Association between short interpregnancy intervals and term birth weight: the role of folate depletion[1–3]

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ABSTRACT

Background: Maternal folate depletion has been proposed as a primary explanation for the excess risk of fetal growth restriction associated with short interpregnancy intervals.

Objective: We aimed to evaluate the folate depletion hypothesis in a community-based cohort of pregnant women.

Design: Using a subsample of the cohort (multiparous participants who delivered a liveborn singleton infant, $n = 3153$), we investigated the relation between an increase in the interpregnancy interval (from 1 to 24 mo, natural log transformation) and birth weight and the risk of small-for-gestational-age (SGA) in 3 strata of maternal periconceptional folic acid use: nonuse, late use (begun after conception), and early use (begun before conception).

Results: Each increase in the interpregnancy interval on the natural log (ln) scale was associated with a mean (±SE) increase of 63.1 ± 20.3 g in birth weight ($P = 0.002$). This relation was mitigated by folic acid use: the change in birth weight was increases of 165.2 ± 39.6 g for nonuse ($P < 0.001$) and 33.5 ± 35.6 g for late use ($P = 0.347$) and a decrease of 5.9 ± 33.6 g for early use ($P = 0.861$). The birth weight differences were directly translated into SGA risk. Odds ratios per 1-mo increase in ln(interpregnancy interval) were significant for the total group (0.61; 95% CI: 0.46, 0.82) and for nonuse (0.38; 0.24, 0.60) and nonsignificant for late (0.83; 0.48, 1.44) and early (1.28; 0.58, 2.84) use.

Conclusions: Folate depletion apparently contributes to the excess risk of fetal growth restriction that is associated with short interpregnancy intervals. As a preventive option, postnatal supplementation may be beneficial, but confirmation is needed. *Am J Clin Nutr* 2008;88:147–53.

INTRODUCTION

Several studies have reported greater risks of the adverse pregnancy outcomes low birth weight and small-for-gestational-age (SGA) after short interpregnancy intervals (1–13). Yet, a general explanation for these excess risks, estimated in a recent meta-analysis to be just over 60% for low birth weight and 25% for SGA (14), is still lacking. Some investigators have attributed the higher risk of poor pregnancy outcomes to factors associated with, rather than causally related to, short interpregnancy intervals, such as maternal sociodemographic characteristics and lifestyle (15–17). However, accumulating evidence from the studies that extensively controlled for such risk factors (3–5, 7, 10–12) suggests that the adverse outcomes are not merely the results of confounding.

A plausible hypothesis, more likely to reflect causality, that has been put forward to explain the excess risk is the nutritional depletion hypothesis (18, 19), which states that women with closely spaced births have insufficient time to restore the nutritional reserves needed to support fetal growth and development in the subsequent pregnancy. Folate depletion, in particular, has been proposed as the nutritional factor that contributes most to the risk of fetal growth restriction (20). During pregnancy, folate is mobilized from maternal stores to meet the increasing demands of mother and child. If dietary supply is low, concentrations begin to decline from the fifth month of pregnancy onward, and they continue to decline until several weeks after delivery (21, 22). Repletion of stores may then take several months (22), and thus mothers who conceive a subsequent child within these first months after delivery are at greater risk of folate deficiency. As a consequence, their offspring may be at higher risk of intrauterine growth restriction and low birth weight, which have previously been associated (23–28) with both low folate and high homocysteine concentrations [as a marker for folate deficiency (29)].

In the present study, we evaluated the folate depletion hypothesis as an explanation for short interval–associated adverse outcomes, by examining in different strata of folic acid supplement use the relation of interpregnancy interval with infant birth weight and SGA risk at term. If the hypothesis is true, we expected, first, to observe a greater risk of fetal growth restriction (ie, lower birth weight and higher SGA risk) at short intervals—ie, a risk that diminishes with greater interval length—and, second, to find a mitigating influence of folic acid supplement use on these risks. More specifically, lower birth weight and higher SGA risk were particularly expected among nonusers of folic acid supplements, who are at highest risk of folate depletion, and not—or to a lesser extent—among early (begun before conception) or late (begun after conception) supplement users. If our

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findings corroborated the hypothesis, new avenues could open for the prevention of adverse pregnancy outcomes in women conceiving their second or a subsequent child, particularly those women who become pregnant shortly after their previous pregnancy.

