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Maternal Obesity, 25(OH)D Concentration and Bone Density in Breastfeeding Dyads

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Abstract

Objective—To examine the association between maternal body mass index (BMI) and SERUM 25-hydroxy vitamin D (25(OH)D) concentration and bone density in mother-infant pairs.

Study design—The study was a secondary analysis of 234 exclusively breastfeeding dyads who were recruited in the first post-partum month for a randomized controlled trial of maternal versus infant vitamin D supplementation. Mean 25(OH)D concentrations and bone mineral density were compared by BMI group. The adjusted association between maternal BMI and 25(OH)D and bone density was examined at one, four and seven months postpartum.

Results—Obese breastfeeding women had lower 25(OH)D concentrations and higher bone mineral density than lean women at all three time points ($p < 0.01$). Higher maternal BMI was associated with lower maternal serum levels of 25(OH)D at one, four and seven months postpartum (adjusted β adjusted per kg/m², 95% CI $-0.76, -0.14$, at one month) and higher bone mineral density (BMD) at the same time points (ointsy BMD Z-score; 95% CI 0.003, 0.01 at one month). Seventy-six percent of infants were vitamin D deficient at one month of age. Infants born to overweight and obese mothers had lower 25(OH)D concentrations than infants of lean mothers ($p < 0.01$). For infants in the maternal supplementation group, higher maternal BMI was associated with lower 25(OH)D concentrations at four months (onthstra 95% CI $-1.17, -0.20$) and lower bone density at seven months (onthsyat 95% CI $-0.002, -0.0001$).

Conclusions—In exclusively breastfeeding dyads, maternal obesity is associated with lower maternal and infant serum 25(OH)D concentrations, which may impact infant bone density.

Keywords

maternal obesity; vitamin D; breastfeeding; bone mineralization

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Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov): NCT00412074

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In addition to the established role of vitamin D in bone health, 25-hydroxy vitamin D (25(OH)D) deficiency in pregnancy has been associated with other adverse outcomes in mothers and infants. In pregnancy, maternal 25(OH)D deficiency is associated with increased risks of gestational diabetes (1) and impaired fetal growth (2). Long-term follow-up studies have shown that offspring of vitamin D deficient mothers have higher rates of obesity and atopic disease (3–4).

Obesity during pregnancy increases the risk of both maternal and infant vitamin D deficiency. In the Hyperglycemia and Adverse Pregnancy Outcomes cohort, Josefson et al reported that for every kg/m^2 increase in maternal Body Mass Index (BMI), maternal serum and cord blood 25(OH)D levels decreased by 0.4ng/ml and 0.26ng/ml, respectively (7). A similar association was found in an earlier study, with a two-fold increased odds of maternal and cord blood vitamin D deficiency with an increase in maternal BMI from 22 to 34kg/m^2 (8). However, there is a paucity of studies examining the role of maternal obesity in maternal and infant vitamin D concentrations and bone health in the postpartum period.

Although obesity is a risk factor for vitamin D deficiency, in non-pregnant adults, obesity appears to be protective of bone density (5). However, breastfeeding women have significantly lower bone mineral density than matched controls, due to infant bone accretion and maternal-infant calcium transfer during breastfeeding (6). These physiologic differences during pregnancy and lactation suggest that results from studies of non-pregnant adults cannot be extrapolated to postpartum and breastfeeding dyads. The objective of our study was to determine the association between maternal BMI and vitamin D levels and bone density in breastfeeding mother-infant dyads. We hypothesized that higher maternal BMI would be associated with lower maternal and infant 25(OH)D concentrations and bone density.

