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Vitamin D in pregnancy – current perspectives and future directions

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Abbreviations used: 1,25$(OH)_2$D [1,25-dihydroxyvitamin D], 25(OH)D [25-hydroxyvitamin D], AI [Adequate Intake], BMC [bone mineral content], BMD [bone mineral density], DBP [vitamin D binding protein], EAR [estimated average requirement], EFSA [European Food Safety Authority], FGR [fetal growth restriction], IOM [Institute of Medicine], MAVIDOS

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[Maternal Vitamin D Osteoporosis Study], NORDEN [Nordic Council of Ministers], PE [preeclampsia], PTH [parathyroid hormone], PTHrP [parathyroid hormone-related protein], SACN [Scientific Advisory Committee on Nutrition], SGA [small for gestational age], RDA [Recommended Dietary Allowance], RI [Recommended Intake], RNI [Recommended Nutrient Intake]

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Abstract

As neonatal vitamin D status is determined by circulating maternal 25-hydroxyvitamin D [25(OH)D] concentrations, prevention of maternal vitamin D deficiency during pregnancy is essential for the avoidance of neonatal deficiency. However, a high prevalence of vitamin D deficiency has been extensively reported among gravidae and neonates from ethnic minorities and white populations resident at high latitude. Currently, regulatory authorities recommend vitamin D intakes for pregnant women that are similar to non-pregnant adults of the same age, at 10-15 μg/day [400-600 IU], to meet 25(OH)D thresholds of 25-50 nmol/L. The lack of pregnancy-specific dietary recommendations is due to inadequate data indicating whether nutritional requirements for vitamin D during pregnancy differ from the non-pregnant state. In addition, there are few dose-response studies to determine the maternal 25(OH)D response to vitamin D intake throughout pregnancy at high latitude. These data are also required to determine vitamin D requirements during pregnancy for prevention of neonatal deficiency, an outcome which is likely to require a higher maternal 25(OH)D concentration than prevention of maternal deficiency only. With regard to the impact of vitamin D on perinatal health outcomes, which could guide pregnancy-specific 25(OH)D thresholds, dietary intervention studies to date have been inconsistent and recent systematic reviews have highlighted issues of low quality and a high risk of bias as drawbacks in the trial evidence to date. Many observational studies have been hampered by a reliance on retrospective data, unclear reporting, suboptimal clinical phenotyping and incomplete subject characterization. Current investigations of vitamin D metabolism during pregnancy have potentially exciting implications for clinical research. This paper provides an update of current dietary recommendations for vitamin D in pregnant women and a synopsis of the evidence relating vitamin D status with maternal and infant health.

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Introduction

As well as promoting healthy perinatal and maternal outcomes, nutritional requirements during pregnancy also need to consider, where possible, whether the intrauterine nutritional supply will promote life-long health.[1] In this context, vitamin D requirements during pregnancy are unknown. As fetal and neonatal circulating 25-hydroxyvitamin D [25(OH)D] concentrations are dependent on maternal vitamin D status, it is widely accepted that at minimum, vitamin D deficiency during pregnancy should be prevented to protect fetal skeletal development.[2, 3] However, vitamin D deficiency, albeit using various 25(OH)D cut-offs, has been reported extensively among gravidae from ethnic minorities[4, 5] and white women resident at high latitude.[6-8]

A recent systematic literature review by Saraf and colleagues[9] reported that on a worldwide basis, 54% of pregnant women and 75% of newborns had 25(OH)D concentrations < 50 nmol/L, a commonly-used threshold to describe vitamin D deficiency.[10] The Institute of Medicine [IOM],[11] the UK Scientific Advisory Committee for Nutrition [SACN][12] and the International consensus on prevention of nutritional rickets[3] identified individuals with 25(OH)D concentrations < 25-30 nmol/L as vitamin D deficient, due to a concomitant increase in the risk of metabolic bone disease. Although there were many limitations to the data available to Saraf et al., notably inconsistent reporting of unstandardized 25(OH)D data, they reported a global prevalence of 18% of pregnant women and 29% of newborns with 25(OH)D < 25 nmol/L.[9] This evidence of endemic vitamin D deficiency among mothers and infants, particularly in low-resource countries, has serious implications for maternal and child health. We recently described the first CDC-accredited gold-standard 25(OH)D data in a large maternal-infant dyad in Ireland, at 51º N.[8, 13] Overall, 11% and 17% of women at 15 weeks gestation and 35% and 46% of umbilical cord sera were < 25 and 30 nmol/L, respectively, comparable to the data reported by Saraf et al. in low-resource settings.[9]

