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Vitamin D May Be a Link to Black-White Disparities in Adverse Birth Outcomes

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In the United States, significant, intractable disparities exist in rates of major pregnancy outcomes between non-Hispanic black and non-Hispanic white women. A previously unexplored candidate influence on the black-white disparity in adverse birth outcomes is maternal vitamin D status. This review summarizes the evidence relating maternal vitamin D to preeclampsia, spontaneous preterm birth, gestational diabetes, and fetal growth restriction, and addresses gaps in our understanding of the contribution of vitamin D to the intractable black-white disparity in these conditions. The literature reviewed highlights strong biologic plausibility of role for vitamin D in the pathophysiology of these poor pregnancy outcomes. Data also suggest that maternal vitamin D deficiency may increase the risk of preeclampsia and fetal growth restriction. Less research has been done in support of relations with spontaneous preterm birth and gestational diabetes, and fetal and infant survival have rarely been studied. Few trials of vitamin D supplementation have been conducted in pregnant women with adequate power to test effects on birth outcomes. Importantly, black pregnant women have rarely been studied in vitamin D—birth outcomes research. Although vitamin D is a promising candidate influence on black-white disparities in preeclampsia, spontaneous preterm birth, fetal growth restriction, and gestational diabetes, these associations require further study in large samples of black US women. Because vitamin D deficiency is widespread and black-white disparities in pregnancy outcomes and infant survival have been resistant to previous interventions, research to test vitamin D as a causal factor is of major public health significance.

Target Audience: Obstetricians & Gynecologist, Family Physicians.

Learning Objectives: After completion of this educational activity, the reader will be able to appreciate risk factors for inadequate vitamin D status. Understand the basic aspects of vitamin D metabolism. Become aware of recent literature linking inadequate vitamin D status and adverse pregnancy outcomes such as preeclampsia and preterm birth.

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In the United States, significant, intractable disparities exist in rates of major pregnancy outcomes between non-Hispanic black and non-Hispanic white women. In 2005, black mothers were 2.3 times as likely as white mothers to experience an intrauterine fetal death (11.1 vs. 4.8 fetal deaths at 20 weeks gestation or greater per 1000 live births) or death of their infant (13.5 vs. 5.8 deaths per 1000 live births) (1,2). Major causes of fetal and infant death also demonstrate striking racial disparities. Compared with white women, black women are at 1.5- to 2.5-fold greater risk of delivering a preterm (<37 weeks gestation; 18.5% vs. 11.7%) or very preterm infant (<32 weeks gestation; 4.1% vs. 1.7%) as well as a term low birth weight infant (<2500 g birth weight at ≥37 weeks; 5.6% vs. 2.6%) (3). Black women are also more likely to develop preeclampsia and have more severe complications of the disorder than white women, even after excluding women with chronic hypertension (4–7). Similar black-white differences have been noted for gestational diabetes (8). Adjustment for many maternal factors does not fully account for the higher incidence of these adverse pregnancy and birth outcomes in blacks, and attempted interventions have yielded disappointing results. Despite decades of study, scientists and clinicians understand little about why black-white disparities exists in adverse birth outcomes and how to prevent them (1).

A previously unexplored candidate influence on the black-white disparity in adverse birth outcomes is maternal vitamin D status. This purpose of this review is to summarize the evidence relating maternal vitamin D status to poor pregnancy outcomes, and address gaps in our understanding of the contribution of vitamin D to the intractable black-white disparity in these conditions.

VITAMIN D METABOLISM AND PRODUCTION IN PREGNANCY

Vitamin D is a prohormone that is either ingested orally or is produced photochemically in the skin. During sunlight exposure, 7-dehydrocholesterol in the skin absorbs ultraviolet B (UVB) (3) radiation to form cholecalciferol (vitamin D_3). Dietary vitamin D and cutaneous vitamin D_3 bind to vitamin D binding protein and are transported to the liver, where they are metabolized to form 25-hydroxyvitamin D (25(OH)D). The major circulating vitamin D metabolite, 25(OH)D, is widely recognized as the best marker of vitamin D nutritional status (9–11). 25(OH)D reenters circulation bound to vitamin D binding protein and is converted in the kidney by 1α-hydroxylase to 1,25-dihydroxyvitamin D (calcitriol; 1,25$(OH)_2$D), the hormonally active form of vitamin D. Like other steroids, 1,25$(OH)_2$D interacts with specific receptors vitamin D receptors, (VDR) to regulate the expression of vitamin D-responsive genes.