SUBJECTS AND METHODS

Study population and design

The present study is part of the Amsterdam Born Children and their Development (ABCD) study, a prospective, community-based cohort study that examines the relation between maternal lifestyle and psychosocial conditions during pregnancy and the child's health at birth and in later life. The design of the study was previously described in detail (30). In short, between January 2003 and March 2004, pregnant women living in Amsterdam were invited to enroll in the ABCD study during their first antenatal visit to the obstetric care provider (approximately week 12 of gestation) and were asked to complete a questionnaire covering sociodemographic data, obstetric history, lifestyle, dietary habits, and psychosocial factors. The questionnaire was available in Dutch and, for immigrant women, in English, Turkish, and Arabic. In total, 8266 of the 12 373 pregnant women invited to participate returned the pregnancy questionnaire (response rate: 67%). Of this group, 7738 women gave birth to a viable singleton infant for whom information on birth weight and pregnancy duration was available. For the present study, we excluded all women with preterm ($n = 410$) and first-time ($n = 3993$) deliveries. A total of 3335 women were available for analysis.

All participants gave written informed consent. The study was approved by the medical ethics committees of the participating hospitals and by the Registration Committee of Amsterdam.

Measurements

Primary outcome variables for the present study were birth weight (continuous; in g) and SGA (yes or no) at term, with SGA defined as a birth weight below the 10th percentile for gestational age on the basis of sex- and parity-specific Dutch standards as available from the Netherlands Perinatal Registry (for the data, see Table S1 under "Supplemental data" in the current online issue). Data on date of delivery, infant sex, birth weight, and gestational age [based on ultrasound or, if that measurement was not available (<10% of cases), on the timing of the last menstrual period] as recorded by the obstetric care providers were obtained via the Youth Health Department at the Municipal Health Service in Amsterdam.

Interpregnancy interval was calculated as the number of months between the date of delivery and the date of the preceding birth, minus the duration of the pregnancy. The latter was defined by the gestational age (in d) at the time of delivery. The use of folic acid supplements was assessed by the question, "Have you taken folic acid, either as a single supplement or as part of a multivitamin supplement, before or during your pregnancy?" Because the general recommendation is to start taking supplements ≥4 wk before conception (31), women were also asked to indicate when they had started taking supplements—either before or after conception. Women who took folic acid supplements and had begun doing so before conception were classified as "early users" of folic acid; those who took folic acid supplements but had begun after conception were classified as "late users"; and those who did not use folic acid supplements at all were classified as "nonusers."

A number of maternal physiologic, obstetric, lifestyle, and sociodemographic characteristics obtained via the questionnaire were considered covariables. Physiologic and obstetric variables included age (<25, 25–34, or ≥35 y), parity (1, 2, or ≥3), height (in cm), pregnancy intention as measured by questioning whether the respondent had wanted to become pregnant (yes or no), and start of prenatal care (<18, 18–23, or ≥24 wk of gestation). Lifestyle variables included alcohol consumption before or during early pregnancy (self-reported previous week's behavior and behavioral change since pregnancy, recoded as no; yes, but not since pregnancy; or yes, also during pregnancy), smoking habits before and during early pregnancy (self-reported previous week's behavior and behavioral change since pregnancy, recoded as no; yes, but not since pregnancy; or yes, also during pregnancy), prepregnancy body mass index (in kg/m^2) based on self-reported height and weight, and psychosocial stress (presence of 0, 1, or ≥ 2 stressors). A random imputation procedure using linear regression analysis was used to complete missing data on height (3.8% missing) and weight (9.9% missing) (32). Psychosocial stressors were measured by using validated Dutch versions of internationally accepted questionnaires; they included depression (33), general anxiety (34), pregnancy-related anxiety (35), parenting stress (36), and work stress (37). Thresholds for nonnormal scores, assuming a representative group of pregnant women, were by design chosen at the 90th percentile. Finally, sociodemographic factors were cohabitant status (living with partner or living alone), length of education after primary school (<6, 6–10, or ≥11 y), and country of birth (the Netherlands, Surinam, Turkey, Morocco, other non-Western country, or other Western country).

