ORIGINAL ARTICLE

Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth

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ABSTRACT

BACKGROUND

It is unclear whether maternal vitamin D supplementation during pregnancy and lactation improves fetal and infant growth in regions where vitamin D deficiency is common.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial in Bangladesh to assess the effects of weekly prenatal vitamin D supplementation (from 17 to 24 weeks of gestation until birth) and postpartum vitamin D supplementation on the primary outcome of infants' length-for-age z scores at 1 year according to World Health Organization (WHO) child growth standards. One group received neither prenatal nor postpartum vitamin D (placebo group). Three groups received prenatal supplementation only, in doses of 4200 IU (prenatal 4200 group), 16,800 IU (prenatal 16,800 group), and 28,000 IU (prenatal 28,000 group). The fifth group received prenatal supplementation as well as 26 weeks of postpartum supplementation in the amount of 28,000 IU (prenatal and postpartum 28,000 group).

RESULTS

Among 1164 infants assessed at 1 year of age (89.5% of 1300 pregnancies), there were no significant differences across groups in the mean (±SD) length-for-age z scores. Scores were as follows: placebo, −0.93±1.05; prenatal 4200, −1.11±1.12; prenatal 16,800, −0.97±0.97; prenatal 28,000, −1.06±1.07; and prenatal and postpartum 28,000, −0.94±1.00 (P=0.23 for a global test of differences across groups). Other anthropometric measures, birth outcomes, and morbidity did not differ significantly across groups. Vitamin D supplementation had expected effects on maternal and infant serum 25-hydroxyvitamin D and calcium concentrations, maternal urinary calcium excretion, and maternal parathyroid hormone concentrations. There were no significant differences in the frequencies of adverse events across groups, with the exception of a higher rate of possible hypercalciuria among the women receiving the highest dose.

CONCLUSIONS

In a population with widespread prenatal vitamin D deficiency and fetal and infant growth restriction, maternal vitamin D supplementation from midpregnancy until birth or until 6 months post partum did not improve fetal or infant growth. (Funded by the Bill and Melinda Gates Foundation; ClinicalTrials.gov number, NCT01924013.)

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Infants who are small for gestational age or have impaired postnatal linear growth continue to be of major concern with regard to public health in low- and middle-income countries.[1,2] However, environmental and dietary regulation of fetal and infant growth remain inadequately understood. Observational studies have shown numerous early-life risk factors for later anthropometric outcomes,[3,4] but there is limited evidence of benefit of prenatal micronutrient interventions on childhood linear growth.[5]

Vitamin D may influence fetal and postnatal growth through effects on calcium absorption,[6] parathyroid hormone expression,[7] phosphate metabolism,[8] growth-plate function,[9,10] and regulation of the insulin-like growth factor axis.[11] Meta-analyses of observational studies[12] and clinical trials[13] have suggested that vitamin D may have a beneficial effect on fetal growth, but most previous trials have had methodologic limitations.[13] In a previous small trial in Bangladesh, we found that early postnatal linear growth was higher in infants born to women who had received vitamin D supplementation as compared with those who had not received supplementation.[14]

In Bangladesh, approximately 30% of newborns are small for gestational age,[1] and the growth of 36% of children younger than 5 years of age is stunted (height-for-age z score, <–2).[15] Vitamin D deficiency is common in Bangladeshi women of reproductive age.[16] In the Maternal Vitamin D for Infant Growth (MDIG) trial conducted in Dhaka, Bangladesh, we evaluated the dose-dependent effects of prenatal vitamin D supplementation, with and without postpartum supplementation, on infant growth and other maternal, newborn, and infant outcomes.

Methods

Trial Design and Oversight

The MDIG trial was a randomized, double-blind, placebo-controlled, dose-ranging trial of maternal vitamin D supplementation.[17] The protocol is available with the full text of this article at NEJM.org, and the statistical analysis plan is included in the Supplementary Appendix, also available at NEJM.org. The trial was overseen by a steering committee and an independent data and safety monitoring board. The protocol was approved by research ethics committees at the Hospital for Sick Children in Toronto and the International Center for Diarrheal Disease Research, Bangladesh (icddr,b). All authors attest to the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol. The trial funder had no role in the trial design, data collection and analysis, or interpretation of the results. No support from a commercial entity was provided.

Participants

Participants were generally healthy pregnant women between 17 and 24 weeks of gestation. They were enrolled after providing written informed consent between March 2014 and September 2015 at the Maternal and Child Health Training Institute, a public hospital in Dhaka, Bangladesh. The criteria for inclusion and exclusion are shown in Table S1 in the Supplementary Appendix.

