Pregnancy, Breastfeeding, and Vitamin D

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Vitamin D metabolism manifests significant changes in pregnant women in comparison to the non-pregnant state, but several questions about the role of vitamin D in pregnancy remain unanswered. Vitamin D deficiency has been reported among pregnant women and nursing mothers globally, constituting a risk group for vitamin D deficiency. Vitamin D deficiency during pregnancy has been associated not only with pregnancy outcomes but also with the posterior physical and mental health of the offspring.

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1. Vitamin D Deficiency in Pregnant and Nursing Mothers

Vitamin D status is usually conditioned by various factors, such as skin pigmentation, physical agents that block exposure to solar radiation (clothing, sunscreens, etc.), and geographical variables (latitude, climate, season, altitude, etc.) [1][2]. Therefore, these factors should be considered before making comparisons between vitamin D deficiency prevalence figures from countries with different ethnic, cultural, and/or geographical characteristics. In fact, vitamin D deficiency in pregnant women and/or nursing mothers ranges from 24–77% in Western countries (Belgium, Canada, Germany, Spain, United States, Netherlands, United Kingdom) to 46–97% in Asian and African countries (China, India, Iran, Nigeria, Pakistan, Kenya, Kuwait, Turkey) [1][2][3][4].

In summary, regardless of ethnic, sociocultural, or geographical differences, vitamin D deficiency among pregnant women represents a health problem of considerable global dimensions, constituting a relative risk group for vitamin D deficiency. Therefore, it would be a priority to develop prevention strategies (sufficient sun exposure, intake of vitamin D-fortified foods, and pharmacological vitamin D supplementation) and generalized screening of pregnant women (serum 25(OH)D determination).

2. Consequences of Vitamin D Deficiency during Pregnancy

Vitamin D deficiency during gestation, in addition to potentially causing connatal or early postnatal rickets in the newborn [5], has been associated with repeated embryo implantation failure and recurrent fetal loss [6]. It has also been associated with an increased risk of gestational hypertension and preeclampsia, gestational diabetes, and cesarean delivery, as well as prematurity and/or intrauterine growth retardation [7][8][9]. It has also been suggested that maternal–fetal vitamin D deficiency could condition various long-term pathologies through phenomena of “fetal

programming” and/or epigenetic modification, such as mineralization defects, alterations in body composition, bronchial asthma, atopic and/or autoimmune diseases, and neurodevelopmental diseases (psychomotor and/or language delay, attention deficit hyperactivity disorder, autism, etc.) [1][5][10][11][12].

3. Maternal Vitamin D Supplementation during Pregnancy

There is great controversy among professionals as to whether or not to institute generalized pharmacological vitamin D supplementation during pregnancy; moreover, there is not even a clear consensus on the optimal time period and dose of vitamin D to be administered among those countries that have decided to recommend selective and/or generalized vitamin D supplementation for pregnant women.

The authors, who question generalized pharmacological supplementation with vitamin D and advocate for more moderate measures, such as regulated sun exposure and intake of vitamin D-fortified foods in combination with analytical screening during pregnancy and pharmacological supplementation with vitamin D exclusively in pregnant women with hypovitaminosis D (deficiency and insufficiency), argue that the changes in vitamin D metabolism that take place during pregnancy are still largely unexplained. For example, circulating levels of 1,25(OH)2D during pregnancy reach “supraphysiological” values, even up to 300 pg/mL, whereas in other conditions (non-pregnant women), levels of only 80 pg/mL could be accompanied by severe hypercalcemia [13].

Fetal and/or neonatal serum 25(OH)D levels are directly related to maternal 25(OH)D levels. In this way, vitamin D deficiency in the pregnant woman would result in a lower placental transfer of 25(OH)D and, consequently, a lower accumulation or deposit of vitamin D in the newborn [14][15][16][17]. Given the high prevalence of vitamin D deficiency in pregnant women, as well as the importance of its potential consequences on maternal–fetal health, it seems risky to rely exclusively on sun exposure and the frequent intake of vitamin D-fortified foods as priority measures to achieve sufficient vitamin D status. Therefore, pharmacological supplementation of vitamin D (cholecalciferol) during pregnancy would be recommended [18][19]. In fact, a recent meta-analysis published by the Cochrane Library corroborates that vitamin D supplementation during gestation would reduce the maternal risk of preeclampsia and/or gestational diabetes, as well as intrauterine growth retardation and prematurity [8].

