Review Article

Vitamin D in pregnancy: A metabolic outlook

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ABSTRACT

Vitamin D deficiency is a preventable health problem. Vitamin D deficiency among pregnant women is frequent in many populations over the world. Research indicates that adequate vitamin D intake in pregnancy is optimal for maternal, fetal and child health. Adverse health outcomes during pregnancy are preeclampsia; gestational diabetes mellitus and caesarean section. Consequences in newborns are low birth weight, neonatal rickets, a risk of neonatal hypocalcaemia, asthma and/or type 1 diabetes. Vitamin D deficiency during pregnancy is the origin for a host of future perils for the child, especially effect on neurodevelopment and immune system. Some of this damage done by maternal Vitamin D deficiency gets evident after many years. Therefore, prevention of vitamin D deficiency among pregnant women is essential. The currently recommended supplementation amount of vitamin D is not sufficient to maintain a value of 25 hydroxy vitamin D above 30 ng/ml, during pregnancy. Studies are underway to establish the recommended daily doses of vitamin D in pregnant women. Clearly, further investigation is required into the effects of vitamin D, of vitamin D supplementation, and of vitamin D analogs for improvement in human health generally and mothers and children specifically. This review discusses vitamin D metabolism, dietary requirements and recommendations and implications of vitamin D deficiency during pregnancy and lactation.

Key words: Child health, pregnancy, vitamin D

Introduction

Vitamin D has been a hot topic in the medical world for the past 10 years. Concerns about vitamin D have resurfaced in medical and scientific literature owing to its multiple effects on human health. We are beginning to learn that it plays a much wider role in health and disease prevention. The classical and non-classical pathways of this hormone affect calcium metabolism, the immune system, cell proliferation and differentiation, infection, and cancer.[1] The question scientists have been working on for almost a decade is why and how vitamin D is affecting conception, pregnancy and the health of the newborn.[2] Also the media has been taking increasing interest, and public expectations have been raised regarding the enhanced roles for vitamin D in pregnancy. It is an unrecognized epidemic common among children, adults and pregnant women throughout the world, across ethnicity and season.[2] There are increasing studies worldwide reporting poor vitamin D status, including those in tropical countries. The prevalence of vitamin D deficiency has been reported to range from 15% to 80%.[3,4] It is now recognized that everyone is at risk for vitamin D deficiency. Skin color and modern practices of cosmetic dermatology (sun tan lotions and creams, etc.) have significantly rendered the sun redundant. Modern day cosmetology and our urbanization has eclipsed the sunlight and it is impossible is to fulfill daily intake via diet as a large amount of vitamin D needs to be consumed. Vitamin D deficiency is prevalent in India, a finding that is unexpected in a tropical country with abundant sunshine. There are few data from India about the prevalence of hypovitaminosis D in pregnancy and in the newborn.[5] The increasing prevalence of disorders linked to vitamin D deficiency is reflected in the several hundred children with rickets treated each year. However, these children represent a small proportion of the individuals with a suboptimal vitamin D status in the population.

The daily dietary calcium intake of both the urban and rural populations was low compared with the recommended

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dietary allowances issued by the Indian Council of Medical Research.[6] Low dietary calcium intake and 25(OH) D concentrations were associated with deleterious effects on bone mineral homeostasis. In the last 3 years, an increasing amount of research suggests that some of the damage done by Vitamin D deficiency is done in-utero, while the fetus is developing. Much of that damage may be permanent, that is, it cannot be fully reversed by taking Vitamin D after birth.

Vitamin D Metabolism

Vitamin D is a misnomer. The 4-carbon ring backbone of this molecule makes it more of a steroid hormone than a vitamin. It is structurally similar to estrogen, testosterone, progesterone and all the steroid hormones. Because of its steroid structure and function, vitamin D plays an important role in priming cells for other hormones to do their action.[7]

