

VITAMIN D SUPPLEMENTATION FOR PREGNANT WOMEN

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ABSTRACT

Supplementation for pregnant women must take into account their diet, which of course depends on cultural tastes and habits, but also on the socio-economic level of each patient. Vitamin D supplementation should be systematic. Vitamin D is central to calcium-phosphorus homeostasis and bone metabolism, but it is also involved in many other tissues. Vitamin D deficiency in pregnant women is common in all populations. It is associated with an increased risk of preeclampsia, gestational diabetes, and cesarean section. The consequences in the newborn are low birth weight, a risk of neonatal hypocalcemia, neonatal rickets, and of developing asthma and / or type 1 diabetes. Prevention of vitamin D deficiency in pregnant women is therefore essential. Current recommendations for vitamin D supplementation, however, are inadequate to maintain 25 hydroxy-vitamin D levels around 30 ng / ml during pregnancy. Randomized, controlled trials of vitamin D supplementation during pregnancy are needed to assess the correct dosage to avoid the consequences of vitamin D deficiency.

KEYWORDS: Vitamin D, Supplementation, Pregnancy, Hypovitaminosis.

INTRODUCTION

Vitamin D has long been considered the key hormone in the regulation of phosphocalcic metabolism and bone mineralization.^[1,2] In recent years, epidemiological and experimental data have constantly reported a pleiotropic effect of vitamin D,^[2] in particular on the muscular, cardiovascular and immune systems, cognitive functions and the onset of cancer.

The assessment of vitamin D status is easily performed by measuring the circulating form, which is serum 25-hydroxy-vitamin D (25OHD).^[3] The concentration of Circulating 25OHD constitutes a biological marker which reflects vitamin D impregnation.^[3] Currently, it is recommended to have an optimal concentration of 25OHD greater than 30 ng / ml,^[3,4] a concentration below which deleterious effects on health are observed, particularly in the bones and muscles.^[5] However, this threshold remains very difficult to obtain in practice, apart from oral supplementation.^[6]

However, there are many publications that report lowered vitamin D levels in apparently healthy subjects.^[7-9] This has been more often reported in sunny countries such as countries around the Mediterranean and the Middle East (Middle East-North Africa: MENA).^[8] This area would probably be at high risk of bone and cardiovascular complications, etc. Nous avons effectu

une revue de la littérature pour définir le rôle de la supplémentation en vitamine D au cours de la grossesse. We will discuss the maternal and fetal consequences of vitamin D deficiency, and current recommendations for vitamin D supplementation during pregnancy.

MATERIALS, METHODS AND RESULTS

Vitamin D Dosage

To diagnose vitamin D deficiency, you need to measure 25 OH vitamin D, which represents the body's vitamin D stores. It is not necessary to measure the 1.25 OH vitamin D, except when a hereditary rickets or other phosphate pathology is suspected. This is because 25 OH vitamin D circulates in the body at significantly higher concentrations and has a much longer half-life. The assessment will be completed by a determination of calcium, phosphate and renal function (urea, creatinine). Parathyroid hormone (PTH) can also be assayed but its assay is only indicated if there is a suspicion of a pathology of the bone or of the underlying phosphocalcic metabolism or if the calcium and phosphate assays are pathological.

1) The form to be dosed

Taking into account its regulation, the dosage of 1,25 (OH) 2 D does not make it possible to evaluate the vitamin D status. Only the dosage of 25 (OH) D makes it possible to assess the body's stocks.^[10,11,12,13,14,15,16]

For patient supplementation, two forms of vitamin D are available on the market, vitamin D2 and vitamin D3.^[17] Assay kits must be able to dose both forms of vitamin D, otherwise the results of an assay performed in a person supplemented with vitamin D2 will be minimized.^[12,16]

2) Reference values

The definition of insufficiency has been the subject of much debate.^[18] The threshold has been revised upwards several times and most experts currently agree to retain

the value of 30 ng / ml. Vitamin D deficiency corresponds to a rate of less than 10 ng / ml. This threshold was retained primarily because the beneficial effects of vitamin D, in particular bone and muscle, were found for values greater than or equal to 30 ng / ml. As regards the maximum "authorized" value, it is often set at around 80 or 100 ng / ml. It should be noted that published cases of vitamin D poisoning reported blood levels often above 150 ng / ml.^[19]

Table 1: 25 OH _vitamin D level.