During pregnancy, 25(OH)D diffuses across the placental barrier. Cord concentrations of 25(OH)D are lower than maternal concentrations (12,13). In fact, the fetus relies entirely on the vitamin D stores of the mother, so if the mother is deficient, so is the fetus (12). Some evidence suggests that 25(OH)D concentrations decline slightly with advancing gestation (14). Maternal decidual cells are among the tissues that locally synthesize 1,25$(OH)_2$D (15), the efficiency of which may depend on available 25(OH)D in circulation as substrate for 1α-hydroxylase (16). The optimal 25(OH)D level for promoting health is being debated, but it is thought to be approximately 75 to 80 nmol/L (17–20). This cutoff was derived from populations of nonpregnant individuals. Less is known about the optimal concentrations for pregnant women.

MAJOR DETERMINANTS OF VITAMIN D STATUS

The most important source of vitamin D is the skin's synthesis of the vitamin from casual exposure to sunlight (21). Therefore, anything that reduces UVB photons from entering the epidermis will reduce or eliminate vitamin D_3 production. The skin pigment melanin slows the rate at which UVB radiation transmits through skin and converts to vitamin D_3 (22), so persons with deeply pigmented skin produce vitamin D_3 less efficiently than do persons with light skin color. A deeply-pigmented African-American adult requires 10 to 50 times the UVB exposure of a medium-skinned Caucasian adult to synthesize the same amount of vitamin D_3 (23). Topical sunscreens absorb UVB radiation. When used properly, a sunscreen with sun protection factor 8 reduces cutaneous vitamin D_3 synthesis by 97.5% (24). Today in the United States, sunscreen use and other sun avoidance behaviors (e.g., wearing sun-protective clothing, seeking shade) are common in all racial groups (25,26), primarily because of fears of skin cancer and premature aging. Season and latitude dramatically alter vitamin D_3 production (27,28). In the United States in wintertime, the angle of the sun is very oblique, thus reducing the UVB radiation that reaches the earth. At latitudes less than 35 degrees, the angle of the sun is so oblique from November to March that virtually none of the UVB photons capable of synthesizing vitamin D_3 reach the

earth; formation of vitamin D_3 in the skin is reduced or entirely inhibited (28). Serum 25(OH)D significantly drops in winter because the vitamin D stored during summer cannot be sufficiently mobilized to buffer the seasonal change in sunlight. At below 35 degree latitude, vitamin D_3 synthesis is possible year-round (28).

Vitamin D intake from diet and supplements is crucial to maintain vitamin D status when vitamin D_3 synthesized from sunlight is limited (29). Unfortunately, rich sources of natural vitamin D (e.g., wild salmon, organ meats) are rarely consumed. Fortified foods (e.g., milk, ready-to-eat cereals) and dietary supplements are the largest contributors to vitamin D intake (30), but contain moderate amounts of the vitamin. In 1999–2000, 27% of non-Hispanic white women and 42% of non-Hispanic black women aged 19 to 50 in the United States failed to meet the recommended intake of 200 IU vitamin D (30). This racial difference in diet may be attributable to the tendency for black Americans to consume less milk and cereal than their white counterparts (31). Even so, consuming the recommended level of vitamin D does not prevent vitamin D insufficiency in vulnerable populations (32–34). This is not surprising, given that the current dietary reference intakes are thought to be arbitrary (35) and are under revision. Recent data have led vitamin D experts to argue that at least 1000 IU of vitamin D_3 per day may be required to optimize vitamin D status of adults (17,35–37) and as much as 6000 IU per day may be optimal for pregnant and lactating women (38).

In summary, lack of adequate sun exposure due to residence in northern US cities, winter season, sun avoidance and indoor jobs, coupled with low vitamin D intakes from diet and supplements compromise vitamin D status in all racial groups. The problem is compounded in African Americans because of their high concentrations of melanin, which dramatically limit the amount of vitamin D that can be synthesized in the skin (23) and their lower intakes of oral vitamin D (30).