Methods

The study was a secondary analysis from participants who provided informed consent to participate in a double-blind, randomized controlled trial of vitamin D supplementation during lactation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00412074): NCT00412074) (9). Dyads were recruited between 4 and 6 weeks postpartum from either the Medical University of South Carolina (MUSC) or the University of Rochester (U of R) and were randomized to receive one of three daily doses of vitamin D supplementation. The control group received 400 IU of vitamin D per day maternal supplementation and 400IU per day for infant and the intervention group received 6400IU of maternal supplementation per day and a placebo for infant. The 2400IU group, which was stopped early, was not included in this analysis. At each time point, dyads were included if they were exclusively breastfeeding and had BMI recorded (at the given study visit) and at least one outcome measure (mother or infant 25(OH)D or bone density) available. Mother-infant dyads were evaluated at three time points: V1 at recruitment (before randomization, N=234), V4, four months post-partum (after randomization, N=181), and V7, seven months postpartum (N=130). Twenty-eight infants who were already receiving vitamin D supplementation were excluded for V1 only (see Figure, available at www.jpeds.com, for study flow.)

Maternal BMI—Height and weight were measured, and BMI (units kg/m²) was calculated for each visit using the following formula: [(weight in kg)/(height in m)²]. Maternal BMI was grouped according to the World Health Organization categories: lean (<25kg/m²), overweight (>25kg/m² and <30kg/m²) and obese (≥30kg/m²).

The primary outcome was maternal serum 25(OH)D concentration at V1, V4 and V7. Secondary outcomes were maternal bone density and infant 25(OH)D and bone density at V1, V4 and V7. For 25(OH)D measurements, maternal and infant blood were collected in a non-fasting state, immediately separated and stored at −80°C for batched assays. As described previously, 25(OH)D was measured using radioimmunoassay (9). Based on the Endocrine Society's Clinical Guidelines, deficiency was defined a priori as total circulating 25(OH)D <20 ng/mL (10). The inter- and intra-assay coefficient of variation was 10%. The laboratory participated in the Vitamin D External Quality Assessment Scheme (DEQAS) throughout the study period to ensure the analytical reliability of the 25(OH)D assay using National Institute of Standards and Technology standards.

Maternal and infant bone mineral density (BMD) was measured at visits V1, V4 and V7 by dual-energy X-ray absorptiometry (DXA) (Hologic, Bedford, MA) as previously described (11). A single research assistant at each site checked scans for positioning, movement, and artifacts, and defined the body regions. DXA machines were cross-calibrated in Charleston and Rochester twice over the course of the study with standard deviations of 0.005 and 0.019. Differences in cross-calibration of the machines were not significant. DXA scans had inter- and intra-assay coefficients of variation of less than 1% (11). All scans were performed by the same technologist at each site; results were machine generated using validated software, and machine results were validated by the same radiologist.

At V1, 224 mothers and 197 infants had DXA scans results; at V4, 177 mothers and 170 infants had DXA scan results; and at V7, 129 mothers and 116 infants had DXA scan results. For this analysis, spine and hip BMD Z-scores were averaged to obtain a mean maternal BMD Z-score. For infants, a global BMD Z-score was utilized.

In questionnaires and interviews, mothers reported information about their age, education, race and insurance status. Insurance status was used as a proxy for income. Center of randomization (MUSC or U of R) was included as a covariate given that latitude is a potential confounder. Subjects also completed a Nutrition Quest Food Frequency Questionnaire at enrollment to measure the dietary vitamin D intake at baseline. Total vitamin D intake was included per participant based on dietary intake plus study-assigned supplement intake. Lastly, season (categorically) at study assessment was included as an additional covariate.

Statistical Analyses

Descriptive statistics were used to characterize and compare sociodemographic variables by BMI category. Mean maternal and infant 25(OH)D and BMD Z-scores were evaluated across three maternal BMI groups (categorically) and results were compared across groups using analyses of variance with a Bonferroni adjustment for multiple comparisons. Percentages with deficient vitamin D concentrations were evaluated using Chi-square tests.

Unadjusted associations were examined between maternal and infant serum 25(OH)D concentration and BMD Z-scores with maternal BMI (continuously) in all women using linear regression. Finally multivariable linear regression analyses were conducted for all four outcomes (maternal and infant 25(OH)D and BMD Z-score) with maternal BMI. All models met assumptions for linear regression and were sequentially adjusted for maternal race in model 1 and model 1 plus maternal education, insurance, center and season in model 2. A stratified analysis was conducted to examine the same linear regression models among the control and intervention groups separately at V1, V4, and V7. Confounders were chosen based on their association with the exposure and outcome in forward modeling, to obtain the most parsimonious final models. Statistical analyses were performed using STATA Statistical Software: Release 13.

