (5.36% vs 12.16%), neonatal pneumonia (0.19% vs 0.79%), neonatal sepsis (0.07% vs 1.13%), and fetal intrauterine infection (1% vs 9.1%) ($P < 0.001$) (Table 1). In cases with placental pathology, which represented specified high-risk pregnancies, maternal vitamin D levels before 13 weeks of gestation were much lower correspondingly ($P = 0.003$).

We compared maternal and neonatal characteristics and outcomes between the PIP and PIN groups (Table 2). The incidence of very early preterm birth (delivery before 31 weeks of gestation) was significantly increased in the PIP group than in the PIN group (1.3% vs 3.1%; $P < 0.01$), whereas the proportion of preterm birth at 34–36 weeks of gestation was significantly decreased in the PIP group (16.6% vs 6.6%; $P < 0.01$). These results were related to different causes of premature delivery in each gestational age group: delivery before 31 weeks of gestation was almost always spontaneous, whereas delivery at 34–36 weeks of gestation was almost always iatrogenic prematurity. This was further confirmed by an increased incidence of pregnancy-induced hypertension (11.3% vs 3.6%; $P < 0.001$), intrahepatic cholestasis of pregnancy (7.3% vs 0.3%; $P < 0.001$), and caesarean section (52.3% vs 36.4%;

Table 1
Neonatal characteristics and outcomes according to the availability of placental pathology.

	Infants without placental pathology (n = 20,748)	Infants with placental pathology (n = 2648)	*P*-value
Maternal characteristics			
Age(y)			0.004
<25	583 (2.8)	59 (2.2)	
25–29	8853 (42.7)	1135 (42.9)	
30–34	8405 (40.5)	1137 (42.9)	
>35	2907 (14.0)	317 (12.0)	
Gestational age(w)			<0.001
28–31	6 (0.0)	52 (2.0)	
31^{+1}–34	30 (0.1)	151 (5.7)	
34^{+1}–36^{+6}	680 (3.3)	348 (13.1)	
≥37	20,032 (96.5)	2097 (79.2)	
Gestational Diabetes Mellitus (GDM)	2224 (10.7)	360 (13.6)	<0.001
Pregnancy-induced Hypertension (PIH)	385 (1.9)	228 (8.6)	<0.001
Intrahepatic Cholestasis of Pregnancy (ICP)	25 (0.1)	129 (4.9)	<0.001
Premature Rupture of Membranes (PROM)	2 (0.01)	28 (1.1)	<0.001
Neonatal characteristics			
Birth weight (kg)	3.38 ± 0.40	3.11 ± 0.65	<0.001
Male	10,694 (51.54)	1370 (51.73)	0.850
Cesarean	8806 (42.44)	1239 (46.79)	<0.001
Apgar scores<7 at 1 min	113 (0.54)	83 (3.13)	<0.001
Preterm birth	717 (3.46)	552 (20.84)	<0.001
Respiratory distress syndrome	12 (0.06)	20 (0.76)	<0.001
Wet lung	194 (0.94)	192 (7.25)	<0.001
Hyperbilirubinemia	1113 (5.36)	322 (12.16)	<0.001
Neonatal pneumonia	40 (0.19)	21 (0.79)	<0.001
Neonatal sepsis	15 (0.07)	30 (1.13)	<0.001
Fetal intrauterine infection	213 (1.03)	242 (9.14)	<0.001
Maternal vitamin D levels (<13w) (median, Quartiles)	42.1 (30.8,53.9)	41.6 (20.1,52.4)	0.003
Vitamin D testing seasons			0.019
Spring (March–May)	5148 (24.8)	730 (27.6)	
Summer (June–August)	4947 (23.8)	607 (22.9)	
Autumn (September–November)	5331 (25.7)	643 (24.3)	
Winter (December–February)	5322 (25.7)	668 (25.2)	

Data are expressed as n (%).Chi-square test and Student t-test were used to evaluate the data.

Table 2
Maternal and neonatal characteristics and outcomes by presence and absence of placental inflammation lesion.

