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Relationship Between Vitamin D During Perinatal Development and Health

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J Midwifery Womens Health. 2010;55(6):550-560.

Abstract and Introduction

Abstract

Vitamin D deficiency is a highly prevalent condition that is present in 40% to 80% of pregnant women. There is emerging evidence that vitamin D deficiency may be a risk modifying factor for many chronic diseases, including osteomalacia, rickets, multiple sclerosis, schizophrenia, heart disease, type 1 diabetes, and cancer. Heightened susceptibility to these diseases may originate in early life during the development of tissue structure and function. It is suspected that biologic mechanisms can "memorize" the metabolic effects of early nutritional environment through fetal and neonatal imprinting. Inadequate vitamin D nutrition during perinatal life may establish a poor foundation that may produce long-term threats to human health. This review summarizes the risks of vitamin D deficiency for human health and provides the current vitamin D recommendations for mothers and their newborns.

Introduction

The United Nations Standing Committee on Nutrition has proposed that a window of opportunity exists from prepregnancy to 24 months of a child's life during which nutrition can affect the structural and functional development of an organism.[1] Such changes in structural or functional development can result in long-term consequences on human health.[2] Vitamin D, a fat-soluble molecule acquired through exposure to sunlight or diet, has been identified as a steroid hormone precursor that modulates long-term programming of human health. Low vitamin D intakes during perinatal development have traditionally been linked to poor bone health. However, scientists are beginning to realize that vitamin D deficiency during perinatal development is a risk modifying factor for a range of diseases, including multiple sclerosis, schizophrenia, heart disease, type 1 diabetes, and cancer.

Historically, humans obtained most of their vitamin D through sun exposure. However, in contemporary society, sun avoidance and the use of topical sunscreen are strongly encouraged because of the association of sun exposure with skin cancer. To sustain adequate vitamin D levels in such an environment, oral consumption of vitamin D is required. However, very few foods in nature contain vitamin D. Fish (e.g., salmon, tuna, and mackerel) and fish liver oils are among the best sources.[3] Small amounts of vitamin D are found in beef liver, cheese, egg yolk, and some forms of mushrooms.[3] Given the importance of vitamin D and its lack of availability from the sun and diet, vitamin D supplementation is required. This need is even more significant during sensitive stages of development, such as the prenatal and neonatal stages of life.

The purpose of this review is to illustrate that inadequate vitamin D nutrition during perinatal development is a threat to human health and to provide health care professionals with current recommendations for vitamin D supplementation.

Vitamin D Metabolism

Vitamin D belongs to a group of sterols, with the two most important sterols being vitamin D_2 and vitamin D_3. The major difference between the two vitamin D sterols is the source from which they are obtained. When skin is exposed to ultraviolet sunlight, it synthesizes vitamin D_3, the most readily available form.[3] However, the ability of skin to synthesize vitamin D_3 from sunlight exposure is adversely affected by factors that diminish the intensity of the exposure, such as poor air quality, extreme latitudes, and the winter season.[4] In addition, factors that limit the skin's absorption of sunlight, such as increased pigmentation, the use of sunscreen, and advanced age, can also limit vitamin D_3 synthesis.[4] Foods such as oily fish are an additional source of vitamin D_3, whereas plant sources provide vitamin D_2.[3] However, the amount of vitamin D obtained through diet is often low and limited by malabsorption syndromes. Therefore, many people rely on fortified foods and dietary supplements to meet their vitamin D needs during times of insufficient sunlight. Vitamin D_3 supplements may be more effective at increasing serum levels of 25-hydroxyvitamin D (25(OH)D) than vitamin D_2 supplements.[5] This may be because vitamin D_3 has a stronger affinity for vitamin D–binding protein, a transporter that mediates its delivery to muscle or fat for storage, or liver and kidney for bioactivation.

Both forms of vitamin D are biologically inert and must undergo two metabolic steps before becoming physiologically active. The first step occurs in the liver, which converts vitamin D to 25(OH)D, the main circulating form and the usual measure of vitamin D status. This conversion to 25(OH)D is impeded in those with liver disease. According to a recent study, 92% of patients with chronic liver disease are vitamin D deficient. Vitamin D deficiency is defined by serum 25(OH)D concentrations below 10 ng/mL (25 nmol/L), because values below this cut-off are associated with rickets and myopathy.[6]

The second metabolic step occurs in the kidney and many other tissues (i.e., heart, brain, skin, reproductive tissue, skeletal muscle, spinal cord, and the placenta) and forms the physiologically active hormone 1,25-dihydroxyvitamin D [$1,25(OH)_2D$].[7] The $1,25(OH)_2D$ is released into the circulatory system and can stimulate target cells in close proximity through its autocrine and

paracrine functions.[7, 8] Moreover, 1,25(OH)$_2$D can bind to vitamin D receptor (VDR) and modulate many cellular and immunologic processes.[9] The expression of VDR has been identified in most organs and several types of white blood cells, indicating that the vitamin D endocrine system is essential for the development and maintenance of tissue structure and function.