BLACK-WHITE DISPARITY IN VITAMIN D DEFICIENCY DURING PREGNANCY

Not surprisingly, there is a striking black-white disparity in the prevalence of vitamin D deficiency. In 2000–2004, poor vitamin D status was substantially more common in black than white pregnant women in the United States (39). Serum 25(OH)D concentrations <37.5, <50, and <75 nmol/L were found in 2.4%, 8.5%, and 49.1% of non-Hispanic white pregnant women (n = 340), respectively (1), compared with 55.4%, 74.6%, and 92.2% of non-Hispanic black pregnant women (n = 124), respectively (1). These black-white disparities are similar to our findings in a cohort residing in Pittsburgh (latitude 40 degree N) at 4 to 21 weeks gestation and at term (13). The extremely high rates of vitamin D inadequacy in our cohort occurred despite widespread use of prenatal vitamins. Other investigators have reported similar high rates of poor vitamin D status in US black pregnant women (12,40) and pregnant women around the world (41–46). These data taken together indicate that prenatal vitamin D insufficiency is prevalent in all racial groups, but black women carry the major burden of vitamin D deficiency.

VITAMIN D AND ADVERSE PREGNANCY OUTCOMES

Although the function of vitamin D is best understood vis-à-vis its effect on bone metabolism and mineral homeostasis (47), the influence of vitamin D on biologic processes is diverse and protean. Indeed, vitamin D has been linked with a wide range of adverse health outcomes, including cancer, cardiovascular disease, diabetes, mental health disorders, infectious diseases, and autoimmune disorders (17,48,49). Comparably less work has been done to explore the effect on pregnancy outcome. In fact, a 2000 Cochrane Library review concluded that there is not enough evidence to evaluate the effect of prenatal vitamin D supplementation on adverse pregnancy outcomes (50). Nevertheless, the fact that the placenta-decidua has VDR and expresses 1α-hydroxylase for synthesis of $1,25(OH)_2D$ (51) highlights many potential pathways linking vitamin D to birth outcomes. We review this evidence for preeclampsia, spontaneous preterm birth, gestational diabetes, and fetal growth restriction.

Preeclampsia

Preeclampsia is a pregnancy-specific disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. At its roots, preeclampsia is thought to originate in abnormal angiogenesis and immunologic adaptation occurring during implantation and trophoblast invasion at the beginning of pregnancy. Pregnancy establishment and implantation depend on the harmonious confluence of complex molecular events related to angiogenesis, hormone production, and inflammation (52–54). There is evidence that vitamin D affects

transcription and function of genes responsible for trophoblast invasion, angiogenesis critical for implantation, and fetal allograft immunologic "tolerance" (55,56). Through actions in these domains, vitamin D may be an important factor in preeclampsia causation.

Preeclampsia is hypothesized to be a 2-stage disorder (57). Stage 1 is reduced placental perfusion and in many cases is secondary to failed remodeling of the maternal vessels. The poorly perfused placenta produces materials that, in an appropriate maternal environment, initiate the coagulation cascade and ensuing multisystem sequelae (stage 2). These pathophysiologic changes are proposed to be secondary to abnormal endothelial function, which is a component of a generalized increase in the inflammatory activation that characterizes normal pregnancy (58).

Vitamin D deficiency could contribute to both of the proposed stages of preeclampsia. Relevant to stage 1, the remodeling of the maternal vessels perfusing the placenta appears to be directed by normal invasion of trophoblast. Vitamin D regulates genes associated with normal implantation and angiogenesis (56). The maternal response to reduced perfusion leading to stage 2 may be equally affected by vitamin D. Maternal vitamin D deficiency may predispose to the increased inflammatory response that characterizes preeclampsia (59–61). Vascular structure and elastic properties including vascular compliance, elasticity, and intima-media thickness are more favorable among women supplemented with vitamin D (62). Vitamin D deficiency may also elevate blood pressure (63,64). This effect may be related to the ability of $1,25(OH)_2D$ to downregulate renin in the kidneys (65). The proteinuria of preeclampsia is mediated by renal vascular endothelial growth factor (VEGF). Reducing VEGF by overexpressing s-Flt, its soluble receptor, leads to increased protein excretion and a renal lesion similar to that present in women with preeclampsia (66). Vitamin D regulates angiogenic processes through direct effects on angiogenesis gene transcription, including VEGF (67,68). Vitamin D protects against renal injury in rats (69). Other mechanisms relate to insulin resistance, which when present early in pregnancy, is a risk factor for preeclampsia (70). Vitamin D inadequacy increases insulin resistance and reduces insulin secretion (71).

