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Vitamin D in Pregnancy

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1. Introduction

Vitamin D has an increasingly recognised repertoire of nonclassical actions, such as promoting insulin action and secretion, immune modulation and lung development. It therefore has the potential to influence many factors in the developing fetus. This paper investigates the effects of vitamin D on the placento-fetal unit and the mother, in terms of calcium metabolism (classical actions) and noncalcium effects (nonclassical actions). There is little information on vitamin D intake in pregnancy and lactation and few studies on clinical outcomes. Some have suggested that the requirement for vitamin D in these women may be up to 6000 iu/day¹ and the ideal vitamin D regimen to prevent and treat vitamin D insufficiency in utero is unknown.

2. Vitamin D deficiency

Vitamin D and its active metabolite 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) have classical actions on calcium balance and bone metabolism. Without sufficient $1,25(\text{OH})_2\text{D}$, the intestine cannot absorb calcium and phosphate adequately, which leads to secondary hyperparathyroidism and a lack of new bone mineralisation (rickets in children and osteomalacia in adults). Rickets is a childhood vitamin D insufficiency and usually develops many months after delivery. However, the neonate is at risk of hypocalcaemic tetany consequent on maternal hypovitaminosis D. Calcium levels are normal in utero when maternal vitamin D is insufficient. However, when maternal calcium delivery is interrupted at birth, the neonate may develop hypocalcaemia. While the developing fetus requires approximately 30 g of calcium, the maternal gut adapts and can overcome some vitamin D insufficiency with increased calcium transport.

Vitamin D deficiency is common in northern Europe, especially in women with pigmented skin. Vitamin D deficiency is three times more common in the winter and spring compared to the summer and autumn in the UK.² In a London antenatal population, a vitamin D level of less than 25 nmol/l was found in 47% of Indian Asian women, 64% of Middle Eastern women, 58% of black women and 13% of Caucasian women.³ In the general adult population, reduced vitamin D concentrations are found in obese subjects. Prepregnancy obesity has been associated with lower levels of vitamin D in both pregnant women and their neonates; 61% of women who were obese (body mass index [BMI] ≥ 30) prior to pregnancy were found to be vitamin D deficient, compared to 36% of women with a prepregnancy BMI of less than 25.⁴

3. Physiology

There are two forms of vitamin D. Vitamin D₃ (cholecalciferol) is produced from the conversion of 7-dehydrocholesterol in skin and vitamin D₂ (ergocalciferol) is produced in mushrooms and yeast. The biologically active form of vitamin D is $1,25(\text{OH})_2\text{D}$. This requires hydroxylation of vitamin D in the liver to $25(\text{OH})\text{D}$ (25-hydroxyvitamin D), which then undergoes renal hydroxylation to form $1,25(\text{OH})_2\text{D}$. Although $25(\text{OH})\text{D}$ has low biological activity, it is the major form of circulating vitamin D. Serum $25(\text{OH})\text{D}$ concentrations are generally thought to reflect nutritional status. Production of $1,25(\text{OH})_2\text{D}$ in the kidney is tightly regulated by plasma parathyroid hormone (PTH) as well as serum calcium and phosphate levels.

The interaction of $1,25(\text{OH})_2\text{D}$ with nuclear vitamin D receptors influences gene transcription. Nuclear receptors for $1,25(\text{OH})_2\text{D}$ are present in a range of tissues including bone, intestine, kidney, lung, muscle and skin. Similar to steroid hormones, $1,25(\text{OH})_2\text{D}$ acts via signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Its biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such

as osteoblasts and skeletal muscle. The biological effects of 1,25(OH)₂D are diverse. It inhibits PTH secretion and adaptive immunity, while promoting insulin secretion and innate immunity. It also inhibits cell proliferation and stimulates their differentiation.

The largest source of vitamin D in adults is synthesis from solar radiation; half an hour of sunlight delivers 50 000 iu of vitamin D with white-complexioned skin.³ Dietary intake of vitamin D makes a relatively small contribution to overall vitamin D status as there is little vitamin D that occurs naturally in the food supply. Melanin absorbs ultraviolet B (UVB) from sunlight and diminishes cholecalciferol production by at least 90%.⁵ Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein.