Vitamin D Metabolism During Pregnancy and Lactation

At 4 weeks of gestation, the placenta is formed, allowing nutrients to be transferred from the mother to the fetus (Figure 1). From 4 weeks of gestation to term, 25(OH)D easily diffuses across the placenta, allowing the 25(OH)D concentrations in fetal cord blood to reach 87% that of the mother's concentrations.[10] The physiologically active metabolite 1,25(OH)$_2$D does not readily cross the placenta.[11] However, the placenta and the fetal kidney express the enzyme 1α-hydroxylase that converts 25(OH)D to 1,25(OH)$_2$D in these tissues, which may contribute to fetal circulating levels of 1,25(OH)$_2$D.[11] In both the mother and the fetus, total 1,25(OH)$_2$D concentrations increase by 100% to 200% starting in the first trimester, but most of this vitamin D is bound to vitamin D–binding protein. It is widely assumed that the nonprotein bound free hormone reflects the more biologic active form of vitamin D. Free 1,25(OH)$_2$D concentrations have only been shown to be elevated in the last trimester[12] and may be implicated in labor initiation. Most recent studies have shown that 1,25(OH)$_2$D regulates the secretion of placental hormones (i.e., estradiol and progesterone)[13] and prevents the induction of inflammatory cytokines that stimulate preeclampsia and premature labor.[14] These findings at least in part explain the observation that vitamin D–deficient women have a fivefold increased risk of developing preeclampsia.[15] After birth, maternal serum 25(OH)D and 1,25(OH)$_2$D concentrations drop significantly, which is partially why breastfed infants need to be supplemented with vitamin D.

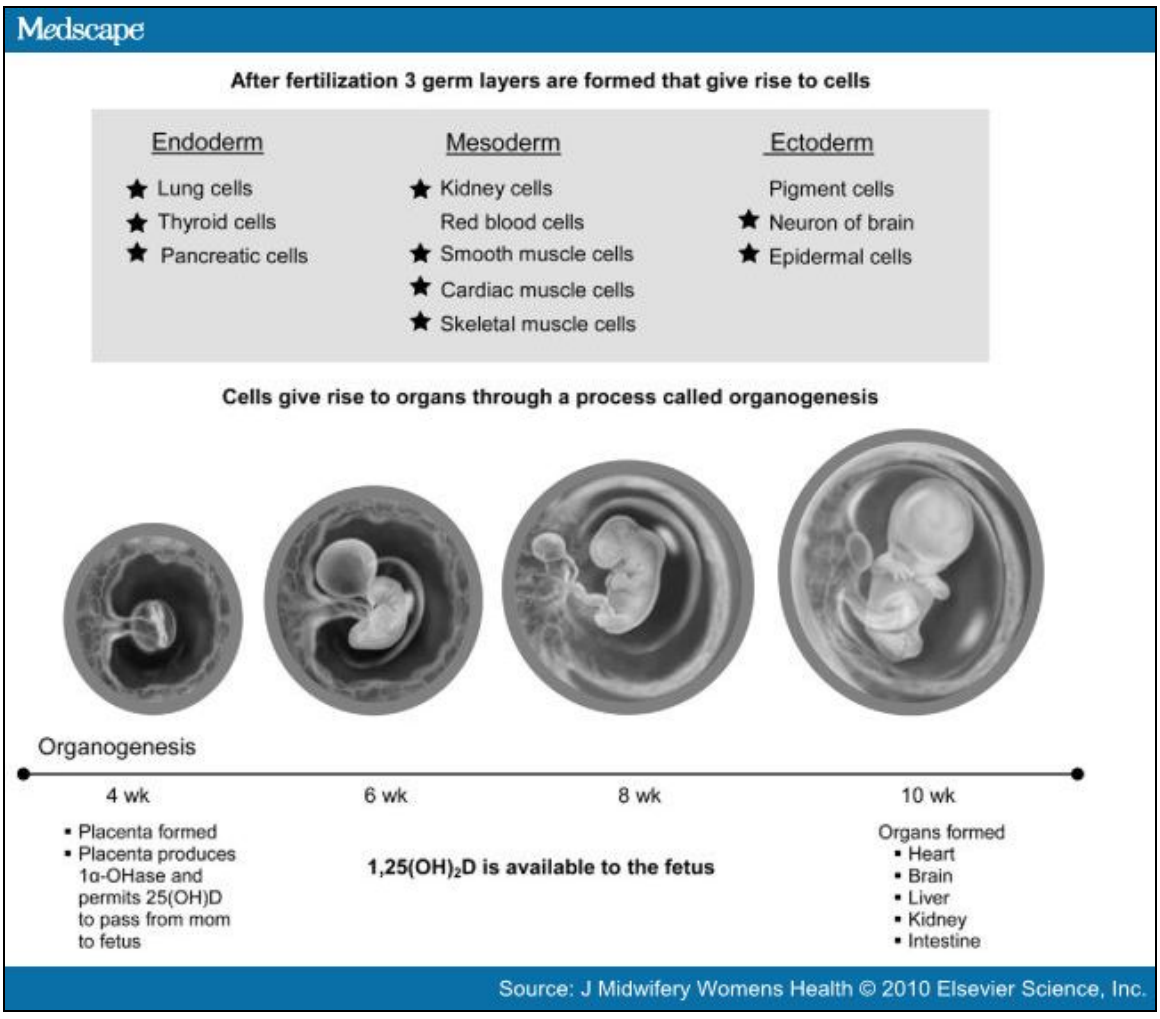

Figure 1.

