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Symposium 3: Vitamin D and immune function: from pregnancy to adolescence

Vitamin D and adverse pregnancy outcomes: beyond bone health and growth

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Concerns exist about adequacy of vitamin D in pregnant women relative to both maternal and fetal adverse health outcomes. Further contributing to these concerns is the prevalence of inadequate and deficient vitamin D status in pregnant women, which ranges from 5 to 84% globally. Although maternal vitamin D metabolism changes during pregnancy, the mechanisms underlying these changes and the role of vitamin D during development are not well understood. Observational evidence links low maternal vitamin D status with an increased risk of non-bone health outcome in the mother (pre-eclampsia, gestational diabetes, obstructed labour and infectious disease), the fetus (gestational duration) and the older offspring (developmental programming of type 1 diabetes, inflammatory and atopic disorders and schizophrenia); but the totality of the evidence is contradictory (except for maternal infectious disease and offspring inflammatory and atopic disorders), lacking causality and, thus, inconclusive. In addition, recent evidence links not only low but also high maternal vitamin D status with increased risk of small-for-gestational age and schizophrenia in the offspring. Rigorous and well-designed randomised clinical trials need to determine whether vitamin D has a causal role in non-bone health outcomes in pregnancy.

Vitamin D: Pregnancy: Adverse outcomes

Although the role of vitamin D during pregnancy is not well understood, concerns exist about the adequacy of vitamin D in pregnant women because of observational evidence linking low maternal vitamin D levels with adverse health outcomes in the mother, fetus and older offspring. Contributing to these concerns is the prevalence of vitamin D deficiency and inadequacy during pregnancy, which ranges from 5 to 84% globally based on low maternal blood levels of 25-hydroxyvitamin D (25OHD)[1]. Following a brief summary of vitamin D metabolism during pregnancy, this review assesses the evidence linking vitamin D and adverse non-bone health outcomes in the pregnant woman including pre-eclampsia, gestational diabetes, obstructed labour or Caesarean (C)-section and infectious disease; the fetus on gestational duration; and the offspring on developmental programming of type 1 diabetes, inflammatory and atopic disorders and schizophrenia. The impact of maternal vitamin D status on bone and related growth outcome is discussed elsewhere in these conference proceedings[2]. In addition, this review considers genetic interactions and emerging U-shaped risk relationships of maternal vitamin D levels with these outcomes as well as knowledge gaps and research needs.

Abbreviations: C, Caesarean; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; DBP, vitamin D binding protein; RCT, randomised clinical trial.

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Maternal and placental vitamin D metabolism

Unique among nutrients, vitamin D can be obtained either from the diet or endogenous synthesis in the skin upon exposure to UVB radiation in sunlight. Endogenously produced vitamin D binds to vitamin D binding protein (DBP) for transport to the liver whereas absorbed dietary vitamin D is first packaged into chylomicrons, released into the periphery, and subsequently transported to the liver in the resultant remnant particles. Irrespective of its source, vitamin D must be activated by two sequential hydroxylations, the first in the liver to 25OHD by 25-hydroxylase and the second in the kidney to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by 1-α-hydroxylase. Both 25OHD and $1,25(OH)_2D$ are transported in the blood bound to DBP and can be degraded to inactive metabolites by 24-hydroxylase. The 1-α-hydroxylase is also found in a number of tissues besides the kidney, including the placenta and maternal decidua; evidence for extra-renal activation of 25OHD exists from *in vitro* studies but has not yet been demonstrated *in vivo*[3]. Nonetheless, extra-renally produced $1,25(OH)_2D$ might act locally in an intracrine, autocrine or paracrine manner through vitamin D nuclear receptor to regulate transcription of a wide array of target genes involved in Ca–P homoeostasis, cell growth and differentiation and immune function.

