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Original Contribution

Self-reported Vitamin Supplementation in Early Pregnancy and Risk of Miscarriage

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Miscarriage is a common and poorly understood adverse pregnancy outcome. In this study, the authors sought to evaluate the relation between self-reported use of prenatal vitamins in early pregnancy and the risk of miscarriage. Between 2000 and 2008, 4,752 US women were prospectively enrolled in Right From the Start. Information about vitamin use was obtained from a first-trimester interview. Discrete-time hazard models were used, candidate confounders were assessed, and the following variables were included in the model: study site, maternal age, gravidity, marital status, education, race/ethnicity, smoking, and use of progesterone in early pregnancy. Approximately 95% of participants reported use of vitamins during early pregnancy. A total of 524 women had a miscarriage. In the final adjusted model, any use of vitamins during pregnancy was associated with decreased odds of miscarriage (odds ratio = 0.43, 95% confidence interval: 0.30, 0.60) in comparison with no exposure. These results should be viewed in the context of a potentially preventive biologic mechanism mitigated by possible confounding by healthy behaviors and practices that are also associated with vitamin supplement use during pregnancy.

abortion, spontaneous; pregnancy trimester, first; vitamins

Knowledge about the biology and factors influencing the early pregnancy period is sparse. The consequences of common early-pregnancy exposures remain unclear because of the challenges associated with prospective enrollment of a large, nonclinical cohort of women early in pregnancy.

Vitamin supplementation is recommended for pregnant women and women planning to become pregnant (1, 2). The documented benefits of supplementation relate mainly to the lowered risk of certain birth defects, such as neural tube defects (3). Because vitamin supplementation is widespread among women intending to become pregnant (4, 5), studying the relation between this common exposure and early pregnancy outcomes is of great value, particularly since the causes of miscarriage are unknown and this exposure is known to affect specific developmental processes.

Prior studies have been conducted to relate vitamin exposure to perinatal outcomes. Specific mechanisms that underlie these relations have not been clarified. Exposure during pregnancy has been associated with a 34%–71% reduction in risk of preterm birth (6–8). Similar reductions in risk estimates have been reported for other pregnancy outcomes, including low birth weight, small-for-gestational-age birth, and preeclampsia (6–10). A challenge for all of these studies, however, is isolating the effect of the vitamins from the effect of other health-seeking behaviors of a woman using vitamins during pregnancy.

Investigators in several studies have examined the relation between vitamin exposure and miscarriage, reporting both decreased and elevated risks (11–14). Research focusing on the early pregnancy period is of interest, because maternal nutritional deficiencies during critical time windows in fetal development may have detrimental consequences for fetal well-being, including structural malformations. Studies focusing on early pregnancy outcomes have mostly examined the effect of only 1 specific supplement component (primarily folic acid) rather than the effect of exposure to the range of micronutrients found in prenatal and multivitamin formulations.

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In light of this limited evidence, we sought to explore this relation within Right From the Start, a large prospective pregnancy cohort study. Our objective was to evaluate the association between self-reported vitamin use and the risk of miscarriage.

MATERIALS AND METHODS

Study population

Right From the Start is a community-based pregnancy cohort study that has enrolled women in the United States since 2000. Women were enrolled prior to 12 completed weeks of pregnancy in several metropolitan areas: Galveston, Texas; Memphis, Tennessee; and the Greater Triangle region of North Carolina (including Raleigh, Durham, and Chapel Hill). Women who had their last menstrual period before February 20, 2008, were included in this analysis. The institutional review boards of all host institutions approved the study, and informed signed consent was obtained from each participant. Participants were at least 18 years old, spoke English or Spanish, had not used assisted reproductive technologies to conceive, and intended to carry the pregnancy to term at enrollment.

Women who were not yet pregnant could pre-enroll in the study prior to pregnancy and were followed until formal enrollment at the time of a positive pregnancy test. To avoid the overenrollment of subfertile women, nonpregnant participants in the study must have been attempting pregnancy for fewer than 6 months and were eligible for up to 12 months of pre-enrollment. Formal enrollment occurred, on average, at 54 days of gestation for women who enrolled while pregnant and at 38 days of gestation for women who pre-enrolled.

