Maternal 25-hydroxyvitamin D correlates with weight gain and bone metabolism during pregnancy

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Abstract

Background: Vitamin D is involved in the regulation of 3% of the human genome, which encode proteins affecting bone health, immune system and other systems. The status of maternal vitamin D may program neonatal skeletal development. Besides, vitamin D is associated with obesity during pregnancy. Obesity has a detrimental effect on bone metabolism and the level of several hormones related to bone metabolism

Methods: This cross-sectional study recruited 103 families who visited Anzhen Hospital from January 2017 to June 2017. The age of included pregnant women ranged from 21 to 42 years old. Patients were assigned to different groups according to their body mass index (BMI) and weight gain during pregnancy. The level of 25-hydroxyvitamin D (25-(OH)D) in serum, parathyroid hormone (PTH), total procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (OC), and C-terminal telopeptides type I collagen (CTX) from mothers and neonates were compared.

Results: The results showed that the average level of 25-(OH) D in serum from mothers was 15.09ng/ml during pregnancy and 16.23ng/ml in the umbilical cord. The maternal P1NP increased significantly when the weight gain increased during pregnancy ($P<0.01$), as well as the fetal weight ($P<0.05$).

Conclusions: Vitamin D deficiency is prevalent during pregnancy and led to more weight gain during pregnancy, also influence the fetal bone health. Obesity negatively correlates with 25-(OH)D level in serum and has a detrimental effect on bone metabolism.

Background

Vitamin D, a group of fat-soluble nutrient, responsible for increasing intestinal absorption of calcium, magnesium, and phosphate. Recently, the accumulating evidence has shown that vitamin D also plays pivotal roles in many other biological processes, such as the pathogenesis of diabetes, obesity, cardiovascular disease, cancer, and regulation of immune system (1), especially during the development of obesity. It has been found that obese people are more likely to suffer from vitamin D insufficiency or deficiency (2–5), similarly, decreasing vitamin D level will increase the risk of obesity (6, 7). Therefore, (8) maintaining vitamin D level by taking vitamin D supplements can prevent those population in high-risk groups from obesity and its related symptoms. A lower level of vitamin D in obese people is consistently found across age, ethnicity, and geography, though it may not always reflect a clinical symptom. 25-hydroxyvitamin D 25-(OH)D is a secosteroid hormone. The serum level of 25-(OH)D is used as an index of vitamin D in the body. The obese population may need to take higher-level vitamin D to achieve the same level of serum 25-(OH)D in people with normal weight. Obesity is a notable risk factor for vitamin D deficiency, which may be caused by vitamin D3 sequestration in adipose tissue (9). Although many researchers have demonstrated a dramatic change of 25-(OH) D concentration along with the overweight severity (3, 10–24), we are unaware of any study investigating the relationship between 25-(OH)D level

and obesity in the context of pregnancy. Pregnancy is a particular period of time susceptible to vitamin D deficiency, in that mothers must sustain their vitamin D level as well as those of their fetuses (25).

Furthermore, hormonally active form of vitamin D play important roles in placental development and function, inflammation, angiogenesis, immunomodulation, and insulin sensitivity (25–29). All of these findings indicate the potential roles of vitamin D deficiency in several well-known adverse pregnancy outcomes related to the overweight during pregnancy, including miscarriage, preeclampsia, and gestational diabetes (30). The level of serum 25-(OH)D in pregnant women not only affect the health of the mother's, but also the health of their children's.

Subjects And Methods

Subjects

This study was approved by the Anzhen Hospital Ethics Committee (Anzhen18029X), the signed consent form from each patient/parents/legal guardians was obtained. And written informed consent was obtained from the patient/parents/legal guardians for publication of any accompanying images and videos. A copy of the written consent is available for review by the editor of this journal. This study was a cross-sectional study analyzing data from 103 pregnant women who visited Anzhen Hospital to have a delivery from January 2017 to June 2017. The mean (±SD) values of age, BMI, and pregnancy weight gain of mothers were 31.09 (±4.1) years old, 25.8 (±3.8) kg/m^2, and 13.1 (±4.4) kg respectively. Ninety-six cases were full-term delivery, seven cases were premature delivery. Blood samples were collected from mothers during pregnancy and from umbilical cords at birth for analysis of serum 25-(OH)D, PTH, and bone remodeling markers.

