Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort[1–4]

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ABSTRACT

Background: The intake of periconceptional multivitamins may decrease the risk of preterm births (PTBs) or small-for-gestational-age (SGA) births.

Objective: We related the timing and frequency of periconceptional multivitamin use to SGA births and PTBs and its clinical presentations (ie, preterm labor, premature rupture of membranes, and medical induction).

Design: Women in the Danish National Birth Cohort (n = 35,897) reported the number of weeks of multivitamin use during a 12-wk periconceptional period. Cox regression was used to estimate the relation between any multivitamin use and PTBs (<37 wk) or SGA births (birth weight adjusted for gestational age >2 SDs below the mean on the basis of fetal growth curves). The timing (preconception and postconception) and frequency of use were also analyzed. Regular users (4–6 wk) and partial users (1–3 wk) in each period were compared with nonusers.

Results: The association between periconceptional multivitamin use and PTBs varied according to prepregnancy overweight status (P-interaction = 0.07). Regular preconception and postconception multivitamin use in women with a prepregnancy BMI (in kg/m^2) <25 was associated with reduced risks of a PTB (HR: 0.84; 95% CI: 0.73, 0.95) and preterm labor (HR: 0.80; 95% CI: 0.69, 0.94). No similar associations were shown for overweight women. The adjusted risk of an SGA birth was reduced in multivitamin users regardless of their prepregnancy BMI (HR: 0.83; 95% CI: 0.73, 0.95), with the strongest association in regular users in the postconception period.

Conclusion: Regular periconceptional multivitamin use was associated with reduced risk of SGA births and PTBs in nonoverweight women. *Am J Clin Nutr* 2011;94:906–12.

INTRODUCTION

PTB[5] and fetal growth restriction are leading risk factors of neonatal morbidity and mortality. Although a PTB and growth restriction are thought to have distinct pathogeneses, risk factors overlap. Black race (1–3), maternal smoking (3–5), nulliparity (3, 6), and a lean maternal BMI (in kg/m^2) (6, 7) were reported risk factors for PTB and growth-restricted births. Women with a first pregnancy complicated by a PTB or growth restriction are more likely to have other complications in subsequent pregnancies, such as a stillbirth (8). In addition, preterm infants are more prone to impaired fetal growth than are infants born at term (9).

Nutrition is believed to play a role in the pathogenesis of adverse pregnancy outcomes including a PTB and fetal growth restriction as measured by SGA (10–15). We showed reduced risk of these outcomes in a cohort of 1823 women who reported periconceptional multivitamin use, which was a finding that was limited to women with a BMI <30 (16). We aimed to reexamine these associations in the Danish National Birth Cohort, which is a large, well-characterized cohort of pregnant women recruited early in gestation who reported multivitamin use during each week immediately before and after conception. We also considered that the timing and frequency of weekly supplement intake may be important in these associations, and to our knowledge, these factors have not been previously examined.

The objective of this study was to relate the timing and frequency of periconceptional multivitamin use to risk of a PTB or delivery of SGA infants. We hypothesized that the relation of multivitamin supplementation with these pregnancy outcomes would be strongest for women with regular use throughout the periconceptional period because this would provide the most comprehensive supplementation. We considered that the timing of use (preconception and/or postconception) may also be important in these associations because of our earlier finding that multivitamin use immediately after conception appeared to be the relevant exposure associated with preeclampsia risk (17). Informed by our previous reports, we

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[5] Abbreviations used: LMP, last menstrual period; PTB, preterm birth; SGA, small-for-gestational-age.

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evaluated if these associations varied by pregravid overweight status. We also considered that any relation may have been more pronounced for infants delivered both preterm and SGA because these cases may have involved a placental pathogenesis.