	Taux de 25-(OH)-vitamine D	
	ng/mL	nmol/L
Carence vitaminique D	<10	<25
Insuffisance vitaminique D	10 à <30	25 à <75
Taux recommandés	30 à 70	75 à 175
Possible intoxication vitaminique D	>150	>375

3) 25 (OH) D assay techniques

a- The different techniques

Currently, two types of methods are used, immunological methods and separative, non-immunological, direct detection methods. Competitive immunological methods consist of an assay system in which 25 (OH) D and a labeled tracer compete for recognition by an anti 25 (OH) D antibody. The markers can be isotopes (radioimmunological methods), enzymes (enzymological methods) or phosphorescent molecules (luminoimmunological methods). Separative, non-immunological, direct detection methods are based on a process of physical separation of the molecules to be analyzed, by high performance liquid chromatography (HPLC) or mass spectrometry. In France, radioimmunological techniques tend to disappear in favor of automated enzymological or luminoimmunological techniques. Separation techniques (HPLC and mass spectrometry) due to heavy and difficult technicality are currently rather reserved for research or toxicology. According to de la Hunty, the weaknesses of all these techniques are their low specificity, matrix effects and non-homogeneous standardization.^[20,21]

b-Reference technique and standardization of dosing techniques

Some assay techniques would present interferences overestimating the results due to lack of specificity and others (certain radio immunological techniques) would underestimate them due to lack of sensitivity. All in all, no assay appears to be free from specificity or sensitivity issues According to the Joint Committee for Traceability in Laboratory Medicine (JCTLM), to date there is no reference method for assaying 25 (OH) D3 and 25 (OH) D2, which makes it difficult to standardize methods and compare techniques with one another,^[12,16,22] However, the National Institute of Standards and Technology

(NIST) has developed a technique of tandem mass spectrometry coupled with liquid chromatography using which it provides a reference material (SMR972) with certified values of 25 (OH) D2, 25 (OH) D3 and 3-epi-25 (OH) D (inactive isomer of vitamin D).^[23] The problems of standardization of assays should therefore be resolved in the coming years,^[12,22,24] This lack of homogeneity is at the origin of the differences in measurements observed between laboratories and between methods and the establishment of the vitamin D status of patients depends on the laboratory where it is carried out. The recent development of a reference technique and efforts to standardize assay methods are expected to improve the definition and management of hypovitaminosis D.^[20,25,26]

DISCUSSION

Numerous epidemiological data support a role of vitamin D in the prevention of certain cancers, in reducing the risk of cardiovascular morbidity and mortality and in the occurrence of autoimmune diseases. These different effects of vitamin D have sparked particular interest in evaluating the link between vitamin D and pregnancy. Our aim is to present the state of current knowledge on vitamin D and its implication during pregnancy.

Physiology of vitamin D metabolism during pregnancy

During pregnancy, changes in vitamin D and calcium metabolism occur to provide the fetus with the calcium necessary for bone development. The fetus accumulates about 30 g of calcium during pregnancy, 80% of which during the last trimester. Serum calcium is higher in the fetus than in the mother, indicating an active transplacental transfer of calcium. There is an increase in calcium absorption during early pregnancy, which peaks in the last trimester. In contrast, vitamin D concentrations are lower in the fetus than in the mother. The 1,25 (OH) 2D concentrations increase from the start

of pregnancy in order to meet the needs of maternal and fetal calcium. In the third trimester and late in pregnancy, 1,25 (OH) 2 D levels reach their maximum. This increase in the synthesis of 1,25 (OH) 2D is linked to an acceleration of maternal renal hydroxylation, but also to hydroxylation in maternal decidual cells.^[27] Hyperparathyroidism has been suggested to explain this increase in the synthesis of 1,25 (OH) 2D, but various studies have found normal PTH levels.^[28] The increase in intestinal calcium absorption cannot be explained only by the increase in 1,25 (OH) 2D, because it occurs long before that of 1,25 (OH) 2 D. In rodents, there is an increase in intestinal calcium absorption even in the absence of the vitamin D receptor.^[29] Another potential signal allowing placental transfer of calcium and synthesis of active vitamin D is PTHrP (PTH-related peptide), produced by fetal parathyroids and the placenta. By acting at the renal and bone PTH / PTHrP receptor, PTHrP increases 1,25 (OH) 2D.^[30] Note that many other signals may be involved in the regulation of vitamin D and calcium during pregnancy: prolactin, placental lactogenic hormone, calcitonin, osteoprotegerin, and estrogens.^[28]