Results

The baseline characteristics of this cohort, recruited between November, 2005 to August, 2012, are summarized in Table I. The mean maternal BMI was 27.6 kg/m². Of the participants, 37% were overweight and 30% were obese. Participants were more likely to be white, hold private insurance or have graduated from college if they were lean, compared with women in the overweight or obese groups. Dietary intake of vitamin D was similar across all three groups at enrollment (Table I). The mean $\pm$ S.D. age of V1, V4, and V7 encounters for infants was 5.2 $\pm$ 1.2 weeks, 17.8 $\pm$ 1.0 weeks, and 30.7 $\pm$ 1.0 weeks respectively and did not differ among study groups.

Maternal Outcomes

Mean maternal serum concentrations of 25(OH)D at V1, V4, and V7 were lower in obese and overweight, compared with lean women (Table II). The proportion of mothers who were vitamin D deficient at baseline was higher in overweight and obese women compared with lean (at V1: Lean: 8.1% Overweight: 12.5%, Obese: 19.4%). Higher maternal BMI was associated with lower serum 25(OH)D concentration (Table III), after adjustment for maternal race, education, insurance, and center (β =−0.45 decrease in 25(OH) for each kg/m² increase in BMI, 95% CI −0.76, −0.14). This association was strengthened in the fully adjusted model at four (V4) (β =−0.64, 95% CI (−1.15, −0.14) and seven months (V7) postpartum (β =−0.77, 95% CI (−1.39, −0.15) (Table III).

Mean BMD was higher in overweight and obese women compared with lean women at V1, V4, and V7 (p <0.01). At V1, higher maternal BMI was associated with higher BMD Z-score in a fully adjusted analysis (β =0.008, 95% CI 0.003, 0.01). At V4 and V7, there was a similar association after additional adjustment for vitamin D intake per randomization group (V4: β =0.007, 95% CI 0.004, 0.01; V7: β =0.007, 95% CI 0.004, 0.011) (Table III). Associations between maternal BMI and maternal outcomes were similar at V1, V4 and V7 in the treatment and control groups in the stratified analysis.

At V1, the mean infant 25(OH)D concentration was 14.2ng/ml and 76.2% of infants had insufficient 25(OH)D concentrations. Infants born to overweight and obese mothers had lower 25(OH)D concentrations at V4 and V7, but not at V1 (Table II). At V1, 42% of infants of overweight and obese mothers had severe deficiency (<10ng/ml) compared with 27% of

infants born to lean mothers ($p<0.05$.) By four months postpartum (V4), higher maternal BMI was associated with lower infant 25(OH)D concentration in a fully adjusted model ($\beta=-0.68$, 95% CI -1.17 , -0.2). At V7, higher maternal BMI was associated with lower infant 25(OH)D concentrations in an unadjusted analysis ($\beta=-0.45$, 95% CI -0.90 , -0.002), but was fully attenuated after adjustment for maternal race ($\beta=-0.38$, 95% CI -0.83 , 0.07) (Table III). When stratified by treatment group, maternal BMI was found to be significantly associated with infant 25(OH)D concentrations at V4 only in the intervention group ($\beta=-0.95$, 95% CI -1.48 , -0.42). The mean $\pm$ SD 25(OH)D concentrations in the control group at V4 for infants born to lean, overweight and obese women were 48.7 ± 20.1 , 38.6 ± 16.4 and 45.7 ± 19.7 ng/mL respectively ($p=0.18$). The mean 25(OH)D concentrations in the intervention group at V4 for infants born to lean, overweight and obese women were 49.9 ± 14.7 , 39.7 ± 12.4 and 34.5 ± 9.2 ng/mL respectively ($p<0.001$).

