VITAMIN D AND PREGNANCY

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In pregnant women, especially during the first phases, the role of vitamin D appears to be mainly immunomodulatory, rather than – more traditionally – a calcium-regulating factor, although this function does retain its importance. Interestingly, vitamin D inadequacy in the early stages of pregnancy could be an instance of the "Barker Hypothesis" [1]. According to this theory, certain diseases in adults might have their roots in nutrient insults experienced in the perinatal period (either *in utero* and/or during the early months of life).
Still today there is little agreement on the optimal vitamin D dosages to be utilized as supplementation during pregnancy.

VITAMIN D: METABOLISM IN PREGNANT AND NONPREGNANT WOMEN

Marked differences exist in vitamin D metabolism in pregnant women, non-pregnant women and developing fetuses. Although scientists have long known about these differences, they have received little attention until recently [2, 3].
The rate of conversion of vitamin D to 25(OH)D appears unchanged during pregnancy, in line with zero-order enzyme kinetics. (We should point out here that zero-order kinetics is observed in an enzyme catalyzed reaction when, in response to high substrate concentrations, the velocity of the reaction reaches a maximum value which becomes constant following complete substrate saturation; in other words, no more enzyme is available) [4].
Conversely, the conversion of 25(OH)D to $1,25(OH)_2D$ has a unique profile during pregnancy. In fact, at no other time during life is 25(OH)D associated with the production of $1,25(OH)_2D$. Starting at 12 weeks of gestation, $1,25(OH)_2D$ concentration is double that of a nonpregnant woman, and continues to rise two to three times with respect to baseline values, reaching levels that would be toxic – because of hypercalcemia – to a nonpregnant woman, but which are essential during pregnancy [5]. The rise in $1,25(OH)_2D$ levels in mother and fetus has been thought to be a mechanism to regulate calcium levels and to preserve the maternal skeleton, in addition to maintaining fetal skeletal development. In reality, it seems that calcium homeostasis is not linked with $1,25(OH)_2D$, because from the twelfth week of gestation there is no demand for calcium increase in either mother or fetus. By contrast, the increase of $1,25(OH)_2D$ levels sustained during pregnancy is not preserved during breastfeeding, when the demand for maternal calcium is as high as during pregnancy [6].
Therefore, the increase in $1,25(OH)_2D$ in mother and fetus during pregnancy is dependent on substrate availability, that is, of 25(OH)D, but it is largely independent of calcium homeostasis [5].
Various hypotheses have been used to explain why calcium metabolism is uncoupled during pregnancy and not during breastfeeding. One theory is that $1,25(OH)_2D$ is an important modulator of the immune system, correlated to maternal tolerance to the fetus. For instance, epidemiologic studies involving pregnant women with preeclampsia, a condition characterized by inflammation and vasculitis, has demonstrated an association between this disorder and vitamin D deficiency [7]. Moreover, animal studies have shown that vitamin D deficiency could be potentially related to placental dysfunction (one of the pathogenic mechanisms of preeclampsia) [8].
We should also emphasize that the placenta represents the most active extra-renal site for the conversion of 25(OH)D to calcitriol. At such a level, the expression of the codifying gene for the enzyme catabolizing the active form of vitamin D (24-hydroxylase) is reduced. Additionally, $1,25(OH)_2D$ cannot cross the placental barrier, while it seems that 25(OH)D can [9].
However, as we have already mentioned, $1,25(OH)_2D$ maternal levels have the tendency to increase during the first trimester and to continue to rise during the entire gestational period, during which its concentration is double that of a nonpregnant woman or during

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puerperium. In this respect, the progressive increase of calcitriol levels during pregnancy plays a crucial role in the modulation of maternal and fetal phosphate and calcium homeostasis, with a possible increase of calcium absorption during pregnancy [10].

A number of randomized trials and placebo-controlled studies [5, 11-17] have dealt with the topic of safety in vitamin D supplementation during pregnancy, with dosages of 400 to 4,000 IU per day: these showed no safety profile abnormalities.