Interventions

Participants were randomly assigned at enrollment to one of five groups to receive vitamin D or placebo. One group received placebo throughout the prenatal period and for 26 weeks post partum. Three groups received prenatal supplementation only, in the following doses: 4200 IU per week (prenatal 4200 group), 16,800 IU per week (prenatal 16,800 group), or 28,000 IU per week (prenatal 28,000 group). The fifth group received prenatal supplementation as well as 26 weeks of postpartum supplementation in the amount of 28,000 IU per week (prenatal and postpartum 28,000 group). A computer-generated, simple randomization scheme was created independently by the trial statistician. The master list linking participant identifiers to supplementation groups was held by the supplement manufacturer and not accessed by any trial personnel until final group assignments were revealed. Concealment of trial-group assignments was ensured with the use of prelabeled and sequentially numbered but otherwise identical supplement vials, which were provided to participants in accordance with the assignment sequence. Oral vitamin D_3 and placebo tablets were manufactured by the Toronto Institute for Pharmaceutical Technology (Toronto). The vitamin D content of each batch of tablets was verified in product testing.[17] Tablets with different doses were identical in appearance and taste. Tablets were routinely administered under direct observation by trial personnel; however, up to four consecutive doses may have been unobserved

when participants were unavailable for scheduled visits. Missed doses were administered up to 7 days after the scheduled date. Calcium (500 mg per day), iron (66 mg per day), and folic acid (350 μg per day) were provided to all participants throughout the intervention phase.[17] If a participant reported use of a vitamin D or a calcium supplement for more than 1 week that had not been provided through the trial, trial supplements were suspended until nontrial supplement use was discontinued. Supplementation was discontinued in participants with confirmed hypercalcemia (as defined below), fetal or infant death, or a new condition or medication that could alter vitamin D metabolism.

ASSESSMENTS AND OUTCOMES

Trial personnel contacted participants weekly from enrollment until 26 weeks post partum, and infants were further assessed at 9 months and 12 months of age. Visits were conducted in the home or at a clinic and included the use of standardized questionnaires, point-of-care tests, anthropometric measurements, and specimen collection (Table S2 in the Supplementary Appendix). Data on socioeconomic and household characteristics were collected at baseline. Weekly prenatal questionnaires included health care encounters and a checklist of clinical symptoms. Postnatal follow-up visits included assessment of both the infant's health and feeding practices as well as a basic physical examination. Maternal blood pressure was measured at enrollment, at 24 and 30 weeks of gestation, and weekly from 36 weeks of gestation to delivery. Trial personnel tracked pregnancy outcomes, visits with trial physicians, hospitalizations, and deaths, and they attended all facility-based deliveries and home births when feasible. Participants were provided with free medical care and encouraged to seek medical attention from trial physicians and to notify trial personnel of concerns about their health. Pregnancies were completed from June 25, 2014, through February 29, 2016. One-year postnatal visits were conducted from June 24, 2015, through March 1, 2017.

Infant crown-to-heel length (to the last completed millimeter), head circumference, upper-arm length, mid–upper-arm circumference, and rump-to-knee length — all to the last completed millimeter — and weight (to the nearest 5 g up to 10 kg and to the nearest 10 g for >10 kg) were measured by trained personnel according to standardized procedures[17] adapted from the protocols of the INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) Project.[18] Each measurement was obtained independently by two trial personnel and repeated if the difference between paired measurements exceeded specified thresholds. Means of the final pair of values were used in analyses. Interrater reliability was high, and few measurements were excluded due to implausibility or temporal inconsistencies (see Methods, section 1, and Table S3 in the Supplementary Appendix).[19] Length, weight, weight for length, body-mass index, head circumference, and mid–upper-arm circumference were expressed as sex- and age- (or gestational age–) standardized z scores according to INTERGROWTH-21st standards for newborn size,[20] postnatal growth standards for preterm infants to 64 weeks of postmenstrual age (weight, length, and head circumference only),[21] or World Health Organization (WHO) child growth standards.[22]

The primary outcome was length-for-age z score at 1 year (364 to 420 days). Secondary outcomes included other infant anthropometric variables; preterm birth (<37 weeks of gestation); gestational hypertension; delivery characteristics; stillbirth; mother and infant symptoms, clinical encounters, and hospitalizations; deaths; congenital anomalies; infant neurologic disabilities; and infant rickets (for a complete list of secondary outcomes, see Table S4 in the Supplementary Appendix). Biochemical screening for rickets was scheduled at 6 months of age (see Methods, section 2, in the Supplementary Appendix). Radiologic confirmation was based on interpretations of images of the wrist, knee, or both by a pediatric radiologist who was unaware of other data. Post hoc classifications of infants' neurologic disabilities, congenital anomalies, and physician-assigned diagnostic codes for clinical encounters and hospitalizations were made by trial investigators who were unaware of treatment allocation.

The primary safety measure was maternal total serum calcium concentration at enrollment, 30 weeks of gestation, delivery, 3 months and 6 months post partum, or during hospitalization (if feasible). "Possible hypercalcemia" was defined as any serum calcium concentration of more than 2.60 mmol per liter (>10.4 mg per deciliter), and "confirmed hypercalcemia" (primary safety outcome) as a serum calcium concentration greater than 2.60 mmol per liter on a repeat specimen

or a single serum calcium concentration greater than 2.80 mmol per liter (>11.2 mg per deciliter).