Neither maternal BMI category (Table II) nor maternal BMI (Table III) was associated with infant BMD Z-scores at V1, V4 or V7 in all infants. However, when we conducted a stratified analysis by treatment group, higher maternal BMI was associated with lower infant bone mineral density at seven months in the intervention group ($\beta=-0.001$, 95% CI -0.002 , -0.0001), after adjustment for confounders. Maternal and infant 25(OH)D concentrations were strongly correlated at all three time points: V1 ($r^2=0.43$, $p<0.0001$), V4 ($r^2=0.28$, $p<0.001$), and V7 ($r^2=0.42$, $p<0.0001$).

Discussion

Our study has shown that in exclusively breastfeeding dyads higher maternal BMI was associated with lower maternal and infant serum concentrations of 25(OH)D in the postpartum period. Interestingly, higher maternal BMI was protective for maternal bone density but associated with lower infant bone density. In pregnancy, maternal calcium is transferred to the fetus mainly in the last trimester for bone accretion resulting in a net loss of 2–3% of maternal total body calcium content (12). Postpartum, a breastfeeding mother loses 300–400mg of calcium daily (13). Additionally, obese women are thought to have reduced bioavailability of 25(OH)D (14). These findings suggest that an obese lactating mother may require higher vitamin D supplementation than her lean counterpart.

Obesity in non-pregnant adults has been shown to be associated with 25(OH)D deficiency, but protective of bone health (5). Mechanisms proposed to explain these counterintuitive associations include the protective effect of mass on mineralization and hormonal protections through estrogens. Although it is reassuring that obesity appears to be protective of bone health in mothers in the first seven months postpartum, vitamin D status has been implicated in non-bone health-related outcomes such as modulation of cell growth, inflammation, neuromuscular and immune function (15). Future studies should examine the long-term maternal impact of breastfeeding in obese women on health outcomes such as infections, cancer and neuromuscular disease.

In breastfeeding infants, our finding that maternal and infant vitamin D levels were strongly correlated suggests that vitamin D supply in breastfeeding infants is dependent on maternal systemic, and thus breast milk, concentrations of vitamin D. The American Academy of

Pediatrics recommends that exclusively breastfeeding infants receive 400 IU vitamin D supplementation, beginning in the days after birth (16). Factors such as infant skin pigmentation and less sunlight exposure are known risk factors for 25(OH)D deficiency in infants. It is remarkable that at V1, three out of four infants had a 25(OH)D concentration less than 20ng/ml. A 2010 study found only 5% of breastfeeding infants receive vitamin D supplementation by one month of life (17). Our study findings provide further support to the AAP recommendation for early supplementation, particularly for infants at high risk such as those born to obese mothers.

By four and seven months postpartum, the mean 25(OH)D concentrations in the infants were no longer deficient, suggesting that supplementation of the infant had been initiated and served to raise systemic 25(OH)D concentrations, particularly in the control group. In this trial, it is likely that there was higher compliance with infant vitamin D supplementation recommendations than in the general population. Nationally at 4 and 7 months postpartum, only 10.8% and 11.3% of exclusively breastfeeding infants receive vitamin D supplementation. This may be explained by a recent study showing that mothers prefer to take a supplement themselves than provide one to their infants (18). This suggests that trials assessing maternal-neonatal 25(OH)D transfer through breast milk at varying maternal BMI-based dosages of vitamin D should be undertaken. Given that one out of three US women is obese, our findings also suggest the need for the incorporation of maternal BMI in determination of risk for infant vitamin D deficiency in the exclusively breastfeeding infant. These data should guide counseling and supplementation practices for these higher-risk infants.

By seven months postpartum, higher maternal BMI was negatively associated with BMD in infants in the intervention group. It is likely that there was no association at one and four months because the effect of 25(OH)D deficiency on bone health is cumulative and may appear later in the first year of life. The hormonal and mechanical protections afforded obese weight-bearing adults on bone mineralization may not apply to infants, placing them at higher long-term risk for bone demineralization. In this study, we were not able to measure the non-bone health risks of 25(OH)D deficiency including asthma, allergy and atopic disease, infections and later obesity. Our findings suggest that long-term follow-up of 25(OH) concentration and bone and non-bone health-related outcomes in breastfeeding dyads is particularly important for pregnancies complicated by maternal obesity.