Participants had an early-pregnancy ultrasonogram for assessment of fetal viability and confirmation of dating in ongoing gestations. Gestational age was assigned using an algorithm that gave precedence to the self-reported date of the last menstrual period. The mean and median differences between the ultrasound gestational age and the last menstrual period-based gestational age were less than 1 day, giving us confidence in the use of last menstrual period dating for pregnancy losses. Ultrasonograms were completed by 93.4% of participants. Forty percent of ultrasonograms were completed by the seventh week of pregnancy, and 75% were completed by gestational week 9.

A comprehensive interview was targeted towards the end of the first trimester (no later than the 16th week of pregnancy). In the interview, information regarding a variety of covariates was obtained from the participant, including her personal medical history, reproductive history, and health behaviors during pregnancy. All women, regardless of whether they were still pregnant or had experienced a miscarriage, completed the detailed interview.

Vitamin exposure assessment

Vitamin use was assessed in the first-trimester interview. Questions were asked separately for prenatal vitamins and multivitamins (see Appendix); for the purpose of this analysis, both categories of supplements were combined because of potential misclassification by participants. In this report, both types of supplements will be referred to simply as ''vitamins.'' Participants were asked whether they were currently taking vitamins or, in the case of a miscarriage, whether they had taken vitamins during pregnancy. Information about the frequency and timing of vitamin use in an average week was also obtained. Participants who reported any use of vitamins during pregnancy were considered exposed.

Outcome

Pregnancy was verified by ultrasonography or repeat pregnancy tests. Miscarriage was defined as loss of a recognized pregnancy prior to 20 completed weeks of gestation. Outcomes were self-reported by participants and verified by medical records. Participants with ectopic/molar pregnancies were excluded from this analysis.

Data analysis

We used discrete-time hazard models to evaluate the relation between vitamin exposure and miscarriage and calculated week-specific odds ratios for the probability of having a miscarriage in a given week, conditional on a woman's still being pregnant at the beginning of that week and having formally enrolled by the beginning of that week. Participants were followed from the time of enrollment in the study and contributed to analysis risk sets until an outcome or loss to follow-up occurred.

We followed a backwards elimination strategy to identify important confounders in the vitamin-miscarriage relation. A change in estimate of at least 10% was used to classify a variable as a confounder. Candidate confounders included study site, maternal age, progesterone use in early pregnancy, gravidity, smoking, race/ethnicity, education, and marital status. To optimize fit, maternal age was specified by the inclusion of linear and quadratic terms in the model. Additionally, categorical time interactions (comparing the effects of vitamin use occurring at >10 weeks' gestation and ≤ 10 weeks' gestation) and interactions with consistency of vitamin use (defined as exposure at least 5 times per week) were assessed using likelihood ratio tests. As an additional step, to evaluate the potential effects of recall error, we stratified the analysis by whether the miscarriage occurred prior to or after the time of interview. We also assessed the relation between vitamin use and early miscarriage (≤ 10 weeks) and late miscarriage (>10 weeks).

Of the 4,752 women who comprised the original data set, 5 women with ectopic pregnancies were removed. Subsequent pregnancies of women who enrolled in the study more than once were excluded ($n = 228$). Twenty participants were excluded for having missing or inconsistent essential data, and 151 participants who did not complete the first-trimester interview were excluded. A total of 4,348 participants contributed to this analysis, and 524 miscarriages were observed during the study period. All other participants were censored at 20 completed weeks of pregnancy

Table 1. Characteristics of Participants, Right From the Start, United States, 2000–2008

