Vitamin D status among preterm and full-term infants at birth

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BACKGROUND: Risk factors for maternal vitamin D deficiency and preterm birth overlap, but the distribution of 25-hydroxyvitamin D (25(OH)D) levels among preterm infants is not known. We aimed to determine the associations between 25(OH)D levels and gestational age.

METHODS: We measured umbilical cord plasma levels of 25(OH)D from 471 infants born at Brigham and Women's Hospital in Boston. We used generalized estimating equations to determine whether preterm (<37 wks' gestation) or very preterm (<32 wks' gestation) infants had greater odds of having 25(OH)D levels below 20 ng/ml than more mature infants. We adjusted for potential confounding by season of birth, maternal age, race, marital status, and singleton or multiple gestation.

RESULTS: Mean cord plasma 25(OH)D level was 34.0 ng/ml (range: 4.1–95.3 and SD: 14.1). Infants born before 32 wks' gestation had increased odds of having 25(OH)D levels below 20 ng/ml in unadjusted (odds ratio (OR): 2.2; 95% confidence interval (CI): 1.1–4.3) and adjusted models (OR: 2.4; 95% CI: 1.2–5.3) as compared with more mature infants.

CONCLUSION: Infants born in <32 wks' gestation are at higher risk than more mature infants for low 25(OH)D levels. Further investigation of the relationships between low 25(OH)D levels and preterm birth and its sequelae is thus warranted.

Preterm birth is a leading cause of infant mortality and morbidity in the United States, with 12% of infants born preterm (<37 wks' gestation) (1–3). Risk factors for preterm birth, including African-American race (4), poverty (5), young maternal age (6), and obesity (7), also overlap with risk factors for vitamin D deficiency (8–11). Vitamin D status in the fetus and newborn infant is largely determined by maternal vitamin D status (12). Because maternal vitamin D insufficiency is common (13), it is likely that many newborns are also relatively deficient in 25-hydroxyvitamin D (25(OH)D).

Investigators have recently demonstrated an adverse role of low vitamin D levels on health conditions beyond the traditionally understood calcium metabolism and bone health, such as health status throughout pregnancy (14) and during infancy and childhood (15). Low maternal 25(OH)D concentrations during pregnancy also have been shown to be associated with increased risks of specific conditions, including gestational diabetes (16), preeclampsia (17), and poor fetal growth (18,19). These perinatal complications can precipitate preterm birth, and thus, preterm infants may be at higher risk of vitamin D deficiency. However, the current distribution of 25(OH)D levels at birth among neonates across the gestational age spectrum is unknown.

To evaluate the association of umbilical cord plasma 25(OH)D concentrations with gestational age, we analyzed data from a prospective cohort of 471 newborn infants born in Boston (latitude 47.32° north). We hypothesized that preterm infants would have lower 25(OH)D levels than their full-term counterparts.

RESULTS

Mean umbilical cord plasma 25(OH)D level was 34.0 ng/ml (SD: 14.1; range: 4.1–95.3) (**Figure 1**). We found that 40.1% of subjects had 25(OH)D levels below 30 ng/ml, including 14.4% with levels below 20 ng/ml. We did not detect a clear linear association between 25(OH)D levels and gestational age (**Figure 2**).

Infants had lower mean umbilical cord plasma 25(OH)D levels if they were born in the winter or spring (vs. summer or fall) and if their mothers were black (vs. white), young (<30 vs. ≥30 y old), single (vs. married), or insured by Medicaid (vs. private insurance or a health maintenance organization) (**Table 1**). More of these infants had 25(OH)D levels below 20 ng/ml as compared with their counterparts (**Table 2**). Notably, infants born in the winter or spring had 25(OH)D levels below 20 ng/ml more than twice as often as infants born in the summer, and black infants had 25(OH)D levels below 20 ng/ml six times more often than white infants (39.3 vs. 6.3%, respectively).

Twenty-five percent of infants born before 32 completed wks' gestation had 25(OH)D levels below 20 ng/ml vs. 7% of infants born during 32 to <37wks' and 14% of full-term infants (**Figure 3**). Infants born before 32 wks' gestation had significantly higher odds of having 25(OH)D levels below 20 ng/ml as compared with more mature infants (odds ratio

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(OR): 2.2; 95% confidence interval (CI): 1.1–4.3). This association persisted after adjustment for season of birth, singleton vs. multiple gestation, maternal race/ethnicity, age, and marital status (adjusted OR: 2.4; 95% CI: 1.2–5.1). Additional adjustment for year of study (2004–2005 vs. 2010–2012), insurance status, and infant sex did not alter these results, and thus, these covariates were omitted from the final, most parsimonious model.