Vitamin D itself is devoid of any biological activity, but enzymatic conversion to 1α,25-dihydroxyvitamin D [1,25(OH) 2D] generates the hormonal form with diverse biological activities.[8] The active form of vitamin D (1,25-dihydroxyvitamin D3, 1,25[OH] 2D3) has well-established effects on bone metabolism and mineral homeostasis. However, recently it has become clear that 1,25(OH) 2D3 has potent anti-proliferative and immunomodulatory actions that are not immediately linked to its role as a skeletal regulator.[9] The actions of 1,25(OH) 2D are mediated through specific, high affinity binding to the vitamin D receptor (VDR), which is present in multiple tissues. Important changes occur in the maternal concentration of vitamin D and in calcium metabolism to provide the calcium needed for fetal bone mineral accretion during pregnancy. Calcium is transported from the mother to the fetus through the placenta. Approximately 25-30 g of calcium are transferred to the fetal skeleton by the end of pregnancy, most of which is transferred during the last trimester. The requirement for vitamin D in maintaining normal calcium metabolism throughout pregnancy and lactation in mothers, fetuses and newborn infants is still controversial. It is clear, however, that vitamin D requirements are increased in mothers during pregnancy and lactation. Established as the chorioallantoic placenta at the end of the first trimester, villous tissues secrete multiple hormones that maintain pregnancy and regulate placental physiology.[10] The synthesis, metabolism and function of vitamin D compounds during pregnancy are complex. The human endometrial decidua makes 1,25(OH) 2D and 24,25(OH) 2D and the placenta synthesizes only 24,25(OH) 2D. Data suggest that 1,25(OH) 2D aids implantation and maintains normal pregnancy, supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines. Notably, the 24,25(OH) 2D synthesized by the placenta accumulates in bone and may be involved in ossification of the fetal skeleton.[10]

In rats, the placenta transports 25(OH) 2D and 24,25(OH) 2D but not 1,25(OH) 2D. Although transplacental transport has not been studied in humans, vitamin D passage from the mother to the fetus would be facilitated by serum concentrations of 1,25(OH) 2D being higher in the maternal compared to the fetal circulations. Synthesis of 1,25(OH) 2Din the kidney increases during pregnancy.[11] Roles of vitamin D are to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resobption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels.[12] Vitamin D deficiency can result in lower bone mineral density and an increased risk of bone loss (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body.

Sources of vitamin D

The most important source of vitamin D is the skin's synthesis of the vitamin from sunlight. This vitamin is photosynthesized by ultraviolet-B radiation in the epidermis.[13] Use of sun blocks, increased coverage of clothing and time spent indoors increase the risk of Vitamin D deficiency.

It has been estimated that exposure to sunlight for usually no more than 5-15 min/d between 10 AM and 3 PM, in the spring, summer, and fall at latitudes above and below 35° (and all year near the equator) to exposed parts of the body involving "arms, legs and face "provides the body with its required 1000 IU of cholecalciferol.

Sunshine in not adequate in many parts of world. In the United States staple foods like milk, breakfast cereals and margarines are artificially fortified with vitamin D.[14] At present, the number and variety of vitamin D fortified foods available on the market differs significantly between countries and is attributed to the country-specific policies on food fortification which are not yet unified. Vitamin D is present in a small number of foods, although, for an average person food will only supply about 10% of the amount needed. Dietary sources of vitamin D include: Fatty fish species, such as Catfish, Salmon, Mackerel, Tuna etc., egg, beef and fish liver oils. Although liver and cod liver oil contain vitamin D, they are not recommended in pregnancy as they also contain too much vitamin A.

Vitamin D is a unique nutrient because its requirement can be met by both endogenous production from sunlight as well as exogenous dietary sources, which complicates determining the body's daily nutritional requirements. Methods are currently available to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure, but serious limitations remain in accurately estimating dietary vitamin D intake because of the incompleteness of nutrient databases for both vitamin D-fortified food and vitamin D supplements. Thus, increasing vitamin D intake from vitamin D fortified foods, and vitamin D supplements, in combination with sensible sun exposure, maximize a person's vitamin D status to promote good health. Women with darker skin Fitzpatrick Class 6 are more prone to Vitamin D deficiency as they need four to ten times sunlight than Fitzpatrick Class 1-4 skinned people for adequate Vitamin D synthesis.[15] Thus, Daily vitamin requirement varies with ethnicity, and this is relevant in case of Indian population.