Our study's strengths lie in the recruitment of dyads from two sites at different latitudes. Our population was racially and socioeconomically heterogeneous and had high rates of exclusive breastfeeding and follow-up. Additionally, our measurements of 25(OH)D and bone density were performed using gold-standard techniques. Given that this was a secondary analysis of a parent trial, we were limited by study group assignment of maternal and infant supplementation, dietary vitamin D intake and sunlight exposure, for which we adjusted in our analysis. We were also limited in the length of our study follow-up, and the lack of non-bone health-related outcomes.

We conclude that higher maternal BMI is a risk factor for 25(OH)D deficiency in exclusively breastfeeding dyads. The repercussions of these findings on long-term maternal and infant

outcomes should also be examined. These findings may lay the foundation for future studies to examine supplementation practices in obese mothers and infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

25(OH)D	25-hydroxy vitamin D
BMI	Body Mass index
BMD	Bone Mineral Density
DXA	Dual-energy X-ray absorptiometry

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Table 1

Maternal demographic characteristics for all women exclusively breastfeeding at V1, V4 and V7 and by BMI subgroup

		Maternal BMI, kg/m ²		
Maternal Characteristic	Total	<25 kg/m ²	25 – <30 kg/m ²	30 kg/m ²
N at V1 (%)	234	74 (32)	88 (37)	72 (31)
N at V4 (%)	181	73 (40)	55 (31)	53 (29)
N at V7 (%)	130	59 (46)	33 (25)	38 (29)
Mean (SD) Age at Enrollment (years)	28.4 (5.9)	28.1 (6.2)	28.5 (5.9)	28.5 (5.8)
Mean (SD) Body Mass Index (kg/m ²)				
V1	27.8 (4.8)	23.0 (1.4)	27.1 (1.5)	33.7 (3.5)
V4	27.6 (5.8)	22.7 (1.5)	27.3 (1.5)	34.8 (4.8)
V7	27.1 (5.9)	22.3 (1.8)	27.2 (1.3)	34.6 (4.6)
Education = College Graduate N (%):				
Yes	92 (39)	35 (47)	34 (39)	23 (32)
Insurance = Private N (%)				
Yes	99 (42)	37 (50)	37 (42)	25 (35)
Race/Ethnicity: N (%)				
Black	60 (26)	13 (17)	18 (21)	29 (40)
Hispanic	70 (30)	22 (30)	30 (34)	18 (25)
Asian	5 (2)	3 (4)	2 (2)	0 (0)
White	99 (42)	36 (49)	38 (43)	25 (35)
Parity: N (%)				
0	13 (6)	2 (3)	4 (5)	7 (10)
1	76 (32)	32 (43)	25 (28)	19 (26)
>1	145 (62)	40 (54)	59 (67)	46 (64)
Center: N (%)				
MUSC	132 (56)	43 (58)	54 (61)	35 (49)
Rochester	102 (44)	31 (42)	34 (39)	37 (51)
Dietary Maternal Vitamin D Intake (IU) Mean (SD) at V1	205.8 (126.0)	182.7 (120.8)	215.2 (135.8)	217.2 (117.5)

Table 2

Mean 25(OH)D concentrations and bone mineral densities in all participants and by BMI subgroup at V1, V4 and V7

