Special Article

Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions

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A high prevalence of maternal vitamin D inadequacy during pregnancy and at delivery has been demonstrated in various ethnic populations living at different latitudes. Because placental transfer of 25(OH)D is the major source of vitamin D to the developing human fetus, there is growing concern about adverse health impacts that hypovitaminosis D during pregnancy may have on the mother as well as the offspring in utero, in infancy, and later in life. While there is lack of consensus regarding the optimal circulating 25(OH)D concentration in pregnancy, it is evident that prior levels used to establish intake recommendations and vitamin D content of prenatal vitamin supplements were too conservative. This review summarizes vitamin D metabolism in the perinatal period, examines evidence regarding outcomes of insufficiency in the mother and offspring, discusses risk factors and prevalence of insufficiency, and considers strategies for public health intervention.

INTRODUCTION

The discovery of multiple functions of vitamin D that are important for growth and development, including regulation of cellular differentiation and apoptosis,[1] immune system development,[2] and brain development,[3] has led to increased interest in the role of this vitamin during pregnancy. Despite the fact that pregnant women in most countries are encouraged to take a daily prenatal vitamin supplement containing vitamin D, a disturbingly high prevalence of hypovitaminosis D has been demonstrated amongst pregnant women in nearly all populations studied. Reported prevalence of maternal vitamin D deficiency at or near term, defined as circulating 25(OH)D <25–50 nmol/L, has ranged from 5–20% in light-skinned populations to 30–70% amongst dark-skinned or veiled populations living at various latitudes.[4–14] Because the human fetus is entirely dependent on the maternal pool of vitamin D, there is growing concern about the functional impacts that hypovitaminosis D during gestation may have on the offspring in utero, in infancy, and later in life. The present review summarizes vitamin D metabolism in the perinatal period, examines potential outcomes of insufficiency in the mother and offspring, discusses risk factors and prevalence of insufficiency, and considers possible strategies for public health intervention.

OVERVIEW OF VITAMIN D METABOLISM AND DETERMINATION OF STATUS

Vitamin D is obtained by humans through cutaneous synthesis from the precursor 7-dehydrocholesterol upon ultraviolet B (UVB) irradiation of the skin or from dietary intake. Fatty fish and fish liver oils are the main natural dietary sources, with an additional contribution in the United States from fortified foods including milk, breakfast cereals, and some orange juices. Once synthesized in the skin or ingested, vitamin D as cholecalciferol (D_3) or ergocalciferol (D_2) is absorbed into the bloodstream and transported to the liver by the vitamin D binding protein (VDBP). In the liver, the mitochondrial

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enzyme 25-hydroxylase rapidly converts vitamin D to 25-hydroxy-D [25(OH)D], the main circulating and storage form of the vitamin and that which is accepted as being a biomarker of vitamin D status. In the kidney and a wide range of other target tissues, the 1-α-hydroxylase CYP27B1 converts 25(OH)D to the active form of vitamin D, $1,25(OH)_2D$. Both 25(OH)D and $1,25(OH)_2D$ are catabolized to more polar metabolites by vitamin D 24-hydroxylase CYP24A1, a mitochondrial cytochrome P450 enzyme.

The circulating 25(OH)D concentration sufficient to meet the physiological needs of humans is an ongoing subject of debate. In adults, optimal circulating 25(OH)D has often been defined as the concentration that maximally suppresses serum parathyroid hormone (PTH), a criterion grounded in the fact that hyperparathyroidism promotes bone loss. A serum 25(OH)D level of <37.5 nmol/L in adults is defined as deficient by the Centers for Disease Control and Prevention based on this criterion.[15] However, the concentrations of 25(OH)D that have been found to suppress PTH actually vary from 20 to 110 nmol/L, in part because PTH concentrations are influenced by diet, time of day, renal function, and physical activity in addition to vitamin D status.[16] As research in the field of vitamin D nutrition has developed, other outcomes such as bone mineral density, calcium absorption, dental health, and risk of falls, fractures, and colorectal cancer have been used to determine optimal circulating 25(OH)D concentrations. A review of randomized controlled studies evaluating threshold concentrations of 25(OH)D associated with these health outcomes concluded that advantageous serum concentrations begin at 75 nmol/L and are best between 90 and 100 nmol/L.[16] Many experts are of the opinion that 25(OH)D levels <50 nmol/L should be considered deficient and 51–74 nmol/L insufficient.[17] Overall, evidence is lacking regarding appropriate cut-points to define vitamin D status during pregnancy.[18]

MATERNAL-FETAL VITAMIN D NUTRITION

Based on direct evidence from animal studies and correlations between cord and maternal blood concentrations of 25(OH)D in humans, it is known that 25(OH)D readily crosses the human placenta and that the vitamin D pool of the fetus is entirely dependent on that of the mother.[19] Concentrations of 25(OH)D in cord blood at delivery range from 68 to 108% of maternal concentrations according to numerous investigators.[20] At physiological concentrations, there is inconsistent evidence of transplacental transfer or correlation between maternal and fetal concentrations of $1,25(OH)_2D$. The placenta itself contains 1-α-hydroxylase and, in addition to the fetal kidney, may contribute to the production of fetal $1,25(OH)_2D$. However, based on studies of infants with renal agenesis, it appears that most of the $1,25(OH)_2D$ in fetal plasma is synthesized in the fetal kidney.[19] Little is known regarding placental transfer of cholecalciferol in humans, though its contribution to fetal status is likely minor given that 25(OH)D is the main circulating form of the vitamin.