Vitamin D effects on fetal development. In pregnancy, the fertilized egg undergoes a series of reproductive cell divisions to form three germ layers (i.e., endoderm, mesoderm, and ectoderm) that give rise to different types of cells, many of which express vitamin D receptors (VDR; denoted by a *star*). Different types of cells give rise to different organs through a process called organogenesis that extends from 4 to 10 weeks of gestation. During this time, localized concentrations of diverse nutrient (i.e., vitamin D) and their metabolites [i.e., 25(OH)D and 1,25(OH)$_2$D] can interact with various signalling systems to regulate organ

development. If we examine the timeline in Figure 2, the placenta is formed at 4 weeks of gestation. Placenta permits the transfer of 25(OH)D from the mother to the fetus. The placenta also produces 1α-OHase, allowing it to locally synthesize $1,25(OH)_2D$. The biologically active hormone $1,25(OH)_2D$ binds to VDR in specialized cells to induce genomic and nongenomic responses that stimulate organ development. By 10 weeks of gestation, the organs are formed (i.e., heart, brain, liver, kidney, and intestine).

How Does Vitamin D Modulate Human Health?

The mechanism by which vitamin D modulates human health has not yet been identified. However, it has been proposed that metabolic imprinting may be responsible for the long-term program effects of 25(OH)D. Metabolic imprinting is an adaptive process that fine tunes the expression of specific genes, without directly altering the DNA sequence, to produce a phenotype that is best suited to survive in its predicted environment.[16]

To better understand the concept of metabolic imprinting, the human body can be thought of as a factory and metabolic imprinting as quality control. In a factory, quality control ensures that the product is designed and produced to meet or exceed consumer requirements. If the product is defective or if there is a possibility that it may malfunction in its given environment, minor modifications are used through various processes to optimize product success and longevity. However, these modifications can only be made if appropriate tools and resources (i.e., raw material) are available. Similarly, in the human body, metabolic imprinting, which takes place during critical windows of development such as the prenatal and neonatal stages of life, ensures that an array of differentiated tissues produces a phenotype that can survive in its given environment.[17] If the phenotype is well matched to its environment, the organism will remain healthy; however, if there is any sort of mismatch, the organism's ability to respond to environmental challenges may be inadequate and risk of disease may be high.[16] An overview of how vitamin D modulates system development and chronic disease susceptibility is summarized in Figure 2 and and expanded upon below.

Table 1. Epidemiologic Evidence Linking Vitamin D and Disease

	Variables Used in Epidemiology to Infer a Relationship to Vitamin D				
Disease Relationship	**Sun Exposure**	**Migration Away From High Sun Exposure**	**Season of Birth**	**Skin Pigmentation**	**Dietary Vitamin D**
Osteomalacia and rickets	Decreased sun exposure in third trimester is associated with decreased bone mass[29]	Afro-Caribbean immigrants in the UK are associated with an increased incidence of rickets[68]	To our knowledge, no epidemiologic studies have shown this relationship	Children with darker skin have a higher prevalence of having poor bone health and rickets[17,69,70]	Low maternal 25(OH)D concentrations during pregnancy are associated with decreased bone mineral content in children at 9 years of age[29] Vitamin D deficiency in early life is associated with rickets, mild respiratory distress, weak muscle tone, decreased calcium and increased parathyroid hormone levels[71]
Multiple sclerosis (MS)	Increased sun exposure during early life is associated with a decreased risk of MS[72] MS relapse is inversely associated with UV exposure and 25(OH)D levels[73]	Indian and Pakistani immigrants who enter the UK between 0–4 years of age are at increased risk of having MS[74] Second-generation Afro-Caribbean immigrants in the UK are associated with an increased MS risk[75]	Data pooled from 4 countries shows that spring births are associated with an increased MS risk and fall births are associated with a decreased MS risk[76]	Having white skin lowers the prevalence of MS disability[77]	Consumption of fish 3 –4 times a week is associated with a decreased MS risk[72] Diets low in fish but high in meat and dairy products are associated with an increased prevalence of MS[78] Intake of vitamin D from supplements is inversely associated with MS risk[79]
Schizophrenia	Increased sun exposure is associated with decreased risks of having schizophrenia, and	Second-generation immigrants from Morocco and Surinam to the Netherlands are associated with an	Data pooled from 6 countries shows that winter births are associated with an increased incidence	Having black skin may be associated with an increased incidence of schizophrenia[85]	Vitamin D supplementation during the first year of life lowered the risk of developing schizophrenia in

	schizophrenia-induced symptoms are weaker and less regular[80]	increased risk of schizophrenia[81] Afro-Caribbean immigrants to the UK are associated with an increased risk of schizophrenia[82]	of schizophrenia[83, 84]		males, but not females[86] Maternal 25(OH)D was not a risk factor for schizophrenia. But the results in the black subgroup raise the possibility that below a certain threshold low levels of 25(OH)D may be associated with an increased risk of schizophrenia[85]
Type 1 diabetes	Monthly sunshine availability is inversely associated with having type 1 diabetes[87]	Children who migrated to an area prevalent in diabetes (northern region) had a greater risk of developing type 1 diabetes[88]	Winter and spring births are associated with higher frequency of type 1 diabetes[89–91] than summer births[91]	Children with black skin are at a higher risk of having type 1 diabetes than children with white skin[92]	In a meta-analysis, vitamin D supplementation was associated with a decreased risk of type 1 diabetes[93] Children who consumed vitamin D supplements had an 80% lower risk of having type 1 diabetes[55] Use of cod liver oil by mothers during pregnancy and infants in the first year of life lowered the infants' risk of developing type 1 diabetes[56]