When we analyzed cord blood 25(OH)D levels in preterm infants by indication for preterm delivery, we found no statistically significant differences among preterm infants born due to maternal preeclampsia, chorioamnionitis, premature rupture of membranes, or preterm labor (**Table 3**). Similarly, we found no statistically significant differences between cord blood 25(OH)D levels of small-for-gestational-age infants and appropriate-for-gestational-age infants in the overall cohort (data not shown) as well as in the preterm subset (**Table 3**).

Because maternal BMI data were available for only a subset (134/471) of infants, we performed secondary analyses to evaluate whether adjustment for BMI might affect our findings. Mean 25(OH)D levels were highest among infants born to lean women (38.9 ng/ml; SD: 16.2) as compared with infants born to overweight (31.6 ng/ml; SD: 15.9) and obese women (32.3 ng/ml, SD: 10.7) ($P = 0.03$). Gestational age was not associated with BMI in this cohort. Among lean, overweight, and obese women, mean gestational ages were 36.2 (SD: 3.4), 36.8 (SD: 4.7), and 37.0 (SD: 3.9) wk, respectively ($P = 0.6$).

An analogous, adjusted model from the primary analysis in this subset revealed that infants born before 32 wks' gestation had similar odds of having 25(OH)D levels below 20 ng/ml before and after additional adjustment for maternal BMI (OR: 1.5; 95% CI: 0.3–7.9 and OR: 1.5; 95% CI: 0.3–7.8, respectively).

We analyzed cord blood plasma from infants born in two distinct time periods: 59 infants from 2004 to 2005 and 412 infants from 2010 to 2012. We chose to include the earlier sample because it was enriched for extremely preterm infants. Eight of the 35 infants born before 28 wks' gestation came from this time period. Because of potential influences of prolonged storage on the 25(OH)D levels from the earlier time period and secular trends in clinical and nutritional practices between the two time periods, we performed a secondary analysis to evaluate the effect of time period. Although we observed a trend in the direction of lower 25(OH)D levels in the earlier cohort, when we performed the same analysis (final adjusted model) on the later time period alone, we found that our results were not different than when the cohorts were combined: infants in the later cohort born before 32 wks' gestation had increased odds of having 25(OH)D levels <20 ng/ ml (OR: 2.4; 95% CI: 1.0–5.9). Further adjustment for time period on our final combined cohort model had no impact on the final adjusted estimate (OR: 2.5; 95% CI: 1.2–5.3).

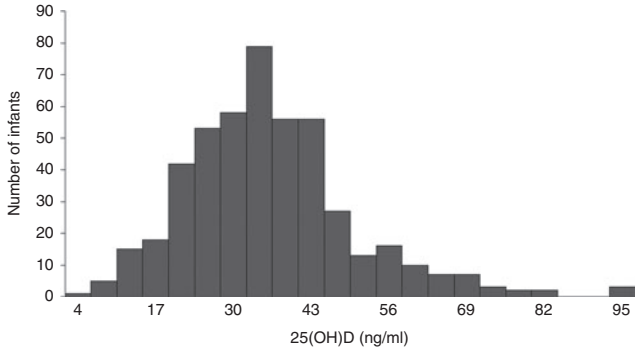

Figure 1. Distribution of umbilical cord plasma 25-hydroxyvitamin D (25(OH)D) levels from 471 infants at Brigham and Women's Hospital, Boston, MA. Mean 25(OH)D: 34.0 ng/ml; SD: 14.1. Histogram created by assigning values into 22 bins between the minimum value of 4 to maximum value of 95 ng/ml.