SUBJECTS AND METHODS

The Danish National Birth Cohort is a nationwide longitudinal study of pregnant women and their children approved by the Danish National Ethics Board (18). Thirty percent of all pregnant women in Denmark were recruited between 1997 and 2003, and effects of differential participation on risk estimates for PTB or SGA births have been shown to be small (19).One-half of the women in the Danish National Birth Cohort (n = 48,102) completed a revised version of the recruitment form used in the second wave of enrollment that allowed women to report in a tabular format each week of multivitamin use from 4 wk before the LMP through 14 wk after the LMP. For the purposes of this study, the periconceptional period was defined as 4 wk before the LMP through 8 wk after the LMP, and this period was further categorized as preconception and postconception (**Figure 1**). Women with a questionable recruitment date or who joined the cohort <5 wk gestation (n = 944; 2%) were excluded because they had incomplete information for the periconceptional period evaluated. Women who reported only single-supplement use (other than folate) were also excluded (n = 3698), as were women who did not report weeks of use, had multifetal gestations, or had missing covariate information (n = 7563). The final study population was 35,897 pregnancies.

The Danish National Birth Cohort recruitment form was completed at a mean (±SD) gestational age of 11.1 ± 3.9 wk (range: 5–24 wk). Very few women stopped multivitamin use once initiated (n = 490; 1.4%); thus, for the 4547 women who were recruited during gestation weeks 5 through 7, we imputed the supplement use for the remainder of the periconceptional period on the basis of the use reported during the week of enrollment. Multivitamin supplementation was evaluated as any use in each of the 12 wk that comprised the periconceptional period, and the contents of the most commonly used multivitamin are provided in **Table 1**. The frequency of use was categorized as partial use (1–3 wk of use out of 6 possible weeks) or regular use (4–6 wk out of 6 possible weeks) for the preconception and postconception periods. Patterns of multivitamin use for each woman were categorized by combining their preconception and postconception use (ie, regular and regular; partial and regular; no use and regular; and no use or partial and no use or partial). Folate-only supplement use was analyzed in the same way as multivitamin use and was evaluated to determine whether the effect appeared to be different in this group than in multivitamin users.

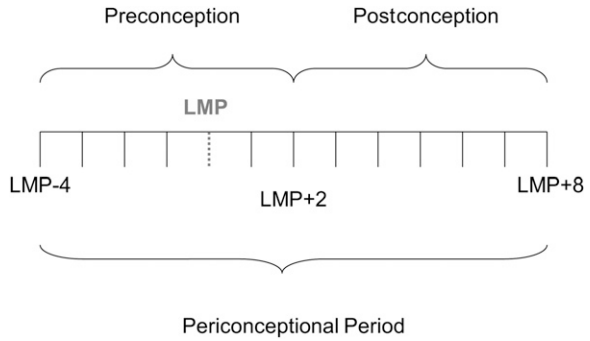

FIGURE 1. Periconceptional exposure period. LMP, last menstrual period; LMP-4, 4 wk before the LMP; LMP+2, 2 wk after the LMP; LMP+8, 8 wk after the LMP.

TABLE 1
Contents of the most commonly used multivitamin supplement in the Danish National Birth Cohort, 1997–2003

Nutrient	Content
Vitamin A (μg)	800
Thiamin (mg)	1.4
Riboflavin (mg)	1.6
Vitamin B-6 (mg)	2
Vitamin B-12 (μg)	1
Folic acid (μg)	200
Niacin (mg)	18
Pantothenic acid (mg)	6
Vitamin C (mg)	60
Vitamin D (μg)	5
Vitamin E (mg)	10
Iron (mg)	14
Zinc (mg)	15
Copper (mg)	2
Iodine (μg)	150
Manganese (mg)	2.5
Chromium (μg)	50
Selenium (μg)	50
Molybdenum (μg)	150

Gestational age was based on the best clinical estimate at birth, which was checked and adjusted according to early ultrasound in >90% of cases (20). When missing, the estimate of gestational age was based on a woman's LMP that was reported at recruitment. A PTB was defined as a delivery before day 259 (<37 wk), and PTBs after a medical indication (n = 68), spontaneous preterm labor (n = 763), or premature preterm membrane rupture (n = 205) were categorized. SGA was defined according to the criteria of Marsal et al (21) as a birth weight >2 SD below the mean for a given gestational age on the basis of fetal weights derived from serial ultrasounds in a Scandinavian population. This categorization was further divided into term SGA (≥37 wk) and preterm SGA (<37 wk).