Maternal concentrations of $1,25(OH)_2D$ double or triple starting in the first trimester of pregnancy.[18] This rise may be attributed to increased expression of 1-α-hydroxylase and VDR in placental and decidual cells of early pregnancy[20,21] as well as placenta-specific methylation in the promoter region of the CYP24A1 gene resulting in decreased expression of the catabolic enzyme 24-hydroxylase.[22] It is notable that PTH, the usual stimulus for increased renal hydroxylation of 25(OH)D, may actually fall to the lower end of the normal range during pregnancy.[18,23]

VITAMIN D, CALCIUM, AND BONE HOMEOSTASIS DURING PREGNANCY

During gestation, the fetus accrues an average of 30 g of calcium, 99% of which is contained in the skeleton.[18] An increased efficiency of maternal calcium absorption from approximately 35% in the nonpregnant state to approximately 60% during the third trimester of pregnancy appears to be the primary mechanism to support fetal calcium accretion.[23] The near doubling of intestinal calcium absorption has commonly been attributed to the similar rise in $1,25(OH)_2D$ during pregnancy; however, vitamin D-deficient or VDR-null animal models have demonstrated an upregulation in calcium absorption similar to controls.[18,24] It has been hypothesized that prolactin and placental lactogen stimulate intestinal calcium absorption independently of $1,25(OH)_2D$ during pregnancy.[18]

Although maternal bone resorption may contribute to fetal calcium accretion, the evidence is inconclusive. Results of longitudinal studies of BMD during pregnancy are conflicting; while some have shown decreases in bone density in the spine, hip, and ultradistal radius,[25–30] others have shown no change[31–34] or even an increase in bone density at cortical sites.[29] Bone resorption markers are modestly increased during pregnancy[18] while osteocalcin, a marker of bone formation, is decreased from midpregnancy through delivery.[35,36] In vitamin D-deficient rats, skeletal mineral content was shown either to increase[37] or to decrease[38] during pregnancy. No human studies have focused specifically on the relationship between vitamin D status during pregnancy and maternal bone turnover.

VITAMIN D STATUS AND REPRODUCTIVE HEALTH

In vitamin D-deficient, VDR-ablated, or 1-α-hydroxylase-null animal models, adult females demonstrate reduced fertility and give birth to small litters. In pregnant vitamin D-deficient rats and mice, sporadic deaths have occurred late in pregnancy, possibly due to hypocalcemia during the period of rapid calcium transfer to the fetus.[18] Reduced fertility in conjunction with vitamin D deficiency has not been investigated extensively in humans, but a recent study demonstrated significantly higher serum and follicular fluid 25(OH)D concentrations in women who achieved clinical pregnancy following in vitro fertilization.[39] It has been speculated that adequate $1,25(OH)_2D$ concentrations for dampening Th1 immune function may be required for the immune tolerance of implantation and successful maintenance of pregnancy.[20,40] This theory is supported by the increased expression of 1-α-hydroxylase and VDR genes in human placental and decidual tissue during the first and early second trimesters of pregnancy.[20]

There has been limited research on the association between maternal vitamin D status and pregnancy complications such as preeclampsia, gestational diabetes, cesarean section, and bacterial vaginosis. One nested case-control study of women who were followed from 16 weeks of pregnancy demonstrated a doubled risk of preeclamsia for every 50 nmol/L decline in serum 25(OH)D concentration prior to week 22 of gestation (adjusted odds ratio [OR] 2.4, 95% confidence interval [CI] 1.1–5.4).[41] Another prospective cohort study found a 27% reduction in the risk of preeclampsia in women receiving 400–600 IU/day of vitamin D from supplements at midpregnancy compared to women not reporting supplementation (adjusted OR 0.73, 95% CI 0.58–0.92).[42] Serum concentrations of $1,25(OH)_2D$ were found to be lower in preeclamptic compared to normal pregnant women,[43] although it is possible that this is due to a decreased ability of preeclamptic placentas to convert 25(OH)D to $1,25(OH)_2D$.[44]

Some evidence exists for an association between gestational diabetes and circulating maternal 25(OH)D.[45,46] Zhang et al.[46] found plasma 25(OH)D at 16 weeks gestation to be significantly lower in women who subsequently developed gestational diabetes than in controls matched by season of conception, with the relationship remaining significant following adjustment for maternal age, race, family history of diabetes, and pre-pregnancy BMI. The authors reported a 1.29-fold increase in risk of gestational diabetes for every 12.5 nmol/L decrease in plasma 25(OH)D in non-Hispanic white subjects (adjusted OR 1.29, 95% CI 1.05–1.69).[46] Another study found a borderline significant inverse association between fasting plasma glucose and serum 25(OH)D at midgestation after adjusting for ethnicity, age, and BMI (adjusted correlation coefficient −0.13, 95% CI −0.26–0.01). However, the odds ratio for gestational diabetes with serum 25(OH)D <50 nmol/L did not reach significance (OR 1.92, 95% CI 0.89–4.17).[47] It has been suggested that the relationship between gestational diabetes and vitamin D status may be mediated by a single nucleotide polymorphism in the CYP27B1 (1-α-hydroxylase) promoter region.[48]