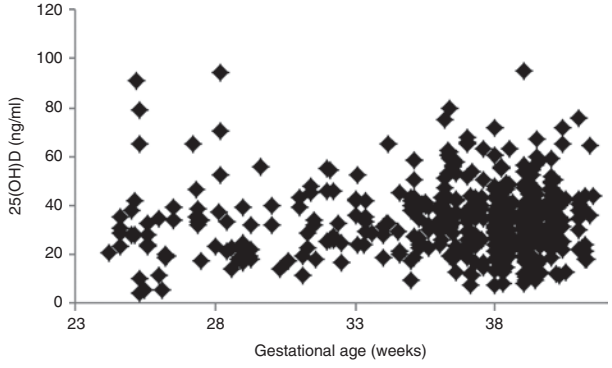

Figure 2. Umbilical cord plasma 25-hydroxyvitamin D (25(OH)D) levels from infants of gestational ages 24–41 wk, $n = 471$; $r = 0.03$, $P = 0.4$.

DISCUSSION

We found that, compared with more mature infants, those born before 32 wks' gestation had higher odds of having umbilical cord plasma 25(OH)D levels below 20 ng/ml. This population of preterm infants suffers from multiple morbidities, including not only metabolic bone disease (20), which is directly related to the well-known physiological effects of vitamin D and calcium metabolism, but also respiratory sequelae and immune system dysfunction, which also might relate to vitamin D status (21,22). Our study describes the distribution of umbilical cord plasma 25(OH)D levels at birth across the gestational age spectrum and also highlights the high risk of low 25(OH)D levels among very preterm infants. Whether such low levels contribute to any of the morbidities of preterm birth remains unknown and should be evaluated in future studies.

In our cross-sectional analyses, we were unable to address whether suboptimal maternal vitamin D status contributed to the preterm births in our cohort. Furthermore, our study is limited by lack of data on prenatal vitamin D supplementation and maternal 25(OH)D levels and therefore not allowing for better risk prediction of suboptimal vitamin D status. Because umbilical cord plasma 25(OH)D concentrations are typically within ~90% of the mother's concentration, and maternal concentrations do not vary significantly throughout pregnancy (12), we do not believe that we are demonstrating a physiological transition at 32 wks' gestation. However, given that fetal and newborn concentrations of 25(OH)D depend on and correlate with maternal serum levels, vitamin D insufficiency among pregnant women places newborns at a greater risk for vitamin D deficiency (23).

Table 1. Maternal and infant characteristics and umbilical cord plasma 25(OH)D levels from 471 infants

		Cord plasma 25(OH)D (ng/ml)	
	n (column %)[a]	Mean (SD)	
All subjects	471 (100)	34.0 (14.2)	
Characteristics			ANOVA *P*
Season of birth			<0.0001
Spring	85 (18.0)	30.4 (11.9)	
Summer	152 (32.3)	38.3 (15.3)	
Fall	130 (27.6)	36.3 (14.5)	
Winter	104 (22.1)	27.7 (10.3)	
Race/ethnicity			<0.0001
White	269 (52.7)	37.2 (13.6)	
Black	61 (13.0)	25.3 (15.0)	
Hispanic	75 (15.1)	33.8 (12.8)	
Asian	54 (10.6)	29.9 (11.7)	
Other	7 (1.5)	29.9 (13.7)	
Maternal age (y)			<0.0001
<20	13 (2.8)	23 (7.5)	
20 to <30	115 (24.4)	30.0 (13.0)	
30 to <40	299 (63.5)	35.8 (14.0)	
≥40	41 (8.7)	35.5 (16.7)	
Marital status			0.006
Married	343 (72.8)	35.0 (14.0)	
Single	118 (25.1)	30.9 (14.4)	
Insurance status			0.01
Private	13 (2.8)	44.1 (19.7)	
HMO	341 (72.8)	34.6 (14.0)	
Medicaid	111 (23.6)	31.0 (13.6)	
Self-pay	3 (0.6)	30.7 (8.7)	
Period of birth			0.07
2004–2005	59 (12.5)	30.9 (13.8)	
2010–2012	412 (87.5)	34.4 (14.2)	
Gestational number			0.07
Singleton	328 (69.6)	33.2 (14.4)	
Multiple	143 (30.4)	35.8 (13.5)	
Infant sex			0.8
Female	220 (46.7)	33.8 (14.4)	
Male	251 (53.3)	34.1 (13.9)	
Gestational age (wk)			0.06
<32	71 (15.1)	31.7 (18.1)	
32 to 36 6/7	108 (22.9)	36.5 (13.1)	
≥37	292 (62.0)	33.6 (13.3)	
Maternal BMI[b] (kg/m^2)			0.03
<25	68 (50.7)	38.9 (16.2)	
25 to <30	40 (29.9)	31.6 (15.9)	
≥30	26 (19.4)	32.3 (10.7)	

25(OH)D, 25-hydroxyvitamin D; HMO, health maintenance organization.