Statistical analysis

Of the 3335 women included, 75 did not provide information on interpregnancy interval ($n = 55$) or folic acid supplement use ($n = 20$), whereas 107 women had ≥1 missing values on the abovementioned covariables (per-item rate of missing: ≤ 2%). After exclusion of these respondents, the final sample for analysis consisted of 3153 women.

After a descriptive analysis of the infant and maternal characteristics, we performed univariate and multivariate regression analyses to estimate the association of interpregnancy interval as a categorical variable with term birth weight (linear regression) and SGA (logistic regression). For interpregnancy interval, the previously defined categories of 0–5, 6–11, 12–17, 18–23, 24–59, and ≥ 60 mo were used (14). Models were adjusted for the abovementioned maternal physiologic, obstetric, lifestyle, and sociodemographic characteristics (*see* "Measurements"). For birth weight as outcome variable, adjustments were also made for infant sex and gestational age. These analyses allowed us to evaluate the actual presence of an association in the current population and to relate the present findings to those of previous studies.

To specifically test the folate depletion hypothesis, we performed a previously defined multivariate regression analysis, including the natural log transformation of the interpregnancy interval as a continuous variable. First, multivariate models were fitted to describe the relation between greater length of interpreg-

nancy interval (from 1 to 24 mo) and birth weight (linear regression model) or SGA (logistic regression model). Although both short and long interpregnancy intervals were previously associated with adverse outcomes, the latter association is not expected to be influenced by folate depletion (14, 20); therefore, long intervals were excluded for this part of the analysis. The cutoff of 24 mo and the use of natural log transformation were chosen because the risks associated with short intervals have been shown to normalize within this time frame, following an inverse J-shaped pattern (after an initial steep decline in risk, a gradual leveling off with increasing interval length) (3, 6, 9–14). Second, stratified analysis using the previously defined models for birth weight and SGA was performed to evaluate the mitigating influence of folic acid supplement use. Strata were no use, late use, and early use (*see* Measurements). The hypothesized mitigating influence of folic acid use was subsequently tested statistically by including in the models both supplement use and interaction terms for supplement use and interpregnancy interval (test for effect modification).

Associations were considered significant at $P < 0.05$. All analyses were conducted with the use of SPSS software (version 15.0; SPSS Inc, Chicago, IL).

RESULTS

Characteristics of the mother-infant pairs ($n = 3153$) are presented in **Table 1**. Mean (± SD) infant birth weight was 3579 ± 497 g, and mean gestational age at birth was 40.0 ± 1.2 wk. In total, 12.5% of the infants were born SGA. Sixty-four percent of the mothers had used folic acid supplements during pregnancy; 29% started taking these supplements after conception, and 35% started taking these supplements before conception.

Less than 4% of the women ($n = 124$) became pregnant within 6 mo after the previous delivery, and 16% of the women ($n = 513$) had interpregnancy intervals of ≥5 y (**Table 2**). In univariate analyses, both short (<6 mo) and long (24–59 or ≥60 mo) interval categories reduced birth weight, with a corresponding increase in SGA risk for intervals < 6 and ≥ 60 mo. After adjustment for relevant maternal and infant characteristics, these associations persisted for the short interval category [mean (± SE) estimated difference in birth weight: −142.1 ± 44.1 g; odds ratio (OR) for SGA: 2.12; 95% CI: 1.23, 3.65; reference category: 18–23 mo] but not for the 24–59-mo interval category. Intervals ≥ 60 mo were no longer associated with SGA risk but remained negatively associated with birth weight (−66.6 ± 30.8 g; reference category: 18–23 mo).