Vitamin D status was associated with risk of primary cesarean section in a study conducted in Boston, USA, between 2005 and 2007; women with 25(OH)D concentrations <37.5 nmol/L were nearly four times more likely to have a cesarean delivery than women with 25(OH)D concentrations ≥37.5 nmol/L (adjusted OR 3.84, 95% CI 1.71–8.62).[17] The authors hypothesized that the increased incidence of cesarean deliveries in vitamin D-deficient women may have been mediated by suboptimal muscle performance and strength during labor. However, no significant association between mode of delivery and vitamin D status was found in a population-based study of 971 pregnant women in Sydney, Australia.[5]

One trial has investigated an association between vitamin D status during pregnancy and bacterial vaginosis, a vaginal infection associated with preterm delivery. Among African American women tested at <16 weeks gestation, an inverse dose-response relation was observed between serum 25(OH)D and prevalence of bacterial vaginosis (adjusted prevalence ratio 0.82 per 15 nmol/L increase in serum 25(OH)D, 95% CI 0.68–0.99).[49] The same trend was not observed in Caucasian women, possibly due to the small number with severe vitamin D deficiency.

VITAMIN D STATUS DURING PREGNANCY AND FETAL AND INFANT OUTCOMES

Because vitamin D is involved in a wide variety of physiological processes, including skeletal development and cell differentiation, a number of studies have investigated the impact of maternal vitamin D status on infant birth outcomes.

Anthropometry

While some studies have demonstrated shorter knee-heel length[50] or lower birth weight[51,52] in infants born to mothers with low dietary vitamin D intake or low circulating 25(OH)D concentrations, other studies have shown no differences[6,53,54] or even greater birth weight[13] among infants of vitamin D-deficient mothers. Any relationship between maternal vitamin D status and birth weight or size is likely to be obscured by multiple confounding factors including maternal ethnicity, pre-pregnancy BMI,

weight gain during pregnancy, gestational diabetes, smoking, and parental stature.

Bone mineralization

Despite the recognized role of vitamin D in bone metabolism and the prevention of rickets, the effect of subclinical vitamin D deficiency during pregnancy on fetal and neonatal bone mineralization remains to be elucidated. Advances in the ability to measure bone mineral content (BMC) directly through single-photon X-ray absorptiometry, dual-energy X-ray absorptiometry, quantitative ultrasound, and computerized tomography have provided quantitative tools for comparison of bone development.[55] Epidemiological evidence comparing infant whole-body mineral content in countries in which milk products are or are not fortified with vitamin D suggests that BMC values are approximately 20% lower in countries without fortification.[56,57] In South Korea, where vitamin D supplementation during pregnancy is uncommon, Namgung et al.[58] reported significantly lower mean cord serum 25(OH)D concentrations and total body bone mineral content in winter-born compared to summer-born newborns.

Other evidence contradicts an association of bone mineral content with vitamin D status in neonates. In studies of vitamin D-deficient rats, 1-α-hydroxylase-deficient pigs, and VDR-null mice, offspring skeletal mineral and calcium content were normal.[18] A human study conducted in The Gambia found no significant relationships between maternal 25(OH)D concentration at 20 or 36 weeks gestation and bone mineral content, bone width, bone area, or bone mineral density measured by single photon absorptiometry at 2, 13, and 52 weeks postpartum.[54] It should be noted, however, that only 20% and 16% of the population studied had 25(OH)D concentrations <80 nmol/L at 20 and 36 weeks gestation, respectively. Another study investigating the effect of supplementation with 1,000 IU/day vitamin D during the third trimester of pregnancy on neonatal bone mineralization, forearm BMC measurements were not correlated with cord serum 25(OH)D concentrations and no differences in BMC were found between supplemented and control groups.[59]

Rickets

Severe vitamin D deficiency during gestation and early life is a primary cause of rickets in infants and children. A severe bone-deforming disease, rickets is characterized by growth retardation, enlargement of the epiphyses of the long bones, deformities of the legs, bending of the spine, knobby projections from the ribcage, and weak and toneless muscles[60]; it is often accompanied by hypocalcemic seizures in young infants.[61,62] Because infants of vitamin D-deficient women are born with limited stores[63] and breast milk is a poor source of vitamin D, breast-fed infants of mothers with marginal or low vitamin D status are highly susceptible to rickets. The incidence of rickets in the United States and other countries decreased significantly after fortification of milk and other food products with vitamin D was initiated. Resurgence in rickets has been observed in the last decade, mainly in exclusively breastfed infants of highly pigmented or veiled mothers.[62,64–66] Rickets is diagnosed with maximum frequency between the ages of 4 and 12 months, once fetal vitamin D stores are depleted and during the period of rapid bone growth.[60]