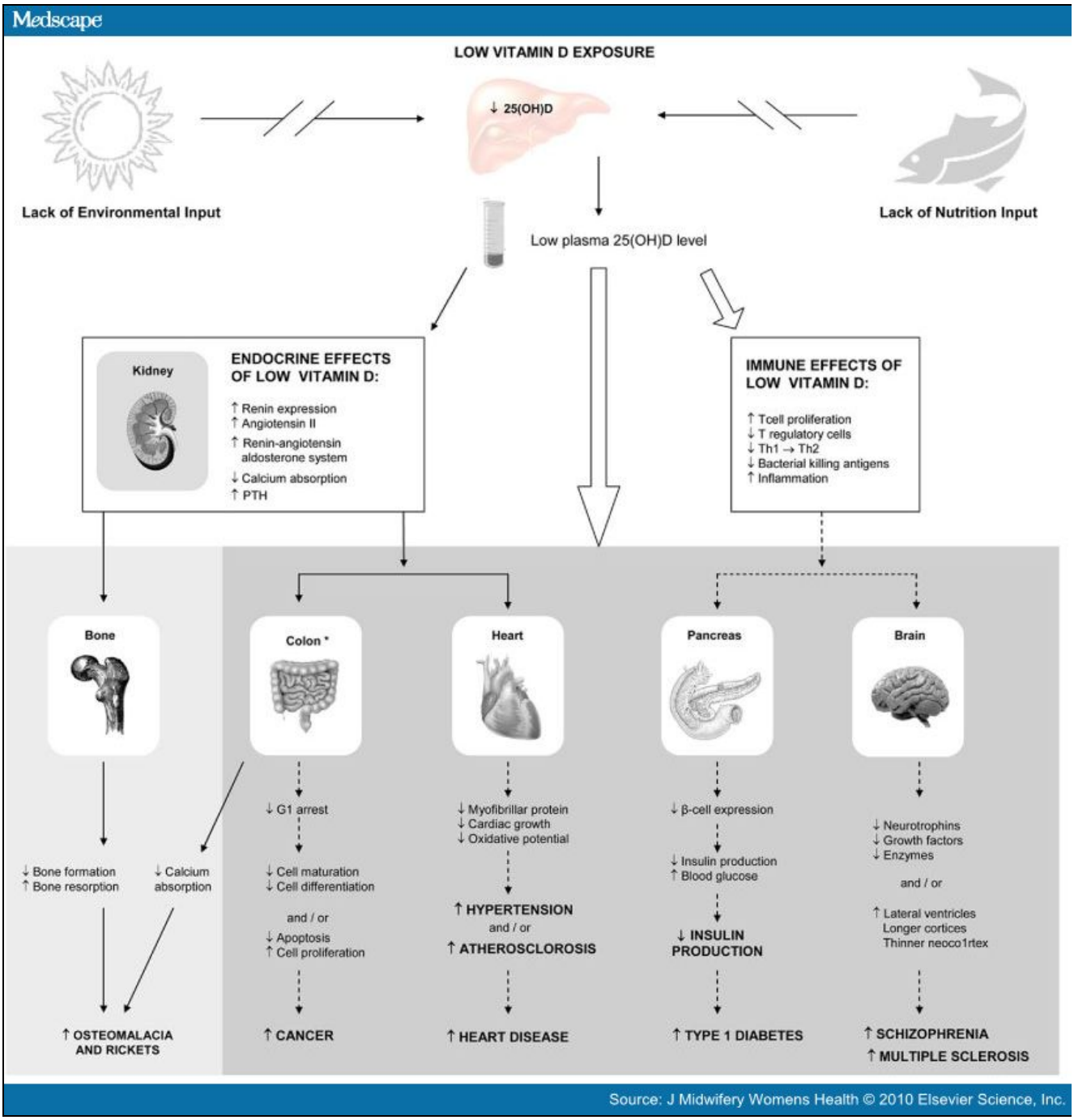

Figure 2.

Summary of mechanisms by which a lack of vitamin D leads to disease. The *arrows* indicated by *solid lines* represent endocrine signals (i.e., molecules moving via the circulation to produce their effects). The *large block arrows* represent paracrine action of 25 (OH)D (i.e., the effects of vitamin D produced by the local production of $1,25(OH)_2D$ to permit communication between cells within each tissue). The *arrows with light dashed lines* represent mechanistic pathways. The *asterisk* (*) signifies that through a similar pathway, low plasma 25(OH)D can promote breast, prostate, or brain cancer.