Indeed low levels of vitamin D during pregnancy have been linked to the following conditions:

- intrauterine growth restriction
- preterm birth
- small for gestational age (SGA)
- bacterial vaginosis
- gestational diabetes
- preeclampsia

In particular, a 2018 review [18] evaluated the association between vitamin D deficiency and adverse complications during pregnancy by means of a literature analysis of observational studies performed in developing countries. Included were thirteen studies showing a variation of vitamin D deficiency prevalence between 51.3 and 100%. Results from ten studies have shown at least one association between vitamin D deficiency and adverse maternal and/or neonatal complications, such as preeclampsia, gestational diabetes, postpartum depression, urgent cesarean section, low birth weight, small for gestational age and growth restriction.

The World Health Organization (WHO) does not currently recommend routine vitamin D screening or supplementation during pregnancy [19] because randomized trials and placebo-controlled studies (RCTs) have not provided high quality scientific evidence for which it would be desirable to activate these kind of procedures. Indeed, as we shall see, the relationship between maternal levels of vitamin D and various pathologic conditions encourages us to more carefully assess both vitamin status and the appropriateness of vitamin D supplementation during pregnancy.

We will now review several pregnancy related complications connected to vitamin D levels.

VITAMIN D AND PREECLAMPSIA

In regard to the physiopathology of preeclampsia [20], the following phases have been traditionally described: 1) abnormal placentation and trophoblast invasion; 2) placental ischemia; 3) endothelial damage; 4) vasoconstriction + platelet activation – hemostatic abnormalities; and 5) preeclampsia.

Low vitamin D levels appear to be related to an impaired mechanism of placentation. Observational studies also report that women who developed preeclampsia had lower vitamin D levels than those who did not. Furthermore, it has been found that the risk of developing severe eclampsia is 5 times greater in pregnant women with 25(OH)D levels < 20 ng/mL [20, 21].

Specifically, in a 2007 study Bodnar [21] evaluated the effects of low maternal 25(OH)D levels on the risk of developing preeclampsia, as well as the vitamin D status in newborns of preeclamptic mothers. This was a case-control study on pregnant women who were followed from before the 16th week of gestation until delivery. The patients were nulliparous pregnant women with singleton pregnancies, who either did or did not develop preeclampsia.

Preeclampsia was defined as a new episode of gestational hypertension associated with proteinuria and developing for the first time after 20 weeks of pregnancy. Concentrations of 25(OH)D at early pregnancy were lower in women who subsequently developed preeclampsia compared to controls. A dose-response relationship between 25(OH)D levels at less than 22 weeks of gestation and the risk of preeclampsia was evident. After adjustment for confounding factors and a reduction of 20 ng/mL, the threshold value implied a relative risk of preeclampsia equal to 2.4 (95% confidence interval [CI]: 1.1,5.4). In addition, newborns of preeclamptic mothers were more likely to have levels of 25(OH)D less than 15 ng/mL (adjusted odds ratio [OR]: 2.2; 95% CI: 1.2, 4.1).

This study concluded that maternal vitamin D deficiency was an independent risk factor for preeclampsia and that vitamin D supplementation should be explored for preventing preeclampsia and promoting neonatal well-being.

Baker's case-control study [20], published in 2010, investigated the association between midgestation vitamin D deficiency and development of severe preeclampsia. Midgestation maternal levels of 25(OH)D were lower in women who subsequently developed severe preeclampsia compared with controls. In addition, 25(OH)D maternal levels of less than 20 ng/mL were associated with an almost 4-fold increase of this risk (OR: 3.63; 95% CI, 1.52, 8.65) compared with levels of at least 30 ng/mL. The observed association become more evident after adjustment for confounders (adjusted OR: 5.41; 95% CI, 2.02, 14.52). Findings from this study showed that vitamin D deficiency during maternal midgestation was associated with an increased risk of severe preeclampsia and that vitamin D deficiency could be a modifiable risk factor.