Secondary safety indicators included the serum calcium concentration of infants at 3 and 6 months of age and the urinary calcium:creatinine ratio of mothers at delivery. "Possible hypercalciuria" in mothers was defined as a single urinary calcium:creatinine ratio of more than 1, with both calcium and creatinine measured in millimoles (or >0.35, with both measured in milligrams). Participants with a urinary calcium:creatinine ratio of more than 1 in two consecutive specimens (i.e., confirmed hypercalciuria), symptoms of renal colic, or both underwent ultrasonography for urolithiasis or nephrolithiasis. Infant urinary calcium:creatinine ratios were measured at 6 months of age. Serum calcium concentrations and urinary calcium:creatinine ratios were analyzed at icddr,b.

Vitamin D status was based on serum 25-hydroxyvitamin D[23] concentration, with deficiency defined as a concentration below 30 nmol per liter (<12 ng per milliliter).[24] The C3-epimer fraction was included only in sensitivity analyses. Measurement of 25-hydroxyvitamin D and intact parathyroid hormone (iPTH) was conducted by the Analytical Facility for Bioactive Molecules at the Hospital for Sick Children, Toronto (Methods, section 3, in the Supplementary Appendix).

STATISTICAL ANALYSIS

The primary analysis was a complete-case intention-to-treat analysis. Analysis of variance was performed to compare length-for-age z scores at 1 year of age across all groups. To estimate the effect of weekly administration of prenatal vitamin D, five pairwise comparisons were conducted with the use of t-tests: prenatal 4200 versus placebo, prenatal 16,800 versus placebo, prenatal 16,800 versus prenatal 4200, prenatal 28,000 versus placebo, and prenatal 28,000 versus prenatal 16,800. Statistical significance was tested with a two-sided alpha level of 0.05, with the Holm test applied for multiple comparisons.[25]

The determination of sample size was based on the conservative assumption that if each between-group comparison had a two-sided alpha of 0.01 and 90% power, 220 participants per group would enable detection of a between-group difference in length-for-age z score of at least 0.40.[14] To accommodate an attrition rate of 15%, we aimed to enroll 260 pregnant women in each group.

The effect of postpartum vitamin D on length-for-age z score at 1 year of age was assessed by means of a pairwise comparison of the prenatal and postpartum 28,000 group with the prenatal 28,000 group (with a two-sided alpha level of 0.05) with the use of a t-test. Secondary outcomes were compared across groups with the use of analysis of variance for continuous, normally distributed variables and with the Kruskal–Wallis tests for skewed distributions; chi-square and Fischer's exact tests were used for categorical variables. Zero-inflated negative binomial models were used to compare incidence rates of clinical encounters, hospitalizations, and other adverse events. When the result of a global test was significant ($P<0.05$), post hoc pairwise comparisons were performed, with the Holm test applied for multiple comparisons.[25] We did not control for the multiplicity of comparisons of the secondary outcomes; any significant differences were viewed as exploratory. We conducted sensitivity and stratified analyses of the primary outcome and multiple imputation with chained equations to account for missing anthropometric data at 1 year of age. Trajectories of infant length-for-age z scores and other anthropometric measures were estimated with the use of restricted cubic spline regression models. Per-protocol analyses were restricted to participants who consumed at least 90% of scheduled supplement doses and had no episodes of reported consumption of nontrial vitamin D or calcium (see Methods, sections 4 to 7, in the Supplementary Appendix for additional details). Analyses were performed with the use of Stata, version 13 (StataCorp).

RESULTS

TRIAL POPULATION

A total of 1300 pregnant women were enrolled and randomly assigned to one of five groups (Fig. S1 in the Supplementary Appendix). Baseline characteristics, including vitamin D status, were similar across groups (Table 1, and Tables S5 and S6 in the Supplementary Appendix). Overall, 64% of women had vitamin D deficiency. The groups did not differ significantly with regard to breastfeeding patterns or reported use of micronutrient supplements by infants (Tables S7 and S8 in the Supplementary Appendix). Participants in primary analyses had higher average household-asset indexes than those who were excluded from pri-

mary analyses, but their characteristics were otherwise similar (Table S9 in the Supplementary Appendix). Across all groups, at least 90% of scheduled doses were received by more than 90% of women during the prenatal period and by more than 80% of women during the postpartum period (Table S10 in the Supplementary Appendix).