There is currently no uniform criterion establishing the dose of pharmacological vitamin D supplementation in pregnancy required to achieve maternal circulating levels of 25(OH)D of at least 40 ng/mL in order to optimize renal/placental production of maternal 1,25(OH)2D during gestation [13][15][20]. For example, while the IOM suggests an oral dose of 600 IU daily [21], the US Endocrine Society recommends a daily oral dose of 1500–2000 IU [22]. However, randomized controlled clinical studies have shown that daily supplementation with 600 IU of vitamin D during gestation is inadequate to achieve sufficient maternal circulating levels of 25(OH)DE, whereas maternal vitamin D supplementation with 2000 or 4000 IU daily achieves maternal 25(OH)D levels above 30 and 40 ng/mL, respectively, without any adverse maternal–fetal effects (hypercalcemia, hypercalciuria, hypocalcemia, and hypervitaminosis D) [18][23][24][25]. Recent observational studies have even emphasized the importance of maintaining sufficient maternal vitamin D levels in the first trimester of pregnancy and/or preconception period in relation to the risk of repeated embryo implantation failure in situations of vitamin D deficiency. Although

randomized controlled studies are required, these results suggest that pharmacological supplementation with vitamin D in pregnant women should begin as early as possible [26].

4. Vitamin D Deficiency in the Neonatal Period

Apart from the immediate maternal–fetal consequences of vitamin D deficiency during pregnancy that have been mentioned above, maternal vitamin D deficiency entails the risk of altered fetal and/or postnatal vitamin D status [15][16][17]. A recent meta-analysis involving pregnant women and their newborns from different population groups corresponding to the WHO regions from which data are available (Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific) indicates that more than half of the mothers at the end of pregnancy and their newborns were vitamin D deficient (although with some variability among the different geographic areas included in this research). Furthermore, there was a significant correlation between maternal and newborn umbilical cord 25(OH)D levels, with maternal levels being logically significantly higher, given the impossibility of the fetus to synthesize 25(OH)D acquired from the mother via the transplacental route [3]. In other words, the prevalence of vitamin D deficiency in both pregnant women and their newborns is considerable, making it a priority to standardize prevention strategies that, in the case of the infants, protect them from the potential adverse effects in the short and/or long term, of vitamin D deficiency.

Obviously, vitamin D supplementation would be the simplest and safest measure to prevent not only childhood rickets and/or bone health but also, given its extra-skeletal functions, overall health status. Classically, vitamin D deficiency has been related to recurrent lower respiratory tract infections (pneumonia, bronchiolitis, etc.), a condition classically called “rickets lung”, but hypovitaminosis D has even come to be related to different types of infectious diseases (urinary tract infections, otitis media, acute diarrhea, sepsis, etc.), including COVID-19. Thus, it has been speculated whether exclusive breastfeeding and infant supplementation with vitamin D could have a positive synergistic effect in the prevention of infectious diseases in infancy [27][28][29].

5. Vitamin D Content in Breast Milk

The predominant forms of vitamin D in breast milk are cholecalciferol and 25(OH)D. The estimation of the vitamin D content or its so-called “anti-rachitic activity” is based on the activity and/or biological effects of its metabolites. For example, 40 IU of vitamin D would correspond to the biological equivalent of one microgram of cholecalciferol (1 µg = 40 IU), whereas the biological equivalent of one microgram of 25(OH)D would correspond to 200 IU of vitamin D (1 µg = 200 IU). The reason is that oral administration of 25OHD is five times more effective than cholecalciferol in raising circulating concentrations of 25OHD [17][30][31][32].

Vitamin D content in breast milk is quite stable, even in prolonged breastfeeding, with seasonal variations. Its content depends on the maternal vitamin D status and, consequently, increases with pharmacological vitamin D supplementation to lactating mothers [16][17][32]. Comparative studies carried out in lactating mothers of different ethnic, cultural, and geographical conditions, while confirming the existence of variations among different

population groups, indicate a mean value of vitamin D content in breast milk and/or “anti-rachitic activity” of 45 IU/L (range: 14–88 IU/L) [30][32][33]. In other words, the vitamin D content in breast milk is clearly too low to meet the established vitamin D requirement of 400 IU per day throughout the first year of life [21][22][34]. Moreover, it has recently been noted that the vitamin D content in breast milk, both cholecalciferol and 25(OH)D, seems to have been progressively decreasing in recent decades in relation to changes in lifestyle: less exposure to solar radiation because of health and/or sociocultural reasons [31][33].