Blood 25OHD level is the best biomarker of exposure to vitamin D because it reflects total exposure from endogenous and dietary sources and has a sufficiently long half-life. Controversy exists on the cut-points for blood 25OHD levels to assess vitamin D status because differing cut-points are proposed and in use: deficiency (<10 to <30 ng/ml), insufficiency (<20 to <32 ng/ml), sufficiency (≥20 to ≥32 ng/ml) and 'optimal' (>30 to >40 ng/ml). However, no consensus and evidence-based guidelines exist for the clinical interpretation of blood 25OHD levels as highlighted by the recent Institute of Medicine Dietary Reference Intakes Committee for Ca and vitamin D[3]. The new dietary reference intakes[3] established for pregnant women are (1) an estimated average requirement of 10 µg/d, which meets the needs of 50 % of the generally healthy population and is linked to blood 25OHD levels of 16 ng/ml; (2) an RDA of 15 µg/d, which meets the needs of 97·5 % of the generally healthy population and is linked to blood 25OHD levels of ≥ 20 ng/ml; and (3) a tolerable upper level intake of 100 µg/d, which over a long period poses no risk of adverse outcomes and is linked to a blood 25OHD level >50 ng/ml. Appropriate application of the dietary reference intakes using the linked blood 25OHD levels suggests an increased risk of inadequacy <16 ng/ml and an adequate intake ≥ 20 ng/ml. The reference nutrient intake for Vitamin D is under review presently by the Scientific Advisory Committee on Nutrition in the UK with a report anticipated in 2013–14. The current reference nutrient intake for pregnant women, established in 1998 and reviewed in 2007 by the Scientific Advisory Committee on Nutrition is 10 µg/d[4], which also noted that supplements may be needed to achieve this intake because in most cases it cannot be met from the diet.

During pregnancy, vitamin D metabolism changes, but the mechanisms whereby these changes occur are largely unknown. DBP increases as early as 8–10 weeks of pregnancy[5] and appears to precede the increase in circulating $1,25(OH)_2D$ levels[1]. DBP increases 7–152 % during pregnancy as reported in four cross-sectional[6–9] and two longitudinal studies[5,10] and decreases as early as 2 weeks post-partum returning to non-pregnant[10] or pre-pregnant[5] levels by 1·5–3 months post-partum, respectively. Evidence suggests that oestrogen may play a role in regulating this change in DBP[1]. Likewise, circulating levels of $1,25(OH)_2D$ also increase 124 %[11] to 134 %[1] based on the analyses of over thirty longitudinal, randomised clinical trial (RCT) and cross-sectional studies. Only one cross-sectional study does not report an increase of $1,25(OH)_2D$ in Nigerian adolescents[12]. Generally, circulating 25OHD levels are unchanged except in one cross-sectional study[12] and one longitudinal[13] study, which report increased levels in the third trimester.

Whether the placenta contributes to the increased maternal blood $1,25(OH)_2D$ level is not known[1]. The presence of 1-α-hydroxylase in placental trophoblasts[14] raises this possibility. Expression of placental 1-α-hydroxylase is over 10-fold greater in first and second trimester placenta than in third trimester placenta[14]. Further, a placental-specific methylation of 24-hydroxylase not only reduces expression of this enzyme *in vitro* but also ablates the responsiveness of the 24-hydroxylase promoter to $1,25(OH)_2D$[15]. Taken together, these findings support the possible sustained placental production of $1,25(OH)_2D$ without its local degradation and, perhaps, a placental contribution to circulating maternal hormone level. However, a nephrotic pregnant woman who received oral $1,25(OH)_2D$ until 21 weeks of gestation did not have elevated blood $1,25(OH)_2D$ levels, but did sustain her circulating levels of the hormone when oral treatment was discontinued for 3 weeks until delivery at 24 weeks of gestation[16]. Determining the relative contributions of maternal kidneys and the placenta to maternal circulating levels of $1,25(OH)_2D$ would advance our understanding of these maternal changes in vitamin D metabolism in pregnancy.

Maternal decidua also expresses 1-α-hydroxylase also with markedly higher expression in the first and second trimesters compared with the third trimester[14]. *In vitro*, decidual cells produce $1,25(OH)_2D$[17]. If both tissues in such close proximity to each other produce $1,25(OH)_2D$ *in vivo*, then paracrine regulation of each tissue by the other is possible. Differing genetic polymorphisms in key enzymes in vitamin D metabolism in the maternal decidua and conceptus-derived placenta could result in different genetic–environmental interactions and production of active hormone within the same maternal nutritional environment and blood 25OHD levels. Potentially, these genetic differences could result in differential paracrine regulation of one of these tissues by the other. A highly complex and compartmentalised local vitamin D regulation might exist in the placenta and decidua as depicted in Fig. 1, but our understanding of the physiology and impact of vitamin D metabolism and regulatory actions in the placenta and decidua is limited.