INFANT GROWTH

Infant follow-up at 1 year of age was completed for 90% of pregnancies and 94% of infants who were alive at 1 year (Fig. S1 in the Supplementary Appendix). Overall, the mean (±SD) length-for-age z score at 1 year was −1.00±1.04, and the prevalence of stunting (length-for-age z score, <−2) was 16%. Prenatal or postpartum maternal vitamin D supplementation had no significant effect on infant length or other anthropometric outcomes by 1 year of age (Table 2, and Figs. S2 through S6 and Tables S11 and S12 in the Supplementary Appendix). The lack of effect of prenatal vitamin D on length was evident from birth (Table 3) and was supported by sensitivity and stratified analyses (Tables S13 through S22 in the Supplementary Appendix). Results of multiple imputation analyses (prespecified for length-for-age z score and post hoc for other 1-year anthropometric measurements) were consistent with the complete-case analyses (Table S18 in the Supplementary Appendix); therefore, complete-case analyses only are shown in Table 2.

BIOCHEMICAL EFFECTS OF SUPPLEMENTATION

Vitamin D had dose-dependent effects on concentrations of maternal, cord blood, and infant 25-hydroxyvitamin D (Table 3 and Fig. 1, and Tables S23 and S24 in the Supplementary Appendix) and on concentrations of maternal iPTH at delivery. The prenatal and postpartum 28,000 group continued to have significantly lower iPTH concentrations at 6 months post partum than the other groups (Fig. 1, and Table S25 in the Supplementary Appendix).

SAFETY AND CLINICAL OUTCOMES

There were no episodes of confirmed hypercalcemia during pregnancy. Confirmed hypercalcemia (asymptomatic) occurred post partum in eight women (0.7%) — with five in the prenatal and postpartum 28,000 group — and in six infants (0.6%) — with two in the prenatal and postpartum 28,000 group; frequencies did not significantly differ across groups (Table S25 in the Supplementary Appendix). Although prenatal vitamin D supplementation led to modest elevations in maternal, fetal, and infant mean serum calcium concentrations, at 6 months post partum only the mothers in the prenatal and postpartum 28,000 group continued to have higher calcium concentrations than those in the placebo group (in post hoc comparisons) (see Table S26 in the Supplementary Appendix). The maternal urinary calcium:creatinine ratio at delivery varied significantly across groups, with the median urinary calcium:creatinine ratio for the placebo group being the lowest. The risk of possible maternal hypercalciuria at delivery increased with dose; however, only the prenatal and postpartum 28,000 group differed significantly from the placebo group (as determined in a pairwise comparison after correcting for multiple testing with the use of the Holm test). There were two asymptomatic cases of maternal confirmed hypercalciuria, one each in the placebo group and the prenatal and postpartum 28,000 group. None of the women with confirmed hypercalcemia or confirmed hypercalciuria had serious adverse events (hospitalizations or deaths) or urinary tract stones. Two of the six infants with confirmed hypercalcemia had neonatal hospitalizations for acute illnesses that antedated and were clinically unrelated to hypercalcemia. There was one infant — in the prenatal 4200 group — with confirmed hypercalciuria. There were no significant differences across groups in infant urinary calcium:creatinine ratios at 6 months of age. Detailed biochemical safety data are shown in Tables S25, S26, and S27 in the Supplementary Appendix.

Groups did not significantly differ in the frequencies of hospitalizations or deaths (Table S27 in the Supplementary Appendix). There were no significant beneficial or harmful effects of any vitamin D dose on gestational hypertension, duration of gestation, preterm birth, small size for gestational age (weight for gestational age, <10th percentile[20]), low birth weight (<2500 g), other delivery outcomes, maternal or infant morbidity, maternal self-reported or caregiver-reported infant symptoms, or stillbirth (Table 3, and Tables S27 through S33 in the Supplementary Appendix). Among four infants with radiologically confirmed rickets, three were in the placebo group

Table 1. Maternal Characteristics at Enrollment.*

Characteristic	Maternal Study-Group Assignment				
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)
Age — yr					
Median	23	22.5	22	22	23
Range	18–38	18–40	18–35	18–38	18–38
Gestational age — wk					
Median	20.4	20.1	20.3	20.4	20.1
Range	17–24	17–24	17–24	17–24	17–24
Married — no./total no. (%)	255/257 (99.2)	259/259 (100)	254/254 (100)	257/257 (100)	256/256 (100)
Secondary school education complete or higher — no. (%)	52 (20.1)	70 (26.9)	51 (19.7)	58 (22.3)	55 (21.2)
Occupation outside the home — no./total no. (%)	17/257 (6.6)	19/259 (7.3)	15/254 (5.9)	16/257 (6.2)	14/256 (5.5)
Household-asset index quintile — no. (%)†					
1	55/257 (21.4)	59/258 (22.9)	38/253 (15.0)	61/256 (23.8)	48/256 (18.8)
2	49/257 (19.1)	54/258 (20.9)	57/253 (22.5)	45/256 (17.6)	46/256 (18.0)
3	58/257 (22.6)	41/258 (15.9)	54/253 (21.3)	51/256 (19.9)	52/256 (20.3)
4	49/257 (19.1)	44/258 (17.1)	56/253 (22.1)	53/256 (20.7)	55/256 (21.5)
5	46/257 (17.9)	60/258 (23.3)	48/253 (19.0)	46/256 (18.0)	55/256 (21.5)
Gravidity‡					
Median	2	2	2	2	2
Range	1–9	1–6	1–6	1–7	1–6
Parity					
Median	2	2	2	2	2
Range	0–6	0–5	0–5	0–5	0–4
Height (cm)§	151.2±5.4	150.9±5.0	150.7±5.5	150.2±5.4	151.8±5.5
Weight (kg)	54.5±10.3	53.2±10.1	53.8±9.9	53.3±9.1	55.2±10.6
Serum 25-hydroxyvitamin D concentration — nmol/liter¶	27.7±13.8	27.4±14.3	28.7±14.0	27.0±14.7	26.6±13.2