Although it is known that exposure to solar radiation can increase the vitamin D content in breast milk, there are few references on the effects of long-term continuous sun exposure on vitamin D content in breast milk, given the risk of skin carcinogenesis associated with continued exposure to solar ultraviolet radiation. In fact, research has focused on whether maternal vitamin D supplementation could not only improve the vitamin D status of the mother but also increase the vitamin D content in breast milk to a level that could supply infants with their age-standardized vitamin D requirements. Several randomized controlled clinical trials have verified that supplementation of lactating mothers with high doses of vitamin D (6000–6400 IU daily) significantly increases the antirachitic activity of breast milk, reaching values of vitamin D content in breast milk of more than 800 IU/L [16][35]. The US Endocrine Society currently recommends a daily dose of 1500–2000 IU for breastfeeding mothers to meet their own needs but warns that if it is not possible for the infant to be supplemented with vitamin D (400 IU daily), the mothers of these infants should be supplemented with 4000–6000 IU daily of vitamin D to meet the needs of their children [22].

6. Pharmacological Vitamin D Supplementation in the Infant

Even if circulating levels of 25(OH)D in pregnant women were sufficient, vitamin D stores in the newborn are practically depleted by 6–8 weeks of postnatal life; thus, sun exposure and breast milk would constitute the natural sources for an infant during the first months of life. It is currently recommended that infants under six months of age should not be exposed to direct sunlight as the most appropriate photoprotection measure to reduce the risks of skin cancer [36]; therefore, they need pharmacological vitamin D supplementation. In fact, in exclusively breastfed infants without vitamin D supplementation, the prevalence of vitamin D deficiency ranged from 67% in Japan to 76% in Ohio (United States) and 82% in the United Arab Emirates [32][35].

In 2010, the IOM, after relevant randomized clinical trials [37], updated its previous recommendations (200 IU daily) and advised increasing the prophylactic dose of vitamin D (cholecalciferol) to 400 IU daily. These recommendations have been adopted by the American Academy of Pediatrics [38], the US Endocrine Society [22], the ESPGHAN (The European Society for Paediatric Gastroenterology Hepatology and Nutrition) [39] and, in the country (Spain), the Spanish Association of Pediatrics [40]. In other words, it is currently recommended that newborns should start taking a pharmacological oral cholecalciferol supplement of 400 IU daily as soon as possible, which should be maintained during the first year of life to ensure an adequate supply of vitamin D, the effectiveness of which has been accredited by different authors [34][41][42]. However, it has also been described that the administration of an oral megadose of 50,000 IU of vitamin D in the newborn achieves similar results to supplementation with 400 IU daily of vitamin D in infants without evidence of adverse effects [43][44].

Other alternatives have been tested, such as replacing pharmacological supplementation of the infant with vitamin D with exclusively maternal supplementation, since improving maternal vitamin D status would simultaneously increase the antirachitic activity of breast milk. In fact, several randomized controlled clinical trials have verified that maternal supplementation of high oral doses of vitamin D (6400 IU daily) not only significantly increases maternal circulating levels of 25(OH)D and the antirachitic activity of breast milk but also achieves levels of 25(OH)D in the infant similar to those achieved with supplementation of 400 IU daily of vitamin D in the infant, and without evidence of adverse effects [16][45][46]. Several randomized clinical trials have also evaluated the effects of exclusively maternal and intermittent supplementation of oral vitamin D megadose. For example, with a dose of 60,000 IU of vitamin D in the immediate postpartum period and at 6, 10, and 14 weeks after delivery (240,000 IU in total) [13] or with a monthly dose of 120,000 IU of vitamin D [47], or with a daily dose of 60,000 IU during the 10 days after delivery (600,000 IU in total) [48], with similar results to supplementation with 400 IU daily of vitamin D in infants, and with no adverse effects reported.

However, there is still some concern about supplementation with high-dose and/or megadose of maternal vitamin D, despite the lack of adverse effects, perhaps because these doses are above the established upper limit of 4000 IU/day for lactating mothers [21]; however, these strategies have failed to gain wide acceptance in clinical practice [49]. Although the risk of vitamin D intoxication is unlikely (intoxication would occur if the nursing mother ingested a vitamin D supplement exceeding 10,000 IU daily for a prolonged period), given its potential negative consequences (hypercalcemia, hypercalciuria, and hyperphosphatemia, which, in turn, are responsible for soft-tissue and vascular calcification and nephrolithiasis in the long term) it is important to be aware of this circumstance and, when appropriate, to prescribe the tolerable upper level of vitamin D always established under medical supervision [1]. Future clinical trials will be necessary to ensure the minimum effective dose for the prevention of vitamin D deficiency in the infant through maternal supplementation with high-dose vitamin D, as well as to establish the safety of such regimens for use in the general population. These alternatives could be especially useful in those situations in which, for various reasons (social, cultural, economic, etc.), adherence to daily pharmacological supplementation in the infant would be particularly difficult.

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