Characteristics	PIN group (n = 1726)	PIP group (n = 922)	*P*-value
Maternal characteristics			
Gestational age(w)			<0.001
28–31	23 (1.3)	29 (3.1)**	
31^{+1}–34	104 (6.0)	47 (5.1)	
34^{+1}–36^{+6}	287 (16.6)	61 (6.6)**	
≥37	1312 (76.0)	785 (85.1)	
Gestational Diabetes Mellitus (GDM)	249 (14.4)	111 (12.0)	0.088
Pregnancy-induced Hypertension (PIH)	195 (11.3)	33 (3.6)	<0.001
Intrahepatic Cholestasis of Pregnancy (ICP)	126 (7.3)	3 (0.3)	<0.001
Premature Rupture of Membranes (PROM)	18 (1.0)	10 (1.1)	0.920
Neonatal characteristics			
Birth weight			<0.001
<1500 g	29 (1.7)	26 (2.8)	
1500 g–2500 g	348 (20.2)	99 (10.7)**	
2500 g–4000 g	1287 (74.6)	746 (80.9)	
≥4000 g	62 (3.6)	51 (5.5)	
Male	855 (49.5)	515 (55.9)	0.002
Cesarean	903 (52.3)	336 (36.4)	<0.001
Apgar scores<7 at 1 min	45 (2.6)	38 (4.1)	0.033
Respiratory distress syndrome	17 (1.0)	3 (0.3)	0.062
Wet lung	136 (7.9)	56 (6.1)	0.088
Fetal intrauterine infection	98 (5.7)	144 (15.6)	<0.001
Hyperbilirubinemia	220 (12.7)	102 (11.1)	0.207
Neonatal pneumonia	13 (0.8)	8 (0.9)	0.752
Neonatal sepsis	8 (0.5)	22 (2.4)	<0.001

Data are expressed as n (%). Chi-square test were used to evaluate the data.
**P < 0.01. PIN: placental inflammation negative; PIP: placental inflammation positive.

Table 3
Maternal vitamin D levels at early pregnancy (<13 w) by presence and absence of placental inflammation lesion.

	PIN group (n = 1726)	PIP group (n = 922)	*P*-value
Maternal vitamin D levels (nM)	41.7 (30.3,52.9)	41.0 (29.7,51.2)	0.042
Vitamin D category 1			0.246
Deficient (<27.50 nM) (%)	317 (18.4)	186 (20.2)	
Insufficient (49.99–27.50 nM) (%)	869 (50.3)	474 (51.4)	
Sufficient (≥50.00 nM) (%)	540 (31.3)	262 (28.4)	
Vitamin D category 2			0.025
$<P_5$ (<20.20 nM)	87 (5.0)	63 (6.8)	
P_5–P_{75} (20.2–53.69 nM)	1237 (71.7)	678 (73.5)	
P_{75}–P_{100} (≥53.70 nM)	402 (23.3)	181 (19.6)	
Vitamin D levels (nM) by testing seasons			
Spring	40.5 (28.4,52.9)	41.1 (27.0,50.9)	0.345
Summer	44.0 (35.5,54.5)	43.6 (33.4,52.9)	0.331
Autumn	44.0 (33.4,53.6)	43.1 (33.1,52.1)	0.463
Winter	37.3 (25.8,51.3)	35.8 (26.1,48.7)	0.708

Data are expressed as n (%) and median (the 25th, 75th percentiles).
The chi-square test was used for categorical variables. The Mann–Whitney U test was used to comparing vitamin D levels between the PIN and PIP groups.
Vitamin D category 1: <27.50, 49.99–27.50, and ≥50.00 nM; Vitamin D category 2: $<P_5$, P_5–P_{75} and P_{75}– P_{100} percentiles for the Vitamin D level in the study population.

P < 0.001) in the PIN group. We also found a decreased probability for infants that weighed between 1500 g and 2500 g in the PIP group versus PIN group (20.2% vs 10.7%; P < 0.01), but an increased probability for infants with very low birth weight in the PIP group (1.7% vs 2.8%), which matched gestational age correspondingly. It is also noteworthy that remarkable risk ratios of adverse neonatal outcomes, including sepsis (0.5% vs 2.4%; P < 0.001) and fetal intrauterine infection (5.7% vs 15.6%; P < 0.001), were observed in the PIP group compared with the PIN group.

3.2. Relationship between vitamin D levels and placental inflammation

Maternal vitamin D levels were statistically significant lower in the PIP group than in the PIN group (41.0 nM vs 41.7 nM; P = 0.042) (Table 3), indicating that the incidence of placental inflammation tended to decrease with increasing vitamin D levels. To further analyze the relationship between placental inflammation and vitamin D level, we compared the incidences of vitamin D deficiency, insufficiency, and sufficiency following the global consensus definition of vitamin D level requirement [15,16] (defined as category 1). There was a much higher incidence of vitamin D deficiency or insufficiency in the PIP group, but the difference was not significant (P = 0.246).