Measurements

BMI values ranged in 24.0 to 27.9 kg/m^2 were defined as "overweight," while values equal to or above 28kg/m^2 were described as "obese" according to the reference values for an adult population (31). The overweight gain was defined as a weight gain of 16kg during the pregnancy for the normal-weight women before pregnancy, for the overweight was 11.5kg and for the obese was 9kg, respectively.

A level of total serum 25-(OH)D level less than 20 ng/ml was considered as vitamin D deficiency, and vitamin D insufficiency was defined when its level fell into the range from 20 to 30 ng/ml (32, 33). The method of blood glucose determination was hexokinase method, which was determined by glucose assay kit. Calcium Arsenazo (Beckman Coulter AU Chemistry System, United States) was used to quantitatively determine the calcium concentration, this step was done by the laboratoryChemiLuminescence (DiaSorin Inc.) was the methodology used to measure 25-(OH)D3, PTH and the markers of bone metabolism (P1NP, OC, CTX).

Statistical analyses

Patients were divided into three groups (normal weight, overweight, and obese), according to their BMI before pregnancy. Statistical analyses were performed with the software SPSS, version 22.0 for Windows. T-test for independent samples was performed when comparing two groups; if the variances were not equal, the Wilcoxon test was performed. One-Way ANOVA was used to compare the means among the three groups. Correlation coefficients were calculated by Pearson correlation. Results were presented as mean (±SD), unless otherwise indicated. The differences were considered significant when $P<0.05$; P values between 0.05 and 0.10 were considered different in trends.

Results

The characteristics of the 103 mothers and their newborns were presented separately for vitamin D deficiency or insufficiency (*Table 1*). The mean serum 25-(OH)D level of the whole group was 14.9 ng/ml. Briefly, no difference was found between the vitamin D deficient group and the vitamin D insufficient group in terms of mothers' age, height and BMI before delivery (P=0.359, 0.587, 0.723, 0.676 and, respectively). Meanwhile, the level of PTH in the vitamin D insufficient group was significantly lower than that in the vitamin D deficient group (18.0 vs. 36.4, P=0.029). While no difference was found between vitamin D deficient group and vitamin D insufficient groups regarding the levels of osteocalcin (OC), C-terminal telopeptides type I collagen (CTX), and serum calcium in mothers (P=0.872, 0.723, and 0.946, respectively). Their newborns showed a difference in birth weight between the vitamin D deficient group and the vitamin D insufficient group (3293.7 g vs. 3358.3 g, P=0.019). The two groups showed no difference in terms of the levels of newborns' 25-(OH) D, total procollagen type 1 N-terminal propeptide (P1NP), OC, CTX, and calcium in the umbilical cord blood (P=0.684, 0.263, 0.501, 0.669, and 0.646, respectively).

Table 1. Parameters of indicated markers in vitamin D deficient and insufficient groups.

	Deficient	Insufficient	P value
Mothers			
Number	55	14	
Age (yrs)	31.0(4.2)	31.0(3.1)	0.359
BMI before pregnancy (kg/m^2)	25.8(3.5)	25.7(4.2)	0.723
Height (cm)	162.4(5.8)	163.2(5.0)	0.587
Weight gain during pregnancy (kg)	13.6(4.7)	12.5(4.8)	0.238
Mean 25-(OH)D (ng/ml)	11.1(4.5)	24.5(2.7)	0.000
PTH (pg/ml)	36.4(22.9)	18.0(7.3)	*0.029
P1NP (ng/ml)	90.0(54.8)	92.5(62.8)	*0.026
OC (ng/ml)	16.3(7.5)	17.8(8.8)	0.872
CTX (μg/ml)	0.5(0.2)	0.4(0.3)	0.723
Serum calcium(mg/dL)	2.10(0.3)	2.14(0.3)	0.946
Newborns			
Number	40	9	
Cord 25-(OH)D (ng/ml)	12.7(5.0)	24.4(9.8)	0.684
Weight (g)	3293.7(713.7)	3358.3(570.4)	*0.019
Cord P1NP (ng/ml)	1151.5(232.7)	1200.0(0)	0.263
Cord OC (ng/ml)	53.1(34.2)	72.1(24.6)	0.501
Cord CTX (μg/ml)	0.65(0.20)	0.58(0.25)	0.669
Cord calcium (mg/dL)	2.4(0.4)	2.3(0.5)	0.646

Data represents as mean (±SD). *: *P*<0.05; “cord” means “umbilical cords”.