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The appropriateness of comparing 25(OH)D concentrations in pregnant women with thresholds established in non-pregnant adults is questionable[2] and pregnancy-specific 25(OH)D cut-offs may be required. In addition, application of adult reference intervals to neonates [albeit using *de facto* measurements of 25(OH)D in umbilical cord blood] may be questionable, as neonatal status changes rapidly with infant-feeding and supplementation.[3] As these uncertainties are still outstanding, we refer to vitamin D deficiency in the current review on the basis of 25(OH)D <30 nmol/L, acknowledging that higher thresholds may be desirable in pregnancy to meet fetal requirements. Here we provide a brief overview of the current dietary recommendations for vitamin D during pregnancy and the evidence relating vitamin D status with maternal and infant health. In the context of relatively new data on vitamin D and calcium metabolism during pregnancy, we have highlighted potentially under-researched areas for further exploration in clinical studies.

Current dietary recommendations for vitamin D during pregnancy

Table 1 provides a summary of the current evidence-based recommendations for vitamin D intake in pregnant women. In general, due to a profound lack of evidence on which to set recommendations for pregnancy specifically,[11] most agencies have proposed the same adequacy thresholds for 25(OH)D and dietary recommendations for vitamin D for pregnant and lactating women as non-pregnant adults. Currently in the US and Canada, serum 25(OH)D < 30 nmol/L is the threshold below which there is an increased risk of vitamin D deficiency, 40 nmol/L fulfills the role of an average or median requirement and vitamin D sufficiency is achieved at concentrations ≥ 50 nmol/L, on the basis of skeletal health outcomes.[11] These thresholds correspond to vitamin D intake recommendations of an Estimated Average Requirement [EAR] of 10 μg/day to achieve a median population 25(OH)D concentration of 40 nmol/L and a Recommended Dietary Allowance [RDA] of 15 μg/day to meet the 50 nmol/L sufficiency cut-off.[11] In 2012, the Nordic Nutrition Recommendations for vitamin D, which

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were also based on skeletal health outcomes, recommended an intake of 10 μg/day with a view to achieving an individual 25(OH)D target of 50 nmol/L.[14]

Recently, SACN proposed a 'population protective' serum 25(OH)D concentration of 25 nmol/L as the minimum concentration that should be met or exceeded by almost all individuals, for protection of musculoskeletal health.[12] In line with the other agencies, SACN defined the vitamin D intake recommendation that would achieve this 25(OH)D target by conducting mathematical modeling of dose-response studies conducted in wintertime at high latitude, to minimise potential contributions from UVB exposure. These models provided an estimate of 10 μg/day of vitamin D for almost all individuals [97.5%, corresponding to the Recommended Nutrient Intake [RNI]] aged 11 years and over, including pregnant women, to meet or exceed the target 25(OH)D of 25 nmol/L. To avoid confusion, the RDA, RI and RNI are presented in Table 1 as individual targets. *(Table 1 near here)*

Table 1. Summary of the current dietary recommendations for vitamin D in pregnant women

Agency	**Countries**	**25(OH)D threshold [nmol/L]**			**Vitamin D intake [μg/day]**		
		Deficiency	*Population Average*	*Individual Target*	*EAR*	*RI*	*AI*
IOM [2011][11]	US/Canada	<30	40	≥50	10	15	
NORDEN [2012][14]	Nordic	<30	-	≥50	7.5	10	
SACN [2016][12]	UK	<25	-	≥25	-	10	
EFSA [2016][15]	EU	-	-	≥50	-	-	15

25(OH)D, 25-hydroxyvitamin D; EAR, Estimated Average Requirement; RI, Recommended [Individual] Intake; AI, Adequate Intake; IOM, Institute of Medicine; NORDEN, Nordic Council of Ministers; SACN, Scientific Advisory Committee on Nutrition; EFSA, European Food Safety Authority.