Vitamin D Effects on Bone Health

Skeletal growth is a dynamic process that requires 25 to 30 g of calcium to be transferred from the mother to the fetus during pregnancy.[18] This calcium transfer is achieved through increased intestinal calcium absorption, which increases from 33% to 36% before pregnancy to 54% to 62% in the third trimester.[19] Vitamin D facilitates the intestinal absorption of calcium, but its effects

reach a plateau at 32 ng/mL, beyond which there is no further rise in calcium absorption.[20] At suboptimal levels, vitamin D's availability limits the physiologic control of calcium transport across the mucosal membrane.[20] In severe cases of vitamin D deficiency, secondary hyperparathyroidism or osteomalacia may result. To date, no studies have investigated the optimal level of 25(OH)D during pregnancy.[12]

When pregnant, a women's body will put the physiologic needs of the baby before her own. For example, a vitamin D–deficient mother who develops secondary hyperparathyroidism will leach nutrients from her bones and tissues and transfer them to her fetus. This will have an adverse effect on maternal bone metabolism but will ensure that the pregnancy survives. The net amount of vitamin D transferred to the fetus from a vitamin D–deficient mother will be reduced, which may affect fetal bone mineralization and growth.[21] A fetus that was vitamin D deficient during pregnancy will most likely be born with normal serum calcium concentrations and normal skeletal morphology, but risks developing osteomalacia or rickets within the first few weeks or months of life.[12] These infants may also exhibit severe muscle weakness, which may alter their lung function. In one study, low maternal vitamin D intake during pregnancy was associated with decreased bronchodilator response and increased risk of wheeze symptoms in 5-year-olds.[22] If the lower limbs are weakened or deformed, there may be adverse effects on the development of ambulation in childhood.

Rickets is a persistent global health concern among infants and children[23] and is associated with anatomic deformities, including pelvic distortion. In this case, the anteroposterior diameter of the pelvis is shorter, causing the pelvis to be contracted.[24] If the child is a female, the contracted pelvis may pose a problem during future childbirth.[24] In general, African American women have a narrower pelvic inlet and a narrower pelvic outlet than European American women.[25] Whether these anatomic differences are caused in part by vitamin D status has not been experimentally determined. However, one study found that 5% of white women and 30% to 45% of black women are vitamin D deficient during gestation.[26] These differences result because highly melanized skin acts as a filter that increases the length of exposure to UVB light needed to synthesize vitamin D_3. For this reason, health care providers should take extra caution about monitoring serum 25(OH)D concentrations of African American women, because they are at a greater risk of vitamin D deficiency.

Pregnant women with serum 25(OH)D concentrations below 15 ng/mL are four times as likely to have a caesarean birth than women with 25(OH)D concentrations above 15 ng/mL,[27] even after correcting for confounding variables such as race. Vitamin D deficiency severely impairs muscle function and causes myopathy even before biochemical signs of bone disease develop.[28] As a result, vitamin D–induced myopathy, which often goes undetected because the loss of bone strength persists for months before muscle weakness develops, may affect the strength of muscle contractions needed during labor and contribute to higher rates of caesarean births. Supplementing women with vitamin D may help to prevent bone disease, myopathy, and improve reproductive success.[29]

Vitamin D Effects on Brain Development

In vitro, animal and human data have provided evidence linking vitamin D to brain development. VDR and 1α-hydroxylase, the enzyme that produces $1,25(OH)_2D$, have been identified in the fetal[30, 31] and adult[32–34] brain. The distribution of VDR in the embryonic brain depends on gestational age. In rats, VDR expression increases from the twelfth day of gestation until birth and is most prominent in the neuroepithelium and proliferating zones of the central nervous system.[30] In the human fetus, the pattern of VDR expression has not been well characterized. It is known that serum 25(OH)D and $1,25(OH)_2D$ can cross the blood–brain barrier,[34] bind to VDR, and stimulate a wide range of genomic and nongenomic responses.[35, 36]

Low concentrations of 25(OH)D during critical windows of development have the potential to reprogram brain tissue structure and function. At birth, the brains of rat pups born to vitamin D–depleted mothers had more mitotic cells and fewer apoptotic cells, suggesting that low 25(OH)D concentrations can cause transcriptional deregulation in the brain.[37] Over time, this transcriptional deregulation may promote tumor growth and lead to brain cancer. Epidemiologic evidence suggests a possible link between brain cancer and vitamin D deficiency; but whether this link is caused by the deregulation of cell cycle arrest is yet to be determined. According to work by Eyles et al.,[37] maternal deprivation of vitamin D can cause profound alterations in the infant's brain on a cellular, molecular, and tissue level,[37] as expanded upon below.

On a molecular level, maternal vitamin D depletion can impair the expression of neurotrophins and growth factors in the developing brain tissue of rat pups.[37] Neurotrophins and growth factors are a family of proteins that regulate neuron production, myelination, cell growth, and the formation of synaptic connections. During fetal development, brain cells multiply at an astonishing rate. At birth, 100 billion brain cells have been established that communicate with each other by sending electrochemical impulses through nerve cells. Each impulse that a brain cell receives creates a neuronal connection inside the nerve cell that helps to strengthen the brain's overall networking system. Each cell in the brain can connect with up to 15,000 other cells, but if these connections are impaired, neurologic disorders, such as multiple sclerosis (MS), can develop.

There is emerging evidence that vitamin D may be a risk modifying factor for MS (). In a large prospective study,[38] the probability of developing MS was significantly higher for individuals with serum 25(OH)D concentrations in the bottom quintile (6–25 ng/mL) than the top quintile (40–60 ng/mL). Importantly, the risk of developing MS for individuals in the bottom quintile decreased by 41% with a 20-ng/mL increase in serum 25(OH)D concentrations.