Pre-eclampsia and neonatal hypocalcaemia are the most prevalent complications of maternal hypocalcaemia and are clearly associated with substantial morbidity. A statistical association of glucose intolerance and hypovitaminosis D has been demonstrated. Maternal vitamin D is important to fetal bone development.^{6,7} Fetal lung development and neonatal immune conditions such as asthma may relate in part to maternal vitamin D levels. Although it is not clear whether maternal vitamin D supplementation will prevent these conditions, a strategy for supplementation and treatment of maternal vitamin D deficiency is proposed.

4. Maternal and fetal complications

4.1 Pre-eclampsia

There is conflicting evidence whether hypovitaminosis D in pregnancy is associated with hypertension and pre-eclampsia. In three studies, women who developed pre-eclampsia were found to have lower levels of vitamin D than women who did not⁸⁻¹⁰ with levels less than 50 nmol/l associated with a five-fold increased risk of severe pre-eclampsia.⁹ Low levels in the first half of pregnancy were related to the risk of developing pre-eclampsia and the neonates of these mothers had a two-fold increased risk of having vitamin D levels < 37.5 nmol/l (vitamin D deficient).¹⁰ In a case-control study, women with severe pre-eclampsia before 34 weeks of gestation had reduced levels of vitamin D compared to control women.¹¹ Furthermore, women with early-onset severe pre-eclampsia and a small-for-gestational-age (SGA) infant had significantly lower vitamin D levels than those with early-onset severe pre-eclampsia but non-SGA infants.¹² However, many studies have shown a weak or no relationship between vitamin D and hypertensive disorders in pregnancy. A Canadian study showed that women with low circulating maternal vitamin D levels are more likely to have hypertension in pregnancy in the univariate analysis, but not the multivariate analysis.¹³ Another study failed to show any association between vitamin D levels and the development of pre-eclampsia, gestational hypertension or preterm birth.¹⁴ A similar study from the USA also failed to demonstrate an association between maternal first trimester vitamin D levels and the subsequent development of pre-eclampsia after controlling for BMI.¹⁵ However, two meta-analyses, including a meta-analysis of 31 studies, demonstrated that vitamin D insufficiency was associated with pre-eclampsia and SGA infants.^{16,17}

4.2 Low birthweight

Maternal vitamin D levels have been shown to positively correlate with birthweight centile.¹² In a study from Holland, women with vitamin D deficiency had a 2.4-fold increased risk of having an SGA baby.¹⁸ Another study found that maternal vitamin D levels of < 37.5 nmol/l in the first half of pregnancy were associated with an adjusted odds ratio of 7.5 for SGA infants in white women, but not in black women.¹⁹ Australian researchers found that mean birthweight was 200 g lower ($P < 0.001$) in babies of vitamin D deficient mothers.²⁰

However, other studies demonstrated no relationship between maternal vitamin D levels in the first trimester and birthweight but did demonstrate that low vitamin D levels in late pregnancy were associated with reduced intrauterine long bone growth and lower gestational age at delivery.⁶

4.3 Impaired glucose tolerance in pregnancy

Hypovitaminosis D is associated with impaired glucose tolerance and diabetes in the general population. However, the evidence for an association between low vitamin D levels and gestational diabetes mellitus (GDM) is conflicting.

Low concentrations of 25(OH)D have been related to the risk of developing type II diabetes mellitus (T2DM) through effects on insulin secretion and insulin sensitivity.²¹⁻²³ However, not all studies support these findings. The Third National Health and Nutrition Examination Survey (NHANES III) did not demonstrate an association between 25(OH)D levels and diabetes or insulin resistance in African Americans, in contrast to Caucasians and Mexican Americans.²⁴ In another study of European Caucasian subjects, insulin secretion and action were not associated with levels of 25(OH)D.²⁵ It is vital that such studies are controlled for obesity, a risk factor itself for vitamin D deficiency. GDM is considered to share the same pathogenesis as T2DM and similar associations between 25(OH)D and the development of GDM have been sought. Maternal 25(OH)D concentrations have been related to the risk of developing GDM in various cohorts.²⁶⁻²⁸

