



Impact of Pregnancy Nutrition on Offspring Bone Development

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Osteoporosis is increasingly recognized as a disease with its roots in early life events and exposures. Bone accretion in early life may set the stage for peak bone mass achieved in adolescence, and suboptimal peak bone mass is a well-established predictor of fracture risk. Factors known to influence bone status include genetic inheritance, fetal exposures such as maternal smoking, body composition, physical activity, and nutrition during pregnancy. Because bone growth and bone mass accretion continue throughout childhood, it is important to take the lifestyle influences of diet and activity of the child into account, as well as diseases and therapeutic drugs that may directly or indirectly have adverse effects on skeletal growth.

Fetal/Neonatal Programming of Bone Status

Several candidate genes are proposed to elucidate the genetic basis of adult bone mass, such as the vitamin D receptor (VDR), the gene encoding for type 1 collagen, and the gene for estrogen receptor.¹ Paternal genotype influences fetal skeletal growth, because paternal height and skeletal size and volumetric bone mineral density (BMD) independent of maternal factors predict intrauterine bone mass of newborn infants.² Father's bone mass was significantly correlated to child bone mass at 6 years.³

Emerging evidence supports the concept that intrauterine exposure to specific adverse environmental factors may operate via fetal “programming” of candidate endocrine systems that influence skeletal metabolism, such as the growth hormone/insulin-like growth factor 1 (IGF-1) axis,⁴ which regulates cell proliferation and growth in bone as well as other organs. Retrospective epidemiological cohort studies have established linkages between poor fetal and early infancy growth and reduced bone mass in adults, or greater risk of hip fracture after the 6th decade.⁵ Fetal programming of vitamin D metabolism to its active hormone form (1,25-dihydroxyvitamin D) also is implicated from epidemiological research.⁶

Maternal Nutrition: The Basis of the Dietary Reference Intakes for Calcium and Vitamin D

In the recently revised United States/Canada Dietary Reference Intakes (DRIs) for calcium and vitamin D,⁷ values were established for pregnancy for the estimated average requirement (EAR), Recommended Dietary Allowance (RDA), and upper intake level (UL), making them the same as for nonpregnant women of similar age. The calcium demand by the fetus, especially in the 3rd trimester when fetal accrual of bone reaches peak velocity,⁸ is accommodated by natural physiological responses that double the maternal intestinal absorption of calcium, owing to doubling of the synthesis of the active metabolite 1,25-dihydroxyvitamin D via a nonparathyroid hormone mechanism that upregulates the renal 1-alpha-hydroxylase enzyme.⁹ Vitamin D binding protein (DBP) also is upregulated during pregnancy. Whether transplacental transport of calcium is vitamin D-dependent or not remains controversial.

The report from the Institute of Medicine⁷ seemed to base the recommendation for calcium intake in pregnancy on research in animal models in which vitamin D-deficient pregnant rats and VDR-null mice demonstrated a rise in intestinal calcium absorption during pregnancy, regardless of the absence of calcitriol or its receptor for action. The epidemiological evidence supporting a role for maternal dietary vitamin D and possibly calcium in fetal, neonatal, and adult bone outcomes was largely discounted in the deliberations of the review panel in revising the DRIs for calcium and vitamin D.

The RDA for vitamin D was set at 600 IU/day for all individuals 1–70 years of age, with no increase for pregnant or lactating women.⁷ For calcium, the RDA was 1300 mg/day for ages 14–19 years and 1000 mg/day for 19–50 years.⁷ Evidence discounted in the DRI report included several prospective cohort studies that have focused on maternal nutrition during pregnancy as a predictor of offspring bone health up to 16 years of age. Such cohort studies were not considered, partly because they do not sufficiently account for confounders, such as lifestyle factors passed on from mother to child. The DRI panel did not appear to consider the hypothesis that intrauterine programming is a contributing factor to osteoporosis in later life and that maternal suboptimal vitamin D status during pregnancy is a key-related component of potentially adverse environmental exposure for the fetus.¹⁰

Maternal Pregnancy Factors Influencing Bone Outcomes

Several factors other than maternal vitamin D intake may independently predict neonatal bone mass in offspring, including season of birth/ultraviolet B (UVB) exposure,¹¹ maternal smoking,¹² maternal calcium and protein intake,^{13,14} lower fat stores, and more vigorous physical activity during late pregnancy (Figure).^{12,15} This paper will focus on the relationship between modifiable nutritional factors during pregnancy and outcomes of bone mass during fetal life and beyond the newborn period.