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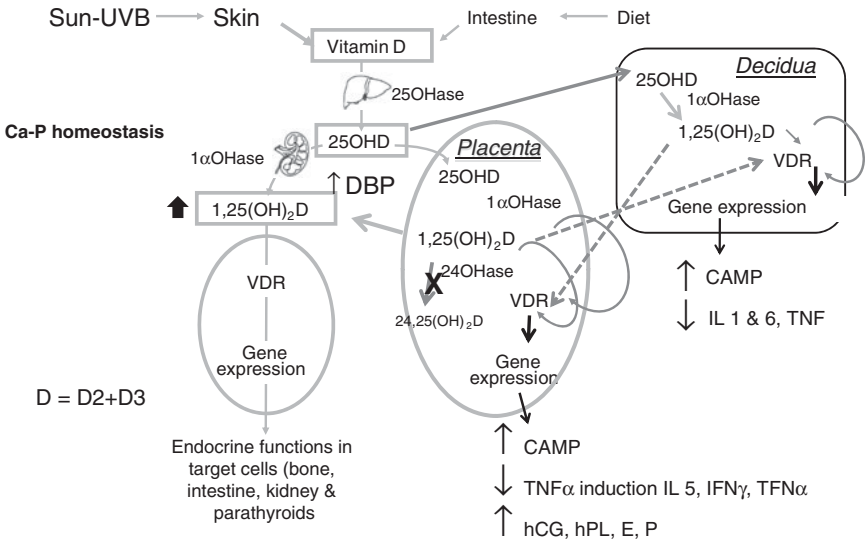

Fig. 1. A model of vitamin D metabolism and function in pregnancy. Vitamin D from either endogenous production upon exposure of the skin to sunlight or from diet must be activated by two sequential hydroxylations, first in the liver to 25-hydroxyvitamin D (25OHD) by 25-hydroxylase (25OHase) and then in the kidney to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by 1-α-hydroxylase (1αOHase). Maternal blood $1,25(OH)_2D$ levels increase in pregnancy, but 25(OH) D levels typically do not. Classic endocrine actions of $1,25(OH)_2D$ maintain Ca–P homoeostasis through its interactions with the vitamin D nuclear receptor (VDR) in target tissues such as bone, intestine, kidney and parathyroid. The 1αOHase also exists in non-renal tissues including the placenta and decidua and *in vitro* activates 25OHD. Extra-renally produced $1,25(OH)_2D$, if it occurs *in vivo*, could act intracinely, autocrinely or paracrinely. The close proximity of the placental and decidual tissue raises the possibility that these two tissues may exert a paracrine action on each other through their production of $1,25(OH)_2D$. In addition, the placenta-specific silencing methylation (X) of 24-hydroxylase (24OHase) may reduce the placental degradation of $1,25(OH)_2D$. Both in the placenta and decidua, $1,25(OH)_2D$ regulates *in vitro* the cathelicidin antimicrobial protein (CAMP) and immuno-modulatory proteins TNFα, IL and interferon-γ (IFN-γ). Additionally in the placenta, $1,25(OH)_2D$ regulates *in vitro* differentiation and production of placental hormones: human chorionic gonadotropin (hCG), human placental lactogen (hPL), oestrogen (E) and progesterone (P).

Vitamin D and adverse maternal outcomes beyond bone health and fetal growth

Maternal risk of pre-eclampsia, gestation diabetes, obstructed labour or C-section and infectious disease has been associated with low maternal circulating levels of 25OHD in a number of observational studies. Only for pre-eclampsia and C-section has a RCT been reported. For most of the observational trials, maternal Ca or P intakes are not considered. Yet, the interrelationships of these two nutrients with vitamin D metabolism are important because of the tight nutrient-responsive hormonal regulation of the production of $1,25(OH)_2D$ and degradation of both $1,25(OH)_2D$ and 25OHD in Ca–P homoeostasis[1]. Low blood Ca levels stimulate parathyroid hormone, which enhances the renal production of $1,25(OH)_2D$. This elevated $1,25(OH)_2D$, itself, enhances its own degradation and that of 25OHD by stimulating 24-hydroxylase. High blood phosphate levels stimulate osteocyte-produced fibroblast growth factor 23, which decreases renal production of $1,25(OH)_2D$ by 1-α-hydroxylase and stimulates the degradation of both $1,25(OH)_2D$ and 25OHD by 24-hydroxylase. To what extent, if any, these observational studies consider other confounders that affect maternal blood 25OHD levels such as season, maternal adiposity, skin pigmentation, physical activity and sun exposure, etc., vary. Further, the evidence for these outcomes, with the exception of maternal infectious disease, is contradictory as discussed in detail later. Thus, the evidence of vitamin D and maternal non-bone health outcomes is presently inconsistent, lacks causality and, thus, is inconclusive.