Table 2 showed the relationships between BMI and maternal 25-(OH)D, PTH, OC, and CTX, respectively. A significant difference of maternal P1NP was found among the three groups. The concentration of P1NP in overweight and obesity were both higher than normal group (P=0.0008, P=0.01). The CTX in normal group was lower than overweight group in trend (P=0.05). There is no significant difference of maternal 25-(OH)D, PTH, OC, and serum calcium. However, both pre-pregnancy BMI and weight gain negatively correlates with maternal 25-(OH) D level in serum (Fig 2.1 and Fig 2.2).

Table 2. Comparisons between pre-pregnancy BMI and maternal 25-OH-D, PTH, OC , and CTX.

	Normal weight	Overweight	Obesity
Mean 25-(OH)D (ng/ml)	15.2(8.2)	15.0(6.5)	15.1(10.0)
PTH (pg/ml)	28.9(14.8)	29.9(14.2)	39.6(34.3)
P1NP (ng/ml)	63.4(34.3)	115.2(64.9)	102.1(53.9)
OC (ng/ml)	14.3(5.9)	19.0(10.2)	17.3(6.1)
CTX (μg/ml)	0.40(0.29)	0.48(0.22)	0.46(0.24)
Serum calcium (mg/dL)	2.02(0.42)	2.02(0.40)	2.21(0.15)
*	***p*** (nw.vs ov.)	***p*** (nw. vs ob.)	***p*** (ov. vs ob.)
Mean 25-(OH)D (ng/ml)	0.66	0.73	0.57
PTH (pg/ml)	0.56	0.77	0.99
P1NP (ng/ml)	0.0008	0.01	0.55
OC (ng/ml)	0.08	0.12	0.68
CTX (μg/ml)	0.05	0.17	0.50
Serum calcium (mg/dL)	0.61	0.33	0.16

“nw” stands for normal weight; “ov” means overweight; “ob” means obesity. Data represents as mean (±SD). *$P<0.05$.

All patients were divided into three groups, normal weight group, overweight group and obesity group, according to their BMI (Table 3). The fetal weight increased along with the BMI increasing of their mothers between normal group and obesity group (3057 vs. 3560, P=0.009). For the normal weight group, there is a negative correlation between BMI and 25(OH)D (t=-2.07, p=0.048). However, there was no difference in other indexes between the three groups.

Table 3. Comparisons between pre-pregnancy BMI and fetal weight, 25-(OH)D, PTH, OC, CTX, and serum calcium.

	Normal weight	Overweight	Obesity
Fetal weight(g)	3057	3280	3560
Mean 25-(OH)D (ng/ml)	14.3(7.9)	15.8(7.2)	19.6(13.2)
OC (ng/ml)	66.8(54.6)	67.6(32.9)	64.4(32.6)
CTX (μg/ml)	0.61(0.27)	0.67(0.14)	0.67(0.11)
Serum calcium (mg/dL)	2.25(0.55)	2.21(0.51)	2.33(0.48)
*	***p***(nw.vs ov.)	***p***(nw. vs ob.)	***p***(ov. vs ob.)
Mean25-(OH)D (ng/mlng/ml)	0.44	0.22	0.54
OC (ng/ml)	0.29	0.50	1.00
CTX (μg/ml)	0.34	0.27	0.83
Serum calcium (mg/dL)	0.56	0.80	0.28
Fetal weight(g)	0.16	0.009	0.06

Data represents as mean (±SD). *P<0.05.

Similarly, the authors also analyzed the relationship between the weight gain of the mother during pregnancy and the level of maternal P1NP, OC, and cord 25-(OH)D occurred. The results (Table 4) demonstrated that the weight gain of mothers during pregnancy was significantly correlated with the level of P1NP, OC, and cord 25-(OH)D. The levels of P1NP, OC, and cord 25-(OH) D in the overweight gain group were higher than those in the normal weight gain group (109.35 vs. 65.86, P=0.0006; 18.24 vs. 14.52, P=0.038; 18.46 vs. 13.31, P=0.039, respectively).

Table 4. Comparisons between weight gain during pregnancy and maternal P1NP, OC, and cord 25-(OH)D.

	Normal weight gain	Over weight gain	p value
P1NP (ng/ml)	65.86	109.35	*0.0006
OC (ng/ml)	14.52	18.24	*0.038
Cord 25-(OH)D (ng/ml)	13.31	18.46	*0.039

*P<0.05.