Depending on the diagnostic criteria used, it has been suggested that GDM complicates up to 16% of pregnancies,^{29,30} although the true incidence can be much greater in some ethnic groups.³¹ There are some data to suggest that the association between 25(OH)D levels and GDM risk is specific to ethnicity. In a majority non-Hispanic white population, 25(OH)D concentrations at 16 weeks of gestation were significantly lower in GDM subjects than in controls, whereas no association was found in Indian mothers where 25(OH)D concentrations were measured at 30 weeks of gestation.^{28,32} Some studies have investigated more than one ethnic group using statistical techniques to correct for the effect of ethnicity, but none have been designed to describe the association in specific ethnic populations.^{27,28} Conversely, a well-conducted study has found no association between maternal 25(OH)D and the development of GDM.³³ A meta-analysis of 31 studies demonstrated vitamin D insufficiency was associated with a higher risk of GDM.¹⁶

4.4 Other complications

Vitamin D deficiency (< 37.5 nmol/l) has been associated with a four-fold increased risk of primary caesarean section (caesarean section performed for the first time),³⁴ although this has not been demonstrated in all studies.¹⁶ Vitamin D deficiency is also associated with bacterial vaginosis in pregnant women.^{35,36}

In conclusion, hypovitaminosis D may be associated with hypertension, pre-eclampsia and increased caesarean section rates. There are no randomised trials showing that vitamin D supplementation alters these putative risks.

5. Neonatal hypocalcaemic seizures

Neonatal vitamin D levels are correlated with those of their mother, with maternal vitamin D deficiency increasing the risk of neonatal vitamin D deficiency.²⁰ In an Australian study, hypovitaminosis D was found in 15% of pregnant women and 11% of neonates.²⁰ Vitamin D deficiency is a major cause of hypocalcaemic seizures in neonates and infants.³⁷ Hypocalcaemia is not uncommon in neonates and is a potentially severe problem.³⁸ Mothers of babies who suffer hypocalcaemic seizures are more likely to be vitamin D deficient (85%) than mothers of babies who do not (50%).³⁷ In another study from Egypt, all mothers of babies with hypocalcaemic seizures had severe vitamin D deficiency.³⁹

Maternal vitamin D deficiency is a common, and potentially preventable, cause of neonatal hypocalcaemia. This is especially common in South Asian women.

6. Skeletal development and growth

Hypovitaminosis D is associated with impaired growth and bone development in the fetus.^{6,7,12,16,18,19} Evidence is accruing to show that less profound maternal 25(OH)D insufficiency may lead to suboptimal bone size and density after birth without overt rachitic change.^{7,40–44} This is likely to lead to an increased risk of osteoporotic fracture in later life.^{45,46} A retrospective cohort study⁴⁷ showed that children who had received supplements with vitamin D in the first year of life had a significant increase in femoral neck bone density at the age of 8 years compared to the group that did not receive supplements.

In a UK mother–offspring cohort, 31% of the mothers had circulating concentrations of 25(OH)D in late pregnancy of 27–50 nmol/l.⁴⁰ There was a positive association between maternal 25(OH)D concentration in late pregnancy and whole body bone mineral content and density, assessed using dual-energy X-ray absorptiometry (DEXA), in the offspring at 9 years of age. Furthermore, maternal UVB exposure and vitamin D supplementation were associated with the bone mass of the child ($P < 0.05$), while lower levels of umbilical-venous calcium were also associated with lower childhood bone mass,⁴⁰ suggesting a possible role for placental calcium transport in this process. Additionally, maternal UVB exposure during pregnancy was positively associated with whole body bone mineral content in the offspring at the age of 9 years in the Avon Longitudinal Study of Parents and Children,⁴¹ although later analysis does not confirm these data.⁴⁸ Similar findings have come from another UK cohort, the Southampton Women's Survey, in which neonatal bone area and bone mineral content were reduced in the female offspring of mothers who had 25(OH)D concentrations < 33 nmol/l in late pregnancy.⁴² These findings of altered neonatal bone mass have been confirmed by a Finnish mother–offspring cohort in which babies born to mothers with circulating 25(OH)D status below the median (42.6 nmol/l) had reduced tibial bone mineral content and cross-sectional area, measured by peripheral quantitative computed tomography (pQCT).⁴³ In a follow-up study, a deficit in tibial cross-sectional area was still observed at 14 months' follow-up,⁴⁴ despite the low vitamin D group catching up with the other group for the bone mineral content.