Pre-eclampsia, a major cause of maternal morbidity and mortality globally, occurs after 20 weeks of gestation with hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) and proteinuria (>300 mg protein in a 24-h urine). Global prevalence ranges from 5 to 10%[1]. Its aetiology is unknown, but abnormal placentation with incomplete placental invasion and remodelling of maternal spiral arteries is considered a key component[18]. Delivery of the placenta after birth resolves the disorder and emphasises the placenta's role. However, the aetiology is multi-factorial with maternal, placental and environmental factors proposed (Fig. 2). Inadequate placental trophoblast differentiation leading to inadequate trophoblast invasion is postulated in these multi-factorial models[19,20]. This abnormal placentation,

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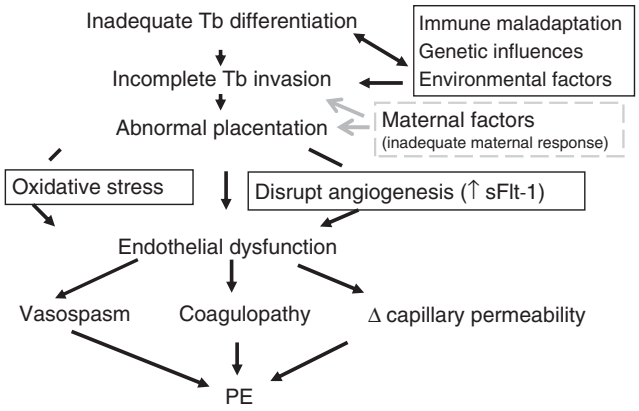

Fig. 2. Multi-factorial model of pre-eclampsia. Intrinsic factors affecting placental trophoblast (Tb) differentiation are proposed to lead to incomplete invasion and abnormal placentation, which through oxidative stress or disrupted angiogenesis causes endothelial dysfunction. This dysfunction is proposed to cause vasospasm, coagulopathy and changes in capillary permeability that result in pre-eclampsia (PE). In addition to these intrinsic factors, other factors also are proposed to affect the development of PE including immune maladaptation, genetic influences, environmental factors and maternal factors that result in an inadequate maternal response to placentation (adapted from[19,20]).

possibly through oxidative stress and disrupted angiogenesis, may lead to endothelial dysfunction resulting in vasospasm, coagulopathy and altered capillary permeability and pre-eclampsia. Yet, maternal factors resulting in an inadequate maternal response to placentation may also contribute to the aetiology[20]. Further, maternal and placental immune maladaptations, maternal and fetal genetic influences and environmental factors that are not well understood may also play a role in this abnormal placentation and the development of pre-eclampsia.

Maternal vitamin D status is one environmental factor that has been proposed to play a role in pre-eclampsia because of the linkage of low maternal vitamin D status with increased risk of pre-eclampsia in some[21–23], but not all[24–27] studies of their association. Two prospective nested case–control studies, both conducted in the USA, with forty-four and forty-nine cases, respectively[21,22], report an increased risk of pre-eclampsia with lower maternal vitamin D for pre-eclampsia[22] and severe early-onset pre-eclampsia[21]. Pre-eclamptic cases had 18% lower blood 25OHD levels on average at mid-gestation (<22 weeks[21,22]) or at term[22] compared with controls. One additional case–control study also reports 43% lower maternal blood 25OHD levels in US women with severe early-onset pre-eclampsia <34 weeks[23]. In contrast, one prospective nested case–control study in the USA reports no difference in maternal blood 25OHD levels at 11–12 weeks[24], and three case–control studies also report no relationship of maternal blood 25OHD levels at 18·5 weeks in Canadian women[27], or in the third trimester in US[25] or Danish women[26]. A single non-placebo controlled RCT conducted in India found no effect of 30 µg vitamin D given daily with 375 mg Ca on the risk of pre-eclampsia in pregnant women habitually consuming diets low in vitamin D (1 µg/d) and Ca (500 mg/d)[28], but did report a small decrease (6%) in systolic blood pressure. The evidence concerning a relationship of maternal vitamin D status with the risk of pre-eclampsia is, thus, inconclusive, and no evidence of causality presently exists.