The European Food Safety Authority [EFSA] recently published Dietary Reference Values [DRVs] for vitamin D,[15] which, although based on a similar risk assessment exercise to the

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other agencies, are substantially different. Citing inadequate data availability as the basis for their decision, the EFSA panel did not publish average requirements or individual intake recommendations, but instead opted for an Adequate Intake [AI] for vitamin D of 15 μg/day to achieve a 25(OH)D concentration of 50 nmol/L. This intake value applies to all persons over 1 year of age, including pregnant women, for maintenance of skeletal health. The option of setting an AI value is typically reserved for nutrients where there is much uncertainty in the data, where it is not possible to recommend an EAR or a RI. The process of setting dietary recommendations is an iterative one, based on the evidence available at that time. In the case of vitamin D, the availability of several published dose-response studies including several hundred individuals have enabled international agencies in recent times to estimate vitamin D recommendations that can be applied in the context of public health nutrition and clinical practice.[11, 12, 14] In terms of public health nutrition policy, development and evaluation [e.g. fortification or supplementation programmes], the EAR, in particular, provides an established framework for assessing the adequacy of nutrient intakes in population groups. At this point, six years after an Average Requirement was proposed for the US and Canada, and in the same year that the UK proposed a RI, we believe that the EFSA decision to set an AI value for vitamin D is a missed opportunity for the European Community. This is because a framework to apply the AI in either the public health or clinical nutrition setting does not exist; by definition an AI value is inherently unreliable and therefore has limited utility.

Implementation of the IOM, SACN and Nordic Council of Ministers [NORDEN] recommendations may protect pregnant women from vitamin D deficiency, if certain outstanding assumptions, for example that pregnancy does not increase the metabolic demand for vitamin D, are met. A recent dose-response trial in Canada[16] showed that circulating 25(OH)D did not decline < 30 nmol/L in pregnant and post-partum women taking 10 μg/day [400 IU] vitamin D_3. However, a critical additional consideration is protection of fetal vitamin

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D availability during pregnancy. Cord blood concentrations, while reflective of circulating maternal 25(OH)D, are usually 60-80% of maternal values collected at delivery.[17, 18] Thus, prevention of maternal vitamin D deficiency at the lower 25(OH)D cut-off of 30 nmol/L will not ensure fetal protection at the same threshold. Notwithstanding the uncertainties around fetal and neonatal requirements, if maternal requirements for vitamin D during pregnancy were established on the basis of prevention of neonatal deficiency at the current minimum threshold of 25-30 nmol/L, a higher maternal 25(OH)D concentration would be required. A longitudinal study of maternal-infant dyads in Denmark, with maternal and cord samples measured at delivery, showed that infants born to women with a serum 25(OH)D concentration of at least 50 nmol/L did not have serum 25(OH)D < 30 nmol/L.[18] Achievement of at least 50 nmol/L required at least 25 μg/day in both the Canadian study[16] and a dose-response trial in pregnant women from New Zealand.[19] As part of the EC-funded ODIN project on vitamin D, we have completed a seasonally-balanced vitamin D dose-response study in pregnant women, which includes measurement of cord blood serum 25(OH)D [NCT 02506439], to estimate the vitamin D requirements during pregnancy and the neonatal period; this trial is now closed and will report in 2017.