Brain development

Human and rodent brains express 1-α-hydroxylase as well as the nuclear VDR, allowing $1,25(OH)_2D$-mediated regulation of cellular proliferation, differentiation, and survival.[3] Rat pups born to dams that were vitamin D deficient 6 weeks before mating and during pregnancy had longer, thinner brain cortices with larger lateral ventricular volumes.[67] Vitamin D deficiency during development was found to reduce the amount of apoptotic cell death normally associated with neuronal differentiation.[68] To test whether vitamin D deficiency during development impairs neurogenesis, neuronal stem cells from the subventricular zone of the offspring of vitamin D-deficient dams were cultured on the day of birth. Proliferation rates were higher in cells isolated from vitamin D-deficient offspring than in controls. Because these cells did not respond to $1,25(OH)_2D$ treatment or differ in VDR mRNA concentrations from controls, it was speculated that the VDR may be rendered nonfunctional in developmentally vitamin D-depleted animals.[69] Other investigators reintroduced vitamin D at birth to pups born to vitamin D-deficient dams. At 10 weeks, ventricle sizes in the brain remained abnormal.[70] While no similar studies have been conducted in humans, a review of existing evidence by McCann and Ames[71] concludes there is ample evidence for a role of vitamin D in brain development and function.

Acute lower respiratory infection

Several studies have demonstrated an association between rickets or low circulating 25(OH)D concentrations and incidence of pneumonia or other acute lower respiratory infections (ALRIs) in infants.[72–74] A Turkish case-control study comparing the vitamin D status of newborns <30 days of age who were admitted to a neonatal intensive care unit with ALRI with those of healthy controls revealed significantly lower serum 25(OH)D

concentrations in the subjects with ALRI. The mothers of newborns with ALRI also had significantly lower serum 25(OH)D concentrations than the mothers of the controls.[75]

HIV transmission

Because of the known immunomodulatory effects of vitamin D as well as the role of vitamin D in fetal immune development, it has been hypothesized that maternal vitamin D status during pregnancy may impact the likelihood of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). A study of HIV-infected pregnant women conducted in Tanzania found that women with serum 25(OH)D levels <80 nmol/L at 12–27 weeks gestation had a 50% higher risk of MTCT of HIV to the infant by postpartum week 6 (95% CI 2%–120%) and a 103% higher risk of MTCT through breastfeeding by 24 months of age (95% CI 8%–282%).[76]

VITAMIN D STATUS DURING PREGNANCY AND CHILDHOOD OUTCOMES

The most comprehensive data regarding later health outcomes in children born to mothers with known vitamin D status was gathered in the United Kingdom. The children, who were 9 years of age at the time of follow-up, were born to mothers who had participated in a nutritional survey during pregnancy that was conducted in 1991 and 1992. There were no statistically significant linear trends between weight, fat mass, and lean mass at the age of 9 years with maternal 25(OH)D concentration in late pregnancy. However, weight, fat mass, and lean mass tended to be lower in children whose mothers had been in the lowest quartile of the distribution of 25(OH)D during pregnancy.[53] Children whose mothers had serum 25(OH)D levels <45 nmol/L late in pregnancy had significantly lower whole body and lumbar spine bone mineral content than children whose mothers were vitamin D replete, a relationship that was not significantly weakened by adjustment for childhood height.[77] No statistically significant associations were found between measures of cognitive function, psychological health, or arterial structure and function.[53]

Asthma is another childhood health outcome of interest in relation to vitamin D status during pregnancy. The onset of asthma occurs in early childhood, with 80–90% of cases occurring before 6 years of age.[78] Three large prospective birth cohort studies estimating maternal vitamin D intake during pregnancy with food frequency questionnaires demonstrated that higher vitamin D intake from food and supplements was associated with lower risk of wheezing and asthma in children aged 3 or 5 years.[79–81] In contrast, in the cohort studied by Gale et al. the risk of reported asthma at 9 years of age was increased in children of mothers with high maternal 25(OH)D concentrations (>75 nmol/L) compared to those of mothers in the lowest quartile of the distribution (<30 nmol/L; OR 5.41, 95% CI 1.09–26.65).[53]

VITAMIN D STATUS DURING PREGNANCY AND ADULT DISORDERS

The work of Barker et al.[82] concerning fetal 'imprinting' with environmental factors that contribute to adult health outcomes has stimulated speculation about the long-term implications of the vitamin D milieu during gestation.[83] Diseases that have been studied include autoimmune conditions such as multiple sclerosis (MS) and type I diabetes, as well as cancers and schizophrenia. Much of the evidence associating perinatal vitamin D with development of disease later in life is ecological, but preliminary results warrant further studies in this area.