Preeclampsia has received a considerable amount of attention in the vitamin D literature, with scientists postulating a strong link (72,73). Two vitamin D supplementation studies to prevent preeclampsia were conducted more than 20 years ago and suggested a beneficial effect. In an uncontrolled trial conducted in the United Kingdom in 1938, supplementation with a multivitamin/mineral supplement and halibut liver oil (containing 900 IU/d vitamin D) provided at 20 weeks gestation reduced the odds of preeclampsia by 32% (95% confidence interval [CI]: 11%–47%) (74,75). Marya et al randomized 400 women at 20 to 24 weeks gestation to vitamin D (1200 IU/d) and calcium (375 mg/d) supplements or no treatment and found a significant reduction in blood pressure ($P < 0.001$) and a nonsignificant reduction in the incidence of preeclampsia in the treated group compared with the untreated (6% vs. 9%) (76). Because both studies used multiple vitamin supplementation, it is impossible to determine whether vitamin D contributed to the protective effects.

Recent observational studies support a role for vitamin D in the protection against preeclampsia. In a nested case-control study of nulliparous, singleton pregnancies in Pittsburgh, we observed that 25(OH)D concentrations at <22 weeks gestation were 15% lower among 55 women who subsequently developed preeclampsia compared with 219 women who did not develop preeclampsia (77). Maternal serum 25(OH)D <37.5 nmol/L was associated with a 5-fold increase in the adjusted odds of preeclampsia (adjusted odds ratio: 5.0 [95% CI: 1.7, 14.1]). Furthermore, there was a monotonic dose-response association between 25(OH)D at <22 weeks and risk of preeclampsia; a 50 nmol/L decline in 25(OH)D approximately doubled the risk of preeclampsia. Because only 12 of the 55 preeclampsia cases were non-Hispanic black mothers, we were unable to specifically examine how maternal vitamin D contributed to the black-white disparity in preeclampsia.

In another recent study conducted among 23,423 Norwegian, nulliparous pregnant women, 15 to 20 μg/d of vitamin D from food and supplements in the first half of pregnancy was associated with approximately a 25% reduction in risk of preeclampsia compared with intake <5.0 μg/d (adjusted odds ratio, 0.77 [95% CI: 0.77 (0.61, 0.96)]) (78). This effect was driven by vitamin D from supplements. Interestingly, this study suggested a reverse J-shaped relation between vitamin D intake and risk, with an attenuated effect among women with the highest intakes of vitamin D (>20 μg/d: adjusted odds ratio, 0.89; 95% CI: 0.75, 1.06). In a cohort of Icelandic women, a U-shaped relation between vitamin D intake at 11 to 15 weeks gestation and the risk of "hypertensive disorders" (cases of transient hypertension of pregnancy combined with preeclampsia) was reported (79). Neither of these vitamin D intake

studies measured maternal 25(OH)D concentrations. A previous study exploring many dietary variables found no association between vitamin D and risk of preeclampsia in a cohort of mostly white Boston mothers (80). However, vitamin in D intake is notorious for being poorly measured in nutrient databases (81,82). Given the significant potential for vitamin D exposure misclassification in such studies, it is debatable how well these results accurately represent the true effect of vitamin D intake on preeclampsia risk. In a unique investigation in a Finish Birth Cohort, Hypponen et al observed that vitamin D supplementation early in the first year of life is associated with a 50% reduction in the likelihood that females will subsequently go on to develop preeclampsia in their first pregnancies (83). These data highlight the potential importance of vitamin D status in early life, not just during pregnancy, to influence disease risk.