The vitamin D concentration distribution in this study population is shown in Fig. 2, which shows a skewed distribution. We sorted the all the 23,396 subjects in this study according to vitamin D level, and the populations in the bottom 5%, middle 70%, and top 25% were considered as $<P_5$, P_5–P_{75}, and P_{75}–P_{100}, respectively (defined as category 2). We found a significant correlation between these vitamin D categories and placental inflammation (P = 0.025). The incidence of placental inflammation was significantly higher in women with extremely low vitamin D levels ($<P_5$). There was no seasonal difference in vitamin D levels between groups.

Using multivariate logistic regression analysis (Table 4), we found that vitamin D deficiency or insufficiency was not associated with the incidence of placental inflammation either with or without adjustment in category 1. However, the odds of placental inflammation were significantly higher in women with extremely low vitamin D levels ($<P_5$; OR = 1.61; P = 0.012) compared with the highest quartile of vitamin D levels in category 2. This effect was slightly decreased but still significant with adjustment for maternal age (OR = 1.57; P = 0.017), gestational age at birth, birth weight, infant sex, and sample collection season (OR = 1.53; P = 0.027). The P_5–P_{75} population showed no significantly higher risk of placental inflammation with or without adjustment. These results show that extremely low vitamin D levels in the first trimester is linked to placental inflammation, confirming that vitamin D deficiency in early pregnancy may be a risk factor for placental inflammation.

We also investigated the risk for placental inflammation using logistic regression models with restricted cubic splines with seven knots at the 5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles, as shown in Supplementary Table 1, in low maternal Vitamin D level (<5th), maternal Vitamin D level was negatively associated with placental inflammation (P = 0.046).

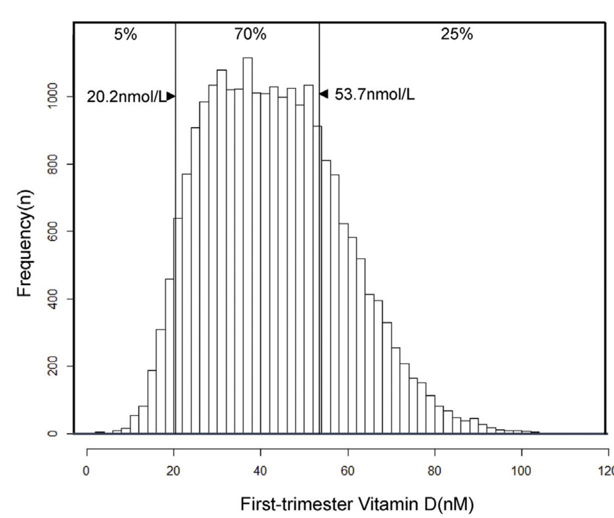

Fig. 2. Vitamin D concentration distribution in this general population database.

Table 4
Multiple logistic regression analyses on the association between maternal vitamin D levels and inflammatory lesions.

	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Vitamin D category 1	Deficient vs. Sufficient		Insufficient vs. Sufficient	
Model 1	1.21 (0.96,1.53)	0.111	1.12 (0.93,1.35)	0.215
Model 2	1.18 (0.94,1.49)	0.162	1.12 (0.93,1.35)	0.244
Model 3	1.17 (0.92,1.48)	0.216	1.11 (0.92,1.34)	0.272
Model 4	1.20 (0.94,1.53)	0.153	1.14 (0.94,1.38)	0.187
Vitamin D category 2	$<P_5$ vs. $P_{75}-P_{100}$		P_5-P_{75} vs. $P_{75}-P_{100}$	
Model 1	1.61 (1.11,2.33)	0.012	1.22 (1.00,1.49)	0.053
Model 2	1.57 (1.08,2.27)	0.017	1.21 (0.99,1.47)	0.066
Model 3	1.53 (1.05,2.24)	0.027	1.20 (0.98,1.47)	0.082
Model 4	1.58 (1.07,2.32)	0.022	1.22 (1.00,1.50)	0.056

Model 1, unadjusted model; Model 2, maternal age was adjusted; Model 3, maternal age, gestational age at birth, birth weight, infant sex and sample collection season were adjusted; Model 4, maternal age, gestational age at birth, birth weight, infant sex and sample collection season, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membranes (PROM) were adjusted.