The results of the regression analyses describing the relation of increasing interpregnancy interval (from 1 to 24 mo) with birth weight and SGA in our cohort are presented in **Figure 1**. Each 1-mo increase in the interpregnancy interval expressed on a natural log scale was associated with an increase in birth weight of 63.1 ± 20.3 g ($P = 0.002$) and, correspondingly, a decrease in SGA risk of ≈40% (OR: 0.61; 95% CI: 0.46, 0.82). To illustrate this relation on the original scale, we calculated the mean birth weight differences and ORs for SGA using month 1 as reference. These differences were 112.9 (95% CI: 41.5, 184.2) g at 6 mo, 156.4 (57.5, 255.3) g at 12 mo, 182.2 (67.0, 297.5) g at 18 mo, and 200.5 (73.8, 327.3) g at 24 mo. Estimated ORs for SGA were 0.42 (95% CI: 0.24, 0.70) at 6 mo, 0.30 (0.15, 0.61) at 12 mo, 0.24 (0.11, 0.56) at 18 mo, and 0.21 (0.08, 0.53) at 24 mo. Stated in reverse, counting down from month 24 as the presumed optimal interpregnancy interval, birth weight differences and 95% CIs were −18.3 (−29.8, −6.7) g, −44.1 (−72.0, −16.2) g, −87.7 (−143.1, −32.2) g, and −200.5 (−327.3, −73.8) g at months 18, 12, 6, and 1, respectively, with corresponding ORs and 95% CIs for SGA of 1.15 (1.05, 1.25), 1.41 (1.15, 1.72), 1.97 (1.33, 2.95), and 4.74 (1.89, 11.84).

TABLE 1
Infant and maternal characteristics[1]

Characteristics	Value
Infant	
Male (%)	50.0
Birth weight (g)	3579 ± 497[2]
Gestational age at birth (wk)	40.0 ± 1.2
Small-for-gestational-age birth (%)	12.5
Maternal[3]	
Folic acid supplement use (%)	
None	36.0
Yes, started after conception (late use)	29.4
Yes, started before conception (early use)	34.6
Age (y)	
<25 (%)	7.1
25–34 (%)	59.6
≥35 (%)	33.3
Parity (%)	
1	71.5
2	20.1
≥3	8.4
Height (cm)	167.7 ± 7.4
Unintended pregnancy (%)	9.3
Started prenatal care (%)	
<18 wk	89.0
18–23 wk	7.6
≥24 wk	3.4
Alcohol consumption (%)	
None	47.1
Yes, but not since pregnancy	30.8
Yes, also during pregnancy	22.1
Smoking (%)	
None	80.9
Yes, but not since pregnancy	10.0
Yes, also during pregnancy	9.1
Prepregnancy BMI (kg/m^2)	23.7 ± 4.3
Psychosocial stressors (%)	
0	71.3
1	17.0
≥2	11.7
Cohabitant status (% living alone)	11.5
Education (y)	
<6 (%)	27.9
6–10 (%)	36.8
≥11 (%)	35.4
Country of birth (%)	
Netherlands	57.4
Surinam	6.9
Turkey	5.6
Morocco	9.3
Other non-Western country	13.8
Other Western country	7.0

[1] $n = 3153$.
[2] $\bar{x}$ ± SD (all such values).
[3] As determined in pregnancy; median (interquartile range) pregnancy duration at questionnaire completion was 16 (14–19) wk.

TABLE 2
Results of the regression analyses relating birth weight and small-for-gestational-age (SGA) to interpregnancy interval as defined in categories[1]

	Interpregnancy interval (mo)					
	<6	6–11	12–17	18–23	24–59	≥60
Subjects (*n*)	124	487	510	407	1112	513
Birth weight (g)	3461 ± 495[2]	3610 ± 480	3617 ± 462	3658 ± 508	3577 ± 501	3482 ± 512
B ± SE						
Crude[3]	−197.1 ± 50.8[4]	−48.3 ± 33.2	−40.8 ± 32.8	0.0	−80.8 ± 28.6[4]	−176.5 ± 32.8[4]
Adjusted[5]	−142.1 ± 44.1[4]	−6.0 ± 28.9	−14.0 ± 28.4	0.0	−22.2 ± 25.2	−66.6 ± 30.8[4]
SGA (%)	22.8	10.5	8.4	11.5	12.1	17.5
OR (95% CI)						
Crude	2.26 (1.34, 3.78)[4]	0.90 (0.59, 1.36)	0.71 (0.46, 1.09)	1.00	1.06 (0.74, 1.51)	1.63 (1.12, 2.38)[4]
Adjusted[6]	2.12 (1.23, 3.65)[4]	0.88 (0.57, 1.36)	0.69 (0.44, 1.08)	1.00	0.85 (0.59, 1.24)	1.06 (0.69, 1.63)