		Total	Maternal BMI category			P*
			<25 kg/m ²	25 – <30	30 kg/m ²	
V1	Mean (SD) maternal 25(OH)D concentration, ng/ml	34.1 (13.3) N=234	37.2 (14.8) N=74	34.7 (13.6) N=88	30.1 (10.0) N=72	0.004 ^B
	Mean (SD) maternal bone mineral density, g/cm ²	1.01 (0.13) N=224	0.97 (0.15) N=70	1.01 (0.11) N=87	1.06 (0.11) N=67	<0.001 ^{B,C}
	Mean (SD) infant 25(OH)D concentration, ng/ml	14.2 (9.4) N=206	15.5 (9.4) N=67	13.1 (9.2) N=80	14.5 (9.8) N=59	0.31
	Mean (SD) infant bone mineral density, g/cm ²	0.21 (0.02) N=197	0.21 (0.02) N=61	0.21 (0.02) N=79	0.20 (0.02) N=57	0.37
V4	Mean (SD) maternal 25(OH)D concentration, ng/ml	45.1 (20.1) N=181	47.4 (22.1) N=73	49.0 (20.9) N=55	37.9 (14.1) N=53	0.007 ^{B,C}
	Mean (SD) maternal bone mineral density, g/cm ²	0.99 (0.12) N=177	0.94 (0.10) N=72	0.99 (0.12) N=54	1.05 (0.12) N=51	<0.001 ^{B,C}
	Mean (SD) infant 25(OH)D concentration, ng/ml	44.3 (17.7) N=173	49.2 (17.8) N=71	39.3 (13.9) N=52	40.1 (16.3) N=48	0.001 ^{A,B}
	Mean (SD) infant bone mineral density, g/cm ²	0.23 (0.02) N=170	0.23 (0.02) N=66	0.23 (0.02) N=52	0.23 (0.02) N=52	0.40
V7	Mean (SD) maternal 25(OH)D concentration, ng/ml	44.9 (22.0) N=130	50.7 (24.7) N=59	41.3 (19.7) N=33	39.2 (17.4) N=38	0.02 ^B
	Mean (SD) maternal bone mineral density, g/cm ²	0.97 (0.12) N=129	0.94 (0.11) N=59	0.97 (0.12) N=33	1.02 (0.11) N=37	0.007 ^B
	Mean (SD) infant 25(OH)D concentration, ng/ml	42.8 (13.7) N=111	46.6 (13.6) N=52	38.8 (13.1) N=26	40.1 (13.4) N=33	0.02 ^A
	Mean (SD) infant bone mineral density, g/cm ²	0.25 (0.02) N=116	0.25 (0.02) N=55	0.25 (0.03) N=25	0.24 (0.02) N=36	0.42

* P value calculated with ANOVA with Bonferroni correction. A=overweight vs. lean, B=obese vs. lean, C=obese vs. overweight

Table 3

Association between maternal BMI and maternal and infant outcomes

Study Visit	Models	Vitamin 25(OH)D	Bone Mineral Density Z-score
Maternal Outcomes		β (95% CI)	
V1	unadjusted	−0.59 (−0.94, −0.24)	0.008 (0.005, 0.012)
	Model 1	−0.40 (−0.71, −0.09)	0.006 (0.003, 0.010)
	Model 2	−0.45 (−0.76, −0.14)	0.006 (0.003, 0.010)
V4	unadjusted	−0.79 (−1.29, −0.28)	0.008 (0.005, 0.011)
	Model 1	−0.61 (−1.12, −0.11)	0.006 (0.004, 0.009)
	Model 2	−0.64 (−1.15, −0.14)	0.007 (0.004, 0.010)
V7	unadjusted	−1.05 (−1.68, −0.43)	0.007 (0.003, 0.010)
	Model 1	−0.89 (−1.49, −0.29)	0.006 (0.003, 0.009)
	Model 2	−0.77 (−1.39, −0.15)	0.007 (0.004, 0.011)
Infant Outcomes		β (95% CI)	
V1	unadjusted	−0.05 (−0.32, 0.23)	−0.0003 (−0.0008, 0.0002)
	Model 1	0.02 (−0.25, 0.28)	−0.0001 (−0.0007, 0.0004)
	Model 2	0.03 (−0.23, 0.30)	−0.0002 (−0.0007, 0.0004)
V4	unadjusted	−0.75 (−1.20, −0.29)	−0.0004 (−0.0009, 0.0001)
	Model 1	−0.71 (−1.19, −0.23)	−0.0005 (−0.001, 0.00005)
	Model 2	−0.68 (−1.17, −0.20)	−0.0005 (−0.001, −0.00003)
V7	unadjusted	−0.45 (−0.90, −0.002)	−0.0004 (−0.001, 0.0002)
	Model 1	−0.38 (−0.83, 0.07)	−0.0006 (−0.001, 0.00004)
	Model 2	−0.36 (−0.84, 0.11)	−0.0007 (−0.001, 0.00005)

Model 1: adjusted for maternal race, Model 2: Model 1+ education, insurance, center, season