The following key points were made in a detailed review by Lucas et al.[84] regarding health implications of prenatal and early-life vitamin D status. A season-of-birth pattern has been demonstrated for MS, glioma, meningioma, and schizophrenia, with greater disease incidence in individuals born in winter or spring when maternal vitamin D deficiency is presumably more prevalent.[85–88] Though not consistent amongst all studies, there is some evidence that the incidence of type I diabetes peaks in individuals born in summer, which is consistent with an effect of low vitamin D status during a critical point of gestation.[84,89–91] A strong latitudinal gradient has been demonstrated for MS, type I diabetes, colorectal, breast, and prostate cancers, and schizophrenia, with higher disease incidence in individuals located further from the equator.[92–98]

Several studies provide additional support for an association between the in utero vitamin D environment and the risk for later development of type I diabetes and schizophrenia. Recalled maternal vitamin D intake from food but not supplements during the third trimester of pregnancy was associated with a lower risk of pancreatic islet cell antibody appearance in children aged 0.8–7.3 years (adjusted hazard ratio 0.37, 95% CI 0.17–0.78).[99] In a Norwegian population-based case-control study, maternal intake of cod liver oil during pregnancy was associated with less risk of type I diabetes incidence in offspring (adjusted OR 0.36, 95% CI 0.14–0.90).[100] In relation to schizophrenia, the enlargement of lateral ventricles seen in the brains of rat pups born to vitamin D-deficient dams is also a common pathophysiological finding in schizophrenic patients.[3] Furthermore, low

plasma concentrations of nerve growth factor and synapsin II, a protein involved in synaptogenesis, are consistent in vitamin D-deficient rat models and adult humans with schizophrenia.

RISK FACTORS FOR VITAMIN D DEFICIENCY DURING PREGNANCY

In addition to conditions that predispose the general population to hypovitaminosis D, including darker pigmentation, sunscreen use, clothing coverage, latitude of residence, urban pollution, and poor intake, several risk factors have a particular significance in relation to pregnancy.

Seasonal variation in serum 25(OH)D is a well-established phenomenon due to reduction in UVB penetration through the atmosphere during the winter months when the sun's zenith angle is increased.[101] Because pregnancy traverses several seasons, it is evident that maternal status at a given point in pregnancy is influenced by season of measurement as well as other environmental and physiological factors. It has been speculated that the timing of vitamin D deficiency during gestation may be pivotal in predicting health outcomes in the offspring.[84] Several studies of vitamin D status in pregnancy have shown higher rates of deficiency at term in women delivering in spring and winter months.[4,5,7,11] Only one study published to date has compared seasonal variations in vitamin D status between pregnant women and nonpregnant controls living in the same community.[7] Because all women participating in the study were recruited at the same time of year, it remains to be elucidated whether progressively poorer vitamin D status in pregnant women compared with controls was due to differential effects of season in pregnant and nonpregnant women or to the physiological demands of pregnancy itself.

Multiple studies have demonstrated that circulating 25(OH)D concentrations are lower in obese than lean individuals, including several studies conducted during pregnancy.[46,52,102–106] Proposed mechanisms include sequestration of vitamin D in adipose tissue[105] or subcutaneous fat,[106] enhanced production of calcitriol with negative feedback on hepatic synthesis of 25(OH)D,[102] avoidance of sun exposure,[104] or lower vitamin D intake.[52] In a subset of subjects participating in a prospective pregnancy cohort study in Pittsburgh, Pennsylvania, Bodnar et al.[103] demonstrated that pregravid obese women had significantly lower serum 25(OH)D concentrations than lean women at 4–22 weeks of gestation and at term after adjustment for race/ethnicity, season, gestational age, periconceptional vitamin use, preconception physical activity, and maternal age. Cord blood concentrations were also significantly lower in neonates of pregravid obese women compared with lean women.

PREVALENCE OF VITAMIN D DEFICIENCY AND INSUFFICIENCY IN PREGNANCY

Numerous studies have estimated the prevalence of vitamin D deficiency and insufficiency amongst pregnant women in various ethnic populations and living at different latitudes (Table 1). Though direct comparisons between studies are not possible due to inconsistent definitions of deficiency and insufficiency, there is a disturbingly high prevalence of hypovitaminosis D amongst pregnant women in nearly all of the populations studied. This is true despite the fact that pregnant women in most countries are encouraged to take a daily prenatal vitamin-mineral supplement containing 400 IU of vitamin D. In "high-risk" pregnant populations consisting of highly pigmented or veiled women, the prevalence of vitamin D deficiency and insufficiency is generally greater than in lighter skinned or less covered women living at the same latitude.

Although it has been assumed that cut-points for defining vitamin D deficiency and insufficiency in pregnancy are the same as in the general population, few studies have compared circulating 25(OH)D in pregnant women and in nonpregnant controls. A recent longitudinal study of vitamin D deficiency and insufficiency in Caucasian pregnant women and age-matched nonpregnant controls in Northern Ireland (54–55°N) found that 96, 96, and 75% of pregnant women were classified as vitamin D insufficient (plasma 25(OH)D <50 nmol/L) at 12, 20, and 35 weeks of gestation, respectively. At the same time points, which corresponded to winter, spring, and summer measurements, 92, 74, and 42% of nonpregnant women were vitamin D insufficient. The authors speculate that lower vitamin D status after 12 weeks gestation may be due to increased fetal demand for the nutrient.[7] Because all pregnant women in this study conceived in late fall or early winter and delivered in summer, interpretation of results is complicated by the confounding effect of season. Ardawi et al.[107] collected blood from 40 pregnant Saudi Arabian women in each trimester, at delivery, and 6 weeks postpartum. A single blood sample was collected from nonpregnant controls. Serum $25(OH)D_3$ levels in pregnant women decreased significantly from the first trimester (54 ± 10 nmol/L) to the third trimester (33 ± 8 nmol/L) and remained depressed at delivery and postpartum. However, the mean 25(OH)D values at each time point were within the reference range obtained from nonpregnant controls, and the authors did not address the possible contribution of season to the variations seen during pregnancy. Based on preliminary evidence, it