2. The consequences of maternal vitamin D deficiency

2.1. At the mother

a) Preeclampsia

Preeclampsia and hypertension (hypertension) complicate 3 to 10% of pregnancies.^[29] Studies have

shown that women with preeclampsia have lower levels of ionized calcium, urinary calcium excretion, and 1,25 (OH) 2 D, and higher levels of PTH, compared to normotensive pregnant women.^[30] Low serum calcium levels, via a number of mechanisms associated with hypertension, such as increased renin and PTH levels, may increase the risk of preeclampsia. A study conducted in the United States, in 274 pregnant women, showed that vitamin D deficiency before 22 weeks of pregnancy is a predictor of preeclampsia and vitamin D deficiency in newborns. Indeed, a 25 (OH) D level of less than 15 ng / ml multiplies the risk of preeclampsia by 5 (RR = 5.0 [1.7-14.1] 95% CI).^[29] On the other hand, supplementation with halibut liver oil (corresponding to 900 IU / d of vitamin D) started at 20 weeks of pregnancy reduces the risk of preeclampsia by 32%.^[31] In a multicenter study carried out in Argentina, Egypt, India, Peru, South Africa, and Vietnam, supplementation of pregnant women whose calcium intake was less than 600 mg / day did not show a reduction in preeclampsia but a reduction in the severity of the disease.^[32]

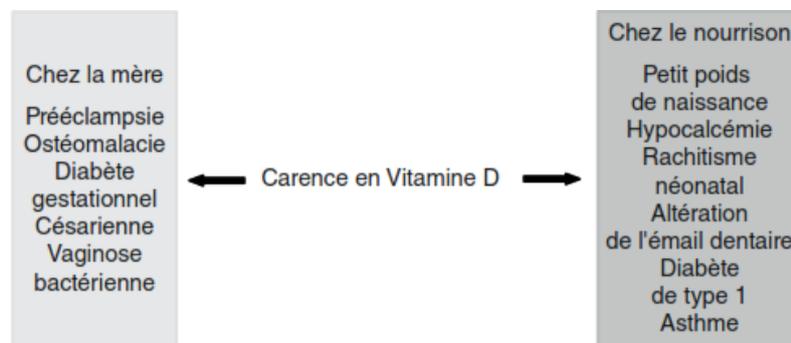


Fig. 1: Potential Impacts of Vitamin D Deficiency During Pregnancy.

A randomized controlled trial has shown that supplementation with vitamin D (1200 IU / d) and calcium (375 mg / d), started between 20 and 24 weeks of pregnancy, significantly reduces blood pressure compared to placebo. In contrast, no significant difference between the two groups was found in the incidence of preeclampsia.^[33] More randomized, controlled studies are needed to find out whether supplementation with calcium, vitamin D, or both can reduce the incidence of preeclampsia.

b). Osteomalacia

Osteomalacia is a defect in the mineralization of the bone matrix on a skeleton that has already reached its adult size. Severe vitamin D deficiency can lead to osteomalacia in the mother.

c) Gestational diabetes

Low 25 (OH) D levels are associated with an increased risk of gestational diabetes and glucose intolerance.^[34] The mechanisms mentioned are the control of insulin secretion and insulin sensitivity by vitamin D.

d) Cesarean section

A vitamin D deficiency would increase the risk of cesarean section. In a study carried out in the United States which included 253 women, 28% of women with a 25 (OH) D level below 15 ng / ml had a cesarean section.^[35] However, there is no evidence of a decrease in the rate of cesarean section after vitamin D supplementation. Randomized controlled trials of vitamin D supplementation during pregnancy are needed to confirm this data.

e). Bacterial vaginosis

Bacterial vaginosis affects 1/3 of women of childbearing age. During pregnancy, bacterial vaginosis before 20 weeks gestation is strongly associated with premature labor, low birth weight, and the risk of chorioamnionitis. One study showed that 25 (OH) D levels between 8 and 20 ng / ml are associated with a greater risk of bacterial vaginosis compared to a level of 30 ng / ml (RR = 1.65 [1.01 -2.69] and RR = 1.26 [1.01-1.57], respectively).^[36]