	Outcome After 20 Weeks' Gestation (n = 3,659)		Pregnancy Loss (n = 524)		Odds Ratio	95% Confidence Interval
	No.	%	No.	%		
Vitamin exposure						
Unexposed	153	4.2	44	8.4	1.0	
Exposed	3,498	95.6	475	90.7	0.47	0.33, 0.69
Missing data	8	0.2	5	1.0		
Maternal age, years						
<35	3,167	86.6	382	72.9	1.0	
≥35	492	13.5	142	27.1	2.39	1.92, 2.98
Missing data	0	0	0	0		
Race/ethnicity						
White, non-Hispanic	2,458	67.2	347	66.2	1.0	
Black, non-Hispanic	767	21.0	124	23.7	1.15	0.91, 1.43
Hispanic	268	7.3	32	6.1	0.85	0.56, 1.25
Other	159	4.4	21	4.0	0.93	0.55, 1.50
Missing data	7	0.2	0	0		
Education						
High school or less	713	19.5	96	18.3	1.0	
Some college	675	18.5	81	15.5	0.89	0.64, 1.23
College or more	2,271	62.1	346	66.0	1.13	0.89, 1.46
Missing data	0	0	1	0.2		
Marital status						
Married/cohabiting	3,229	88.3	453	86.5	1.0	
Other	430	11.8	71	13.6	1.18	0.89, 1.55
Missing data	0	0	0	0		
Gravidity						
Primigravida	1,245	34.0	147	28.1	1.0	
Multigravida	2,411	65.9	375	71.6	1.32	1.07, 1.62
Missing data	3	0.1	2	0.4		
Progesterone use						
No	3,558	97.2	493	94.1	1.0	
Yes	90	2.5	26	5.0	2.08	1.28, 3.29
Missing data	11	0.3	5	1.0		
Smoking during pregnancy						
No	3,195	87.3	460	87.8	1.0	
Yes	460	12.6	59	11.3	0.89	0.66, 1.19
Missing data	4	0.1	5	1.0		
Study site						
Greater Triangle region, North Carolina	1,629	44.5	270	51.5	1.0	
Memphis, Tennessee	745	20.4	86	16.4	0.70	0.53, 0.91
Raleigh, North Carolina	936	25.6	122	23.3	0.79	0.62, 0.99
Galveston, Texas	349	9.5	46	8.8	0.80	0.56, 1.12

(n = 3,659) or at the last time of study contact that occurred prior to the end of the study period (n = 165).

All analyses were conducted in Stata, version 9.2 (Stata Corporation, College Station, Texas).

RESULTS

Nearly all (95%) of the study participants reported exposure to prenatal vitamins or multivitamins at some point

Table 2. Characteristics of Participants Reporting Vitamin Use During Early Pregnancy Compared with Participants Reporting No Vitamin Use, Right From the Start, United States, 2000–2008

	No Vitamin Use (n = 205)		Vitamin Use (n = 4,122)	
	No.	Row %	No.	Row %
Maternal age, years				
<35	183	5.0	3,500	95.0
≥35	22	3.4	622	96.6
Missing data	0		0	
Race/ethnicity				
White, non-Hispanic	54	1.9	2,806	98.1
Black, non-Hispanic	119	12.7	821	87.3
Hispanic	21	6.4	308	93.6
Other	10	5.2	181	94.8
Missing data	1		6	
Education				
High school or less	116	13.4	753	86.7
Some college	49	6.2	743	93.8
College or more	40	1.5	2,625	98.5
Missing data	0		1	
Marital status				
Married/cohabiting	131	3.5	3,666	96.6
Other	74	14.0	456	86.0
Missing data	0		0	
Gravidity				
Primigravida	46	3.2	1,393	96.8
Multigravida	159	5.5	2,729	94.5
Missing data	0		0	
Progesterone use				
No	202	4.8	4,002	95.2
Yes	2	1.7	117	98.3
Missing data	1		3	
Smoking during pregnancy				
No	157	4.2	3,609	95.8
Yes	48	8.6	513	91.4
Missing data	0		0	
Study site				
Greater Triangle region, North Carolina	44	2.2	1,959	97.8
Memphis, Tennessee	73	8.6	777	91.4
Raleigh, North Carolina	53	5.0	1,015	95.0
Galveston, Texas	35	8.6	371	91.4

Table 3. Relation Between Vitamin Use During Early Pregnancy and Miscarriage After Adjustment for Selected Factors, Right From the Start, United States, 2000–2008

	No. of Pregnancy Losses	Odds Ratio[a]	95% Confidence Interval
Vitamin exposure			
Unexposed	44	1.0	
Exposed	475	0.43	0.30, 0.60
Maternal age			
Continuous variable (per year)		0.83	0.72, 0.96
Maternal age squared		1.00	1.00, 1.01
Race/ethnicity			
White, non-Hispanic	347	1.0	
Black, non-Hispanic	124	1.28	1.00, 1.64
Hispanic	32	0.88	0.59, 1.31
Other	21	0.95	0.61, 1.49
Education			
High school or less	96	1.0	
Some college	81	0.91	0.66, 1.25
College or more	346	1.01	0.73, 1.38
Marital status			
Married/cohabiting	453	1.0	
Other	71	1.30	0.96, 1.76
Gravidity			
Primigravida	147	1.0	
Multigravida	375	1.07	0.87, 1.31
Progesterone use			
No	493	1.0	
Yes	26	1.66	1.10, 2.51
Smoking during pregnancy			
No	460	1.0	
Yes	59	0.97	0.72, 1.30
Study site			
Greater Triangle region, North Carolina	270	1.0	
Memphis, Tennessee	86	0.84	0.65, 1.10
Raleigh, North Carolina	122	0.98	0.79, 1.23
Galveston, Texas	46	1.20	0.85, 1.70