Covariates included the maternal age at delivery, self-reported smoking status at the first interview, self-reported height and prepregnancy weight, which were used to calculate BMI, parity, alcohol use, physical activity, and socioeconomical status, which was based on a woman's job classification or education. A high status was assigned to women in management or jobs that required >4 y of education beyond high school. Office, service, or skilled manual workers and women in the military were classified in the middle category; unskilled workers or unemployed women were classified in the low category. Women were categorized with hypertension if they reported, at the first interview, that they were diagnosed before pregnancy and also reported the use of an antihypertensive medication or indicated that the hypertension persisted (22). Women with preeclampsia were identified via *International Classification of Diseases, 10th revision*, codes O14 to O15, which is an approach that has been validated (23). Dietary data were collected via a food-frequency questionnaire in midpregnancy from a subset of women (n = 22,938; 64%). Diet was characterized as Western (high-fat dairy and red meat), health conscious (highest intake of fruit and vegetables, poultry,

and fish), and intermediate as previously reported (24). For example, women in the health-conscious group consumed, on average, 228 g fruit/d compared with 97 g fruit/d in the Western group. Self-reported information about smoking status and number of cigarettes smoked, alcohol consumption, and physical exercise came from the first interview.

We compared maternal characteristics of women with periconceptional multivitamin use, folate-only use, and no use of supplements. Risk of a PTB or SGA birth associated with multivitamin use was estimated as HRs with 95% CIs by using Cox regression with gestational days as the underlying time variable. Follow-up started at gestational day 155 and ended at the date of birth, date of fetal death, or date of emigration. Nonusers were the referent for all models. Absolute risk associated with the timing and frequency of use during the 12-wk periconceptional period was described. Women with more than one birth (n = 324) were included, and models used a robust sandwich covariance matrix estimate to account for the possible intracluster dependence (25). Because off the evidence that the effect of vitamin supplementation during pregnancy differs by BMI (10, 16, 26, 27), we modeled the relation between multivitamin use (any) and overweight status (pregravid BMI $\geq$25) with an interaction term, and results were stratified by overweight status when appropriate (α = 0.10). We also evaluated if the relation between multivitamin use and PTB differed for early compared with moderate preterm deliveries by testing for interaction between any multivitamin use and deliveries before or after day 238 (34 wk). In SGA models, differential effects for term compared with preterm SGA were also evaluated with an interaction term (less than day 259 compared with at least day 259).

Potential confounders were selected on the basis of evidence that related them to vitamin use and/or pregnancy outcomes. These included maternal age, smoking status, BMI, parity, and marital status. Additional covariates were included (ie, gestational age at recruitment and socioeconomic status) that may have accounted for confounding by health-promoting behaviors that were also associated with multivitamin use. Because of our earlier findings (17), we considered that preeclampsia may be on the pathway relating multivitamin use to PTBs or SGA births. Therefore, we evaluated models with and without cases of preeclampsia. SAS software (version 9.2; SAS Institute) was used for analyses, and results were considered significant with a 2-sided $P < 0.05$.

RESULTS

Overall, 21,785 women (60.7%) reported any multivitamin use in the periconceptional period (**Table 2**). Multivitamin users

TABLE 2
Maternal characteristics according to any periconceptional multivitamin or folate-only supplement use

	Nonusers (n = 11,503)	Multivitamin users (n = 21,785)	Folate-only users (n = 2609)
Maternal age (%)			
≤25 y	17.2	11.4	10.3
26–30 y	38.7	43.4	40.7
31–35 y	31.1	32.9	35.5
≥36 y	13.1	12.3	13.6
BMI (%)			
<18.5 kg/m^2	4.2	4.3	4.5
18.5–24.9 kg/m^2	63	67.6	67.1
25–29.9 kg/m^2	21.9	19.4	19.5
≥30 kg/m^2	10.9	8.7	8.9
Smoking during pregnancy (%)	21.5	13.2	11.3
Alcohol consumption (%)			
None	56.0	56.3	56.2
0.5–3 drinks/wk	41.3	41.7	42.3
>3 drinks/wk	2.7	2.0	1.5
Physical exercise (%)			
None	67.2	61.9	62.6
1–180 min/wk	25.8	30.6	29.7
>180 min/wk	7.0	7.5	7.8
Dietary pattern (%)[1]			
Western	20.0	13.4	14.7
Intermediate	66.9	65.5	63.8
Health conscious	13.1	21.2	22.1
Socioeconomic status (%)			
High	57.9	71.2	73.3
Medium	35.8	25.7	26.6
Low	6.3	3.1	3.1
Time to pregnancy >12 mo (%)	13.9	14.7	18.5
Nulliparous (%)	44.0	52.1	55.8
Preeclampsia (%)	2.3	2.2	2.5
Chronic hypertension (%)	1.8	1.8	2.2
Gestational age at recruitment (wk)[2]	11.4 ± 4.3	10.9 ± 3.8	10.7 ± 3.5