[1] $n = 3153$. OR, odds ratio. Linear regression analysis for birth weight as dependent variable and interpregnancy interval in categories as primary independent variable; logistic regression analysis for SGA as dependent variable and interpregnancy interval in categories as primary independent variable. SGA was defined as birth weight < 10th percentile for gestational age based on sex- and parity-specific standards.

[2] $\bar{x} \pm$ SD (all such values).

[3] Crude regression coefficient ± SE.

[4] Significantly different from reference category (18–23 mo), $P < 0.05$.

[5] Regression coefficient ± SE adjusted for gestational age at birth (linear and quadratic), infant sex, maternal age, height, parity, maternal prepregnancy BMI (linear and quadratic), smoking before and during pregnancy, alcohol consumption before and during pregnancy, psychosocial stress, pregnancy intention, cohabitant status, education, and ethnicity.

[6] Adjusted for maternal age, height, maternal prepregnancy BMI (linear and quadratic), smoking before and during pregnancy, alcohol consumption before and during pregnancy, psychosocial stress, pregnancy intention, cohabitant status, education, and ethnicity (SGA was already adjusted for gestational age, infant sex, and parity).

In line with the hypothesis, we observed a mitigating effect of folic acid supplement use on the relation of interpregnancy interval with birth weight (**Figure 2**) and SGA (**Figure 3**). Stratified analysis showed that, in both early and late supplement users, the association between interval and birth weight or SGA no longer existed; the change in birth weight per 1-mo increase in ln(interpregnancy interval) was a decrease of 5.9 ± 33.6 g for early users and an increase of 33.5 ± 35.6 g for late users; the corresponding OR for SGA was 1.28 (95% CI: 0.58, 2.84) for early users and 0.83 (95% CI: 0.48, 1.44) for late users. In contrast, for nonusers, we observed a significant birth weight increase of 165.2 ± 39.6 g, $P < 0.001$) per 1-mo increase in