2.2. In infants

Vitamin D deficiency during pregnancy can affect infants in the short, medium and long term.

a) short term

Low birth weight: A case-control study reported an association between maternal 25 (OH) D levels and the risk of low birth weight for gestational age in newborns, born to Caucasian women, for values less than 15 ng / ml or greater than 30 ng / ml. The risk is three times greater when the 25 (OH) D level is less than 15 ng / ml.^[37] This relationship has not been found in black women. Another multi-ethnic cohort study showed that pregnant women with vitamin D deficiency (<11 ng / ml) in early pregnancy, have a higher risk of having low birth weight newborns.^[38]

Early or late neonatal hypocalcaemia: Numerous studies have demonstrated a risk of early or late neonatal hypocalcaemia in relation to maternal vitamin D deficiency during pregnancy. Dilated cardiomyopathies were observed in these children, whose serum calcium ranged from 4.6 to 5.8 mg / dl (normal: 9-11 mg / dl) and whose 25 OH vitamin D level was less than 5 ng / ml.^[39]

b) in medium and long term

Neonatal rickets: Vitamin D is important for the bone development of the fetus. Vitamin D deficiency during pregnancy is responsible for insufficient mineralization of the fetal skeleton. It manifests itself at birth by congenital rickets, cranio tabès and / or osteopenia.

Alterations of dental enamel: Tooth decay could originate during the life of the fetus or newborn. Studies show that infants of mothers with vitamin D or calcium deficiency during pregnancy are likely to have temporary and permanent tooth enamel abnormalities, despite taking enough supplements later on. in their life.^[40,41]

Type1 for diabetes

Vitamin D is an immunomodulator, and could be involved in the onset of type 1 diabetes. Several studies have found that vitamin D supplementation during pregnancy or in childhood decreases the risk of developing type 1 diabetes. 1.^[42,43] On the other hand, a recent Finnish study did not find an association between the intake of vitamin D during pregnancy, of food or in supplements and the risk of developing type 1 diabetes in children at high genetic risk of type 1 diabetes.^[44]

Asthma

Studies have found that increasing vitamin D intake during pregnancy decreases the risk of asthma in children during the first years of life.^[45,46]

Multiple Sclerosis

A recent American study correlated vitamin D levels during pregnancy with the risk of multiple sclerosis in children. The authors showed a halving of the risk of developing multiple sclerosis in children of mothers who took more than four glasses of milk per day or who had high vitamin D intakes.^[47] The immunomodulatory action of vitamin D may be one of the mechanisms behind this relationship.

3. Recommendations for vitamin D supplementation during pregnancy

Vitamin D supplementation during pregnancy is currently systematic. The recommended dosage is a single ampoule of 100,000 IU of vitamin D in the seventh month of pregnancy.^[48] Recent recommendations, established by the American Society of Endocrinology, recommend giving 600 IU per day of vitamin D to pregnant women. This dosage is probably insufficient to reach the target of 30 ng / ml and it is likely that a dose of 1500-2000 IU / d of vitamin D is necessary. Vitamin D supplementation at 4000 IU per day is more effective in maintaining sufficient 25 (OH) D plasma levels (> 32 ng / ml) in mothers and their newborns, regardless of ethnicity. No increased risk of toxicity was found at this dosage.^[49]

On the other hand, infants who receive exclusive breastfeeding are at high risk for vitamin D deficiency.^[50] Indeed, breast milk contains a very low concentration of vitamin D (approximately 20-60 IU / l) which represents approximately 1.5 to 3% of the maternal plasma level. These infants should receive vitamin D supplementation into their teens. A recent study showed that giving 4,000 IU per day of vitamin D to breastfeeding women who were deficient in breastfeeding could prevent complications in them and their infants.

CONCLUSION

Vitamin D deficiency is common in pregnant women. The discovery of the role of vitamin D in different conditions has shed new light on the importance of vitamin D supplementation during pregnancy. Assessment of vitamin status can be assessed by measuring 25 (OH) D in plasma. Current recommendations for vitamin D supplementation appear insufficient to maintain 25 (OH) D levels around 30 ng / ml during pregnancy. Randomized, controlled trials of vitamin D supplementation during pregnancy are however needed in order to assess the correct dosage to avoid the consequences of vitamin D deficiency.

CONFLIS OF INTEREST: No.

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