Table 1 **Prevalence of vitamin D deficiency and insufficiency during pregnancy and at term.**

Reference	Location	No. of subjects	Ethnicity	Time of sampling	Definition of deficiency	Definition of insufficiency	Percent deficient	Percent insufficient	Percent taking PVM*	Other findings	Comments
Farrant et al. (2008)[6]	Mysore, India (12.3 °N)	559	South Indian	30 wk gest*	Serum 25(OH)D <50 nmol/L	–	Mothers: 66	–	NA	No association between maternal 25(OH)D and gestational diabetes risk, fetal growth, or altered cord plasma insulin	D status assessed in stored serum samples (1997–8)
Sachan et al. (2005)[12]	Lucknow, India (26.8 °N)	207	Indian	Delivery	Serum 25(OH)D <25 nmol/L 37.5 nmol/L 50 nmol/L	–	 Mothers: 42.5 Mothers: 66.7 Cord: 95.7	–	NA	PTH sig higher and cord serum 25(OH)D sig lower in D def versus normal mothers (cutoff <25 nmol/L)	Samples collected from Sept–Nov
Maghbooli et al. (2007)[10]	Tehran, Iran (35 °N)	552	Iranian	Delivery	Serum 25(OH)D <35 nmol/L	–	Mothers: 66.8 Cord: 93.3	–	70		All samples collected in winter (Oct–Feb)
Kazemi et al. (2009)[8]	Zanjan City, Iran (36.7 °N)	67	Iranian	Delivery	Serum 25(OH)D <25 nmol/L	–	Mothers: 71 Cord: 67	–	NA	No sig differences in maternal or cord 25(OH)D between urban ($n = 28$) and rural ($n = 39$) groups	Samples collected in March and Sept
Bowyer et al. (2008)[5]	Sydney, Australia (40 °S)	971	Mixed; 55% born in Australia, 17% in Asia, 7% in Lebanon	23–32 wk gest in mothers, cord at delivery	Serum 25(OH)D ≤25 nmol/L	Serum 25(OH)D 26–50 nmol/L	Mothers: 15 Cord: 11	Mothers: 33 Cord: 29	NA	Serum 25(OH)D in cord sig higher than maternal; frequency of def* and insuff* varied with maternal skin phototype; babies of deficient mothers had sig lower birth weight	Skin phototype classified by Fitzpatrick criteria
Bodnar et al. (2007)[4]	Pittsburgh, Pennsyl-vania (40 °N)	Total 400; 200 of each ethnicity	Black (B); white (W)	4–21 wk gest and pre-delivery	Serum 25(OH)D <37.5 nmol/L	Serum 25(OH)D 37.5–80 nmol/L	B (4–21 wk): 44.9 W (4–21 wk): 2.0 B (37–42 wk): 29.2 W (37–42 wk): 5.0 Cord B: 45.6 Cord W: 9.7	B (4–21 wk): 51 W (4–21 wk): 60.3 B (37–42 wk): 54.1 W (37–42 wk): 41.2 Cord B: 46.8 Cord W: 56.4	B: 94.3; W: 91.9	After adjustment for BMI and PVM use, seasonal differences in 25(OH)D were smaller in B women than in W women	All nulliparous
Lee et al. (2007)[9]	Boston, Massachusetts (42 °N)	40	Mixed: 62.5%; black, 25%; white, 7.5%; Asian	24–48 h post delivery	Plasma 25(OH)D <30 nmol/L	–	Mothers: 50; cord: 65	–	NA	No sig correlations between maternal or cord 25(OH)D and infant anthropometrics	All samples collected in winter
Nicolaidou et al. (2006)[11]	Athens, Greece (37.5 °N)	123	Mixed: 50%; Greek, 23%; Albanian	Delivery	Serum 25(OH)D <25 nmol/L	–	Mothers: 19.5; cord: 8.1	–	NA	Serum 25(OH)D in cord sig higher than maternal; association between maternal 25(OH)D and skin phototype	Skin type classified by Fitzpatrick criteria
Weiler et al. (2005)[13]	Winnipeg, Canada (49.5 °N)	50	Mixed: 60%; white, 20%; First Nations: 10%; Asian	0–48 h post delivery	Plasma 25(OH)D <37.5 in mother; <27.5 in cord	–	Mothers: 46; cord: 36 *Different cutoffs used*	–	78	Vitamin D-deficient infants had higher birth weight but lower whole body and femur BMC* relative to weight	Bone mineral content in infants measured at 15 d
Yu et al. (2009)[14]	London, United Kingdom (51.5 °N)	Total 180; 45 of each ethnicity	Indian Asian (IA) Middle Eastern (ME), Black African (A) Cauc (C)	26–27 wk gest	Serum 25(OH)D <25 nmol/L	Serum 25(OH)D 25–50 nmol/L	IA: 47 ME: 64 A: 58 C: 13	IA: 51 ME: 33 A: 36 C: 60	NA	PTH* sig higher in IA, ME, and BA compared to C	26–27 wk samples collected before randomization to treatment
Holmes et al. (2009)[7]	Belfast, Ireland (54–55 °N)	120	Caucasian	12 wk gest 20 wk gest 35 wk gest 3 d PP* ($n = 21$)	Plasma 25(OH)D <25 nmol/L	Plasma 25(OH)D 25–50 nmol/L	12 wk: 35 20 wk: 44 35 wk: 16 PP: 10	12 wk: 61 20 wk: 52 35 wk: 59 PP: 52	22	Plasma 25(OH)D sig lower in pregnant women than non-preg women at 20 wk, 35 wk, and 3 d PP (spring and summer, respectively)	Non-pregnant control group ($n = 41$)