* Plus–minus values are means ±SD. One participant in the group receiving no prenatal vitamin D and no postpartum vitamin D (placebo group) and one participant in the group receiving 16,800 IU of prenatal vitamin D and no postpartum vitamin D (prenatal 16,800 group) were found to be ineligible for trial participation after randomization and were excluded from the analyses. The prenatal 4200 group received 4200 IU of vitamin D prenatally and placebo post partum, the prenatal 16,800 group received 16,800 IU of vitamin D prenatally and placebo post partum, the prenatal 28,000 group received 28,000 IU of vitamin D prenatally and placebo post partum, and the prenatal and postpartum 28,000 group received prenatal supplementation as well as 26 weeks of postpartum supplementation in the amount of 28,000 IU. Prenatal dosing began between 17 and 24 weeks of gestation and ended at birth, and postpartum dosing was provided for 26 weeks. Administration of all doses of vitamin D and of placebo occurred weekly. To convert the values for 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

† Higher quintiles indicate greater household-asset ownership relative to other participants. See Methods, section 7, in the Supplementary Appendix for a description of the construction and interpretation of the asset index.

‡ Gravidity is defined as the number of pregnancies, including the current pregnancy.

§ P=0.02 for the comparison of maternal height based on analysis of variance. Post hoc pairwise comparisons conducted with the use of t-tests showed significant pairwise differences in maternal height between the prenatal and postpartum 28,000 group and the prenatal 28,000 group, after adjustment for multiple comparisons conducted with the Holm test.

¶ Calculations were based on 253 participants in the placebo group, 258 participants each in the prenatal 4200 group, the prenatal 16,800 group, and the prenatal 28,000 group, and 256 participants in the prenatal and postpartum 28,000 group. Vitamin D deficiency was defined as a concentration of 25-hydroxyvitamin D of <30 nmol per liter (<12 ng per milliliter).

and one was in the prenatal 4200 group (Table S27 in Supplementary Appendix).

DISCUSSION

In a region of the world where there is widespread vitamin D deficiency and fetal–infant growth restriction, vitamin D supplementation from midpregnancy to delivery or 6 months post partum had no significant effect on length-for-age z scores at 1 year or on other anthropometric measures from birth to 1 year. Similarly, vitamin D supplementation had no significant effect on numerous clinical outcomes during pregnancy or infancy.

These findings do not support the hypothesis that prenatal vitamin D status in the second half of pregnancy is a determinant of newborn size. Our findings are contrary to the conclusions of earlier meta-analyses of observational studies[12] and mostly small trials[13] but consistent with those of higher-quality trials in areas where the prevalence of vitamin D deficiency and fetal growth restriction is lower.[26-29] Our earlier trial, also conducted in Bangladesh,[14] and a trial in the United Kingdom[30] showed that prenatal vitamin D supplementation increased infant linear growth. However, these studies were small, each involving fewer than 135 participants, and included postnatal growth as a post hoc outcome, and the between-group differences may have been due to chance. A meta-analysis of six trials of prenatal, multiple-micronutrient supplementation that included relatively low doses of vitamin D (200 to 400 IU per day) in low- and middle-income countries showed no effect on height at 2 to 8.5 years of age.[5] The findings of our current trial confirm the lack of effect on growth across a range of prenatal doses of vitamin D up to 28,000 IU per week (the equivalent of approximately 4000 IU per day).

Effects on fetal or infant growth were absent despite the robust dose–response effects of vitamin D on serum concentrations of 25-hydroxyvitamin D, iPTH, and calcium and on the urinary calcium:creatinine ratio. The dose that was equivalent to the dietary allowance recommended by the Institute of Medicine[24] (4200 IU per week) was sufficient for eliminating maternal vitamin D deficiency (defined as a 25-hydroxyvitamin D concentration <30 nmol per liter) in nearly all women without elevating 25-hydroxyvitamin D concentration above a conservative long-term risk threshold (125 nmol per liter [50 ng per milliliter]).[24] In nearly all women who received supplementation of 16,800 IU per week, concentrations of 25-hydroxyvitamin D did not fall below 50 nmol per liter (<20 ng per milliliter). In these women there was also maximal suppression of iPTH concentrations, and cord concentrations of 25-hydroxyvitamin D did not fall below 30 nmol per liter. Maternal postpartum supplementation of 28,000 IU per week maintained infant 25-hydroxyvitamin D concentrations at or above 30 nmol per liter up to 6 months of age, despite variation in feeding patterns. Although higher vitamin D doses increased serum calcium and urinary calcium excretion, hypercalcemia and hypercalciuria were infrequent, even in the group receiving the highest dose, and clinical adverse events did not differ significantly across groups.