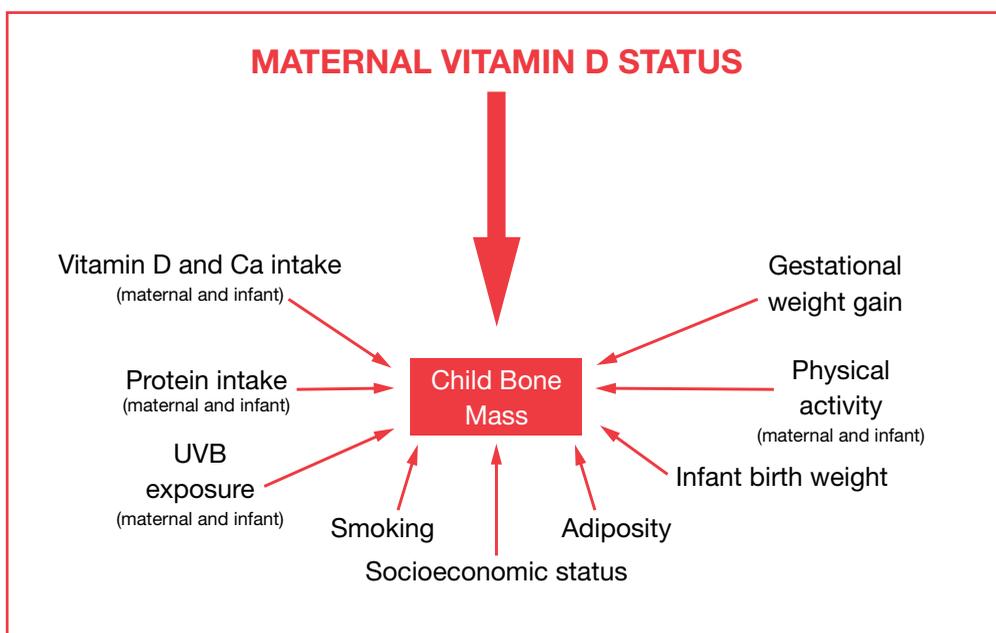


Figure. Potential maternal and infant influences on programming of child bone mass.

Maternal Vitamin D Status and Bone Health of Offspring

Observational studies have demonstrated that offspring of vitamin D-deficient women are born vitamin D deficient,¹⁶ have reduced intrauterine long-bone growth and slightly shorter gestation,¹⁷ lower bone mass at birth,¹⁸ lower fetal long-bone growth,¹⁹ lower infant bone mass,¹⁸ and risk of neonatal rickets.²⁰

Maternal vitamin D status may program a larger body size in utero.^{17,21-23} This also could explain any effect on bone mass, because a larger body size potentially means having a larger skeleton with longer and/or thicker bones that contain higher mineral content. Maternal vitamin D deficiency (serum 25-hydroxyvitamin D [25OHD] <28 nmol/L) during late pregnancy is linked with reduced knee-heel length

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at birth, indicative of reduced intrauterine long-bone growth.¹⁷ Fetuses of vitamin D-deficient mothers had a pattern of femoral growth that resembled childhood rickets, including an increased splaying index and metaphyseal cross-sectional area measured by 3-D ultrasound at 19 weeks of gestation.¹⁹

Although femur length was not affected, a higher velocity of femur growth was observed in mothers with higher vitamin D status. During pregnancy, a lower dairy intake in the mother predicted a shorter fetal femur length in the 3rd trimester,²⁴ and lower UVB exposure predicted reduced birth length.^{21,23} Small size at birth was observed in infants of mothers with lower vitamin D status.²⁵ Evidence of effect modification by infant FokI genotype for the vitamin D receptor was suggested by observations of lower birth weight in infants of vitamin D-deficient mothers.²⁶