Evidence that 25(OH)D-related changes may be detectable early in gestation has come from the Southampton Women's Survey.⁷ In this cohort, fetal distal femoral metaphyseal cross-sectional area was increased relative to femur length at 19 and 34 weeks of gestation in those babies whose mothers had low levels of circulating 25(OH)D, changes reminiscent of those seen in postnatal rickets.

These findings suggest that the adverse consequences of maternal vitamin D deficiency for the offspring are manifest early in pregnancy. There are no data from randomised controlled trials to show benefit from maternal vitamin D supplementation in terms of fetal or longer term growth of the child.

7. Fetal lung development and childhood immune disorders

Low maternal vitamin D intake in pregnancy is associated with wheeze and asthma in the offspring.⁴⁹ Low cord blood 25(OH)D concentrations have been associated with respiratory syncytial virus bronchiolitis⁵⁰ and respiratory infections.⁵¹ There are plausible physiological mechanisms for an association between prenatal vitamin D status and immune development. The metabolite 1,25(OH)₂D has been shown in animal and in vitro models to have an immune-modulatory role and low levels of neonatal vitamin D have been linked to childhood asthma.^{49,52} Maternal vitamin D supplementation is associated with cord blood gene expression of tolerogenic immunoglobulin such as immunoglobulin-like transcripts 3 and 4 (ILT3 and ILT4).⁵³ Cord blood 25(OH)D is correlated with mononuclear cell release of IFN- γ and hence Th1 cell development.⁵⁴

More research is needed on the potential association between maternal vitamin D in fetal lung development and childhood allergy; there are ongoing studies investigating long-term neonatal putative benefits of adequate maternal vitamin D.

8. Screening for vitamin D deficiency in pregnancy

There are no data to support routine screening for vitamin D deficiency in pregnancy in terms of health benefits or cost effectiveness. There is an argument that some groups of women who are pregnant should have a screening test: for example, on the basis of skin colour or coverage, obesity, risk of pre-eclampsia, or gastroenterological conditions limiting fat absorption. As the test is expensive, offering it to all at-risk women may not be cost effective compared to offering universal supplementation, particularly as treatment is regarded as being very safe. At present, there are no data to support a strategy of measurement followed by treatment in the general female population.⁵⁵ Measurement of vitamin D in a hypocalcaemic or symptomatic woman as part of their management continues to be applicable. This includes women with a low calcium concentration, bone pain, gastrointestinal disease, alcohol abuse, a previous child with rickets and those receiving drugs which reduce vitamin D.

9. Supplementation and treatment in pregnancy

Daily vitamin D supplementation with oral cholecalciferol or ergocalciferol is safe in pregnancy. The 2012 recommendation from UK Chief Medical Officers and NICE guidance state that all pregnant and breastfeeding women should be informed about the importance of vitamin D and should take 10 micrograms of vitamin D supplements daily.^{56,57} Particular care should be taken over high-risk women. The recommendations are based on the classical actions of vitamin D, although many of the nonclassical actions of vitamin D may be beneficial. As mentioned above, the review and meta-analysis by Aghajafari et al. found associations between vitamin D insufficiency and risk of gestational diabetes, pre-eclampsia, bacterial vaginosis and SGA infants.¹⁶ Of course this does not necessarily demonstrate that correction during pregnancy will reduce these risks.

Three categories of vitamin D supplementation are recommended.