*, The overweight gain was defined as a weight gain of 16kg during the pregnancy for the normal-weight women before pregnancy, for the overweight was 11.5kg and for the obese was 9kg, respectively.

Discussion

Vitamin D is a fat-soluble nutrient which is mainly obtained from consuming dairy supplements and fish oils. Also, it can be produced endogenously in the skin with exposure to sunlight. To be active, vitamin D must undergo hydroxylation in the liver, being converted to 25-(OH)D, then hydroxylized to the physiologically active 1,25-dihydroxyvitamin D primarily in kidney. This active form is nesessary to promote absorption of calcium in the gut, and enables normal bone mineralization and growth. The newborn disordered skeletal homeostasis, congenital rickets, and fractures is highly considered with severe maternal vitamin D deficiency (34, 35).

The level of vitamin D is affected by many different factors, such as the geographical region, race, weight, gender, lifestyle diet and so on. This group of pregnant women were from north of China and their lifestyle diet are short of vitamin D. The mean serum 25-(OH)D level of the whole group was 14.9 ng/ml, that may be because of not enough vitamin D intake and UVB exposure.

Pregnant women, as a special group of people, are more likely to suffering from vitamin D deficiency, especially for those people who are high-risk pregnancies, such as vegetarians and women with limited sun exposure and insufficient exercise (36-38). Women who have vitamin D deficiency usually do not expereience any clinical symptom, but some may have muscle weakness and weakened bones. The level of vitamin D in newborns is mainly dependent on the level of maternal vitamin D. Consequently, infants of those mothers with or at high risk of vitamin D deficiency are also at risk of vitamin D deficiency (38,

39). Lower maternal vitamin D level is associated with lower bone mineral concentration in newborn infants (40).

Vitamin D and obesity

Obesity is a significant health problem worldwide, particularly in developed nations. Recently, the relationship between obesity and vitamin D drew more and more attention around the world. Some researchers have found that obese people tend to suffer from vitamin D decline or deficiency; consistently, the decrease in the level of vitamin D increases the risk of obesity. Parikh and his co-workers found that the serum level of 25-(OH)D in the obesity group was significantly lower than that in non-obesity group (3). Konradsen et al. reported a significant decrease of both serum 25-(OH)D and 1,25-(OH) D ($P<0.001$) along with the increasing of BMI. Also, those people with BMI >39.9 kg/m^2 had 24% lower level of serum 25-(OH)D and 18% lower level of 1,25-(OH)D than those with BMI <25 kg/m^2. The previous reports indicated that relevant evidence was insufficient that high levels of circulating 1,25-(OH)D contribute to the development of obesity (2). Some reports claim that the occurrence rate of vitamin D deficiency increased from 21% to 81% among obese people (3, 41-43). The Fig 2.1 shows that pre-pregnancy BMI negatively correlates with 25-(OH) D level in serum($t=-1.03$) and Fig 2.2 indicates the negative correlation between weight gain and maternal 25-(OHD) ($t=-0.68$). The reason might be that obese people may prefer conservative clothes to cover up their figures and seldom do exercise outside to get enough sun exposure. Furthermore, pregnant women join less outdoors activities, while need more vitamin D, which resulted in the vitamin D deficiency.

Obesity-associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D(3) from cutaneous and dietary sources, because of its deposition in body fat compartments (9).

Volumetric dilution can also explain the finding. The researchers gave healthy adults a small dose of vitamin D supplement and did the regression analyses of body size variables against serum 25-(OH)D concentration. They found that obese people need higher loading doses of vitamin D to achieve the same serum 25-(OH)D as normal weight people do. Thus, vitamin D replacement therapy needs to be adjusted by body size, if the desired serum 25-(OH)D concentration is to be achieved (44).On the other hand, the low serum vitamin D level is a risk factor of obesity. A prospective study evaluated 1226 subjects and concluded that vitamin D deficiency is associated with an increased risk of developing obesity (45). Lai et al. found that 25-(OH)D was inversely related to truncal fat mass ($P = 0.02$) (46).

A study of the relationship between 25-(OH)D and maternal metabolic index indicated that the vitamin D level of the pregnants was generally low. The BMI and the weight gain in the vitamin D deficiency group were significantly higher than those in the vitamin D sufficient group, which suggested the correlation between the low vitamin D level and overweight gain during pregnancy (47)·This finding is consistent with current results that the weight gain during pregnancy in the vitamin D insufficient group was less compared to the vitamin D deficient group. A previous clinical trial was done on 2018 described that the overweight and obese women population received vit D supplements compared to the placebo, after 6

weeks high dosage of vitamin D (50,000IU/week) pretreatment ,the means of weight, BMI, waist circumference, and hip circumference decreased significantly (48).