The question of whether constrained bone growth is long lasting is partially addressed by studies where maternal UVB exposure during pregnancy positively correlated with the child's height until as late as 9 years of age.^{22,23} Consistent with this, a study in guinea pigs showed that the effect of vitamin D metabolites on longitudinal growth in utero is possibly not reversible, even with sufficient postnatal supplementation with the vitamin.²⁷

Information on bone size and mass derived from whole body and specific bone sites using dual-energy X-ray absorptiometry (DXA) in neonates and young children provides some insights into the possible role of maternal diet in offspring bone health. Size at birth, which sometimes is a function of maternal prepregnant body mass and/or diet during pregnancy, and early infant growth are possible determinants of later bone status. A recent systematic review²⁸ conducted in 14 retrospective and longitudinal studies explored the relationships between birth weight and weight at 1 year of age and later bone mass. Meta-analysis revealed that higher birth weight and weight at 1 year predicted significantly greater bone mineral content (BMC) of the lumbar spine and hip, but not whole body in adulthood.²⁸ However, no impact of birth weight on areal or volumetric bone density was noted. In a single study, fetal femur length also predicted whole-body bone size and mass at 4 years of age.²⁹

Vitamin D status during pregnancy is also a determinant of bone mass in the offspring. Mothers in the United Kingdom with lower UVB exposure (assessed by using local meteorological data) in their 3rd trimester had children with lower bone mass at 9.9 years of age.²³ Similarly, children of mothers who were vitamin-D deficient during pregnancy by serum measures had significantly lower whole-body BMC and lower lumbar-spine BMC at 9 years of age.³⁰



Maternal vitamin-D status, based on intake from food and supplements, as well as serum 25OHD status, was explored as a determinant of bone size and mass using peripheral quantitative computed tomography (pQCT) at birth and 14 months of age.³¹ Maternal serum 25OHD >35.6 nmol/L as compared to <35.6 nmol/L was associated with significantly higher tibia BMC and cross-sectional area in newborn infants, even after adjustment for z-score for birth weight, maternal height, and age.³¹ At follow-up in the infants at 14 months of age, the cross-sectional area still was advantaged in the high-maternal vitamin-D group, but tibia BMC demonstrated catch-up in the low vitamin-D group.³²

The recent publication of the one randomized clinical trial of vitamin D supplementation in pregnancy provides insight into the amount of vitamin D intake to achieve various levels of vitamin D status.³³ Of 494 women randomized in early pregnancy to vitamin D supplements of 400, 2000, or 4000 IU/day, 350 women were followed to term birth. Intake of vitamin D from food was about 200 IU/day and calcium was about 1000 mg/day. For the groups receiving 2000–4000 IU/day, >80% of subjects achieved a serum 25OHD of >80 nmol/L, and both maternal and cord blood 25OHD (Table) was significantly higher than for the group randomized to 400 IU/day vitamin D.³³ No adverse effects were reported for hypercalcemia, hypocalcemia, hypercalciuria, or parathyroid hormone level.

Maternal Supplement	Infant Birth 25OHD, nmol/L Mean ± SD
400 IU/day	45.5 ± 25.3
2000 IU/day	57.0 ± 24.5
4000 IU/day	66.3 ± 25.8
<i>P</i> value	<0.0001

❖ No clinical outcomes in infants reported; birth weight similar

Table. Vitamin D status at birth in infants born to mothers who received 400, 2000, or 4000 IU vitamin D/day during pregnancy.³³

Source: Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res.* 2011;26:2341-2357. Reproduced with permission of Blackwell Publishing Ltd.

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One limitation of the study by Hollis et al³³ is that no clinical outcomes of infant growth (other than birth weight, which was similar across vitamin D-supplement groups) or bone size or mass were reported. In a previous study in 125 Gambian women who all achieved serum vitamin D in pregnancy >50 nmol/L,³⁴ no differences were observed in birth weight, infant length, or whole-body or radius-bone measures by DXA at 1 year of age between groups from mothers with a serum 25OHD status during pregnancy above or below 80 nmol/L. Thus, the need to achieve vitamin D status in pregnancy of more than 80 nmol/L in order to optimize bone size and mass outcomes in the offspring remains open for further investigation.