[a]Percentages may not add up to 100% due to missing data: maternal race/ethnicity (*n* = 5), maternal age (*n* = 3), insurance (*n* = 3), and marital status (*n* = 10).
[b]Maternal BMI data available for just 28% of the infants.

Table 2. Categories of umbilical cord plasma 25(OH)D status by maternal and infant characteristics (*n* = 471)

	25(OH)D category			
	<20 ng/ml	20 to <30 ng/ml	≥30 ng/ml	
	n (row %)[a]	*n* (row %)	*n* (row %)	
All subjects	68 (14.4)	121 (25.7)	282 (59.9)	
Characteristics				Mantel-Haenszel χ^2 *P*
Season of birth				0.03
Spring	12 (14.1)	35 (41.2)	38 (44.7)	
Summer	11 (7.2)	32 (21.1)	109 (71.7)	
Fall	17 (13.1)	22 (16.9)	91 (70.0)	
Winter	28 (26.9)	32 (30.8)	44 (42.3)	
Race/ethnicity				<0.0001
White	17 (6.3)	60 (22.3)	192 (71.4)	
Black	24 (39.3)	19 (31.2)	18 (29.5)	
Hispanic	10 (13.3)	21 (28.0)	44 (58.7)	
Asian	13 (24.1)	17 (31.5)	24 (44.4)	
Other	2 (28.6)	3 (42.9)	2 (28.6)	
Maternal age (y)				<0.0001
<20	5 (38.5)	6 (46.2)	2 (15.4)	
20 to <30	25 (21.7)	35 (30.4)	55 (47.8)	
30 to <40	32 (10.7)	69 (23.1)	198 (66.2)	
≥40	5 (12.2)	10 (24.4)	26 (63.4)	
Marital status				0.002
Married	39 (11.4)	86 (25.1)	218 (63.6)	
Single	29 (24.6)	31 (26.3)	58 (49.2)	
Insurance status				0.001
Private	1 (7.7)	2 (15.4)	10 (76.9)	
HMO	45 (13.2)	78 (22.9)	218 (63.9)	
Medicaid	22 (19.8)	38 (34.2)	51 (46.0)	
Self-pay	0 (0)	2 (66.7)	1 (33.3)	
Period of birth				0.06
2004–2005	11 (18.6)	20 (33.9)	28 (47.5)	
2010–2012	57 (13.8)	101 (24.5)	254 (61.7)	
Gestational number				0.1
Singleton	55 (16.8)	81 (24.7)	192 (58.1)	
Multiple	13 (9.1)	40 (28.0)	90 (62.9)	
Infant sex				0.5
Female	33 (15.0)	59 (26.8)	128 (58.2)	
Male	35 (13.9)	62 (24.7)	154 (61.4)	
Gestational age (wk)				0.1
<32	18 (25.4)	19 (26.8)	34 (47.9)	
32 to 36 6/7	8 (7.4)	30 (27.8)	70 (64.8)	
≥37	42 (14.4)	72 (24.7)	178 (61.0)	
Maternal BMI[b] (kg/m^2)				0.4
<25	9 (13.2)	11 (16.2)	48 (70.6)	
25 to <30	7 (17.5)	12 (9.0)	21 (52.5)	
≥30	4 (15.4)	5 (19.2)	17 (65.4)	

25(OH)D, 25-hydroxyvitamin D; HMO, health maintenance organization.

[a]Percentages may not add up to 100% due to missing data: maternal race/ethnicity (*n* = 5), maternal age (*n* = 3), insurance (*n* = 3), and marital status (*n* = 10).
[b]Maternal BMI data available for just 28% of the infants.