Obesity is a growing epidemic. Pre-pregnancy obesity is also associated with significant increases in the odds of maternal and neonatal vitamin D deficiency, independent of other factors such as ethnicity.[16] This deficiency is because body fat stores much of the vitamin D made in the skin, making it less available to the body. Certain medications like steroids, anti-epileptic medications, cholesterol-lowering drugs, and some diuretics reduce absorption of vitamin D from the intestines. Women who have intestinal malabsorption diseases like celiac disease and Crohn's disease or partial removal or bypass of the stomach or intestines absorb less of both dietary and supplemental vitamin D are at increased risk of deficiency.

Overdose

Hypervitaminosis D is a serious, albeit very rare, condition. There is controversy concerning levels of nutrient intake, and at times the concept that "more is better" emerges. It is said that serum 25-hydroxyvitamin D concentrations above 75 nmol/L (30 ng/mL) are "not consistently associated with increased benefit". For vitamin D, there are still underlying questions: How much is the daily requirement and How much is too much?[17] New research suggests that women who take high doses of vitamin D during pregnancy have a greatly reduced risk of complications, including gestational diabetes, preterm birth, and infection.[18] This recommendation may be controversial because very high doses of vitamin D have long been believed to cause birth defects.W

Epidemiological analyses implicated high dietary vitamin D intake during pregnancy results in birth of syndromic babies. In the early 1960s, Williams, *et al.*[19] described a syndrome of supravalvular aortic stenosis, peripheral pulmonic stenosis, and body features indistinguishable from those in survivors of the syndrome of idiopathic hypercalcemia of infancy. Friedman and colleagues developed a model for this disorder in rabbits by administering near-fatal amounts of ergocalciferol during pregnancy.[20] Based on these accumulated observations, the uncertain teratogenic potential of high doses of calciferol analogs or of the associated disturbances in mineral homeostasis continues to cause concern.

Various human studies are done so far involving pharmacological doses of vitamin D during pregnancy. A study in human subjects involved the administration of 100,000 IU vitamin D per day (2.5 mg/day) throughout pregnancy to hypoparathyroid women to maintain serum calcium with no fatal outcome. Goodenday, *et al.* reported that as hypoparathyroid patients have completed many pregnancies while receiving ergocalciferol,[21] it is unlikely that material vitamin D, 25(OH) D, or 24,25(OH) 2D per se are teratogens.

Most prenatal vitamins have around 400 IU of vitamin D, and most health groups recommend taking no more than 2,000 IU of the vitamin in supplement form daily. Eventually, as circulating 25(OH) D increases to toxic concentrations, the classic situation of hypercalciuria, hypercalcemia, and, finally, extraskeletal calcification becomes evident. Hypercalciuria due to excessive vitamin D intakes is always accompanied by circulating 25(OH) D concentrations >250nmol/L (100 ng/mL).[18,19] To attain circulating 25(OH) D concentrations that exceed 250 nmol/L (100 ng/mL), a daily vitamin D intake well in excess of 10,000 IU/d (250 μg/d) for several months would be required. However, hypervitaminosis D has never occurred when physiologic amounts of vitamin D are ingested. In addition, no case of hypervitaminosis D from sun exposure has ever been reported. This is supported by the recent finding from a randomized, double-blind, placebo-controlled trial examining the effects of a single annual megadose of vitamin D3 (500,000 IU, equivalent to approximately 1370 IU/d) on fall and fracture outcomes in community-dwelling elderly women with a history of fall or fracture.

Role of vitamin D in pregnant women

Adequate vitamin D intake is essential for maternal and fetal health during pregnancy, and prevention of adverse outcomes. Recent work emphasizes the importance of non-classical roles of vitamin D in pregnancy and the placenta. Vitamin D deficiency during pregnancy is associated with the non-classical actions of this hormone, being linked with preeclampsia, insulin resistance,