[1] Data were available for 22,938 women (63.9%)
[2] Values are means ± SDs.

compared with nonusers were more likely to be >25 y of age, have a prepregnancy BMI <25, nulliparous, and to report a midpregnancy diet that was classified as health conscious and a >12-mo waiting time to pregnancy. They were also less likely to smoke and report a lower socioeconomic status. Folate-only users (n = 2609; 7.3%) were similar to multivitamin users. There were 1754 (4.9%) PTBs and 1209 (3.4%) SGA births; 217 (0.6%) were births were both preterm and SGA. Women with regular preconception and postconception multivitamin use had modestly lower rates of a PTB than did nonusers (4.3% compared with 5.3%; P = 0.02; **Figure 2**). PTB rates in folate-only users were similar to those in nonusers. Women with regular postconception multivitamin use, regardless of the preconception use pattern, had lower rates of an SGA than did nonusers (2.4–2.8% compared with 4.3%; $P < 0.01$ for each comparison with nonusers). Rates of SGA appeared more variable in folate-only users.

Multivitamin use and risk of PTB

Any multivitamin use in the periconceptional period was associated with reduced risk of a PTB after adjustment for maternal age, parity, BMI, smoking, and socioeconomic status, which was a relation that may have differed according to pregravid BMI (P-interaction = 0.07; **Table 3**). In nonoverweight women (pregravid BMI <25), multivitamin use was associated with a 16% reduced risk of preterm delivery [HR (95% CI): 0.84 (0.73, 0.95)]. There was no association between multivitamin use and PTB risk in overweight women [HR (95% CI): 1.03 (0.85, 1.26)]. This relation did not differ in women who delivered in <34 wk gestation and women who delivered in 34–36 wk (P-interaction = 0.43). Although the precision was low when the analysis was limited to women with dietary data (n = 22,938), additional adjustment for this covariate did not affect the magnitude of the HR associated with multivitamin use in nonoverweight women [HR (95% CI): 0.85 (0.69, 1.04)].

When multivitamin use was evaluated according to timing and frequency, nonoverweight women who reported regular use in the preconception and postconception periods had reduced risk of preterm delivery [HR (95% CI): 0.82 (0.70, 0.97)]. Partial multivitamin use in the preconception and postconception periods was also associated with reduced risk in nonoverweight women [HR (95% CI): 0.77 (0.65, 0.92)]. There was no relation between any patterns of multivitamin use and risk of PTB in overweight women.

The relation of any multivitamin use on risk of PTB in nonoverweight women appeared to be limited to idiopathic cases that presented with spontaneous preterm labor [HR (95% CI): 0.80 (0.69, 0.94)]. All patterns of multivitamin use in the periconceptional period were associated with 17–27% reduced risk of spontaneous labor cases in nonoverweight women, and there were no associations with preterm labor in overweight women. Multivitamin use in nonoverweight women was not associated with premature membrane rupture or medically induced PTBs [HR (95% CI): 0.95 (0.71, 1.27) and 0.95 (0.53, 1.68), respectively].