There were no apparent benefits of improved vitamin D status in the latter half of pregnancy on pregnancy, birth, or infant outcomes, even without adjustment for multiplicity of testing for numerous secondary efficacy outcomes. Consistent with the findings of a recent meta-analysis,[13] we did not find a reduction in the incidence of preterm births. The occurrence of four cases of rickets in the placebo group and the prenatal 4200 group raised the possibility that doses of 16,800 IU per week or higher prenatally may prevent the development of early rickets, but there were too few cases to assess this question. Our trial was not powered to detect differences in infrequent maternal and infant adverse outcomes. Furthermore, the initiation of vitamin D supplementation in midpregnancy did not address the question of whether earlier supplementation might have had beneficial effects. Other potential limitations of the trial were that effects of vitamin D may have been attenuated by cosupplementation with calcium and that untreated maternal nutritional deficits may have limited the effects of vitamin D on fetal growth. Faltering of linear growth was milder in our trial participants than in a recent Bangladeshi national survey,[15] which suggests that participants had relatively better baseline health and access to care; for example, participants had high rates of facility deliveries (85% vs. 37% nationally).[15]

At this time, the WHO does not recommend routine vitamin D supplementation during pregnancy.[31] The present findings support this position, even in communities where vitamin D de-

Table 2. Anthropometric Outcomes in Infants at 1 Year of Age.*

Outcome	Maternal Study-Group Assignment					
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)	P Value†
Age at measurement — days						0.70
Median	364	365	365	365	365	
Range	364–419	365–415	364–418	364–419	364–416	
Length						
No. of children measured	229	237	237	230	231	
Length — cm	72.62±2.76	72.31±2.84	72.56±2.54	72.39±2.80	72.67±2.53	0.53
Length-for-age z score	−0.93±1.05	−1.11±1.12	−0.97±0.97	−1.06±1.07	−0.94±1.00	0.23
Stunted — no. (%)‡	36 (15.7)	46 (19.4)	36 (15.2)	39 (17.0)	31 (13.4)	0.49
Other anthropometric indexes						
Weight-for-age z score§	−0.81±1.12	−1.00±1.14	−0.86±1.09	−0.96±1.09	−0.89±1.04	0.34
Weight-for-length z score§	−0.47±1.07	−0.60±1.03	−0.52±1.08	−0.58±1.01	−0.59±1.01	0.62
BMI-for-age z score§	−0.36±1.05	−0.48±1.00	−0.40±1.07	−0.46±0.99	−0.48±1.00	0.66
Head-circumference-for-age z score¶	−1.11±0.99	−1.25±0.96	−1.21±1.05	−1.22±0.92	−1.22±0.89	0.61
Mid–upper-arm-circumference-for-age z score¶	−0.14±0.97	−0.27±0.92	−0.21±0.93	−0.29±0.88	−0.23±0.86	0.42
Wasted — no. (%)**	14 (6.1)	22 (9.3)	18 (7.6)	18 (7.8)	21 (9.1)	0.72

* Plus–minus values are means ±SD. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

† P values for multiple group comparisons are from analysis of variance or Kruskal–Wallis tests for continuous variables, and chi-square tests for categorical variables. P values were not adjusted for the multiplicity of secondary outcomes.

‡ Stunted was defined as a length-for-age z score lower than −2.

§ Weight-for-age, weight-for-length, and BMI-for-age z scores were obtained for 228 infants in the placebo group, 236 infants in the prenatal 4200 group, 237 infants in the prenatal 16,800 group, 229 infants in the prenatal 28,000 group, and 231 infants in the prenatal and postpartum 28,000 group.

¶ Head circumference-for-age z scores were obtained for 225 infants in the placebo group, 235 infants in the prenatal 4200 group, 234 infants in the prenatal 16,800 group, 229 infants in the prenatal 28,000 group, and 231 infants in the prenatal and postpartum 28,000 group.

‖ The sample sizes for mid–upper-arm circumference-for-age z score were the same as those for length-for-age z score.