Vitamin D, pregnancy and infant health outcomes – an update

Hypertensive disorders of pregnancy

The question of whether maternal and infant health outcomes can be improved by optimizing vitamin D status is of intense interest as this addresses the persistent uncertainties around 25(OH)D concentrations that meet the criteria for "optimal status". Complicating ~ 5% of pregnancies worldwide,[20, 21] preeclampsia [PE] is responsible for > 70,000 maternal and > 500,000 infant deaths annually on a global basis.[22] PE is defined as a multisystem complication with the development of hypertension on at least two occasions, four hours apart, after 20

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weeks of gestation but before the onset of labor, or postpartum, with proteinuria or any multi-system complication in a previously normotensive woman.[23] Gestational or pregnancy induced hypertension is the *de novo* development of high blood pressure after 20 weeks of gestation, without any of the abnormalities that define PE; however up to 25% of women with gestational hypertension go on to develop PE.[23] Risk factors for PE include a previous history, multiple pregnancy, primiparity, underlying metabolic disorders such as pre-existing diabetes, family history, African American race, advanced maternal age and obesity.[23] However, its aetiology is not understood and the existence of several subtypes of the disorder challenges the development of clinical prediction models. In the longer term, hypertensive disorders during pregnancy [as well as gestational diabetes] predispose mothers to cardiovascular and metabolic disorders in later life.[24] Whether increased risk of cardiovascular disease following PE is a direct cost to maternal life-long health or whether the metabolic stress of pregnancy aggravates a pre-existing risk of metabolic dysfunction is unclear. A quarter of the babies born to mothers with PE are growth restricted and a third are preterm, accounting for up to 20% of neonatal intensive care unit admissions. Gestational hypertension, with or without PE, itself predisposes to fetal growth restriction [FGR] and small for gestational age [SGA] birth, with immediate and potentially life-long consequences.

Potential role of vitamin D in the prevention of hypertensive disorders of pregnancy

In their updated Cochrane review of vitamin D supplementation and maternal and infant health outcomes, De-Regil et al. included 15 trials, assessing a total of 2,833 women.[25] Nine trials compared the effects of vitamin D versus no supplementation or a placebo and 6 trials compared the effects of vitamin D and calcium with no supplementation. Data from two trials involving 219 women, both of which were of low quality, suggest that women who received vitamin D supplements may have a lower risk of PE than those receiving no intervention or placebo. A systematic review and meta-analysis of observational studies of 25(OH)D and

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pregnancy outcomes by Aghajafari et al. included 31 studies, of which 9 focused on PE.[26] Heterogeneity in the studies was a limiting factor in the meta-analysis, but there was a substantial difference in serum 25(OH)D concentrations between women who subsequently developed PE and those who did not. The authors were persuaded that, given the mechanistic underpinning and biological plausibility of the associations between vitamin D and metabolic abnormalities including hypertension, plus the relative consistency in the observational data and the likelihood that low 25(OH)D preceded the adverse outcome [therefore reducing the likelihood of reverse causation], intervention studies with defined outcomes were warranted.

Although gestational hypertension is clinically managed in high resource settings and perceived as a 'softer' outcome than PE, it is a meaningful indicator of an unhealthy pregnancy. In their systematic review of observational studies, Harvey et al. identified 11 studies [6 case-control, 4 cohort, 1 cross-sectional] that examined the effect of maternal serum 25(OH)D concentration during pregnancy on gestational hypertension, with inconsistent findings.[27] Similarly, Thorne-Lyman and Fawzi concluded from their systematic review and meta-analysis that the evidence for a benefit of vitamin D on maternal outcomes was insufficient to draw firm conclusions.[28] A recently conducted economic analysis of the burden of vitamin D deficiency in pregnant women in the UK concluded that despite uncertainties in the data, there was enough evidence to propose that addressing vitamin D adequacy in pregnant women in England and Wales would reduce PE cases by a margin sufficient to have a positive impact on the national health budget.[29]

From the perspective of infant health, Aghajafari et al. identified a significant association between maternal 25(OH)D levels and risk of SGA birth.[26] More recently, we reported a 36% lower risk of combined PE and SGA birth at 25(OH)D concentrations > 75 nmol/L among a large cohort of well-characterized, low-risk nulliparous women.[8] A low birth weight, in conjunction with asymmetric growth and a reduced amniotic fluid index, distinguishes FGR