1. In general, vitamin D 10 micrograms (400 units) a day is recommended for all pregnant women in accord with the national guidance.⁵⁶ This should be available through the Healthy Start programme.⁵⁸

2. High-risk women are advised to take at least 1000 units a day (women with increased skin pigmentation, reduced exposure to sunlight, or those who are socially excluded or obese).^{1,59} The RCOG has highlighted the importance of addressing suitable advice to these women.⁶⁰ Women at high risk of pre-eclampsia are advised to take at least 800 units⁶¹ a day combined with calcium.⁶² Vitamin D may be inappropriate in sarcoidosis (where there may be vitamin D sensitivity) or ineffective in renal disease. Deficient renal 1- α hydroxylation necessitates the use of active vitamin D metabolites, such as 1 α -hydroxycholecalciferol or 1,25-dihydroxycholecalciferol. Specialist medical advice should be sought in such cases. The limitation to therapy compliance mostly relates to the calcium which has a side effect of tasting of chalk, rather than the vitamin D element of oral therapy. It is often more appropriate to give vitamin D alone for patient acceptability. However, this is limited by the availability of suitable agents; vitamin D cannot be prescribed at low doses without calcium. 800-unit formulations of cholecalciferol without calcium are available (e.g. Fultium-D₃®, Internis, London; Desunin®, Meda, Bishop's Stortford, UK). There may be particular benefits of vitamin D/calcium supplementation in women at risk of pre-eclampsia.^{62,63}

3. Treatment. For the majority of women who are deficient in vitamin D, treatment for 4–6 weeks, either with cholecalciferol 20 000 iu a week or ergocalciferol 10 000 iu twice a week, followed by standard supplementation, is appropriate.^{64,65} For women who require short-term repletion, 20 000 iu weekly appears to be an effective and safe treatment of vitamin D deficiency. A daily dose is likely to be appropriate to maintain subsequent repletion (1000 iu daily). In adults, very high doses of vitamin D (300 000–500 000 iu intramuscular [IM] bolus) may be associated with an increased risk of fractures and such high doses are not recommended in pregnancy. A 2011 study demonstrated that supplemental doses of 4000 iu cholecalciferol a day were safe in pregnant women and most effective compared to the lower doses.⁶⁶

Table 1. Supplementation and treatment recommendations		
Supplementation		
	Daily units	Combined with
Vitamin D	400 ^a 800 ^b 1000 ^c	N/A Calcium ⁶⁷ N/A
Treatment		
Cholecalciferol	2800	20 000 iu a week
Ergocalciferol	2800 ^d	10 000 iu 2x weekly
^a Recommended for all pregnant women ^b Recommended for women with high risk of pre-eclampsia ^c Recommended for women at high risk of vitamin D deficiency ^d To be taken through and after the high-dose supplementation		

A comment piece in *The Lancet* argued that routine supplementation of vitamin D should be reserved for at-risk women rather than for all women.⁶⁸ This was on the basis of a large prospective cohort study showing no association between maternal serum vitamin D levels and bone mineral content in the children.⁴⁸ However, although large, this was not randomised, did not consider supplementation and only looked at one indication.

10. Safety of vitamin D

In pregnancy there is enhanced intestinal calcium absorption. Vitamin D toxicity is manifested through hypercalcaemia and hypercalciuria. Therefore, there is a hypothetical concern that when secondary hyperparathyroidism follows vitamin D deficiency, calcium given with vitamin D may be associated with temporary hypercalcaemia. However, this is self-limiting due to the associated hungry bone and has not been demonstrated to represent a clinical problem.

11. Opinion

Treatment of vitamin D deficient women and vitamin D supplementation is safe and is recommended for all women who are pregnant or breastfeeding. Low vitamin D concentrations are present in a significant proportion of the population. Women with pigmented or covered skin, obesity and immobility are at a higher risk. Low vitamin D concentrations have been associated with a wide range of adverse maternal and offspring health outcomes in observational epidemiological studies. However, despite a dearth of interventional evidence supporting supplementation/treatment of vitamin D in randomised controlled trial settings, it is generally accepted that supplementation/treatment is not harmful and may have some significant short- and long-term health benefits. Further research should focus on the potential benefits and optimal dosing of vitamin D use in pregnancy.

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