Considering the effects of vitamin D on preeclampsia physiopathology (Table 1), it should be noticed that, at different levels, vitamin D is able to mitigate the principal mechanisms for the onset of this pathology.

Interestingly, Cochrane's review, published in 2012, suggested that pregnant women who received vitamin D and calcium supplementation were less likely to develop preeclampsia compared to pregnant women who received no supplementation and who had a risk ratio of 0.51 (95% CI, 0.32, 0.80).

A more recent study [23] assessed the effect of vitamin D supplementation (4400 vs. 400 IU/day) begun early in pregnancy (8-10 weeks) on the development of preeclampsia. The effects of vitamin D serum levels [25(OH)D] on the incidence of preeclampsia in pregnant women were also examined both at the beginning of the study and during the third trimester (28-32 weeks). Findings from this study revealed that a supplementation started at approximately 10-18 weeks of gestation does not reduce the incidence of preeclampsia. However, vitamin D levels of 30 ng/mL or greater detected at the beginning of the study and during late pregnancy were associated with a lower risk of preeclampsia.

A literature review [24] published in 2018 assessed the association between low maternal vitamin D levels and increased risk of hypertension. This review included all interventional, observational and nutritional studies, thereby providing a broad evaluation of data. The results of this analysis indicated that both vitamin D and calcium have a protective effect with regard to the development of preeclampsia. Conflicting data from observational studies in this area were attributed to several factors, such as high study design heterogeneity, a lack of consistency with the definitions of the obstetric outcomes, the varying quality of laboratory tests for measuring 25(OH)D and uncertainty about vitamin D status.

TABLE I.
Preeclampsia pathogenesis and vitamin D effects.

PATHOGENIC MECHANISMS	EFFECTS OF VITAMIN D
Abnormal placentation associated with inflammatory mechanisms	Reduction of immune response susceptibility
	Regulation of genes associated to placental invasion and implantation
Vascular endothelial dysfunction	Regulation of vascular structure, of elasticity and of intima-media thickness
	Reduced blood pressure (regulation of renin-angiotensin-aldosterone system)
Proteinuria mediated by Vascular Endothelial Growth Factor (VEGF) at renal level	Increase of proliferation of vascular smooth muscle cells through an increase of VEGF gene transcription