gestational diabetes mellitus,[22] bacterial vaginosis, and an increased risk for caesarean section delivery. Women who have vitamin D deficiency do not usually feel any different but in some may have muscle weakness and weakened bones. Pregnancy does not exacerbate hypocalcaemia and secondary hyperparathyroidism in people with pre-existing vitamin D deficiency. A new study finds that women who develop severe preeclampsia tend to have lower blood levels of vitamin D than healthy pregnant women raising the possibility that the vitamin plays a role in the complication. Preeclampsia rates are elevated during winter months, when sunlight-dependent 25(OH) D productions are reduced. Vitamin D supplementation reduces preeclampsia risk, compared to unsupplemented controls.[23] Preeclampsia is associated with low circulating levels of IGF-I and 1,25(OH) 2D and, *in vitro*, IGF-1 increases 1,25(OH) 2D production by primary human syncytiotrophoblasts from placentas from normal pregnancies but not from preeclamptic pregnancies. Studies by other groups have reported abnormal expression of 1α-hydroxylase, a vitamin D—activating enzyme in preeclamptic pregnancies, revealing a potential role for 1,25(OH) 2D3 as a regulator of placentation. Induction of the 1α-hydroxylase in early gestation might provide a mechanism by which environmental or dietary vitamin D can influence fetal-placental development. Two clinical trials support a potential role of vitamin D in the prevention of preeclampsia, although neither of these treated with vitamin D supplements alone. In an uncontrolled trial, supplementation with a multivitamin/mineral supplement and halibut liver oil (containing 900 IU/d vitamin D) provided at 20 wk gestation reduced the odds of preeclampsia by 32% (95% CI, 11-47%).[24] Vitamin D supplementation in early pregnancy should be explored for preventing preeclampsia and promoting neonatal well-being.

Vitamin D is known to influence insulin secretion. 1,25(OH) 2D regulates insulin secretion by pancreatic β-cells and thereby affects circulating glucose levels.[25] As expected, low concentration of 25(OH) D is a risk factor for insulin resistance, glucose intolerance, and features of metabolic syndrome in normoglycemic subjects. Vitamin D deficiency during early pregnancy significantly increases the risk for gestational diabetes in later pregnancy.[26]

Vitamin D may influence the course of infectious diseases during pregnancy. Low 25(OH) D levels are correlated with increased bacterial vaginosis in the first trimester. Bacterial vaginosis is more prevalent in black women, who typically have lower serum 25(OH) D concentrations and have a six-fold higher chance of vitamin D deficiency, compared with white women. Vitamin D has effects on the immune system, cytokines, and antibacterial peptides that are likely to regulate the bacterial flora. Nutritional vitamin D status has very recently been linked to the human innate immune system and its ability to contain Mycobacterium tuberculosis.

Serum 25(OH) D levels are inversely related to primary cesarean section in nulliparous women, an unexpected and unexplained maternal outcome recently identified. The risk was four-fold higher in women with serum 25(OH) D levels below 37.5 nmol/L (15ng/mL) controlling for multiple confounding factors. VDR and 1,25(OH) 2D normally increase skeletal muscle function. Conversely, vitamin D deficiency results in proximal muscle weakness and decreased lower extremity muscle function perhaps contributing to the risk for cesarean section.

The Cochrane Library issued a review of vitamin D supplementation during pregnancy and identified 7 relevant studies. The Cochrane review concluded that there is not enough evidence to evaluate the requirements and effects of vitamin D supplementation during pregnancy. Data from three trials involving 463 women show a trend for women who receive vitamin D supplementation during pregnancy to more frequently have a baby with a birth weight below 2500 grams than those women receiving no treatment or placebo, although the statistical significance was borderline. Animal models of vitamin D deficiency have shown just how important adequate nutritional intakes of vitamin D are to skeletal, cardiovascular, and neurologic development in experimental animals.[27] Weishaar and Simpson[28] showed that lengthy periods of vitamin D deficiency in rats are associated with profound changes in cardiovascular function, including increases in cardiac and vascular muscle contractile function. A recent study provides evidence with reference to the consequences of vitamin D deficiency on the neurodevelopment of the fetus during pregnancy in a rat model.[28] A study on rodents showed that hypovitaminosis D trabecular bone loss, and concluded that vitamin D is indispensable for normal bone mineralization during the reproductive period in rats.[29]

Vitamin D appears to have a protective effect against multiple sclerosis (MS). Research has found direct connections between vitamin D and the genes known to be involved in MS, but exact pathology and whether vitamin D supplements during pregnancy or childhood can lessen the likelihood of the child developing MS later in life is not known. While there is interest in the role of vitamin D in the prevention of multiple sclerosis, following epidemiological studies demonstrating an association between vitamin D supplementation and reduced prevalence of the disease, future research, including randomized controlled trials in pregnant or nonpregnant individuals, is awaited to confirm or refute such benefit.