** Wasted was defined as a weight-for-length z score lower than −2.

Table 3. Delivery Characteristics and Pregnancy Outcomes.*

Characteristic or Outcome	Maternal Study-Group Assignment					
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)	P Value†
Live birth — no. (%)	247 (95.4)	254 (97.7)	252 (97.3)	252 (96.9)	249 (95.8)	0.53
Gestational age at birth (wk)						0.62
Median	39.1	39.1	39.0	39.1	39.1	
Range	32–43	34–42	26–43	29–43	30–42	
Preterm (<37 wk) — no. (%)	24 (9.7)	21 (8.3)	31 (12.3)	26 (10.3)	22 (8.8)	0.60
Cesarean section — no. (%)	121 (49.0)	143 (56.3)	131 (52.0)	127 (50.4)	132 (53.0)	0.54
Facility (hospital or clinic) delivery — no. (%)‡	211 (85.4)	216 (85.0)	216 (85.7)	212 (84.1)	207 (83.1)	0.93
Female infant — no. (%)	129 (52.2)	117 (46.1)	132 (52.4)	124 (49.2)	121 (48.6)	0.58
Maternal serum 25-hydroxyvitamin D at or near delivery — nmol/liter§	23.8±13.9	69.7±19.5	100.9±23.6	110.7±28.0	113.6±25.7	<0.001¶
Newborn anthropometry‖						
Birth weight — kg**	2.72±0.36	2.70±0.39	2.72±0.35	2.67±0.34	2.76±0.35	0.25
Length at birth — cm††	47.4±2.1	47.5±1.9	47.4±1.9	47.2±2.1	47.5±2.0	0.74
Head circumference at birth — cm‡‡	33.0±1.3	33.0±1.3	33.0±1.1	32.9±1.2	33.0±1.1	0.73
Size for gestational age and sex according to standardized measures‖						
Weight-for-gestational-age z score at birth**	−1.12±0.83	−1.27±0.89	−1.15±0.90	−1.30±0.82	−1.12±0.85	0.16
Length-for-gestational-age z score at birth††	−0.83±1.04	−0.95±1.00	−0.90±1.05	−1.00±1.02	−0.88±0.95	0.61
Head-circumference-for-gestational-age z score at birth‡‡	−0.58±0.96	−0.66±1.04	−0.57±0.94	−0.72±0.98	−0.58±0.91	0.57
Low birth weight — no. (%)**§§	42 (25.3)	53 (31.0)	42 (25.0)	53 (32.9)	40 (23.7)	0.23
Small for gestational age — no. (%)**¶¶	72 (43.4)	88 (51.5)	77 (45.8)	84 (52.2)	76 (45.0)	0.38

* Plus–minus values are means ±SD. With the exception of maternal serum 25-hydroxyvitamin D concentration at or near delivery, all characteristics and outcomes are for live births only.

† P values were calculated with the use of analysis of variance or Kruskal–Wallis tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. When the overall P value was significant, P values for pairwise tests were adjusted for multiple comparisons with the use of the Holm test; however, the values were not adjusted for the multiplicity of secondary outcomes.

‡ Two infants (one in the placebo group and one in the prenatal 16,800 group) were born at a location other than a hospital or clinic or at home; all other deliveries that did not occur at a medical facility took place at home.

§ The values for maternal serum 25-hydroxyvitamin D at or near delivery were obtained for 128 women in the placebo group, 122 women in the prenatal 4200 group, 135 women in the prenatal 16,800 group, 118 women in the prenatal 28,000 group, and 132 women in the prenatal and postpartum 28,000 group. The median gestational age at the time of the measurements was 274 days (interquartile range, 268 to 281 days).

¶ Post hoc pairwise comparisons calculated with the use of t-tests showed significant pairwise differences between all groups except the two groups that received a prenatal dose of 28,000 IU per week, after adjustment for multiple comparisons with the use of the Holm test.

‖ These data are limited to measurements obtained within 48 hours after birth. Standards are based on those established by the INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) Project.

** These values were obtained for 166 infants in the placebo group, 171 infants in the prenatal 4200 group, 168 infants in the prenatal 16,800 group, 161 infants in the prenatal 28,000 group, and 169 infants in the prenatal and postpartum 28,000 group.

†† These values were obtained for 164 infants in the placebo group, 169 infants in the prenatal 4200 group, 166 infants in the prenatal 16,800 group, 160 infants in the prenatal 28,000 group, and 165 infants in the prenatal and postpartum 28,000 group.

‡‡ These values were obtained for 167 infants in the placebo group, 168 infants in the prenatal 4200 group, 169 infants in the prenatal 16,800 group, 159 infants in the prenatal 28,000 group, and 167 infants in the prenatal and postpartum 28,000 group.

§§ Low birth weight was defined as a weight below 2500 g.