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from SGA. FGR is coupled with an increased risk of preterm birth,[30] which was ranked seventh in the leading causes of global years of life lost.[31] Several investigators have described an association of preterm birth with low maternal vitamin D status.[28, 32, 33] The series of events that initiate preterm birth, including induced uterine contractions, membrane rupture and subsequent dilation and effacement of the cervix,[33] are potentially accompanied by systemic inflammation, which is associated with low 25(OH)D status.[32] It is likely that 25(OH)D concentrations measured at time-points closest to delivery, reflecting maternal vitamin D status at that time, are better predictors of preterm birth than those taken in early gestation.[34]

Longer-term child health outcomes have been examined in several prospective birth cohort studies. Evidence for an inverse association between impaired skeletal development in children[35, 36] and maternal 25(OH)D concentrations throughout gestation have been extended to offspring skeletal health in young adulthood.[37] Maternal vitamin D supplementation during pregnancy significantly reduces the risk of infantile rickets and hypocalcaemia.[38] However, results from the recent Maternal Vitamin D Osteoporosis Study [MAVIDOS] suggest there is no beneficial effect on offspring whole body bone mineral content [BMC] when expectant mothers are supplemented with 25 μg/day [1000 IU] vitamin D_3 compared with placebo.[39] In a pre-specified secondary analysis, the authors noted a significant treatment-by-season interaction, where supplementation had a positive effect on neonatal bone area, BMC and bone mineral density [BMD] for infants delivered during late winter and early spring. Nonetheless, interpretation of such findings are cautioned and clarification of the long-term implications on offspring bone health will be expected following completion of the MAVIDOS childhood study.[39] It should be noted that the incidence of vitamin D deficiency was very low in MAVIDOS, as women were only eligible for randomization if their 25(OH)D was between 25 and 100 nmol/L at screening, and the placebo arm received 10 μg/day [400 IU].

Vitamin D metabolism during pregnancy

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Acquisition of a deeper understanding of vitamin D metabolism during pregnancy is an area of intense research interest,[40, 41] because the physiologic adaptations of pregnancy alter maternal vitamin D metabolism, thereby influencing fetal availability, which may have a pronounced effect on vitamin D requirements during pregnancy. Beginning late in the first trimester and continuing until after delivery, circulating levels of both vitamin D binding protein [DBP][42] and serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D][43] increase. DBP levels begin to rise as early as 8-10 weeks' gestation, preceding the steady increase in serum 1,25$(OH)_2$D, which commences approximately 2 weeks later. The mechanism controlling the elevation of circulating DBP in pregnancy is undefined, however, oestrogen regulation has been suggested.[2] At term, expectant mothers have approximately twice the concentration of circulating 1,25$(OH)_2$D as non-pregnant women,[43] which is generated by increases in renal synthesis of 1,25$(OH)_2$D plus placental and/or decidual tissue production.[2, 44, 45] A surge in 1a-hydroxylase [CYP27B1] expression, the enzyme that catalyses conversion of 25(OH)D to 1,25$(OH)_2$D, is accompanied by decreased expression of the catabolic enzyme, 24-hydroxylase [CYP24A1].[44, 46] In this way, placental/decidual tissues have the potential to generate significant amounts of 1,25$(OH)_2$D without undergoing catabolic inactivation.[47] The purpose of these steep increases in placental-decidual production in 1,25$(OH)_2$D is not clear. While metabolic adaptations to pregnancy that facilitate fetal calcium accretion, outlined in the following section, are not likely to be the target effect, some investigators have proposed an immunomodulatory function for vitamin D within the placenta and maternal decidua. This relies on local availability of 25(OH)D for paracrine production of 1,25$(OH)_2$D,[47] which has implications for maternal 25(OH)D thresholds and vitamin D requirements.