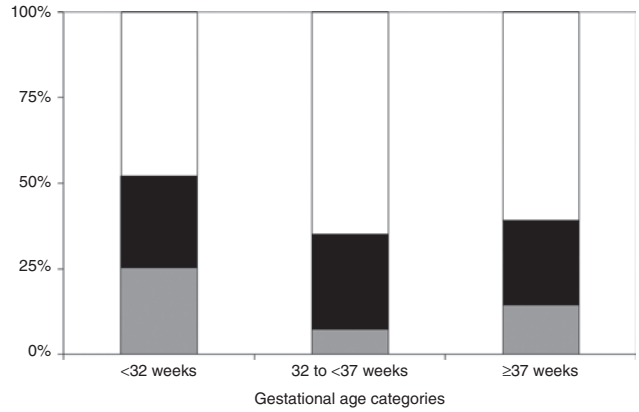

Figure 3. Umbilical cord plasma 25-hydroxyvitamin D (25(OH)D) categories by gestational age group, $n = 471$. White bars, ≥30 ng/ml; black bars, 20 to <30 ng/ml; and gray bars, <20 ng/ml.

Table 3. Pregnancy complications and umbilical cord plasma 25(OH)D levels among preterm infants

		Cord plasma 25(OH)D (ng/ml)	*t*-test *P* value
Pregnancy complication	*n*	Mean (SD)	
Premature rupture of membranes			0.6
Yes	42	33.5 (11.6)	
No	136	35 (16.5)	
Preeclampsia			0.2
Yes	40	32.1 (14.4)	
No	137	35.4 (15.8)	
Preterm labor			0.2
Yes	78	35.9(16.6)	
No	90	32.8(13.7)	
Chorioamnionitis			0.08
Yes	11	26.6(9.3)	
No	166	35.2(15.7)	
Maternal fever			0.2
Yes	7	27.1(10.2)	
No	170	35 (15.8)	
Gestational diabetes			0.2
Yes	15	30.5 (14.4)	
No	145	35.1 (15)	
Small for gestational age (<10th percentile)			0.98
Yes	37	34.7 (11)	
No (10th to 90th percentile)	141	34.7 (16.4)	

25(OH)D, 25-hydroxyvitamin D.

Additionally, even infants born to mothers with marginally sufficient 25(OH)D levels still have a risk for 25(OH)D deficiency, whereas those born to mothers with insufficient 25(OH)D levels are almost certainly deficient themselves (15).

Two recent interventional studies on vitamin D supplementation during pregnancy support a causal relationship between suboptimal vitamin D status and preterm birth (24,25). Hollis *et al.* (24) reported a trend for decreased duration of gestation in the group of pregnant women receiving lower dose of vitamin D supplementation as compared with the group receiving higher doses of vitamin D supplementation. The study population differed from our study population in that it did not include multiple gestations or pregnant women with preexisting hypertension or diabetes. Furthermore, there were no infants born at <36.4 wks' gestation. A subsequent study by Wagner *et al.* (25) showed a statistically significant negative association between preterm labor, infection, and preterm delivery with vitamin D status; however, this finding needs to be confirmed in adequately powered studies. When we analyzed cord 25(OH)D levels in our preterm infants by indication for preterm birth, we found no statistically significant differences between those with maternal risk factors and those without.

Currently, there is limited information on the distribution of 25(OH)D levels in preterm infants. A few studies have documented 25(OH)D levels from infants at birth with sample sizes ranging from 8 to 34 infants (26–30) with mean 25(OH)D levels ranging from 16.3 nmol/ml (~6.5 ng/ml) among preterm infants born to women in the United Arab Emirates (30) to 29.2 nmol/l (~10 ng/ml) in Finland (27). A recent study of 21 full-term infants born to HIV-infected women in Malawi reported mean 25(OH)D levels of 13.8 ng/ml at birth (31). Our study is the first to describe 25(OH)D levels across the gestational age spectrum and to demonstrate that, in the absence of a clear linear association between 25(OH)D levels and gestational age, among the most immature infants, there remains an increased risk of 25(OH)D levels below 20 ng/ml, a level often cited as deficient by vitamin D experts (32). Our study has a number of strengths, including a large sample of infants spanning the entire gestational age spectrum and racial/ethnic diversity (only 52% of infants were born to white mothers). However, in our cohort, adjustment for potential confounders such as BMI and race did not affect our effect estimates. We believe that this is likely due to the particular characteristics of our cohort, in which BMI and race were not associated with preterm birth. Brigham and Women's Hospital serves both urban minority pregnant women seeking routine obstetric care and high-risk suburban (majority white) obstetrical patients. Such referral patterns lead to a higher proportion of white preterm infants than what is seen on a population level. Fifteen percent of white infants and 18% of black infants in our cohort were born before 32 wks' gestation, and this difference was not statistically significantly different ($P = 0.4$). In the United States, very preterm delivery (<32 wk) is more than twice as common among black infants (3.9%) compared with white infants (1.6%) (33).