Conflicting reports also exist on vitamin D metabolism in pre-eclamptic placentas[29,30]. Fischer *et al.*[29] report an increase in 1-α-hydroxylase activity and mRNA levels in term pre-eclamptic placental tissue whereas Díaz *et al.*[30] report only 15% of activity and reduced mRNA levels for the hydroxylase in syncytiotrophoblasts cultured from pre-eclamptic placentas (35–42 weeks). Thus, whether placental vitamin D metabolism is altered in pre-eclampsia is unclear.

Evidence from *in vitro* placental cell culture models does suggest biologically plausible roles for vitamin D in key processes implicated in the multi-factorial models of pre-eclampsia (Fig. 2), however. Vitamin D regulates immunomodulatory cytokines such as TNFα, interferon-γ and IL-6 in cultured trophoblasts and decidual cells[31] and stimulates the anti-infective cathelicidin protein[32]. Vitamin D also regulates aspects of differentiated hormonal function of trophoblasts including enhancing human chorionic gonadotropin, human placental lactogen, oestrogen and progesterone production. As shown in Fig. 1, a complex and interactive model of placental and decidual vitamin D metabolism and its actions raises the possibility that vitamin D regulates relevant placental differentiation and immunomodulatory functions. Determining whether these potential actions of vitamin D in the placenta or decidua affect the development of pre-eclampsia requires mechanistic studies in relevant model systems *in vivo* and *in vitro*.

Gestational diabetes has also been associated with lower maternal blood 25OHD levels (23%) in one cross-sectional study[33]. In contrast, no relationship is reported in two others, one a cohort study[34] and the other a prospective case–control study[35]. Further studies including well-designed, large and prospective cohort studies and placebo-controlled RCT are needed to clarify the relationship and determine the causality of vitamin D and gestational diabetes.

Obstructed labour and C-section have been assessed relative to maternal vitamin D status in only two case–control studies[36,37] and one RCT[38], which report conflicting results. Despite 37% higher maternal blood 25OHD levels in those with obstructed labour in Pakistan, no relationship is found with the risk of obstructed labour[36]. In contrast, maternal blood 25OHD levels are 37% lower in women delivering by C-section in Boston and inversely associated with an increased risk of C-section[37]. The single RCT found no difference in C-section among women receiving 10, 50 or 100 µg supplemental vitamin D daily[38]. Again, further research is needed to clarify the relationship and causality of maternal vitamin D status with obstructed labour and C-section.

Infectious disease is consistently associated with low maternal blood 25OHD levels mid-gestation in four observational studies of vaginosis[39,40], severe periodontal disease[41] and maternal HIV transmission and neonatal death[42]. Increased risk of vaginosis is reported in a cross-sectional study with an OR of 2·7 <30 ng 25OHD/ml[39] and in a cohort study with an OR of 1·26 <20 ng

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25OHD/ml or 1·65 <8 ng 25OHD/ml[40]. The risk of severe periodontal disease increases (OR 2·1) with vitamin D insufficiency defined as <30 ng/ml in a case–control study[41]. Low maternal blood 25OHD levels <32 ng/ml is associated with an increased risk (50 %) of maternal to child HIV transmission[42]. Despite the diversity of the type of infectious disease (bacterial and viral) and primary sites of infection, the association of low maternal vitamin D levels with an increased risk of these infections is the only consistent association of maternal vitamin D status with an adverse maternal health outcome. The consistency of this relationship suggests that rigorous RCT are needed to determine causality of this relationship.

Vitamin D and adverse fetal and offspring outcomes beyond bone health and fetal growth

Studies of maternal vitamin D status during pregnancy on fetal and offspring non-bone health and growth adverse outcomes are limited in number and address gestational duration/pre-term, infant infection, and developmental programming of type 1 diabetes, inflammatory and atopic disorders and schizophrenia. Observational studies report conflicting results for these health outcomes except for schizophrenia, for which only one study exists, and for autoimmune and inflammatory disorders, for which a consistent inverse association is reported in a number of studies. Only one RCT is available, which examines gestational duration. In addition to the limitations noted earlier for studies of adverse maternal non-bone health outcomes, maternal weight gain, maternal pre-pregnant BMI and socio-economic status are considered only in one study[43]. Many of the confounders in these studies during pregnancy might be sustained during postnatal developmental periods, making it challenging to distinguish *in utero* and postnatal relationships. As is true in the case of maternal adverse health outcomes, the relationship of maternal vitamin D status to fetal and offspring health outcomes is inconclusive because of the contradictory nature of the present evidence for most of these outcomes and the lack of evidence of causality for all of these outcomes.