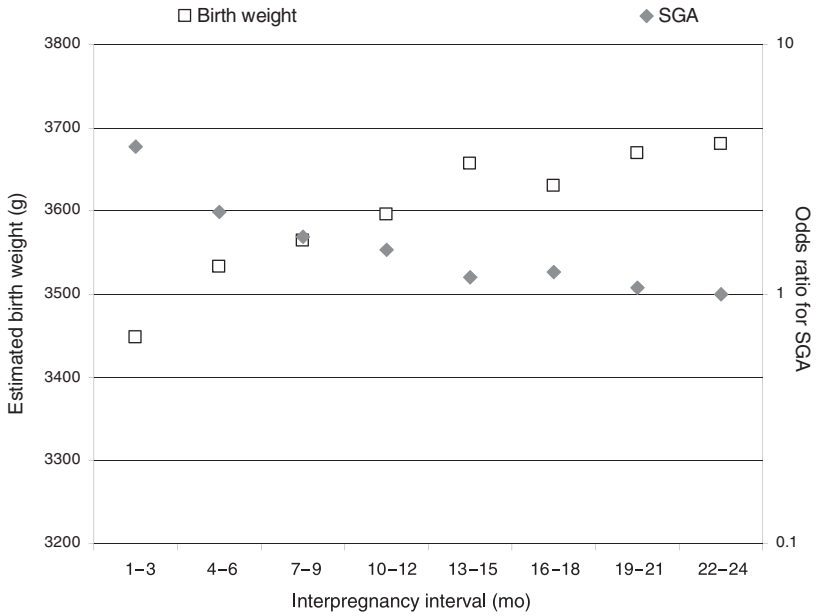

FIGURE 1. Estimated mean birth weight (linear regression) and odds ratios for small-for-gestational-age (SGA) (logistic regression) in the Amsterdam Born Children and their Development cohort as a function of interpregnancy interval. Estimates for birth weight were derived from a continuous multivariate linear regression model with birth weight as dependent and ln(interpregnancy interval) as primary independent variable; odds ratios for SGA were derived from a multivariate logistic regression model with SGA as dependent and ln(interpregnancy interval) as primary independent variable. In both models, adjustments were made for a previously defined set of covariables (*see* Table 2 footnotes). For presentation purposes, monthly intervals were combined in 3-mo categories. $n = 43$, 127, 244, 301, 263, 224, 204, and 180 in the 1–3-, 4–6-, 7–9-, 10–12-, 13–15-, 16–18-, 19–21-, and 22–24-mo intervals (the *n*'s are similar for the birth weight and SGA analyses).

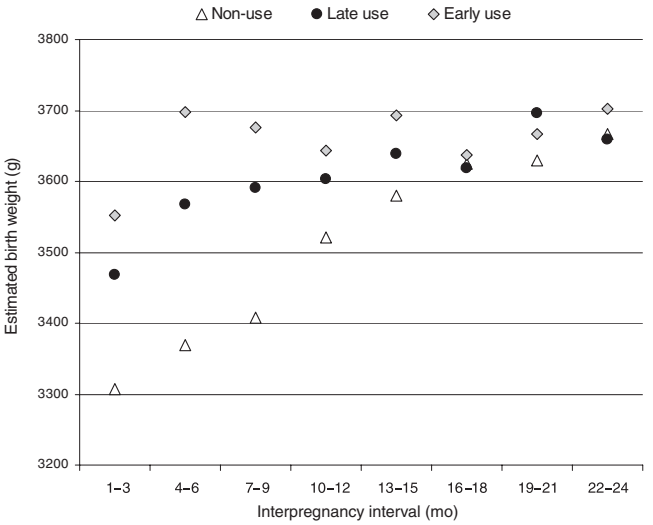

FIGURE 2. Estimated mean birth weight (linear regression) in the Amsterdam Born Children and their Development cohort as a function of interpregnancy interval in 3 strata of folic acid supplement use. Estimates for birth weight were derived from a multivariate linear regression model with birth weight as dependent and ln(interpregnancy interval) as primary independent variable. Adjustments were made for a previously defined set of covariables (*see* Table 2 footnotes). Analyses were stratified for folic acid supplement use: nonuse (n = 414), late use (n = 537), and early use (n = 635). For presentation purposes, monthly intervals were combined in 3-mo categories. In the 1–3-, 4–6-, 7–9-, 10–12-, 13–15-, 16–18-, 19–21-, and 22–24-mo intervals, the numbers of subjects were 21, 37, 69, 77, 60, 53, 47, and 50, respectively, for nonuse; 13, 48, 97, 111, 80, 63, 78, and 47, respectively, for late use; and 9, 42, 78, 113, 123, 108, 79, and 83, respectively, for early use.

ln(interpregnancy interval), with a corresponding decrease in SGA risk of 60% (OR: 0.38, 95% CI: 0.24, 0.60). Consequently, mean birth weight differences in the nonuse group, taking the optimal interpregnancy interval of 24 mo as reference, were −47.9 (95% CI: −70.4, −25.4) g at 18 mo, −115.6 (−170.0, −61.3) g at 12 mo, −229.6 (−337.5, −121.7) g at 6 mo, and −525.3 g (−772.1, −278.5) at 1 mo; corresponding ORs for SGA were 1.33 (95% CI: 1.16, 1.52), 1.98 (1.43, 2.75), 3.89 (2.02, 7.48), and 22.35 (5.01, 99.76). The interaction model confirmed that the effect modification as observed in the stratified analysis was significant for both birth weight (P = 0.001) and SGA (P = 0.008).