Vitamin D and bone metabolism

Taking optimum dose of vitamin D can not only control the weight gain during pregnancy and lower the risk of obesity complication (48),but also benefit fetal bone growth. Our data showed that newborn's 25-(OH)D level in the vitamin D insufficient group was higher than that in the vitamin D deficient group, which was also the case in terms of mothers' 25-(OH)D.

Maternal vitamin D level during pregnancy can program offspring's skeletal development (49)and body composition in the offspring (50)by influencing the interaction between osteoblasts and adipocytes. Low maternal serum 25-(OH)D level is associated with shorter duration of gestation and, consequently, reduced growth of long bones in newborns (51). In vitamin D-deficient mothers, maternal PTH is elevated, probably due to the increased mineral demands of larger babies (51). Children of mothers with low vitamin D status during late pregnancy had reduced whole-body bone mineral content, bone area, and areal bone mineral density (BMD) at the age of 9 (52). This suggests that vitamin D has an influence on skeletal programming, and the tracking of bone mass lasts throughout childhood. Furthermore, birth weight and growth during the first year of life may contribute to skeletal fragility later in life (53-55).

Previous studies showed that maternal vitamin D status, defined by serum 25-OH-D concentration, is tightly associated with cord blood vitamin D concentration (56-58).

Obesity and bone metabolism

Although obesity has been considered as a condition of low risk for osteoporosis traditionally, this classic view has recently been questioned (59). Bodyweight is directly associated with BMD. A low BMI has been identified as an essential risk factor for lower BMD and predicts greater bone loss in older age (60, 61) and in younger persons in the absence of menses and/or an eating disorder (62)· On the other hand, a high body weight can be due to the increased physical activity or obesity, both of which will increase BMD. However, increasing evidence has suggested that excess weight due to adiposity is detrimental to bone and increases fracture risk. In an animal test, short-term and extended high-fat diet-induced obesity caused significant bone loss. Recently, more and more index of bone metabolism has been shown correlated with obesity, such as OC, PTH, P1NP, CTX, and serum calcium.

Osteocalcin

Reinehr and Roth found that OC levels were lower in obese children and increased when weight loss was achieved (63). OC, also known as bone gamma-carboxyglutamic acid-containing protein, is a non-collagenous protein hormone found in bone and dentin, giving bones strength and flexibility. It is secreted solely by osteoblasts and thought to play a role in metabolic regulation. In addition, it is pro-osteoblastic, or bone-building, by nature (64). It is also implicated in bone mineralization and calcium ion

homeostasis. Due to its role in supporting bone strength, the amount of OC increases during periods of rapid growth, notably in children during the first year of life. Therefore, the OC decline will have a negative effect on the bone metabolism. The low OC level in obese people may result from the change of the level of leptin. Leptin is a hormone which is predominantly made by adipose cells that help to regulate energy balance by inhibiting hunger and play a very important role in bone metabolism. Leptin can regulate the OC level in serum. In an animal test, rats with leptin deficiency and leptin resistance had higher OC level. Lepin can also inhibit the production of osteoblasts and the secretion of OC (65). Nevertheless, the OC level of patients in overweight gain group was higher than the normal weight gain group. It might be explained by a feedback mechanism to meet the demand of fetal growth.

Parathyroid hormone

PTH, response to the low level of serum calcium, however, the over-responses of PTH will destroy the balance between the bone remodeling and resorbing. Previous publication indicated that the obese people have higher PTH level (66), and Pitroda thought the reason might be the low 25-(OH)D level in the obese people (67). The PTH in the vitamin D insufficient group is clearly lower than that in the vitamin D deficient group. Meanwhile, the PTH in the obese pregnant women were higher than that in the non-obesity pregnant women, and it is also the case in terms of calcium level in serum.