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Schizophrenia	Increased sun exposure is associated with decreased risks of having schizophrenia, and schizophrenia-induced symptoms are weaker and less regular[80]	Second-generation immigrants from Morocco and Surinam to the Netherlands are associated with an increased risk of schizophrenia[81] Afro-Caribbean immigrants to the UK are associated with an increased risk of schizophrenia[82]	Data pooled from 6 countries shows that winter births are associated with an increased incidence of schizophrenia[83,84]	Having black skin may be associated with an increased incidence of schizophrenia[85]	Vitamin D supplementation during the first year of life lowered the risk of developing schizophrenia in males, but not females[86] Maternal 25(OH)D was not a risk factor for schizophrenia. But the results in the black subgroup raise the possibility that below a certain threshold low levels of 25(OH)D may be associated with an increased risk of schizophrenia[85]
Type 1 diabetes	Monthly sunshine availability is inversely associated with having type 1 diabetes[87]	Children who migrated to an area prevalent in diabetes (northern region) had a greater risk of developing type 1 diabetes[88]	Winter and spring births are associated with higher frequency of type 1 diabetes[89–91] than summer births[91]	Children with black skin are at a higher risk of having type 1 diabetes than children with white skin[92]	In a meta-analysis, vitamin D supplementation was associated with a decreased risk of type 1 diabetes[93] Children who consumed vitamin D supplements had an 80% lower risk of having type 1 diabetes[55] Use of cod liver oil by mothers during pregnancy and infants

					in the first year of life lowered the infants' risk of developing type 1 diabetes[56]

Early development is a crucial exposure period for MS. Individuals who are vitamin D deficient during early life may have a greater susceptibility to MS or greater severity of MS symptoms.[39] The pathology underlying MS involves disruption of the blood–brain barrier, which allows white blood cells called T lymphocytes to cross over and damage the myelin sheaths of the central nervous system.[40] The cause of MS remains unknown, but findings from a cell culture study indicate that, by interacting with VDR on T lymphocytes, the biologically active $1,25(OH)_2D$ hormone can downregulate T cell activity that damages the myelin of the central nervous system.[41] Therefore, supplemental vitamin D may be protective when sun exposure is low for preventing myelin sheet damage and reducing the risk of MS.

On a tissue level, maternal vitamin D depletion alters the brain morphology of the developing offspring.[42] Rat pups born to vitamin D–deprived mothers had enlarged lateral ventricles and longer cortices that were proportionally thinner. Changes in brain morphology have been associated with psychological disorders. Thinning of neocortex and ventricle overgrowth are two changes commonly observed in brains of children with schizophrenia,[43] suggesting that vitamin D may be a risk modifying factor for schizophrenia. There is some epidemiologic evidence supporting the association between vitamin D exposure in early life and schizophrenia ().

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Animal models designed to limit the organism's ability to use vitamin D during brain development have been used to investigate how vitamin D affects both cognitive and behavioral functions. Many of these observational findings are consistent with behavioral patterns of patients with schizophrenia and MS,[44, 45] and may in part be explained by deregulation of brain protein expression. Adult rats that were vitamin D–deprived during gestation had deregulation of 36 brain proteins,[46] many of which are misexpressed in either schizophrenia or MS. If this is also true in humans, vitamin D supplementation in pregnancy and childhood may prove to be a simple yet cost-effective strategy to help to prevent or alleviate debilitating disorders in later life.

Vitamin D Effects on Heart Disease

Findings from the National Health and Nutrition Examination Survey (1988–1994) revealed that serum 25(OH)D concentrations are inversely associated with cardiovascular disease, hypertension, myocardial infarction, congestive heart failure, and stroke in a large sample representative of the US adult population.[47] Exposure to low concentrations of 25(OH)D during early development may alter function in later life because during perinatal life, the mammalian heart undergoes tremendous growth and development. Emerging epidemiologic evidence () suggests that both maternal and neonatal vitamin D deficiency may be associated with heart disease later in life, but the mechanism remains unknown. One hypothesis is that vitamin D deficiency substantially lowers intestinal calcium absorption (50–60%), which triggers parathyroid hormone release.[48] Parathyroid hormone, in addition to its actions on calcium reabsorption and vitamin D production, stimulates insulin resistance, inflammation, and the renin–angiotensin aldosterone system. Over time, these three metabolic modifications upregulate the atherosclerotic process, which can lead to heart disease (Figure 2).[48]

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A study conducted in rodents examined how maternal vitamin D deprivation affected metabolic and contractile development of the neonatal heart.[49] Pups exposed to low levels of vitamin D (<200 IU/day) during perinatal life exhibited a reduction in protein (myofibrillar) accumulation and cardiac growth, which may seriously compromise cardiac functional capacity. In humans, there was no association between maternal 25(OH)D levels and cardiac measures in offspring at 9 years of age.[29] However, changes in

cardiac measures typically manifest in later life, suggesting that human studies need to be followed more long-term to determine the true association between vitamin D and heart disease.

During pregnancy, vitamin D may also affect heart development by modulating kidney function. In humans, nephron synthesis is complete at 36 weeks of gestation. Perturbations in nephrogenesis during the early stages of development may have long-term implications for renal health and hypertension. A study by Maka et al.[50] revealed that rat pups born to vitamin D–deficient mothers had a 20% increase in nephron endowment and a reduction in renal corpuscle size. These changes suggest that vitamin D does modulate nephrogenesis. However, without examining tubule resorption or kidney perfusion, the long-term implications of these changes for hypertension or heart health are unknown.