Gestational duration is examined in three observational studies[44–46] and one RCT[38], which report conflicting results. One cohort study reports a decrease of 0·7 weeks in gestational duration in women with blood 25OHD levels <12 ng/ml at 28–32 weeks[44], but no relationship with maternal blood 25OHD levels in the third trimester is reported in a nested case–control study[46]. No relationship is reported with low maternal vitamin D intake <5 μg in another observational study[45]. In an RCT[38], vitamin D supplementation of 50 or 100 μg/d does not alter gestational duration compared with vitamin D supplementation with 10 μg/d.

Infant infection is examined in a prospective birth cohort study of 156 neonates. Cord blood 25OHD levels are 23 % lower in those who developed respiratory syncytial viral bronchiolitis in the first year with a relative risk of 6·2 in those whose cord blood 25OHD levels were <20 ng/ml compared with those >30 ng/ml[47]. Relative risk was not greater in those with cord blood levels of 20–30 ng/ml compared with those >30 ng/ml.

Developmental programming of offspring's non-bone health outcomes (type 1 diabetes, inflammatory and atopic disorders and schizophrenia) by maternal vitamin D status during pregnancy is examined in several observational studies. As noted earlier, studies of developmental programming by maternal nutritional status on subsequent offspring's health outcomes is challenging because of the difficulty of controlling for confounders in the intervening period from birth to subsequent determination of the outcome. This is particularly true for a nutrient like vitamin D in which environmental and personal confounders occurring during pregnancy might be sustained post-natally. Some studies have considered early infant supplementation with vitamin D and its relationship to later adverse health outcomes such as type 1 diabetes, but are not discussed in this review.

Type 1 diabetes risk is examined in relationship to maternal vitamin D intakes in two longitudinal studies[48,49], which report purportedly conflicting results. Neither study determined maternal blood levels of 25OHD, but such determinations would strengthen the studies and enhance the ability to determine the relationship of maternal vitamin D status to the risk of type 1 diabetes in her offspring. One study only assesses vitamin D intake from foods using an FFQ that further limits the study because supplemental vitamin D intake is not determined and total dietary intake is not assessed[48]. Vitamin D intake from food tends to be positively associated with the risk islet autoimmunity in offspring at 4 years of age ($P = 0{\cdot}059$). Total vitamin D intake during pregnancy retrospectively assessed from foods and supplements is not related to islet autoimmunity in offspring at 9 years of age[49]. Both studies have limitations that weaken the strength of this evidence; neither study supports a relationship of maternal vitamin D status during pregnancy with the risk of type 1 diabetes in the offspring.

Inflammatory and atopic disorders risk consistently associates inversely with maternal blood 25OHD levels or vitamin D intake. Four longitudinal birth cohort studies report an inverse association of maternal blood 25OHD levels[50] or vitamin D intakes[51–53] with asthma and wheezing, although one of these studies is seriously limited by its retrospective assessment of maternal vitamin D intake[53]. Maternal vitamin D intake also positively associates with a reduced risk for allergic rhinitis[50] and allergic sensitisation to food allergens[54]. The consistent association of low maternal vitamin D status with increased risk or higher maternal vitamin D status with reduced risk of inflammatory or atopic disease in their offspring in later childhood merits rigorous RCT to determine whether this relationship is causal.

Schizophrenia risk is examined in a population-based case–control study using 430 case–control pairs from the Danish Psychiatric Registry and Newborn Screening Biobank from 1981 to 1984 matched for age and birth date[55]. A U-shaped risk relationship is reported with cord blood 25OHD levels. Neonates with cord blood 25OHD levels <16·2–20·4 ng/ml had a 2-fold increased risk of schizophrenia compared with those with cord blood levels

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16·2–20·4 ng/ml. However, neonates with cord blood levels >20·4 also had a 1·71 increased risk of schizophrenia.