Because the poor vitamin D stores of the mother may impair vitamin D state in the infant, it is important to know whether rickets can be prevented in breast fed infants by supplementation of the mother.[30] The Canadian Pediatric Society recommended 2000 IU of vitamin D3 for pregnant and lactating mothers with periodic blood tests to check levels of 25(OH) D and calcium.[31] The American Academy of Pediatrics recommendations focus on supplementing the infant and make no specific recommendations about universally supplementing breastfeeding mothers. A sufficient supply of vitamin D to the breast fed infant is achieved only by increasing the maternal supplementation up to 2000 IU/day. As such a dose is far higher than the daily dietary allowance recommended for lactating mothers its safety over prolonged periods is not known and should be examined. Other suggests vitamin D supplementation of 400 IU/day to breast fed infants is the most secure way of preventing rickets in infants.[32]

Role of vitamin D in newborn and infant

Adequate maternal vitamin D levels are also important for fetal and child health. Fetal Vitamin D concentrations are mainly dependent on maternal concentration, and maternal deficiency may lead to adverse outcomes in offspring. Vitamin D-deficiency in mothers have significantly increased risk of infantile rickets due to inadequate maternal–fetal transfer of 25-hydroxyvitamin D.[32] Recent retrospective studies found a significant and previously undetected association of maternal vitamin D deficiency with rickets-associated infant heart failure and with acute lower respiratory tract infection,[33] a serious complication often associated with sepsis without clinical signs of rickets. While vitamin D supplementation in pregnancy has previously been associated with reduced risk of wheezing and type 1 diabetes.[34] A few studies have observed that maternal Vitamin D concentrations are related to offspring birth weight and growth during the postnatal years. Lower maternal vitamin D status was associated with lower bone mineral concentration and impaired glucose homeostasis in newborn infants.[35] Maternal vitamin D deficiency also has been associated with craniotabes,[35] a softening of skull bones that is one of the earliest signs of vitamin D deficiency, in a case study with neonatal seizures of a hypocalcemic infant and with impaired skeletal development in utero.[34] Interestingly, vitamin D deficiency during pregnancy is also associated with risks of health problems later in childhood, including improper bone development at 9 yrs of age, asthma,[36] dental cavities, schizophrenia, and type I diabetes.[37-39]

The concept that maternal nutritional status influences the risk of chronic disorders in the offspring has attracted interest over the past 2 decades. However, very few studies have been in position to examine this association directly in animals.

Women of Indian origin, especially pregnant women, are known to have a high prevalence of vitamin D deficiency. In Indian women calcium intakes are low and the demands on calcium economy are high because of repeated cycles of pregnancy and lactation.

A study in pregnant women in South India assessed maternal vitamin D status by measuring serum 25-hydroxyvitamin D in stored serum samples.[40] More than 60% of the women of the women had low 25(OH) D concentration (<50 nmol/L) at 30-week gestation. Although there was no association between maternal Vitamin D status and offspring birth size. At present, vitamin D supplementation is not a part of antenatal care programs in India.

Testing and treatment for vitamin D deficiency

Women of reproductive age are assumed to be able to obtain the recommended intake for almost all vitamins without the use of supplements, and no national organization recommends routine vitamin D supplementation during pregnancy unless a woman is at nutritional risk.

The US Preventive Services Task Force does not comment for or against routine screening for vitamin D deficiency in pregnant women. One approach is to consider serum testing in patients at high risk for vitamin D deficiency but treating without testing those at lower risk.

The basis for these recommendations was made before it was possible to measure the circulating concentration of 25-hydroxyvitamin D [25(OH) D], the indicator of nutritional vitamin D status.[41,42] Endocrine Society Issues Practice Guideline on Vitamin D and the guideline recommend that clinicians screen for vitamin D deficiency in people at risk for deficiency, including obese individuals, blacks, pregnant and lactating women, and patients with malabsorption syndromes.[43] If electing to test vitamin D status, serum 25-hydroxyvitamin D is the accepted biomarker to be offered early in pregnancy.[44] Although 1,25(OH) 2D is the active circulating form of vitamin D, measuring this level is not helpful because it is quickly and tightly regulated by the kidney. True deficiency would be evident only by measuring 25(OH) D. Of note, questions have been raised regarding the need for standardization of assays. A large laboratory (Quest Diagnostics) recently reported the possibility of thousands of incorrect vitamin D level results. Sunlight expo-sure questionnaires are imprecise and are not currently recommended.