Data from calcium supplementation studies in preeclampsia may also be relevant to the effect of vitamin D on disease risk. Calcium supplementation prevents preeclampsia only among women with very low baseline calcium intake (84). Inadequate dietary intake of calcium can cause a secondary vitamin D deficiency (85). Thus, calcium supplementation may increase the available vitamin D for its hypothesized effect on angiogenesis, vascular physiology, and insulin sensitivity (72).

Finally, seasonal patterns in preeclampsia support a role for vitamin D and sunlight. We and others observed the highest incidence of preeclampsia in winter (when UVB light is limited), and lowest incidence in summer (when UVB light is plentiful) (86–89). Importantly, we found that the clear seasonal pattern in preeclampsia among the 20,794 white women in the cohort was substantially blunted among the 18,916 black women (86). If season is a surrogate for vitamin D status, this differential effect by race may suggest that vitamin D status does not vary to a great enough extent across the seasons among black women to substantially alter preeclampsia risk.

Taken together, the published literature suggests that there is substantial promise for vitamin D in the prevention of preeclampsia. Nevertheless, with a dearth of studies on vitamin D and preeclampsia in African American mothers, it is impossible from the current literature to determine the contribution of vitamin D to the racial disparity in preeclampsia.

Spontaneous Preterm Birth

Spontaneous preterm births are those that occur before 37 weeks gestation after preterm labor or preterm, prelabor rupture of the fetal membranes. With respect to pathophysiology, spontaneous preterm birth is a heterogeneous syndrome (90). The cascade of events that culminate in spontaneous preterm birth has, at its origin, several possible root pathways including pathologic uterine overdistension, decidual hemorrhage, precocious fetal endocrine activation, and intrauterine infection/inflammation. The cross-talk and downstream convergence of these pathways is connected via inflammation. Inflammation leads to stimulation of uterine contractions, rupture of membranes, and cervical dilation and effacement (91,92).

Vitamin D sufficiency may exert a protective effect on spontaneous preterm birth risk through its immunomodulatory and anti-inflammatory properties, which have been demonstrated in a number of cell lines, tissue types, and model systems (93–95). With respect to the cell-mediated immune response, vitamin D reduces the response to microbial pathogens by abrogating production of interleukin-6, interleukin-1, and tumor necrosis factor-α by macrophages (59,60,96). Importantly, the immunomodulatory effects of vitamin D may be important for processes other than the host inflammatory response to pathogen. Exciting new data highlight a novel function of vitamin D in upper genital tract immunity. Investigators observed that human decidual cells are able to synthesize active $1,25(OH)_2D_3$, particularly in early gestation, and this may act in an autocrine/paracrine manner to regulate both acquired and innate immune responses at the fetal-maternal interface (61,97,98).

Immunologic function of reproductive tract cells and, indeed, uterine immune cells themselves such as dendritic cells, macrophages, and natural killer cells, are modulated by vitamin D in vitro and in vivo (60,93). Vitamin D is also important for pregnancy maintenance through its relation to calcium metabolism in the myometrium (99–101). Increases in myometrial contractility are dependent upon increases in intracellular calcium release from sarcoplasmic reticulum within the myometrial cell. In a variety of cell types and model systems, vitamin D is critical to the execution of calcium-dependent cellular processes (102).

The strongest evidence that vitamin D sufficiency may protect against preterm birth comes from preliminary analysis of a large pregnancy vitamin D supplementation study in South Carolina. Hollis and colleagues randomized 600 white, black, and Hispanic mothers to 400 IU, 2000 IU, or 4000 IU per day of vitamin D3 in early pregnancy (1). Their initial findings show that the risk of preterm birth at

<37 and <32 weeks was reduced among women taking the highest doses of vitamin D (personal communication, Bruce Hollis, 2010). Future analyses limited to spontaneous preterm births and stratified by race/ethnicity will undoubtedly yield intriguing insights into the contribution of maternal vitamin D status into the black-white disparity in preterm birth. We are unaware of another vitamin D trial to have tested these effects.