4. Discussion

Our results provide evidence of the potential association between maternal vitamin D deficiency and placental inflammation. Vitamin D deficiency in pregnant and lactating women is highly prevalent in China, including the Shanghai municipalities [37,38]. Foreign guidelines have been recommended to define the cutoff point of serum 25(OH)D for evaluating vitamin D status during pregnancy [16,39]. According to the racial and geographical differences between our study and foreign studies, we identified the bottom 5%, middle 70%, and top 25% of vitamin D levels as severe deficient, relatively insufficient, and absolutely sufficient, respectively. Based on this distribution, we found an association between vitamin D levels in early pregnancy and placental inflammation using a tougher criterion of vitamin D deficiency.

As we know, intrauterine inflammation contributes to adverse maternal outcomes and neonatal infection-related morbidity [40]. In particular, fetal inflammatory response syndrome is overwhelmingly considered to be related to preterm delivery [41] and increased frequency of both chronic lung disease [42] and adverse long-term neurodevelopmental outcome [43]. We also found that women with placental inflammation had much higher incidences of fetal intrauterine infection and neonatal sepsis compared with women without placental inflammation. Placental inflammation initially stimulated the response in the amniotic compartment (amnion/chorion, skin, lung, and the gastrointestinal tract), modulated the immune changes in blood and lymphoid organs, and caused both the systemic disease and the damage of organs [44]. Our study provided additional evidence that intrauterine infection and neonatal sepsis is associated with placental inflammation, suggested that maybe vitamin D in early pregnancy is a protective factor for short-term neonatal outcomes.

Many studies have shown that vitamin D and VDR have an effect on preterm birth [45] and other adverse neonatal outcomes [46], the most important cause of which is intrauterine/placental inflammation [47]. However, the anti-inflammatory effect of vitamin D during pregnancy remains controversial. Other researchers [31] reported that 25(OH)D deficiency at birth was not associated with placental inflammation or neonatal infection among infants with very low birth weight. However, in fundamental research, immune challenge, such as injecting lipopolysaccharide (LPS), elevated the expression of mouse CYP27B1 and VDR, while ablation of fetal (trophoblastic) CYP27B1 or VDR altered placental responses to LPS challenge [28]. Moreover, placental LPS-induced inflammation was suppressed by pretreatment with vitamin D due to activated placental VDR and nuclear factor kappa B [29]. Therefore, it appears that vitamin D has effects on placental immune function and tends to provide a protective effect against inflammation. Likewise, the potential physiologic responses to maternal vitamin D deficiency are countless in basic research. Given the multifaceted role of vitamin D in immune pathways, there remains much work to be done to elucidate how maternal vitamin D status impacts appropriate immune and inflammatory responses in pregnancy.

One of the strengths of our study is that the definition used for placental inflammation was based on histologic examination and included, but was not limited to, chorioamnionitis. This allowed us to explore the correlation between vitamin D levels in early pregnancy and placental inflammation systematically and comprehensively. However, due to the retrospective study design, A limitation of our study is that maternal vitamin D levels during the later periods of pregnancy could not be included in the analysis. In summary, this study provides evidence that placental inflammation is more prevalent in women with extremely low vitamin D levels. A healthy placenta is crucial in fetal intrauterine growth and development, while impaired placental function induces fetal disturbance, which may result in long-term neonatal complications [48,49]. Therefore, this study revealed that the severe vitamin D deficiency may play an important role in placental inflammation which may in turn lead to higher risk of intrauterine growth restriction (IUGR) and other adverse neonatal outcomes.

Future prospective studies are needed to longitudinally examine the impact of maternal vitamin D deficiency on maternal placental inflammation and neonatal health, and the underlying mechanism.

Conflict of interest

The authors declare no conflict of interest.

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Author's contributions

All the authors contributed to the work and approved the final version of the manuscript. Particularly, contributions were: study design: QZ, CZ, ZL; Data collection: HC, YY, HL, YH, ZT; Data analyses and interpretation: QZ, CZ; Manuscript drafting: QZ; Critical revision of the manuscript: QZ, ZL, FO, HH.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.06.978.

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