There is no consensus about the optimal 25(OH) D level, but many experts accept a range 75nmol/L (≥30 ng/mL) as optimal.[44] Controversy exists regarding the optimum concentration of serum 25-hydroxyvitamin D for

defining vitamin D deficiency, especially in pregnancy. Most experts agree that serum vitamin D levels below 50 nmol/L (20 ng/mL) represent deficiency. However this current practice is based on the skeletal actions of the vitamin and may not be applicable for its non-classic actions.

As was recently pointed out in a Cochrane review, the topic of maternal vitamin D requirements during pregnancy has been poorly studied. The reality is that the actual vitamin D requirement during pregnancy is not known. For that matter, the requirement for the general population is not known either. There is no dietary recommended intake (DRI) for vitamin D. What is known today is that for a pregnant woman, the adequate intake for vitamin D is 200 IU per day. However this recommended level, which was largely arbitrarily set, seems to be less helpful to improve the nutritional vitamin D status of pregnant women.

National Osteoporosis Foundation's (NOF) recommends 400-800IU vitamin D for pregnant women. A recent systematic review concluded that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and white women, improves growth in the first year of life in South Asian babies and therefore may contribute to reducing the incidence of rickets in this latter group, without evidence of harm.[45] The NICE guidelines for antenatal care were therefore updated in 2008. Current NICE guidance states clearly that pregnant women are informed, at their first antenatal booking, of the importance of adequate vitamin D during pregnancy and after, to maintain their own and their baby's health. These women are advised to take 10 micrograms per day in the form of a multivitamin supplement.

It is crucial to ensure that at-risk women are aware of this need. Those identified as at-risk include: Women from black and ethnic minorities who are socially-excluded, women with limited exposure to sunlight, especially those who are housebound and obese women with prepregnancy BMI > 30. Current U.S. guidelines call for pregnant women to get 400-600 IU. However, research in recent years has been challenging those ideas on what is enough, and what is too much. The U.S. guidelines are currently under review. For now, though, 600 IU in prenatal vitamins remains the recommended daily intake for pregnant women. However, getting 25(OH) D levels consistently above 75 nmol/L (30 ng/mL) may require at least 1500-2000 IU/day of vitamin D. If a mother is vitamin D deficient, breast milk is not a good source of vitamin D, so infants need to be given vitamin D supplementation until they are weaned. Also women are encouraged to continue to take vitamin D supplements after pregnancy to help protect against health problems such as osteoporosis. It was recently shown that a maternal supplementation of 2100 IU vitamin D/day was needed, when administered during the period of lactation, in order to observe an increase in serum levels of 25(OH) D in the breast-fed infants comparable to that observed in children given 400 IU/day.

Conclusion

Vitamin D has emerged as something of a wonder supplement, according to the claims of dozens of studies published in the past few years. The current lack of evidence of benefit for women at lower risk of vitamin D deficiency points to the need for further research into vitamin D supplementation in pregnant women with clinical neonatal and infant end-points under scrutiny. There is a similar gap in the knowledge base for optimal dosing, as there is little empirical robust evidence to support 600 IU/day. Further research is required, particularly to establish the dose needed to supplement pregnant women with pre-existing deficiency and the optimal gestation at which vitamin D supplementation should be started. Recommendations should be made on informing women of the importance of maintaining adequate vitamin D stores in pregnancy, particularly for those at greatest risk of vitamin D deficiency. Sensible sun exposure and education of the public about the beneficial effects of some limited sun exposure to satisfy their body's vitamin D requirements should be implemented. Future studies are essential to determine the true vitamin D requirement during pregnancy not only for maternal skeletal preservation and fetal skeletal formation, but also for fetal "imprinting" that may affect neurodevelopment, immune function and chronic disease susceptibility soon after birth as well as later in life.

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