¶¶ Infants considered to be small for gestational age had a weight-for-age z score that was below the 10th percentile according to neonatal standards established by the INTERGROWTH-21st Project.[20]

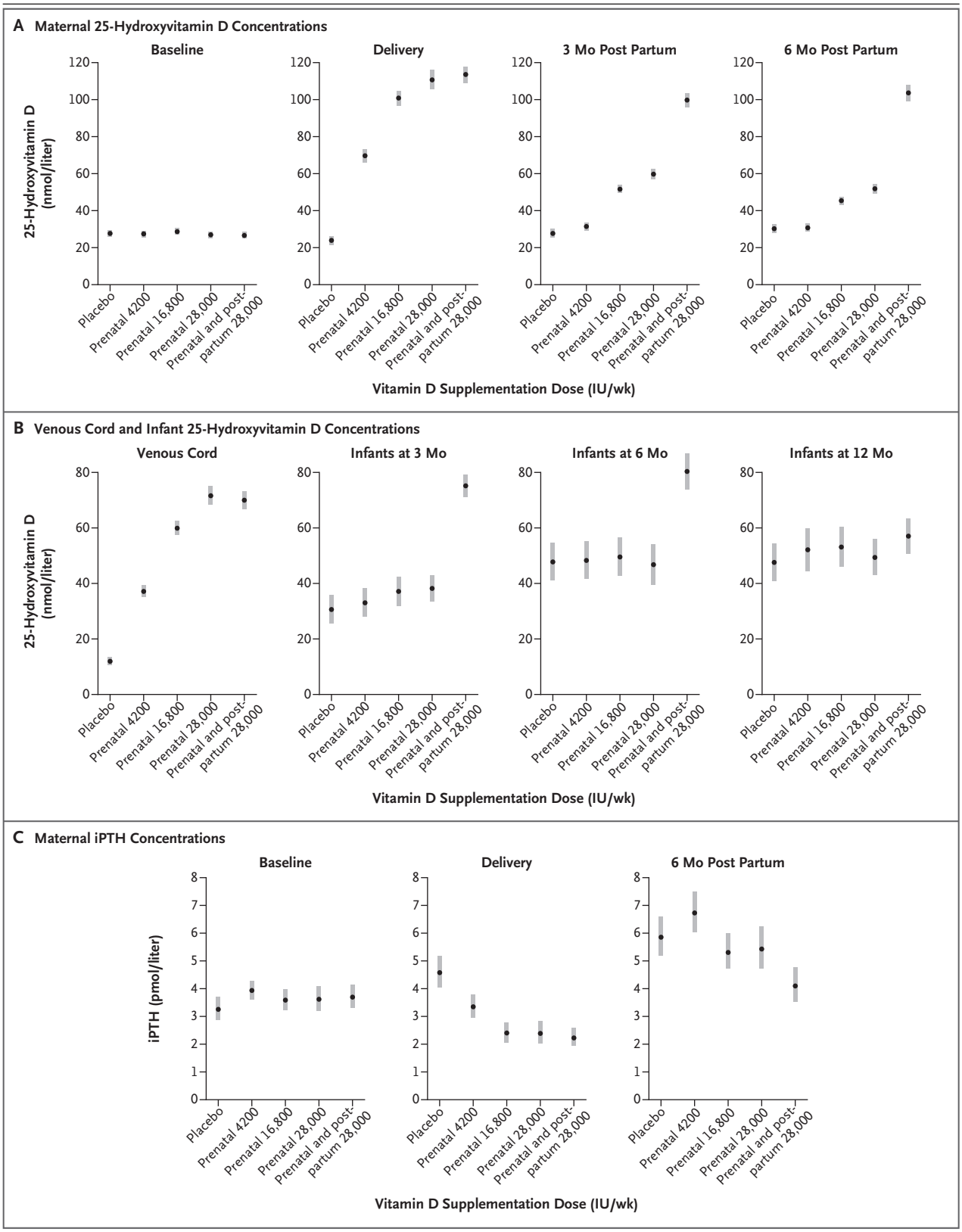

Figure 1 (facing page). Concentrations of Maternal, Venous Cord, and Infant 25-Hydroxyvitamin D and Maternal Intact Parathyroid Hormone (iPTH) According to Maternal Vitamin D Supplementation Group.

Panel A shows the mean maternal 25-hydroxyvitamin D concentration at baseline (1283 women), delivery (635 women, with delivery specimens obtained up to 19 days before or 4 days after delivery [median, 0 days]), 3 months post partum (560 women), and 6 months post partum (569 women). Panel B shows mean 25-hydroxyvitamin D concentrations in venous cord blood (499), infants at 3 months (343), infants at 6 months (250), and infants at 12 months (180). Panel C shows the geometric mean concentrations of maternal iPTH at baseline (587 women), delivery (551, with specimens obtained within 19 days before or 4 days after delivery [median, 0 days]), and 6 months post partum (566). One group received no prenatal vitamin D or postpartum vitamin D (placebo group). Three groups received prenatal supplementation only, in doses of 4200 IU per week (prenatal 4200 group), 16,800 IU per week (prenatal 16,800 group), and 28,000 IU per week (prenatal 28,000 group). The fifth group received both prenatal and postpartum vitamin D at a dose of 28,000 IU per week (prenatal and postpartum 28,000 group). Shading denotes 95% confidence intervals. To convert the values for 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

ficiency and fetal–infant growth restriction are endemic.

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APPENDIX

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