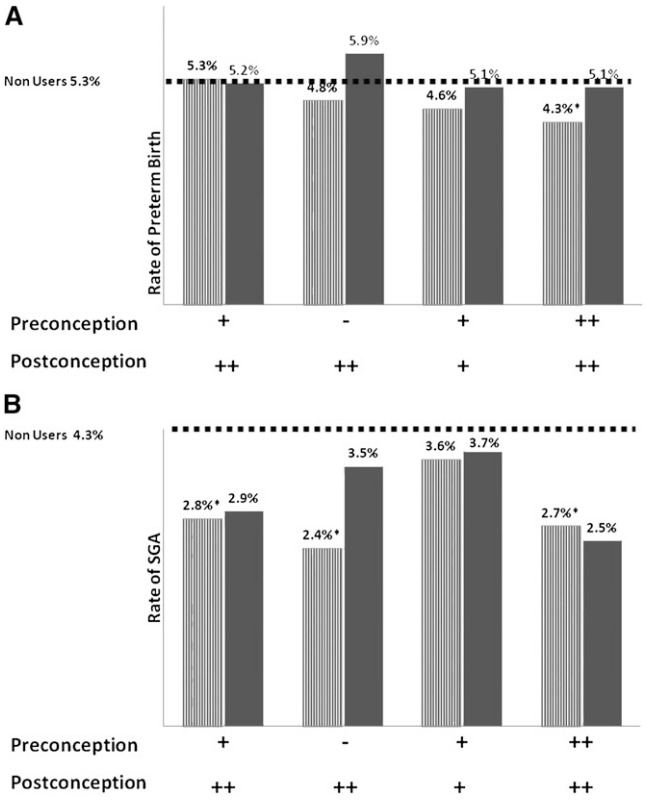

FIGURE 2. Rates of preterm (A) or small-for-gestational-age (SGA) (B) births according to patterns of periconceptional multivitamin (striped bars) and folate-only use (gray bars) compared with nonusers (dashed line). For each 6-wk preconception or postconception period: +, partial use (1–3 wk of use); ++, regular use (4–6 wk of use); -, no use. *Comparison of preterm birth rate was significantly different from that of nonusers, $P < 0.05$ (crude Cox regression results).

Multivitamin use and risk of SGA

Any periconceptional multivitamin use was associated with reduced risk of SGA after adjustment for confounders [HR (95% CI):0.83 (0.73, 0.95); **Table 4**] with no difference in nonoverweight and overweight women (P-interaction = 0.49). In addition, the postconception exposure period appeared to be most strongly related to SGA risk. Although all patterns of periconceptional multivitamin use appeared to be associated with 10–20% reduced risk of SGA, regular postconception only use was associated with a 33% reduction in risk [HR (95% CI): 0.67 (0.54, 0.86)]. Term and preterm SGA risks were similarly related to periconceptional multivitamin use [HR (95% CI): 0.86 (0.74, 0.99) and 0.82 (0.61, 1.14), respectively]. Results were unaffected when cases of preeclampsia were removed and when models were additionally adjusted for dietary patterns.

Folate use and risk of PTBs or SGA births

Analysis was repeated in women who reported folate-only use in the periconceptional period (n = 2609). Compared with women with no reported supplement use, there was no association between folate-only use and PTBs or SGA births [adjusted HR (95% CI): 1.00 (0.91, 1.11) and 0.96 (0.84, 1.08), respectively]. Also, there were no associations between any patterns of preconception and postconception folate-only use and PTBs. There was some indication that regular folate-only users had reduced risk of SGA [HR (95% CI): 0.79 (0.53, 1.19)], but

TABLE 3
HRs for preterm birth (PTB) according to timing and frequency of periconceptional multivitamin use[1]

			All Women		Adjusted HR (95% CI)[2]	
	n	PTB	Crude HR	Adjusted HR (95% CI)[2]	BMI <25 kg/m^2	BMI ≥25 kg/m^2
		n (%)				
Nonuser	11,503	604 (5.2)	1.00			
Multivitamin user (any)	21,785	1013 (4.5)	0.88	0.89 (0.80, 0.99)	0.84 (0.73, 0.95)	1.03 (0.84, 1.26)
Preconception, postconception						
−, −	11,503	604 (5.2)	1.00			
++, ++	8569	376 (4.3)	0.83	0.89 (0.77, 1.02)	0.82 (0.70, 0.97)	1.05 (0.81, 1.35)
+, ++	2281	124 (5.3)	1.01	1.01 (0.82, 1.24)	0.93 (0.73, 1.20)	1.21 (0.83, 1.76)
−, ++	4297	211 (4.8)	0.93	0.92 (0.77, 1.08)	0.90 (0.74, 1.10)	0.93 (0.67, 1.28)
− or +, − or +	6638	302 (4.5)	0.87	0.84 (0.72, 0.97)	0.77 (0.65, 0.92)	1.01 (0.77, 1.32)