[a] Adjusted for maternal age, gravidity, progesterone use in early pregnancy, smoking, race/ethnicity, education, marital status, and study site.

during the first trimester of pregnancy. About half (52%) of vitamin users reported having taken vitamins prior to conception. The majority of participants (95%) reported taking prenatal vitamins at least 5 times per week in a typical week. Approximately 70% of participants were from North Carolina, 20% were from Memphis, and 9% were from Galveston. Sixty-six percent of participants were white, 62% had a college education or more, and 88% were married or living with a partner (Table 1). Women who reported no use of vitamins were more likely to be black, less educated, and unmarried and were more likely to report smoking during pregnancy compared with women who reported vitamin use (Table 2).

In the unadjusted model, the odds ratio for miscarriage in a given gestational week, given that the fetus was at risk during the week of loss, was 0.43 (95% confidence interval: 0.31, 0.59), comparing women who were exposed to

Table 4. Association Between Vitamin Use During Early Pregnancy and Miscarriage, by Timing and Consistency of Vitamin Use and Time of Miscarriage, Right From the Start, United States, 2000–2008

Vitamin Use Characteristic	No. of Pregnancy Losses	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Timing of use during pregnancy					
≤10 weeks' gestation	244	0.40	0.25, 0.63	0.38	0.24, 0.62
>10 weeks' gestation	280	0.50	0.32, 0.76	0.47	0.30, 0.73
Consistency of use					
<5 times per week	59	0.27	0.15, 0.50	0.27	0.15, 0.49
≥5 times per week	457	0.46	0.33, 0.62	0.43	0.31, 0.61
Time of miscarriage					
Interviewed before miscarriage	201	0.39	0.24, 0.63	0.62	0.37, 1.04
Interviewed after miscarriage	317	0.43	0.28, 0.65	0.29	0.19, 0.45
Early miscarriage (≤10 weeks)	244	0.40	0.25, 0.63	0.28	0.17, 0.47
Late miscarriage (>10 weeks)	280	0.50	0.32, 0.76	0.55	0.34, 0.87

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for maternal age, gravidity, progesterone use in early pregnancy, smoking, race/ethnicity, education, and marital status.

vitamins with those who were unexposed. In the final model, results were adjusted for study site, maternal age, hormone use, gravidity, smoking status, race/ethnicity, education, and marital status. In the final adjusted model, exposure to prenatal vitamins was associated with the same odds ratio as it was without adjustment (odds ratio = 0.43, 95% confidence interval: 0.30, 0.60). Because no substantial differences in the magnitude or precision of the results occurred when we compared the final adjusted model with the unadjusted model, results from the final adjusted model are presented (Table 3).

We also considered several dimensions of vitamin exposure related to the timing and consistency of exposure. To evaluate a potential difference in the effect of exposure by time period of pregnancy and to identify whether exposure during early pregnancy further decreased the odds ratio, we included a categorical time interaction denoting the early (≤10 weeks) pregnancy period. This interaction did not contribute substantially to the model ($P = 0.5$). The odds of miscarriage for women reporting less frequent vitamin use (fewer than 5 times per week) were lower than but not substantially different from those for more consistent use ($P = 0.06$) (Table 4). Estimates for the odds of miscarriage stratified by whether the interview occurred before or after the pregnancy loss were similar.

DISCUSSION

In this analysis, we found evidence of a reduction in the odds of miscarriage among women who used vitamins before and during pregnancy. The final adjusted and unadjusted models gave results of similar magnitude and precision.

Vitamin supplementation is widely recommended for all women who are pregnant or planning a pregnancy. Specific components of vitamin formulations are intended to cover gaps in maternal nutrition and to decrease the risk of adverse outcomes such as neural tube defects. The biologic mechanisms underlying these widespread recommendations remain unclear. The early embryo may require specific maternal nutrients at precise critical windows of development; however, little is known about nutritional requirements and exact time periods of importance. Detailed evidence of this nature is required before any conclusions can be drawn about a causal relation between vitamin use and adverse pregnancy outcomes.