There is sparse observational data on vitamin D and preterm birth. Morley et al examined maternal 25(OH)D in relation to length of gestation in a nearly all Caucasian sample, and reported that serum 25(OH)D <28 nmol/L at 28 to 32 weeks was associated with a 0.7 weeks shorter gestation (95% CI: −1.3, −0.1) (103). There was no relation between 25(OH)D at 11 weeks and gestational length. With only 14 cases of preterm birth, the researchers were limited in their ability to study this outcome. Investigators of a study of 884 HIV-infected pregnant Tanzanian mothers reported no significant association between serum 25(OH)D <80 nmol/L at 12 to 27 weeks gestation and risk of preterm birth at <37 weeks (risk ratio [95% CI]: 0.84 [0.65, 1.07]) or preterm birth <34 weeks (0.77 [0.50, 1.18]) (104). The suggestion of a possible protective effect of vitamin D deficiency should be followed up in other cohorts with different underlying nutritional or immunologic status.

Indirect evidence that vitamin D and sunlight exposure may be relevant for preterm birth can also be derived from studies of seasonal patterns in disease occurrence. In a cohort of 82,213 singleton live births between 1995 and 2005 in Pittsburgh, we found that the prevalence of spontaneous preterm birth at 32 to <37 weeks and at <32 weeks was lowest among women who conceived in summer and fall (when vitamin D status is at its peak), and was highest among winter and spring conceptions (when vitamin D status is poorest) (105). Maternal race did not modify the observed seasonal pattern. In a low-income group of black and white women in our region, we also recently noted a strong, negative association between maternal 25(OH)D at <16 weeks gestation and the prevalence of bacterial vaginosis (106), a common vaginal infection strongly linked with spontaneous preterm birth (107).

Certainly, with the strong biologic plausibility linking vitamin D status to spontaneous preterm birth, studies of large, racially diverse populations are needed to explore the contribution of black-white disparities in vitamin D deficiency to risk of this common adverse birth outcome.

Gestational Diabetes Mellitus

Gestational diabetes is a disorder of great public health significance for mothers and offspring (108,109). Gestational diabetes is thought to arise from an inappropriately robust increase in insulin resistance during pregnancy with a failure of pancreatic β cell insulin production to rise sufficiently to meet needs.

Because of both pancreatic and peripheral effects, vitamin D is likely to play a major role in glucose and insulin metabolism and, thus, gestational diabetes. Data support a plausible connection between vitamin D and insulin sensitivity. Vitamin D deprivation decreases and vitamin D treatment increases the insulin content of the whole pancreas or isolated islets and the secretory response of the islets to glucose among rats (110). These changes in insulin release are significant when normalized to the insulin content of the islets. Furthermore, there is a positive correlation of 25(OH)D and insulin release from pancreatic islet cells among rats (110). Human studies have reported correlations between vitamin D status with β-cell function, peripheral insulin sensitivity, and a reduced prevalence of the metabolic syndrome (111–113). These intriguing findings taken together suggest that vitamin D deficiency causes primary alteration of pancreatic B-cell function (71).

Vitamin D deficiency has been associated with diabetes in nonpregnant adults (114), and recently has been studied in relation to gestational diabetes. Zhang et al are the only investigators to have examined maternal vitamin D status before the clinical onset of gestational diabetes (1). In a nested case-control study of predominantly white mothers living in Washington State, they found that vitamin D deficiency at 16 weeks gestation was associated with a 2.7-fold increased risk developing gestational diabetes later in the pregnancy, independent of measured confounders (115). Other researchers measured 25(OH)D contemporaneously with oral glucose tolerance testing. Two reports noted significant positive correlations between 25(OH)D concentrations and insulin sensitivity, as measured by the homeostasis model assessment index (116,117) and fasting insulin (117), whereas no association was observed in another large study (118). However, the cross-sectional nature of these studies hampers the inferences that can be drawn about vitamin D and the development of glucose intolerance in pregnancy.