A limitation of our study was the inability to control for maternal BMI/obesity, a known risk factor for low 25(OH)D levels (32,34,35). On the other hand, we performed secondary analyses on a subset of infants ($n = 134$) for whom maternal

BMI data were available from the medical record, and adjusting for BMI did not influence effect estimates. Furthermore, there exists, among current researchers, some uncertainty regarding the optimal method of measuring 25(OH)D levels (36,37). We measured 25(OH)D using chemiluminescence (38). The laboratory used US National Institute of Standards and Technology level 1 for quality control. Finally, as in all observational studies, it is possible that our results might be affected by other unmeasured confounding variables.

In conclusion, we found that infants born before 32 wks' gestation have an increased risk of low 25(OH)D levels (below 20 ng/ml) as compared with more mature infants. Whether such low levels contribute to the morbidities that these infants suffer in the neonatal period and beyond warrants further study but may be difficult to detect given the multifactorial etiologies of the sequelae of preterm birth. Interventional trials of vitamin D supplementation among pregnant women at risk of delivering preterm should include infant and childhood follow-up to document benefit to the offspring, if any, of vitamin D supplementation during pregnancy.

METHODS

Vitamin D Analysis

The Institutional Review Board at Brigham and Women's Hospital approved the study, which involved discarded samples and chart review and thus did not require informed consent. We collected umbilical cord blood at the time of delivery from a convenience sample of 471 infants born at Brigham and Women's Hospital, a high-risk tertiary care center in Boston, MA, during the two time periods (2004–2005: 59 samples and 2010–2012: 412 samples). We included the earlier, stored samples from a previous study of preterm infants from the same institution because it was enriched in extremely preterm infants (39). We refrigerated and centrifuged the blood samples and stored plasma aliquots at −80°C. We measured the levels of 25(OH)D, a combination of 25(OH)D_2 and 25(OH)D_3, which represent the best analytes for overall vitamin D status (40), using DiaSorin Liaison (DiaSorin Liaison reagent Integral; DiaSorin, Stillwater, MN) that uses a chemiluminescence immunoassay (38), to determine plasma concentrations of 25(OH)D. For quality control, the laboratory used US National Institute of Standards and Technology level 1. Interassay coefficient of variation was 9.6%. We report 25(OH)D levels in ng/ml, which can be multiplied by 2.496 to convert to nmol/l.

Clinical and Demographic Data Ascertainment

We calculated gestational age in weeks at the time of birth based on the best obstetrical estimate using the date of last menstrual period with confirming first-trimester ultrasounds. Through medical record reviews, we collected information on potential confounders including maternal race/ethnicity, age, BMI, marital and insurance statuses, and pregnancy complications, including premature rupture of membranes, maternal preeclampsia, preterm labor, chorioamnionitis, maternal fever, and gestational diabetes. We also collected information on season of birth, infant sex and birth weight, and singleton vs. multiple gestations.

Statistical Analyses

We first performed bivariate analyses to determine maternal and infant characteristics associated with previously described adult clinical categories of vitamin D status (11,41–43): deficiency (25(OH)D level: <20 ng/ml), insufficiency (25(OH)D levels: 20 to <30 ng/ml), and sufficiency (25(OH)D level: ≥ 30 ng/ml) as thresholds for analyses. We performed *t*-tests to determine whether 25(OH)D levels differed by indication for preterm delivery and small-for-gestational-age status. We adjusted for potential confounders (including season of delivery, race/ethnicity, maternal age, insurance and marital statuses, infant sex, and singleton vs. multiple gestation) in multivariable logistic regression models. Maternal prepregnancy BMI data were available for a subset of 134 infants in whom we performed secondary analyses to evaluate the potential impact of BMI on our results. Similarly, we compared results including and then excluding the 59 samples from the earlier time period (2004–2005) to ensure that storage did not affect our findings. We also analyzed these two time periods as potential confounders to ensure that clinical practices that might differ between the two time periods did not explain our findings. To account for clustering by mother among multiples, we used generalized estimating equations (PROC GENMOD). We performed all analyses using SAS 9.2 (SAS Institute, Cary, NC).

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