DISCUSSION

The results of this large, prospective cohort study not only confirm previous research showing a negative association between short interpregnancy intervals and fetal growth (1–14) but also support the explanatory hypothesis of folate depletion (20). Among those most at risk of folate depletion—the nonusers of folic acid supplements—we observed a greater risk of fetal growth restriction (as reflected by a lower mean birth weight and higher SGA risk) at short interpregnancy intervals, which diminished with increasing interval length. In contrast, no significant interval-associated decrease in birth weight or increase in SGA risk was observed among supplement users. These observations imply that the adverse effects of interpregnancy intervals shorter than 6 mo could be prevented by the use of folic acid supplements in the period between the consecutive pregnancies.

In line with the hypothesis, the mitigating influence of folic acid supplementation was expected to be dose-dependent. Indeed, we observed the interval-associated risks of lower birth weight and SGA among late users (ie, started after conception) to be intermediate between the interval-associated risks among nonusers and early users (ie, started before conception). The biological plausibility of this dose-dependency lends further credibility to a true causal role of folate depletion in the association between interpregnancy interval and adverse pregnancy outcomes. Folate has a fundamental role in the process of cell division because of its role in DNA synthesis. Particularly during pregnancy—a time of tissue growth and sustained cell division—the need for folate increases (38). Low maternal folate concentrations may negatively influence fetal growth and development, but folate supplementation to restore folate status may counterbalance these effects. The largest reduction in risk may thus be expected from supplementation starting before conception, which may ensure adequate folate status during the critical stage of embryonic development (20). Indeed, previous studies showed a preventive effect of higher folate intakes on adverse pregnancy outcomes, particularly in women at high risk of folate deficiency (39, 40).

Given the unavoidably nonexperimental setting of our study, alternative explanations for our observations should be considered. We cannot exclude the possibility that our results are explained by maternal characteristics associated with supplement use (eg, being more health-conscious) or, more specifically, by the concurrent intake of other micronutrients relevant to fetal

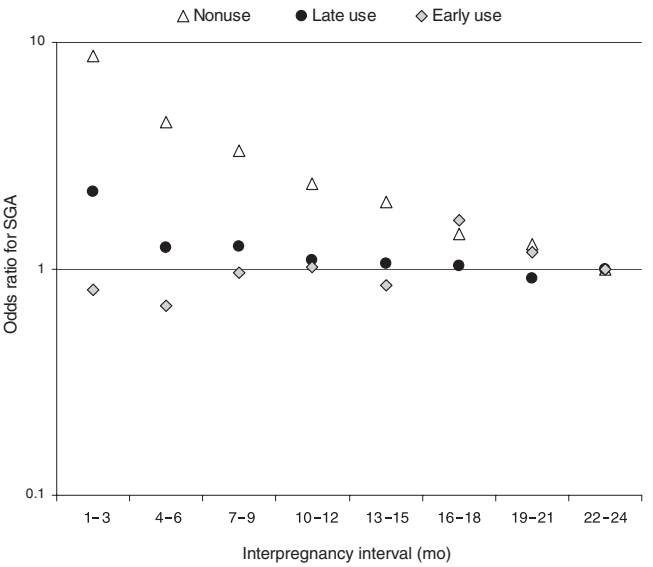

FIGURE 3. Estimated odds ratios for small-for-gestational-age (SGA) (logistic regression) in the Amsterdam Born Children and their Development cohort as a function of interpregnancy interval in 3 strata of folic acid supplement use. Odds ratios for SGA were derived from a multivariate logistic regression model with SGA as dependent and ln(interpregnancy interval) as primary independent variable. Adjustments were made for a previously defined set of covariables (*see* Table 2 footnotes). Analyses were stratified for folic acid supplement use: nonuse (n = 414), late use (n = 537), and early use (n = 635). For presentation purposes, monthly intervals were combined in 3-mo categories. In the 1–3-, 4–6-, 7–9-, 10–12-, 13–15-, 16–18-, 19–21-, and 22–24-mo interval categories, the numbers of subjects were 21, 37, 69, 77, 60, 53, 47, and 50, respectively, for nonuse; 13, 48, 97, 111, 80, 63, 78, and 47, respectively, for late use; and 9, 42, 78, 113, 123, 108, 79, and 83, respectively, for early use.

growth. However, most micronutrient concentrations return to normal fairly soon after delivery (22, 41); in addition, from the available follow-up information, which included a retrospective assessment of the type of supplements used (single compared with multivitamin supplements; available for 1509 of the 2029 supplement users in this study), it can be concluded that most (65%) participants were single supplement users only. In this context, we assume that the role of nutrients other than folate is minor.