VITAMIN D AND LOW BIRTH WEIGHT

A positive correlation exists between maternal vitamin D levels and birth weight. Low birth weight (LBW) refers to both term and near-term newborns with a weight at birth of < 2500 g. These infants may be "small for gestational age" (SGA), or may have intrauterine growth restriction. The mortality rate of "small for gestational age" newborns has increased compared to those with normal weight [25]. Vitamin D plays an important role in fetal growth, both for its relation to parathormone and for its participation in the phosphate and calcium homeostasis. Several studies have in fact shown that insufficient levels of prenatal and postnatal vitamin D play a significant role in inadequate bone mineralization; such levels are also associated with SGA newborns, who are more frequent in winter-month pregnancies characterized by vitamin D deficiency [26, 27].
A Chinese study [28] evaluated the association between maternal vitamin D deficiency during pregnancy and the risk of SGA and LBW infants. A positive correlation was found between the maternal serum 25-hydroxyvitamin D level and offspring birth weight ($r = 0.477$; $p < 0.001$). Further analysis showed that 4.98% of neonates were LBW infants among subjects with vitamin D deficiency (RR = 12; 95% CI, 4.37, 33) and 1.32% among those with vitamin D insufficiency (RR = 3.18; 95% CI, 1.07, 9.48). After adjustment for confounders, the RR for LBW newborns was 12.31 (95% CI, 4.47, 33.89) among subjects with vitamin D deficiency and 3.15 (95% CI, 1.06, 9.39) among those with vitamin D insufficiency. Results from this study again confirmed the association between low maternal vitamin D levels and the risk of giving birth to LBW offspring.
Another Chinese study [29] examined the association between maternal vitamin D status at the first prenatal examination, on one hand, and the measurements of newborns and placental weight, on the other, in a cohort of women with singleton pregnancies (n = 747). In this group of women, 76.9% (95% CI, 74%, 78%) were defined as vitamin D deficient. The incidence of SGA was 13.3% (95% CI, 10.8%, 15.7%).
In addition, a nonlinear relation was found between 25(OH)D levels, birth weight and head circumference ($p < 0.01$). Interestingly, birth weight and head circumference increased by 69 g (95% CI, 38, 122) and 0.31cm (95% CI, 0.22, 0.40), respectively, per each ng/mL increase in 25(OH)D levels, before levelling off.
SGA distribution across the 25(OH)D quartiles ranged between 3.7% in the fourth to 24.1% in the first quartile. In addition, for each unit decrease of the plasma concentration of 25(OH)D, the unadjusted and adjusted risk of SGA increased by 19% (OR = 1.19 [95% CI, 1.13, 1.25], $p < 0.001$) and 9% (1.08 [1.03, 1.16], $p = 0.009$), respectively. By means of a multivariate analysis using vitamin D deficiency vs. other clinical variables, the adjusted risk of SGA increased by 205% (OR= 3.05 [95% CI, 2.24, 4.40], $p = 0.001$).
An analogous association has also been shown by European studies. In a study performed in the Netherlands [30] on a multiethnic cohort of 3,730 women with singleton pregnancies, researchers assessed the association between maternal vitamin D status, measured during the first stages of pregnancy, and neonate birth weight, as well as the prevalence of SGA infants and postnatal growth (weight and length). Vitamin D levels were measured during the first phases of pregnancy (13 weeks on average) for defining vitamin D deficiency, insufficiency or sufficiency.
Six ethnic groups were identified: Dutch, Surinamese, Turkish, Moroccan, other Western and other non-Western. Multilevel regression analysis was used to assess the association between neonatal data. Data showed that women with vitamin D deficiency had more LBW offspring (-114.4 g; 95% CI, -151.2, -77.6) and a higher risk of SGA (OR = 2.4, 95% CI, 1.9, 3.2) compared to women who had normal levels of vitamin D. Neonates born of women with vitamin D deficiency showed an accelerated growth rate for weight and height during the first years of life. Although vitamin D deficiency influenced birth weight, SGA risk and neonatal growth, it played no role in explaining ethnic differences.
Another study conducted in Australia [31] also showed an association between maternal vitamin D deficiency and frequency of LBW infants.

VITAMIN D AND PRETERM LABOR

Vitamin D levels may affect the physiopathological mechanisms of preterm labor through the modulation of inflammation and of some immune activities [32]. Vitamin D plays a role in the activation of the toll-like receptors that trigger innate immune response. Vitamin D deficiency therefore increases the risk of infection by causing a reduction in the production of catelicytines, a peptide with antifungal properties produced by macrophages [33]. At the same time, several observational studies have not found a significant association between maternal vitamin D levels and preterm labor [34, 35].
One study [37] compared vitamin D levels in 120 American women who delivered at term to those of 40 women who delivered between the 23rd and the 35th week of pregnancy. No differences in vitamin D levels between the groups were observed. Another study [32], which evaluated levels of vitamin D in a group of American women of mixed ethnicity with twin pregnancies, found significantly lower vitamin D levels in those who delivered before the 35th week com-