The Effects of Early Vitamin D Exposure on Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that begins in infancy and results in the destruction of insulin-producing β cells in the pancreas. The initiation of this process is not well understood, but it is estimated that by the time type 1 diabetes is diagnosed, 80% to 90% of β cells have been destroyed.[51] Prevention (rather than treatment strategies) may be most effective in the fight against type 1 diabetes.

There is evidence from epidemiology () that vitamin D is a contributing factor in the development of type 1 diabetes. Experimental studies suggest that vitamin D deficiency may be involved in the pathogenesis of type 1 diabetes,[52, 53] possibly because vitamin D is a potent modulator of the immune system and is involved in regulating cell proliferation and differentiation.[54] According to a Finnish study, children who receive a daily dose of 2000 IU of vitamin D starting in the first year of life have a reduced risk of developing type 1 diabetes.[55] Likewise, Norwegian children with rickets who take cod liver oil (rich in vitamin D) in the first year of life have a lower risk of developing type 1 diabetes.[56] The exact mechanism by which vitamin D protects against type 1 diabetes remains unknown, but the identification of VDR in both β cells and immune cells has led to a number of studies of the delineation of these pathways.[57] The scientific evidence thus far suggests that vitamin D supplementation early in life may be important in the protection of β cells' function and prevention of type 1 diabetes.[58, 59]

Table 1. Epidemiologic Evidence Linking Vitamin D and Disease

	Variables Used in Epidemiology to Infer a Relationship to Vitamin D				
Disease Relationship	**Sun Exposure**	**Migration Away From High Sun Exposure**	**Season of Birth**	**Skin Pigmentation**	**Dietary Vitamin D**
Osteomalacia and rickets	Decreased sun exposure in third trimester is associated with decreased bone mass[29]	Afro-Caribbean immigrants in the UK are associated with an increased incidence of rickets[68]	To our knowledge, no epidemiologic studies have shown this relationship	Children with darker skin have a higher prevalence of having poor bone health and rickets[17,69,70]	Low maternal 25(OH)D concentrations during pregnancy are associated with decreased bone mineral content in children at 9 years of age[29] Vitamin D deficiency in early life is associated with rickets, mild respiratory distress, weak muscle tone, decreased calcium and increased parathyroid hormone levels[71]
Multiple sclerosis (MS)	Increased sun exposure during early life is associated with a decreased risk of MS[72] MS relapse is inversely associated with UV exposure and 25(OH)D levels[73]	Indian and Pakistani immigrants who enter the UK between 0–4 years of age are at increased risk of having MS[74] Second-generation Afro-Caribbean immigrants in the UK are associated with an increased MS risk[75]	Data pooled from 4 countries shows that spring births are associated with an increased MS risk and fall births are associated with a decreased MS risk[76]	Having white skin lowers the prevalence of MS disability[77]	Consumption of fish 3–4 times a week is associated with a decreased MS risk[72] Diets low in fish but high in meat and dairy products are associated with an increased prevalence of MS[78] Intake of vitamin D from supplements is inversely associated with MS risk[79]
Schizophrenia	Increased sun exposure is	Second-generation immigrants from	Data pooled from 6 countries shows	Having black skin may be	Vitamin D supplementation

	associated with decreased risks of having schizophrenia, and schizophrenia-induced symptoms are weaker and less regular[80]	Morocco and Surinam to the Netherlands are associated with an increased risk of schizophrenia[81] Afro-Caribbean immigrants to the UK are associated with an increased risk of schizophrenia[82]	that winter births are associated with an increased incidence of schizophrenia[83, 84]	associated with an increased incidence of schizophrenia[85]	during the first year of life lowered the risk of developing schizophrenia in males, but not females[86] Maternal 25(OH)D was not a risk factor for schizophrenia. But the results in the black subgroup raise the possibility that below a certain threshold low levels of 25(OH)D may be associated with an increased risk of schizophrenia[85]
Type 1 diabetes	Monthly sunshine availability is inversely associated with having type 1 diabetes[87]	Children who migrated to an area prevalent in diabetes (northern region) had a greater risk of developing type 1 diabetes[88]	Winter and spring births are associated with higher frequency of type 1 diabetes[89–91] than summer births[91]	Children with black skin are at a higher risk of having type 1 diabetes than children with white skin[92]	In a meta-analysis, vitamin D supplementation was associated with a decreased risk of type 1 diabetes[93] Children who consumed vitamin D supplements had an 80% lower risk of having type 1 diabetes[55] Use of cod liver oil by mothers during pregnancy and infants in the first year of life lowered the infants' risk of developing type 1 diabetes[56]

Current Vitamin D Recommendations and Target Levels for Serum 25(OH)D

In 1997, the Institute of Medicine's Food and Nutrition Board (FNB) recommended that the daily vitamin D intake for pregnant and lactating women be 200 IU (5 mcg).[6] However, most clinicians recommend a daily vitamin D supplement of 400 IU per day (10 mcg), because this amount is included in most prenatal multivitamins in the United States.[7] A dose of 400 IU per day raises serum 25(OH)D by 2.8 to 4.8 ng/mL (7–12 nmoL/L)[60] but is often ineffective for resolving vitamin D deficiency.