Although there is some evidence of a beneficial effect of supplementation for women at risk of preeclampsia or preterm birth (7–9), little is known about the effect of maternal nutrition on early pregnancy outcomes in a general population. Existing evidence suggests that vitamin supplementation may minimally affect the risk of miscarriage (13, 15) or may slightly increase the risk of miscarriage (11, 12). Given that miscarriage is a common pregnancy outcome, even a small increase in risk resulting from a common exposure may have far-reaching implications. In clinical studies of plasma folate measurements taken prior to or during pregnancy, investigators have reported an inverse relation between plasma folate levels and the risk of miscarriage (16–22), a finding that is supported by our results. Plasma markers represent the effective dose of the supplement, which may be affected by actual supplement intake and individual genetic and dietary factors. To better understand the etiologic mechanism underlying the relation between vitamin use and miscarriage, biologic data would be required.

Our study examined the impact of supplementation itself, which may be related to the effect of pregnancy intendedness and other demographic, reproductive, and dietary characteristics associated with the decision to use vitamin supplements. We were unable to account for dietary intake,

a limitation of this analysis. Because we assessed the effect of overall vitamin use, not the effect of specific supplement components, we may have actually been measuring a proxy for other health-conscious or preventive behaviors that are related to vitamin use, such as alcohol intake or physical activity during pregnancy. Of note, we found important demographic differences between participants who reported vitamin use and those who did not, suggesting that the results shown here may partly represent a constellation of lifestyle factors related to pregnancy intendedness and preconception care access, as well as self-selection into our study. The interplay of these dimensions of vitamin use requires further study, and such investigations would be enhanced by inclusion of both biologic and self-reported information. However, this study represents an initial step towards identifying modifiable factors that affect miscarriage risk, and it provides reassuring results suggesting that this very common early-pregnancy exposure does not have a detrimental relation with pregnancy loss.

More consistent vitamin use was associated with an odds ratio slightly closer to the null. This appears counterintuitive, but it could occur if women who are more vigilant about daily supplementation are at higher risk of miscarriage than women who are not as attentive to taking their daily vitamin. We had insufficient statistical power to evaluate the effect of beginning vitamin use prior to the time of conception versus afterwards. Odds ratios for miscarriages that occurred before and after the interview were somewhat different, although the overlap in confidence intervals indicates that the difference between the estimates remains within the bounds of random error. Regardless of when the interview occurred, vitamin use reduced the risk of miscarriage. Similar results were found when comparing early ($\leq$10 weeks) and late ($>$10 weeks) miscarriage.

Our study had several strengths. Our nonclinical study population was recruited directly from the communities in which Right From the Start is active. Because of this, a more generalizable study population was recruited very early during pregnancy. Prior work has shown that clinic-based samples may be demographically different from population-based samples (23). Analyses based on clinical samples may overestimate the occurrence of adverse outcomes. Our participants did not have to change any aspect of their usual prenatal care routine for the study; thus, it is unlikely that our enrollment procedures and study activities influenced our results. Although we recognize that the Right From the Start study population is highly educated and generally of high socioeconomic status, we believe that our results can be informative for pregnant women in the United States.

Because participants enroll in Right From the Start very early in pregnancy, we are able to observe a greater proportion of pregnancy losses in our study population than if prenatal clinic-based recruitment occurred. Our participants have an ultrasonogram conducted by a study sonographer early in pregnancy; thus, fetal viability is confirmed early in pregnancy and our gestational age assignment is accurate. A strength of Right From the Start is that we can accurately time the occurrence of events and exposures in pregnancy in time-varying models.

In conclusion, we found that use of vitamin supplements during early pregnancy was associated with reduced odds of miscarriage. Additional studies would be required to identify specific vitamin components that may have differential effects on early pregnancy outcomes. Further understanding of the interplay between vitamin exposure, biologic mechanisms, and pregnancy intendedness and health behaviors is also warranted.

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APPENDIX

Prenatal vitamins

1. Do you now take prescription or nonprescription prenatal vitamins?
2. In the past 4 months, did you take prescription or nonprescription prenatal vitamins?
3. Did you start taking prescription or nonprescription prenatal vitamins more than 4 months ago?

Multivitamins

4. Do you now take multivitamins other than prenatal vitamins?
5. In the past 4 months, did you take multivitamins other than prenatal vitamins?
6. Did you start taking multivitamins other than prenatal vitamins more than 4 months ago?