* *Abbreviations*: BMC, bone mineral content; BMI, body mass index; def, deficient; gest, gestation; insuff, insufficient; PP, postpartum; PTH, parathyroid hormone; PVM, prenatal vitamins/mineral supplements; sig, significantly.

may be prudent to revisit the definition of vitamin D sufficiency late in pregnancy, when most studies have measured circulating 25(OH)D.

RECOMMENDED DIETARY INTAKES DURING PREGNANCY

In the United States, Australia, New Zealand, and Canada the currently recommended dietary adequate intake (AI) of vitamin D for pregnant women is 200 IU/day[15,108,109] while the United Kingdom recommends 400 IU/day.[110] The existing recommendations are the subject of widespread controversy given the evolving concept of vitamin D sufficiency, currently believed to be serum 25(OH)D levels >75 nmol/L, and many recent studies showing a high prevalence of vitamin D insufficiency using lower cutoffs (Table 1). In the United States, the recommendation of 200 IU/day during pregnancy is based on a study published in 1978, which demonstrated that pregnant women with an estimated intake of 150 IU/day during the last 3 months of pregnancy had a mean plasma 25(OH)D level of 22.75 ± 3.75 nmol/L; this concentration was considered to be sufficient at the time.[111]

SUPPLEMENTATION WITH VITAMIN D DURING PREGNANCY

While a number of vitamin D supplementation trials during pregnancy have been conducted since the early 1980s (Table 2), interpretation of results is complicated by the type of supplement used and the duration and dose of supplementation. It is clear that either daily or high-dose supplementation during the third trimester of pregnancy has been effective at raising circulating 25(OH)D concentrations compared to controls in all populations studied. Some studies have found an increase in maternal third trimester weight gain and infant birth weight in supplemented subjects compared with controls; however, these results have not been replicated in other studies.

No studies to date have compared 25(OH)D concentrations in pregnant women supplemented with different daily doses of vitamin D. One study conducted in nonpregnant adults during the Canadian winter suggested that supplementation with 1,000 IU/day cholecalciferol for 2–5 months was effective for ensuring serum 25(OH)D levels ≥75 nmol/L in 35% of 23 subjects, while supplementation with 4,000 IU/day was effective for achieving serum 25(OH)D levels ≥75 nmol/L in 88% of 25 subjects.[117] In order to revise the recommended level of vitamin D intake for pregnant women, a consensus must be reached regarding the optimal concentration of circulating 25(OH)D to be obtained late in pregnancy and studies should investigate the level of supplementation needed to reach this goal.

VITAMIN D TOXICITY IN PREGNANCY

Historically, vitamin D supplementation during pregnancy was thought to be a risk factor for supravalvular aortic stenosis (SAS) in infants; this was based on the finding in 1964 of an elevated blood concentration of vitamin D in an infant with this condition.[118] Interestingly, when the case report was published there were no quantitative methods for measuring circulating 25(OH)D.[119] It was later determined that the sporadic association between elevated 25(OH)D and SAS was due to a disease now known as Williams Syndrome, a genetic disorder with a prevalence of 1/7,500 that is characterized by dysmorphic facial features, multiorgan involvement including SAS, and an exaggerated response of circulating 25(OH)D to oral doses of vitamin D.[119–122] In pregnant animals receiving doses of 200,000–300,000 IU vitamin D per kilogram body weight (equivalent to 12–15 million IU in a 60 kg human), adverse outcomes have been observed in mothers and offspring.[123–126] The highest dose of vitamin D studied during pregnancy was given to 15 hypoparathyroid women who received 100,000 IU/day in order to maintain serum calcium. No adverse effects were observed in these mothers or their infants.[127]

PUBLIC HEALTH IMPLICATIONS

The alarming prevalence of vitamin D insufficiency during pregnancy demonstrated in a diverse range of populations living at various latitudes, the extensive scope of adverse effects to the offspring during development and later in life, and the lack of evidence of toxicity from physiological doses of vitamin D suggest that the current recommendations for vitamin D intake during pregnancy are grossly inadequate. While it may be argued that increased sun exposure would provide a more natural means of achieving better vitamin D status in pregnancy, this method has dermatological ramifications in terms of skin cancer risk and may not be culturally or socially acceptable in some populations. Most prenatal vitamin and mineral supplements that are commercially available in the United States contain 400 IU/day vitamin D as cholecalciferol. Because compliance with prenatal vitamin and mineral intake has been high (70–94%) in several studies of vitamin D status conducted in the United States,[4,9,13] a sensible public health intervention strategy targeting pregnant women would involve reformulation of prenatal supplements with higher doses of vitamin D. Although large-scale trials are necessary to