Measuring serum 25(OH)D concentrations will identify vitamin D deficiency in pregnancy. Levels of less than 10 ng/mL (<25 nmoL/L) indicate severe vitamin D deficiency that can result in rickets or have adverse effects on overall health.[6] Concentrations between 10 to 20 ng/mL (25–50 nmoL/L) reflect vitamin D inadequacy and are common in northern regions that have low sun exposure. Higher concentrations—those above 32 ng/mL (>80 nmoL/L)—are proposed as adequate for overall health and disease prevention. Ultra high concentrations of 25(OH)D >200 ng/mL (>500 nmoL/L) are considered potentially toxic, although human data are limited. Vitamin D toxicity may lead to nonspecific symptoms, such as nausea, vomiting, poor appetite, constipation, weakness, and weight loss, or more serious conditions, such as hypercalcemia and hyperphosphatemia.

The National Health and Nutrition Examination Survey (1988–2004) found that 4% of white and 42% of black women of childbearing age residing in the United States have serum 25(OH)D levels less than 10 ng/mL, consistent with a diagnosis of severe vitamin D deficiency.[61] A more recent study (2007) revealed similar trends,[26] indicating that the widespread problem of vitamin D deficiency still persists. Emerging research suggests that more than 1000 IU per day (25 mcg/day) may be needed during pregnancy and lactation to achieve adequate levels of serum 25(OH)D.[12, 62] However, the tolerable upper intake limit of 2000 IU per day that was set by the FNB in 1997 (based on a report by Narang et al.[63]) has impeded the ability to change policy.[6] The report, by Narang et al.,[63] showed that mean serum calcium concentrations were abnormally high in six healthy subjects who consumed 3800 IU per day for 3 months.[63] However, this study did not report data on serum 25(OH)D concentrations that would verify the vitamin D dose used, and without other studies being able to replicate these findings, the quality of data is highly questionable. A recent risk assessment study that evaluated 21 available clinical trials of vitamin D supplementation concluded that 10,000 IU per day may be a more appropriate upper limit for vitamin D supplementation.[64] A pilot clinical trial in childbearing women revealed that maternal vitamin D supplementation of 6400 IU per day for 6 months can ensure that both the mother and the infant have adequate 25(OH)D status, and that their serum and urinary calcium are in the normal range.[7]

If ongoing research confirms these results, it may help to change policy on vitamin D intake during pregnancy and lactation. In 2008, the FNB established an expert committee to reevaluate adequate vitamin D intakes for healthy populations and reassess indicators of adequacy, hazard, health outcomes, and risk factors (i.e., skin pigmentation, age, sex, and sunlight exposure). The new report on vitamin D intake is expected in late 2010. As of 2009, however, only the Canadian Paediatric Society has made a recommendation for higher doses of vitamin D (2000 IU daily) to be taken by women during pregnancy.[65]

The high incidence of vitamin D deficiency among mothers is reflected in their newborn infants, with 10% of white and 46% of black neonates having 25(OH)D concentrations below 15 ng/mL.[26] Low concentrations of 25(OH)D will impair neonatal development and pose a threat to adult health. Serum 25(OH)D concentrations that are greater than 10 ng/mL are necessary in infants 0 to 12 months of age to avoid vitamin D–induced rickets and osteomalacia. A lactating mother who consumes a daily vitamin D dose of 200 to 400 IU will have approximately 20 to 70 IU/L in her breast milk, which is inadequate for infant development. Moreover, infants are typically not exposed to ample amounts of sunlight. Therefore, to achieve adequate serum concentrations of 25(OH)D, an infant must consume a minimum of 200 IU (5 mcg) of vitamin D per day. Although this level is deemed adequate by the FNB to minimize the risk of developing diseases, the American Academy of Pediatrics recommends that breastfed, healthy term infants receive a daily vitamin D supplement of 400 IU (10 mcg).[66] For nonbreastfed infants, formulas and baby food products are fortified with 400 IU of vitamin D per litre of formula.[67] However, if an infant is not consuming at least one liter (32 oz) of formula per day, these recommendations for vitamin D intake will not be met because vitamin D is scarce in other sources of an infant's diet. Vitamin D supplementation should begin at birth and continue until the infant's diet includes at least 400 IU (10 µg) of vitamin D per day.

Conclusion

The period from prepregnancy to 24 months of a child's life offers an important developmental window during which vitamin D exposure can have profound effects on human health. Inadequate concentrations of 25(OH)D during perinatal life can adversely affect bone health, brain development, heart disease, type 1 diabetes, and cancer. To achieve optimal health at adulthood, it is imperative that pregnant mothers and their newborn infants receive sufficient amounts of vitamin D during critical developmental windows. The current recommendations for vitamin D supplementation of pregnant and lactating mothers are based on estimated requirements for adults in general, which do not address the needs of the mother and the developing infant. There is an urgent need to determine optimal vitamin D intakes for pregnant and lactating women. It is not practical nor cost-effective to screen all mothers and infants for serum 25(OH)D. Proactive strategies involving appropriate supplementation of mothers and infants are needed.

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Mr. Vieth has received lecture fees from the Council for Responsible Nutrition, Merck, Lilly, Dairy Farmers of Canada, and Carlson Laboratories, and he has received consulting fees from Cytochroma, Ddrops, Fabutan, IADSA, and Whitehall-Robbins. Ms. Kaludjerovic has no conflicts of interest to disclose.

J Midwifery Womens Health. 2010;55(6):550-560.