Emerging evidence of a U-shaped risk of adverse health outcomes with maternal vitamin D status

The Institute of Medicine Committee set the tolerable upper intake level (100 μg/d) well below frank intoxication intakes (≥250 μg/d) in adults including pregnant women because of emerging evidence of U-shaped risk relationships of vitamin D status with adverse outcomes such as all-cause mortality, CVD, selected cancers (pancreatic and prostate), etc.[3]. No evidence of U-shaped risk relationships in pregnancy was available during the time of the committee's deliberations, but since the release of the report, three studies report either a U-shaped risk relationship with adverse maternal outcomes (small-for-gestational age[56]) or offspring outcomes, developmental programming of schizophrenia[55] or increased risk of eczema in offspring of women with higher blood levels of 25OHD during pregnancy (>30 ng/ml)[43]. In all of these studies, the increased risk of adverse maternal or offspring outcomes is seen at maternal blood 25OHD levels >30 ng/ml. The concerns that led the Institute of Medicine Committee to establish the tolerable upper level at 100 μg/d, thus appear to be relevant to pregnancy and warrant further study. Given the ethical limitations of examining adverse outcome during pregnancy in human subjects and the need for long-term evaluation post-natally, rigorous studies in relevant animal models would advance our understanding of the impact of high maternal vitamin D levels on pregnancy outcomes.

Vitamin D–Gene interactions during pregnancy on non-bone health outcomes

Interest in the interaction of relevant polymorphisms of key proteins and enzymes in vitamin D metabolism with vitamin D status is growing as emerging evidence reveals the potential of such interactions to affect availability and action of vitamin D. In pregnancy, few studies exist relating such polymorphisms to adverse maternal, fetal and offspring outcomes, but the ones reported for birth weight[57,58] and maternal blood 25OHD levels[59] demonstrate the potential impact of such gene–vitamin D interactions and the need to research these interactions using genomic and metabolomic approaches.

The vitamin D nuclear receptor polymorphism, *Vdr* Fok (FF/FF), is an effect modifier of birth weight with 8% lower birth weight in maternal vitamin D deficiency (<11·2 ng/ml)[57]. The vitamin D nuclear receptor -rs7975232 SNP affects mRNA stability and is associated with birth weight in non-Hispanic blacks, but not non-Hispanic whites[58]. Finally, the prevalence of the 'AA' allele of 1-α-hydroxylase (CYP27B1(1260)) associates with maternal serum 25OHD levels >20 ng/ml in gestational diabetes patients, whereas the 'CC' or 'CA' allele is more prevalent in those with serum 25OHD levels of <10 or <20 ng/ml[59].

Conclusions and research needs

Despite the concerns about maternal vitamin D deficiency or insufficiency on adverse non-bone health outcomes and the biologically plausible roles of vitamin D in immune and differentiation processes during pregnancy, the evidence is predominantly observational with limited RCT and conflicting for both maternal outcomes of pre-eclampsia, obstructed labour or C-section and gestational diabetes and for fetal and offspring outcomes of gestational duration and developmental programming of type 1 diabetes. The evidence for these outcomes, thus, is inconclusive and lacking causality. Only for maternal infectious disease and developmental programming of inflammatory and atopic disease does the observational evidence consistently associate low maternal vitamin D status with increased risk of these outcomes. For offspring infectious disease, only a single observational study links low maternal vitamin D status with increased risk. However, for schizophrenia, a single observational study reports a U-shaped relationship with increased risk at both low and high maternal vitamin D status. Such a U-shaped risk curve is also reported for small-for-gestational age. Thus, future studies need to analyse their results for potential U-shaped risk relationships and consider carefully analyses with cut-points or sub-groupings of maternal vitamin D status that may mask such important relationships. Presently, little evidence suggests that pregnancy is a time of greater risk relative to maternal vitamin D status for adverse maternal, fetal or offspring health outcomes.

Intriguing evidence also links maternal genetic polymorphisms with risk of adverse birth weight outcomes or maternal vitamin D status. Future studies need to investigate maternal genetic interactions with vitamin D and should also consider conceptus genetic interactions with maternal vitamin D, especially in the placenta.

Finally, more research is needed to elucidate the role of vitamin D in pregnancy. We need to understand the mechanisms underlying maternal changes in maternal vitamin D metabolism and the role of vitamin D of normal and abnormal placentation. We especially need to understand the relationship and causality of maternal vitamin D status to non-bone health outcomes, particularly for maternal and neonatal infectious disease and offspring inflammatory and atopic disease, the only outcomes for which consistent observations link low maternal vitamin D status with increased risk.

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