Calcium metabolism during pregnancy and the PTH-axis

Recently, Scholl and colleagues have described the concept of "calcium metabolic stress", the result of a low calcium-containing diet and/or low serum 25(OH)D. This causes secondary

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hyperparathyroidism in pregnancy, which increases the risk of PE as well as other adverse perinatal outcomes such as SGA.[48, 49] Pregnancy-specific adaptations to vitamin D metabolism parallel alterations in the broader calcium homeostatic system, invoked to meet the demands of the developing fetus. As summarised above, maternal increases in $1,25(OH)_2D$, which increase calcium absorption and reduce calcium excretion, occur independently of the classical parathyroid hormone [PTH]-vitamin D endocrine system.[50] PTH levels fall early in pregnancy and remain low, before rising late in gestation to reach pre-pregnancy levels post-partum.[51] A decrease in serum calcium likely reflects the hemodilution associated with pregnancy.[11] Although the majority of fetal calcium is accrued in the final trimester, maternal calcium absorptive capacity increases markedly early in pregnancy and remains high throughout.[52] To facilitate fetal mineral demands an increase in bone resorption and formation occurs in pregnancy, leading to a transitory reduction in BMD.[53] Special consideration should be given to pregnancy in adolescence, a period associated with active bone accretion, in which additional maternal skeletal adaptation may be required.

Fetal calcium homeostasis differs considerably from that of the mother, uniquely adapted to facilitate skeletal mineralization. Calcium and phosphorous are actively transferred through the placenta but this does not determine fetal levels, which are maintained at higher concentrations than in maternal circulation.[54] $1,25(OH)_2D$ circulates at low levels in the fetus, likely due to suppression of 1a-hydroxylase by the high levels of calcium and phosphorous. Although fetal PTH concentrations are relatively low, PTH-related protein [PTHrP], the origins of which remain unclear, is present at high concentrations. As summarised from Kovacs,[55] both PTH and PTHrP play crucial roles in fetal bone and mineral metabolism; maintaining serum calcium and phosphorous levels and regulating endochondral bone development, with PTHrP [and possibly PTH] also aiding placental mineral transfer. Such observations, largely from animal data, have led some to suggest that alterations to PTH/PTHrP activity, such as those caused by

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calcium metabolic stress, may give rise to a programming effect on bone development.[56] Although PTH and PTHrP exhibit additive effects and utilise the same receptor, they are not interchangeable, having distinct modes of regulation and action.[55, 57]

Despite the many adaptations in the vitamin D/calcium metabolic system during pregnancy, the inverse 25(OH)D/PTH relationship is retained, if slightly weakened.[58, 59] More controversial is the threshold relationship between 25(OH)D and PTH, reflecting the 25(OH)D level at which PTH stops increasing or below which PTH increases rapidly. While many studies identify a plateau level of 25(OH)D, others suggest a negative exponential relationship which is linear when the data is expressed as log values and as such has no threshold value.[60] Such heterogeneity likely results from inter-study population and methodological differences. Challenges in consistent measurement of PTH include the bimodal, pulsatile secretion of PTH,[61] with large sample sizes perhaps the only feasible choice to overcome such inherent biological variability. There is considerable scope for exploring these dynamics in large, well-characterized pregnancy-specific cohorts. Although the interplay between calcium and vitamin D is well established in terms of bone health, the combined effects of vitamin D and calcium are not often considered in pregnancy and perinatal studies. Dairy intake, a proxy for calcium and vitamin D intakes, has been associated with birth weight and fetal femur growth.[62, 63] Interactive effects, in which the detrimental effect of a deficit in one nutrient may be mitigated by sufficiency of the other, should also be considered; such a phenomenon is seen in pregnant adolescents.[64]

Elevated PTH reflects stress in the calcium metabolic system, which may be caused by either insufficient calcium intake or low 25(OH)D status [secondary hyperparathyroidism]. In pregnant Pakistani women, PTH was negatively correlated with crown-heel length and birth weight, neither of which were related to 25(OH)D.[65] This, in combination with a positive relationship between serum ionised calcium and crown-heel length, led the authors to conclude