Total procollagen type 1 N-terminal propeptide and C-terminal telopeptides type I collagen

The organic composition of the bone includes mainly type collagen (90%), bone binding protein (10%) and trace albumin. Collagen is the crucial component for maintaining the bone integrity. P1NP reflects the change of the newly synthesized type collagen, which can be regarded as a symbol of bone remodeling. CTX is the degradation product of the type collagen and it is an index of bone resorbing. Some researchers think that the uncontrollable bone resorbing is the main reason leading to the sharply decline of bone mass in obesity (68). Table 3 and 4 showed that the maternal P1NP increased clearly when the weight gain increased during pregnancy and the CTX of the obese pregnant women was higher than that in the normal weight group. The P1NP and CTX were increased to meet the bigger demand of the baby's bone growth which was indicated by the finding that obese pregnant women have higher probability to deliver a baby whose weight is over 4000 g.

Conclusions

Vitamin D deficiency is prevalent during pregnancy. Obesity negatively correlates with the level of serum 25-(OH)D and has a detrimental effect on bone metabolism and fetal weight. The decrease of vitamin D not only increased the weight of fetal, but also affected their bone health. The levels of PTH, P1NP, CTX and serum calcium of patients in the obesity group were higher than that of patients in the normal weight group. This phenomenon can be explained by a feedback mechanism trying to meet the demand of their own and fetal bone growth. Thus it is significant for pregnant women to maintain a reasonable 25-OHD level.

Declarations

Ethics approval and consent to participate

This study was approved by the Anzhen Hospital Ethics Committee (Anzhen18029X), the signed consent form from each patient/parents/legal guardians was obtained. And written informed consent was obtained from the patient/parents/legal guardians for publication of any accompanying images and videos. A copy of the written consent is available for review by the editor of this journal.

Consent to publish

The authors declare that there is no conflict of interest regarding the publication of this article, and all the authors and the institution are consented to publish.

Availability of data and materials

The data that support the findings of this study included in this manuscript, and the original files are available from the corresponding author upon reasonable request

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article,

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Authors' Contributions

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

L.L. and N.W. carried out the study. L.L. wrote the manuscript with support from D.Y.. D.X., L.W., J.Z. and D.Y. fabricated the analysis. D.Y. and L.L. helped supervise the project.