Table 2 **Vitamin D supplementation studies in pregnancy.**

Reference	Location	No. of subjects	Ethnicity	Supplement	Treatment duration	25(OH)D nmol/L (treatment/control)†	Other findings	Comments
Marya et al. (1981)[112]	Rohtak, India (28.9 °N)	25 Treatment I 20 Treamtent II 75 Control	North Indian (Hindu)	I: 1200 IU/d D_2 II: 600,000 IU D_2 No placebo	I: ~28th wk to term (~3 mo) II: 7th and 8th month (2 doses)	Did not measure	Both treatments significantly increased birth weight compared with controls	Treatment II had a more pronounced effect on birth weight, maternal and fetal calcium and phosphorus
Delvin et al. (1986)[113]	Lyon, France (46°N)	20 Treatment 20 Control	Caucasian	1000 IU/d D_3 Placebo	~27th wk to term (~3 mo)	33 wk: 55.0 ± 10.0/27.5 ± 10.0* Del: 65.0 ± 17.5/32.5 ± 20.0* Cord: : 45.0 ± 5.0/17.5 ± 2.5* 4 d: 32.5 ± 2.5/12.5 ± 2.5*	Significantly higher serum calcium in infants at 4 d in supplemented group	All subjects randomized in December and delivered in June
Mallet et al. (1986)[114]	Northwest France (~47 °N)	21 Treatment I 27 Treatment II 29 Control	Caucasian	I: 1000 IU/d D_2 II: 200,000 IU D_2 Placebo	I: ~28th wk to term (~3 mos) II: 7th mo (single dose)	Del: 25.3 ± 7.7/26.0 ± 6.4/9.4 ± 4.9* Cord: 15.7 ± 5.1/18.2 ± 5.2/5.3 ± 2.5*	No significant modification of maternal calciuria or infant birth weight by treatment	Supplement protocols similarly effective at raising maternal and cord 25(OH)D
Brooke et al. (1980)[115]	London, UK (51.5 °N)	59 Treatment 67 Control	Indian Asian (70% Indian, 17% Pakistani)	1000 IU/d D_2 Placebo	28–32 wk gestation to term (~3 mo)	28–32 wk: 20.1 ± 1.9 Del: 168.0 ± 12.5/16.2 ± 2.7 Cord: 137.9 ± 10.8/10.2 ± 2.0	Greater 3rd trimester weight gain in supplemented mothers, larger fontanelle in control infants, no significant anthropometric effects	Placebo group showed profound hypovitaminosis D
Yu et al. (2009)[14]	London, UK (51.5 °N)	60 Treatment I 60 Treatment II 59 Control	Indian Asian, Mid Eastern, Black, Caucasian	I: 800 IU/d D_2 II: 200,000 IU D_3 No placebo	I: 27th wk to term (~3 mo) II: 27th wk (single dose)	Median (IQR) 27 wk: 26 (20–37)/26 (21–41)/25 (21–38) Del: 42 (31–76)/34 (30–46)/27 (27–39) * Cord: 26 (17–45)/25 (18–34)/17 (14–22) *	Significant differences in 25(OH)D at baseline between ethnic groups; none in maternal weight gain or birth weights by treatment	Supplement protocols similarly effective at raising maternal and cord 25(OH)D levels, but 25(OH)D ≥50 nmol/L achieved in 30%
Cockburn et al. (1980)[116]	Edinburgh, Scotland (56 °N)	82 Treatment 82 Control	Caucasian	400 IU/d D_2 Placebo	12th wk gestation to term (~6 mo)	24 wk: 39.0/32.5* 34 wk: 44.5/38.5* Del: 42.8/32.5* Cord: 28.0/20.0* 6 d: 34.5/20.3*	Incidence of hypocalcemia and convulsions reduced but not abolished in treatment group; no difference in birth weight between groups	Maternal, cord, and infant circulating 25(OH)D was <50 nmol/L in both groups

† Significant differences between treatment(s) and control denoted by*.
Abbreviations: IQR, interquartile range; del, delivery.

confirm a daily dose sufficient to ensure vitamin D adequacy in the majority of the pregnant population, based on existing evidence it appears that this dose would exceed 1,000 IU/day. Subsets of pregnant women who are at higher risk for hypovitaminosis D due to pre-pregnancy obesity, darker pigmentation, or winter/spring due date may require higher-dose supplementation.

CONCLUSION

The widespread global prevalence of hypovitaminosis D during pregnancy and its implications for undesirable health outcomes in present and future generations is an area of growing concern. Because inadequate vitamin D status during gestation may have adverse effects on maternal pregnancy as well as fetal and postnatal growth and development, an increasing number of experts are advocating changes to recommended vitamin D intakes in pregnancy. Although the optimal circulating 25(OH)D concentration throughout pregnancy remains the subject of debate, it is evident that prior levels used to establish intake recommendations were too conservative. In light of existing evidence, public health intervention to reduce the prevalence of hypovitaminosis D in pregnant women in the United States and worldwide is imminently desirable.

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Declaration of interest. The authors have no relevant interests to declare.

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