[1] −, no use; +, 1–3 wk during the 6-wk interval; ++, 4–6 wk during the 6-wk interval.
[2] Cox regression models were adjusted for age, parity, BMI, sociooccupational status, and smoking. $P = 0.07$ for the interaction between multivitamin use and overweight status (BMI, in kg/m^2: ≥25).

numbers were too small to evaluate other patterns of use associated with SGA births.

DISCUSSION

Any periconceptional multivitamin use was associated with reduced risk of PTBs in nonoverweight women and SGA births regardless of pregravid BMI. When examined according to timing and frequency, regular multivitamin use in the preconception and postconception periods was associated with reduced risk of PTBs in nonoverweight women. In contrast, the use in the postconception period appeared to be more robustly related to risk of SGA independent of prepregnancy BMI.

These findings should be interpreted with caution because multivitamin use, as demonstrated in our results, correlated strongly with other lifestyle factors. Although we accounted for many of these factors, we could not rule out the possibility of unmeasured confounding. Randomized trials of vitamin supplementation to reduce risk of chronic disease or adverse pregnancy outcomes on the basis of promising observational data have often given disappointing results (28–31). Because of current recommendations, it is unlikely that a randomized trial of periconceptional multivitamins is feasible. Therefore, methodologically rigorous prospective observational studies may be the only way to investigate if multivitamin supplementation around the time of conception may reduce risk of PTBs or SGA births.

Our results were largely consistent with the few studies of periconceptional multivitamin use and risk of PTBs or growth-restricted births (32–34). These previous studies were carried out in much smaller cohorts derived from more disadvantaged and, therefore, less well-nourished populations, and this may explain why our results were more modest than those previously reported. Our findings indicated that periconceptional multivitamin use may be more robustly related to SGA risk than to PTB risk. There was no differential relation of multivitamin use in early compared with late PTBs or in PTBs that were also growth restricted. This result was in contrast to our earlier finding of a reduced risk only for PTBs delivered <34 wk in periconceptional multivitamin users (16). This may have been due to different underlying risks in different source populations. Studies of mechanisms by which multivitamin use may reduce PTB risk are needed to elucidate these differences.

Similar to our earlier findings related to preeeclampsia (17), risk of SGA was more strongly related to multivitamin supplementation in the immediate postconception period. Therefore, supplementation after conception may be of particular importance. An analysis of folate-only users suggested that SGA, but not PTB, may also be reduced in women with regular folate use. The dominant brand of multivitamin supplements reported in the Danish National Birth Cohort contained 200 μg folic acid. Thus, folate may be involved in the multivitamin-SGA association, but other micronutrients may be important in the association between periconceptional multivitamin use and PTB. Prenatal concentrations of zinc and vitamins C and E have been related to PTB risk (13,14, 35–37), but studies of micronutrient use during the periconceptional period are sparse. One case-control study related the preconception sufficiency of vitamins B-6 and B-12 in maternal serum to 50–60% reduced risk of a PTB (32). Although mechanisms that may link periconceptional multivitamin use to a PTB or SGA are not understood, impaired placentation is one possibility. Placentation is characterized by vascular remodeling, oxidative stress, inflammation, and rapid cell division, all of which may be affected by nutritional status. Nearly all nutrients in typical prenatal/multivitamins may be hypothesized

TABLE 4
HRs for small-for-gestational-age (SGA) according to timing and intensity of periconceptional multivitamin use[1]

	SGA	Crude HR	Adjusted HR (95% CI)[2]
	n (%)		—
Nonuser	489 (4.2)	1.00	—
Multivitamin user (any)	640 (2.9)	0.76	0.83 (0.73, 0.95)
Preconception, postconception			
−, −	489 (4.3)	1.00	—
++, ++	233 (2.7)	0.73	0.89 (0.75, 1.05)
+, ++	63 (2.8)	0.72	0.81 (0.62, 1.07)
−, ++	105 (2.4)	0.67	0.68 (0.54, 0.85)
− or +, − or +	239 (3.6)	0.86	0.87 (0.74, 1.03)