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Figures

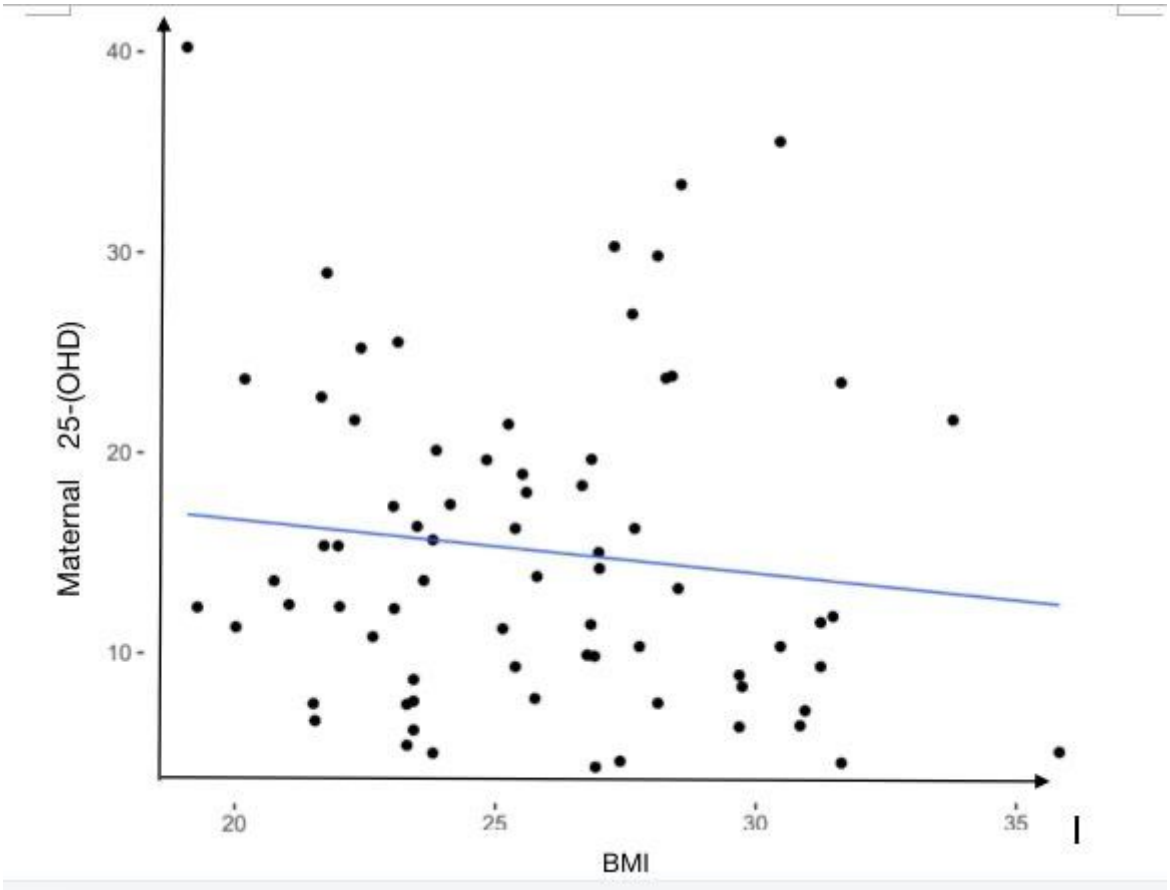

Figure 1

Fig 1.1 The correlation between pre-pregnancy BMI and maternal 25-(OH)D.

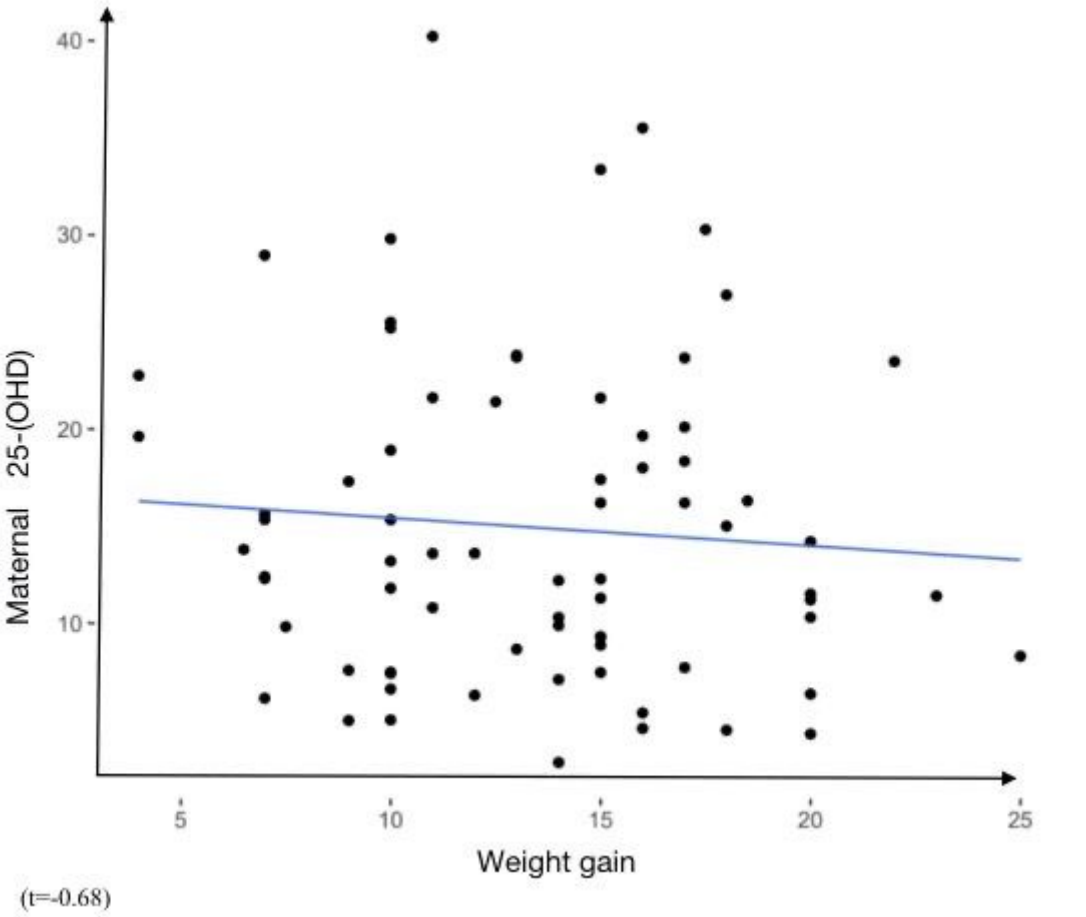

Figure 2

Fig 1.2 The negative correlation between weight gain and maternal 25-(OHD) (t=-0.68).