A strength of our study is the parallel focus on term birth weight and SGA. SGA is the most important outcome in terms of clinical relevance, but the use of birth weight as continuous measure and the planned exclusion of preterm births allowed us also to capture the physiologic evidence of folate's overall effect on weight without the distorting effect of preterm delivery (42). The mechanism through which folate depletion affects preterm delivery is likely to differ from the mechanism through which it affects birth weight, which further justifies this separation. The observed corresponding effects of interpregnancy interval on term birth weight and SGA in the cohort of the present study were adjusted for a large set of simultaneously measured risk factors relevant to fetal growth in the index pregnancy. However, the design of the present study limited our ability to measure factors related to the preceding pregnancy, such as the outcome of pregnancy and maternal breastfeeding. Breastfeeding practices may interact with the association between folate depletion and interpregnancy interval, because women who breastfeed are at greater risk of depletion (20). The outcome of the preceding pregnancy has been shown to relate to the outcome of subsequent pregnancies (43). However, this correlation may reflect ≥1 persisting factors that affect all infants in a sibship, such as smoking (44). To the extent that these factors were known in our cohort, they were adjusted for in our analyses. In addition, in previous studies that did control for the outcome of the preceding pregnancy, the adjustment did not affect the J-shaped relation between interpregnancy interval and the risk of fetal growth restriction (10–12). Another limitation related to the design of our study may be the measurement of folic acid supplement use, which was self-reported. One could assume that overreporting of this socially desirable healthy behavior influenced our observations. However, self-administered questionnaires have been shown to validly measure folic acid use (45); if any overreporting was present, it may imply that our estimates are too conservative.

Throughout the world, the use of folic acid supplements as a proven measure to prevent birth defects has brought about public health policies to promote folic acid intake (46, 47). Whereas the issue presented here is relevant in most of the countries that have supplementation policies similar to those in the Netherlands (46), it is more difficult to generalize the present results to countries in which supplementation policies are integrated with the population-wide fortification of flour, such as the United States. However, recent evidence from the United States has shown the persistent need for supplementation: after an initial rise, folate concentrations in women of childbearing age have declined again in recent years (48), whereas low concentrations are still common among ethnic minority groups, who also are at risk of short interpregnancy intervals (4–7, 9–12).

In summary, this large-scale prospective cohort study suggests that folate depletion contributes to the consistent association between short interpregnancy intervals and fetal growth restriction. One could argue that the evidence is sufficient to implement universal postpartum supplementation, which would also provide the maternal benefit of quick and adequate restoration of folate stores. However, given the current debate on the longer-term benefits and risks of folic acid supplementation in pregnancy (47), caution is warranted. Only prospective postnatal intervention studies that also include other relevant outcome measures (such as preterm delivery) can provide decisive evidence in this regard. Meanwhile, one should keep in mind that primary prevention of interpregnancy interval–associated risks still depends on family planning education, for which the best window of opportunity may lie in the early postnatal period—a critical stage for identifying those women who, intentionally or unintentionally, are most likely to have a short interpregnancy interval.

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The authors' responsibilities were as follows: MFvdW and GJB: conceived and designed the ABCD study; LJMS: proposed the present study as part of the ABCD study; MvE and MFvdW: collected and processed the data; MvE: statistical analysis, under the supervision of GJB; LJMS and MFvdW: provided additional statistical advice; and all authors: interpreted the results, wrote the manuscript, and reviewed and approved the final version. None of the authors had a personal or financial conflict of interest.

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