[1] −, no use; +, 1–3 wk during the 6-wk interval; ++, 4–6 wk during the 6-wk interval.
[2] Cox regression models were adjusted for age, parity, BMI, sociooccupational status, and smoking.

to aid in the process of normal placentation, and folate and vitamin B-12 have been linked to defects in the placental vascular bed (38). Abnormal placentation with failed remodeling of maternal vessels that perfuse the placenta has been associated with spontaneous PTB (38–45) and growth restriction without preeclampsia (42, 45). Our group previously reported that regular multivitamin use in the periconceptional period may reduce risk of preeclampsia, which is a pregnancy complication with a well-established relation with poor placentation (17, 27).

Overweight status modified the relation of periconceptional multivitamin use and PTB risk, similar to other reports of supplement use related to risk of preeclampsia, SGA, and malformations (10, 16, 26, 27). We can only speculate on the mechanisms underlying the varying effects of multivitamin use by BMI. Overweight women may have higher nutrient requirements than do lean women. Perhaps the metabolic dysregulation in obese women blunts any positive effects of modest micronutrient supplementation. It is also possible that these metabolic or physiologic factors might directly or indirectly alter the absorption, transport, or storage of nutrients in overweight women. Our finding of a possible effect-measure modification by overweight status did not appear to be related to smoking because rates of smoking during pregnancy were only modestly higher in overweight than in nonoverweight women in our data (31.3% and 29.4%, respectively). In contrast, there was no interaction between multivitamin use and pregravid BMI in SGA risk in our data. Thus, even in overweight women, regular postconception multivitamin use was associated with reduced SGA risk. Taken together, these results were consistent with the possibility that different mechanisms at different time points and perhaps different micronutrients were involved in the relation between periconceptional multivitamin use and PTBs or SGA births.

Our results should be considered in light of important limitations. Although the Danish National Birth Cohort is a large, well-characterized population cohort, it consists predominantly of white women. Therefore, our results may not be generalizable to other ethnicities. However, the homogeneity of the Danish population helped to reduce the residual confounding. Although we attempted to account for unmeasured confounding by accounting for diet patterns in the subgroup of women who completed the food-frequency questionnaire, we could not rule out the possibility that women who took a multivitamin supplement may also have eaten a diet or had other lifestyles that were more related to PTB or SGA risks. However, multivitamin users in our study were very similar to women who reported folate-only use, and in this group of women, we detected reduced risk of SGA but not PTB, which may have indicated that our findings were not entirely due to residual confounding. Regrettably, a more detailed analysis of the specific micronutrients consumed in food was not feasible in our current study because diet data were collected after 25 wk of gestation, which was well beyond the periconceptional period. Strengths of our study were the large, well-characterized population, data on multivitamins collected early in pregnancy in a systematic fashion to minimize the recall bias, and fetal growth measures that were based on ultrasound-derived standards.

In conclusion, regular multivitamin use around the time of conception was associated with reductions in risk of PTBs in nonoverweight women and of SGA independent of BMI. No patterns of use appeared to be related to increased risks of these outcomes. It may be that multivitamin use around the time of conception could be a safe and simple strategy to improve pregnancy outcomes, similar to folate supplementation. However, before such advice is given, studies are needed to evaluate possible risks of early and late fetal deaths associated with periconceptional multivitamin use as well as other outcomes in the life course of the child.

We thank the pregnant women in Denmark who were recruited between 1997 and 2003 and participated in the Danish National Birth Cohort.

The authors' responsibilities were as follows—JMC: designed research, analyzed data, wrote the manuscript, and had primary responsibility for the final content of the manuscript; LMB: participated in data analysis and in developing and finalizing the manuscript; JO and EAN: participated in the design and conduct of the research, interpretation of data, and in drafting and finalizing the content of the manuscript; SO: participated in the design and conduct of the research; and all authors: read and approved the final version of the manuscript. None of the authors had a conflict of interest.

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