Fetal growth, Growth Restriction, and Growth Velocity

The physiologic trajectory of growth of the human fetus is dependent upon adequate delivery of oxygen

and nutrients from maternal circulation to fetal circulation. The delivery of nutrients and oxygen is among the most important functions of the placenta. In this regard, through effects on angiogenesis and trophoblast invasion of maternal blood vessels, vitamin D can influence placental villous development. In terms of placental development and function, the vitamin D activating enzyme CYP27B1 as well as VDR are present in human placenta (51). The $1,25(OH)_2D$, acting through the VDR and the cAMP/PKA signaling pathway, regulates human chorionic gonadotropin expression and secretion in human syncytiotrophoblast (119) and increases placental sex steroid production (120). As noted earlier, vitamin D is also important in glucose/insulin metabolism and homeostasis. As a regulator of glucose concentration in maternal circulation, vitamin D could play a role in glucose availability for transplacental transport and fetal usage. As a regulator of calcium homeostasis and transport, calcitriol also can influence fetal growth directly through influences on skeletal muscle and bone development (121,122).

A number of randomized clinical trials have been conducted to determine the effect of vitamin D supplementation on infant size at birth. In a randomized, double-blinded trial of 1000 IU vitamin D per day or placebo starting in the third trimester, researchers found that among their population of 126 Asian mothers living in Britain, supplementation significantly reduced the risk of small-for-gestational age (SGA) infants (15% vs. 28%, $P < 0.05$) and increased maternal 25(OH)D concentrations (mean, 168.0 vs. 16.2 nmol/L; $P < 0.001$) (123). In a randomized trial among 145 Hindu women, Marya et al found that the group supplemented with a single dose of 600,000 IU twice in gestational months 7 and 8 delivered infants with significantly higher birth weights (mean birth weight, 3.18 kg) than mothers randomized to receive 1200 IU of vitamin D per day starting in the third trimester (2.89 kg), or mothers randomized to placebo (2.73 kg) (124). In a follow-up study of 200 Asian women, the same investigators reported that 600,000 IU twice in the third trimester reduced the incidence of low birth weight (<2500 g) compared with placebo (4% vs. 19%) (125). In contrast, there were no differences in mean birth weight among groups of French women randomized to a single dose of 200,000 IU of vitamin D in gestational months 7 or 1000 IU/d of vitamin D starting in the third trimester compared with a control group, but the relatively small sample (n = 77) may have limited power to detect differences (126).

A study of 74 Canadian women who restricted milk intake during gestation found a positive association between vitamin D intake from food and infant birth weight (127). In a cross-sectional study of 449 Iranian women at delivery, adequacy of oral vitamin D intake was associated with a decreased odds of low birth weight (128). We recently reported a U-shaped relation between serum 25(OH)D and risk of SGA among white mothers, with the lowest risk from 60 to 80 nmol/L (129). Compared with serum 25(OH)D 37.5 to 75 nmol/L, SGA odds ratios (95% CIs) for levels <37.5, and >75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8), respectively. There was no relation between 25(OH)D and SGA risk among black mothers. We also noted that one single nucleotide polymorphism (SNP) in the VDR gene among white women and 3 SNPs in black women were significantly associated with SGA. Morley et al (130) examined how a functional SNP in the VDR gene (*Fok*I) modified the effect of maternal vitamin D status on low birth weight. They found that low maternal 25(OH)D concentrations were associated with lower birth weight infants only among infants who were either homozygous or heterozygous for the *Fok*I major allele.

In contrast, no relation between maternal 25(OH)D, most often assessed late in pregnancy, and mean birth weight or other continuous measures of size at birth have been reported in observational studies of 30 Pakistani women living in Norway (131), 559 women in South India (118), 374 Austrian, dominantly Caucasian, women (103), 123 Gambian women (132), or 466 Caucasians in the United Kingdom (133). For example, Gale et al measured maternal third-trimester serum 25(OH)D and observed no differences in mean infant birth weight, length, head circumference, or mid-upper arm circumference (133).