pared to those who delivered after the 35th week of pregnancy. Women with vitamin D levels lower than 30 ng/mL delivered prematurely in 49.4% of the cases, compared to 26.2% of preterm deliveries in women with vitamin D concentrations higher than 30 ng/mL.
It is necessary to point out that some of these studies included women with a previous history of preterm birth or twin pregnancies or who were at risk of preeclampsia. It is interesting to note that a meta-analysis [38] failed to show an association between maternal vitamin D levels and preterm birth. This conclusion is perhaps explained by the fact that the meta-analysis considered observational studies which were quite heterogeneous (in terms of dosage types, vitamin D levels measured at different gestational ages, etc.).
By contrast, an American research project [39] on supplementation in a mixed ethnicity population suggests an inverse relationship between maternal vitamin D levels and preterm labor. In this study, vitamin D concentrations were measured at the first examination, at which a supplementation of 5.000 IU capsules of vitamin D was offered. Additional measurements were made at the 24th and 28th weeks of gestation. The study found that women with vitamin D concentrations higher than 40 ng/mL at the time of delivery had a 62% lower risk of delivering prematurely compared to women with vitamin D concentrations lower than 20 ng/mL.
In addition, in women who had vitamin D levels below 40 ng/mL at their first examination, and who reached concentrations higher than 40 ng/mL at the follow-up visit, the risk of preterm birth was lower than 60%. Interestingly, the inverse relationship between vitamin D levels and risk of preterm birth was found to be true for all ethnic groups, suggesting that adequate vitamin D concentration may be beneficial for all women regardless of ethnicity. Similar outcomes were confirmed in another study performed in the United States [12].

VITAMIN D AND BACTERIAL VAGINOSIS

Bacterial vaginosis continues to be a problem during pregnancy: since vitamin D induces the expression of antibacterial proteins and enhances antibacterial activity in various tissues, various studies have focused on the relationship between this condition and vitamin D [40]. In a study in the U.S. on a group of 469 pregnant women, half Caucasian and half Black [41], vitamin D concentrations were measured before the 16th week of gestation, while a vaginal smear was performed simultaneously. It was found that vitamin D deficiency was associated with bacterial vaginosis in Black women, but not in Caucasians.
A meta-analysis on observational studies found an inverse relationship between maternal vitamin D concentrations and the risk of bacterial vaginosis [38]. Meanwhile, two randomized studies failed to show a positive effect of vitamin D supplementation on the occurrence or recurrence of bacterial vaginosis during pregnancy [5, 14].

VITAMIN D AND CAESAREAN SECTION

Regarding the relationship between vitamin D and the risk of caesarean section delivery in women with vitamin D deficiency, it has been proposed that this condition may reduce pelvic muscle strength, leading to prolonged labor [42]. A study conducted in the U.S. showed that in pregnant women of mixed ethnicity a significantly higher risk of caesarean section was associated with vitamin D concentrations below 15 ng/mL, after accounting for race, age and educational level [43].
Another American study examined a cohort of 1,153 low-income women and found a significantly higher risk of caesarean section in women with vitamin D concentrations lower than 12 ng/mL between the 8th and 18th weeks of gestation [42].
A British study analyzed the motivations behind elective and emergency C-sections [44]. After adjusting for such cofactors as BMI, ethnicity and age, no differences were found in vitamin D concentrations measured between the 11th and 13th weeks of gestation in women who would have vaginal deliveries, elective or emergency C-sections.

CONCLUSIONS

Low levels of vitamin D are frequent in the general population during pregnancy and lactation. Maternal vitamin D status during pregnancy may affect fetal and neonatal skeletal developmental mechanisms. This effect may continue after development, even reaching the stage of peak bone mass. (Such data represent an additional and important motivation for a prophylaxis of vitamin D during pregnancy).
On the evidence of results from epidemiologic observational studies and meta-analyses, low concentrations of vitamin D have been associated with a broad range of adverse complications regarding both the mother and the fetus and infant.
In women at risk of vitamin D deficiency who are pregnant or who are breastfeeding, vitamin D supplementation should be at least 600 IU/day, although vitamin D doses of 1500-2000 IU/day may be necessary to maintain 25(OH)D serum levels above 30 ng/mL. Indeed some studies in this review report doses of up to 4000 IU per day of vitamin D supplementation during pregnancy.
Currently, available studies seem to recommend starting prophylaxis with vitamin D at the beginning of the pregnancy, to be continued throughout the entire pregnancy and during lactation.

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