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that any effect of maternal vitamin D deficiency was indirect, through alteration of maternal calcium homeostasis. Thus, investigation of PTH concentrations in pregnancy as a proxy for maternal calcium stress may help clarify the roles of vitamin D and calcium in maternal and fetal health, as disruption to homeostasis in the calcium metabolic system may have non-skeletal effects. Scholl et al. found a 2-3 fold increase in SGA risk, along with lower birth weight, birth length and head circumference, in women who exhibited dysregulation of maternal calcium homeostasis.[49] PTH, but not 25(OH)D, was associated with β-cell dysfunction and dysglycemia in pregnancy, with incident gestational diabetes progressively increasing across the tertiles of PTH.[66] Secondary hyperparathyroidism [defined by elevated PTH in conjunction with low 25(OH)D] increased the risk of PE three-fold, with no increase in risk in those with low 25(OH)D or elevated PTH only.[48] Given that PE is indicative of uteroplacental dysregulation and thus results in FGR, an indirect effect on bone growth must also be considered. Taken in totality, the evidence indicates that further studies addressing calcium metabolic stress, alongside vitamin D, and birth outcomes may be warranted.

Conclusions and future directions

Recent high-profile systematic reviews of vitamin D trials and observational studies have highlighted poor quality and significant heterogeneity in the observational data.[26-28] In their updated Cochrane review of vitamin D [and/or calcium] intervention studies in pregnancy, De-Regil et al. found limited evidence for a role of vitamin D supplementation in preventing PE, low birth-weight and preterm birth, all of which impact fetal and neonatal growth, but urged caution in the clinical interpretation of the data due to low quality, absent reporting of adverse effects and a high risk of bias in most studies.[25] In addition to common design, implementation and analytical differences, some of the discrepancies in study outcomes may be due to incomplete characterization of study populations. For example, nutritional assessment, including a dietary analysis, is often not included in many protocols. Calcium intake is typically

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ignored, despite its intimate metabolic connection with vitamin D and documented potential for reducing blood pressure in some women with PE.[67] Clinical risk factors, such as overweight, and indicators of a healthy lifestyle such as smoking, supplement use and physical activity levels, are also relevant confounders implicated in adverse perinatal outcomes,[23] as well as predictors of vitamin D status,[8] and should always be included in clinical assessment protocols.

Thus, at present, there are insufficient trial data to justify setting pregnancy-specific recommendations for vitamin D. Currently, the dietary intake for vitamin D recommended for non-pregnant individuals is 15 μg/day [600 IU] in the US and Canada[11] and 10 μg/day [400 IU] in the UK[12] and the Nordic countries[14]. Two vitamin D dose-response studies in pregnancy indicate that while 10 μg/day will protect against maternal deficiency at the 30 nmol/L threshold, a higher dose is required to protect against neonatal deficiency at the same threshold.[16, 19] Among calls for larger and better trials, investigators need to consider a further challenge. The minimum *individual* recommendation for vitamin D intake currently proposed by the regulatory agencies is 10 μg/day. Therefore, as the MAVIDOS trial has shown,[39] it is highly unlikely that ethical review boards will consider randomization to a true [zero] placebo in pregnancy trials with vitamin D. In an intervention study, where the "placebo" is 10 μg/day, the minimum of the range of 25(OH)D concentrations among participants will be 30 nmol/L. This will present significant design and resource challenges in implementing sufficiently powered studies to detect a reduction in the incidence of serious outcomes, such as PE, that may be dependent on achieving target 25(OH)D concentrations within a narrow range.

Finally, in the absence of maternal and cord reference ranges for 25(OH)D, different thresholds describing "vitamin D deficiency" are used. In common with Saraf and colleagues,[9] we urge the international community to adopt a policy of transparent data reporting, describing serum

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25(OH)D concentrations across a range of debated thresholds, to enable international comparison.

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