Although the results of studies of maternal vitamin D and infant size at birth are mixed, positive associations are more consistent when studies are limited to those that examined a pathologic outcome such as SGA or low birth weight. Indeed, the problem with studying birth weight or other measures of size on a continuum is that, often, pathologic outcomes do not operate along a continuum. That is, the relation between vitamin D and fetal growth or size may not have as close a relationship in accounting for variation in normal as it would in accounting for variation in a pathophysiologic condition such as growth restriction. The conflicting findings in the overall vitamin D and infant size literature may also be because of the study of maternal vitamin D in late-

pregnancy, rather than early-pregnancy. Vitamin D may exert its effect in early pregnancy, like many other exposures (134). An important final limitation in understanding the relation between vitamin D status and disordered fetal growth is the use of population standards for defining abnormal rather than application of customized fetal growth trajectories and birth weights. Recent work suggests that the use of customized fetal growth trajectories is able to provide a more precise estimate of appropriate fetal growth and size, and, thus, a more specific measure of pathologic growth and increased risk of perinatal morbidity and mortality for any given fetus/newborn (135–137). The use of customized standards is an important advance in understanding environmental contributors to disordered fetal growth and holds great promise for future investigation.

CONTRIBUTION OF VITAMIN D TO THE BLACK-WHITE DISPARITY IN BIRTH OUTCOMES

Black infants are 4 times as likely as whites to have been exposed to in utero vitamin D deficiency (13). They also die at a rate more than twice that of their white counterparts, and experience more frequent morbidity (1–3). Research linking a common, modifiable risk factor such as vitamin D deficiency to the profound and intractable black-white disparity in infant mortality and morbidity could have a tremendous public health impact. To inform this critical question, several key gaps in our current knowledge must be filled.

First, is vitamin D causally related to major adverse birth and pregnancy outcomes? Although the literature reviewed earlier suggests that maternal vitamin D deficiency may increase the risk of preeclampsia and SGA birth, there is currently less research in support of spontaneous preterm birth and gestational diabetes. Moreover, observational studies dominate the field, with few published trials of vitamin D supplementation conducted in pregnant women with adequate power to test effects on birth outcomes. All relations are of strong biologic plausibility and warrant further testing with rigorous study designs.

Second, does maternal vitamin D status contribute to fetal and infant survival? We are aware of only one study to address these relationships. In the aforementioned vitamin supplementation trial among 884 HIV-infected pregnant Tanzanian women, maternal second-trimester serum 25(OH)D <32 ng/mL was not associated with fetal loss, but was associated with a 61% increase in the incidence of infant death (104). Additional studies in diverse populations are urgently needed. Certainly, because the great obstetrical syndromes of preterm birth, fetal growth restriction, and preeclampsia are among the major causes of fetal and infant death, research into these adverse outcomes will contribute meaningful information as to whether vitamin D may be related to offspring survival. However, the vast majority of babies born preterm, to mothers with preeclampsia, or with pathologic fetal growth do not die in the uterus or during infancy; exploration of the epidemiology and mechanisms underlying fetal and infant death go above and beyond understanding the great obstetrical syndromes. Stillbirth and infant death impose a tremendous burden of disease worldwide, and understanding their independent contributors is critically important (138).

Third, is vitamin D deficiency a risk factor for adverse outcomes specifically among black women? Clearly, there is an absence of black pregnant women from published vitamin D—birth outcomes research. Specifically assessing relations between vitamin D and poor birth outcomes among adequate numbers of black women in observational studies and clinical trials is necessary because vitamin D may have a differential effect on certain diseases depending on racial/ethnic group (139–141). If supplementing with vitamin D raises 25(OH)D in all women, but only white women see a benefit in terms of outcome, then such an intervention would only exaggerate the racial disparity. In contrast, if improving vitamin D status reduces risk in both white and black women to a similar extent, vitamin D interventions will likely result in a reduction of the racial disparity because vitamin D deficiency affects more black than white women.

Maternal vitamin D status is a promising candidate influence on black-white disparities in preeclampsia, spontaneous preterm birth, fetal growth restriction, and gestational diabetes, but requires further study in large samples of racially diverse US women. Because vitamin D deficiency is widespread and black-white disparities in pregnancy outcomes and infant survival have been resistant to previous interventions, research to test vitamin D as a causal factor is of major public health significance. After completing the CME activity, learners should be able to describe the extent of the racial disparity in adverse birth outcomes and vitamin D deficiency in pregnant women. Learners should also be able to summarize what is known about maternal vitamin D deficiency

and the risk of preeclampsia, preterm birth, fetal growth restriction, and gestational diabetes.

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