Maternal Calcium Intake and Bone Mass in Offspring

The high demand for calcium by the fetus during pregnancy necessitates sufficient calcium in the mother's diet.³⁵ Maternal consumption of higher amounts of calcium and milk during pregnancy was associated with higher lumbar-spine BMD in offspring at age 16.³⁶ Higher total body and spine BMC and/or BMD also were observed in children (n=698) in rural India at 6 years of age whose mothers had a higher frequency intake of calcium-rich foods, especially milk and milk products, during pregnancy, independent of parental or infant size and other confounding variables.³ This aligns with observations that consumption of less than two dairy servings/day during pregnancy is associated with shorter femur length at 20–34 weeks of gestation, which is an indicator of fetal bone development.²⁴

Cord calcium concentration (corrected for protein) was a determinant of child bone mass at 9 years,³⁰ indirectly indicating a potential role for calcitriol in placental calcium transport, perhaps through modulation of the transcription of placental calcium transporters.³⁷ Supporting evidence is that messenger ribonucleic acid (mRNA) expression of one calcium transporter isoform, PMCA3, predicted neonatal skeletal size, independent of several other maternal predictors.³⁸ However, the dependency of placental calcium transport on vitamin D sufficiency and the impact on programming of skeletal development require further investigation.

Maternal Protein Intake and Bone Outcomes in the Offspring

Maternal protein intake during pregnancy impacts fetal bone development. For example, a higher protein intake during the 3rd trimester is associated with higher whole-body BMD in the offspring.³⁹ It was observed that maternal protein



deprivation during pregnancy in rats delays mesenchymal stem-cell proliferation and differentiation in the skeleton, modifies growth-plate morphology,⁴⁰ and negatively impacts bone composition, length, and mechanical strength.⁴¹

The developing skeleton requires a continuous supply of amino acids for collagen formation and also for modulation of serum IGF-1 levels, which in turn impacts on homeostasis. Cord IGF-1 levels correlated positively with whole-body bone-mineral content of infants after adjusting for other independent predictors of bone mass.^{42,43} Notably, cord-serum IGF-1 concentrations are directly related to protein intake of mothers in late pregnancy, thus maternal dietary protein inadequacy may impact fetal skeletal outcomes.⁴²

Future Research

Further investigations in humans, preferably as randomized clinical trials, are needed to fully examine the influence of variations in maternal nutrition on fetal or infant bone outcomes, which would help to establish science-based recommendations targeted to pregnant women for intake of vitamin D, calcium, protein, and possibly other nutrients important to bone health during fetal development and later in childhood.

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Q & A

Q: Where was the study population from in the paper by Hollis et al [Hollis et al. *J Bone Miner Res*. 2011;26:2341-2357]?

Dr Atkinson: The study took place at the Medical University of South Carolina in Charleston. Of the 350 women studied, more than 60% of them were African American or Hispanic.

Q: Does anybody know what the average compliance is for taking multivitamins during pregnancy for the average American woman? How many take their multivitamins or prenatal vitamins? Does anyone have an idea?

Dr Atkinson: I cannot speak to America. In Canada, based on the most recent population-based survey by Health Canada, 40%–50% of nonpregnant women take mineral/vitamin supplements [Socio-economic status and vitamin/mineral supplement use in Canada. *Health Reports*. 2010;21(4). Statistics Canada, No. 82-003-XPE]. This study did not sample pregnant women.



Q: So do you think your study population of pregnant women represents all of Canada, that 100% are taking their multivitamins?

Dr Atkinson: In our study, more than 83% of mothers took prenatal or other multivitamins that provided 200–400 IU of vitamin D/day, and, in addition, some took single vitamin D supplements containing up to 1000 IU/day during pregnancy. However, our study population represents a middle socioeconomic class that may have different practices for use of supplements and level of food security than those of lower financial status. The study population reflects those in our community who are willing to join long-term studies.

We do not have very many smokers—only about 4% of the women were smoking during pregnancy, although some had smoked prior to pregnancy. In the last 3 years, we have seen a big push through Health Canada, our obstetrical society, and pediatric society about healthy lifestyle practices for nutrition and exercise that they advise mothers to adopt during pregnancy. Maybe our public health people are doing a good job and that is reflected in the nutrition practices that we observed in our study.