Letter

Role of Folic Acid Supplementation on Association between Short Inter-Pregnancy Intervals and Adverse Birth Outcomes: A Retrospective Cohort Study in Changsha, China

Zhiqing Zhao[1,&], Ling Chen[2,&], Wenbin Ouyang[1], Jing Deng[3], Xiaohui Chen[4], and Xin Huang[1,#]

Preterm birth and suboptimal fetal growth remain significant perinatal challenges worldwide. Recent data indicate that China's perinatal profile has improved due to reductions in preterm birth rates. However, the country has a 6.5% prevalence of small-for-gestational-age (SGA), ranking fifth globally in total SGA birth numbers[1,2]. Early life outcomes have long-lasting effects on health. Therefore, identifying effective public health interventions that improve maternal health and reduce adverse birth outcomes is imperative.

The period between childbirth and subsequent conception is known as the inter-pregnancy interval (IPI). A shorter IPI has been associated with an increased risk of adverse birth outcomes[3], such as preterm birth, low birth weight (LBW), SGA, birth defects, and neonatal death. Folate is a critical nutrient for DNA synthesis and cell replication, and its depletion interferes with fetal growth and gestation[4]. Notably, folate levels remain low six months after delivery[5]. Consequently, women with a very short IPI are at high risk of folate deficiency, which may adversely affect their reproductive health.

Accordingly, researchers have hypothesized that folic acid supplementation may prevent adverse birth outcomes associated with a short IPI. However, evidence regarding the role of folic acid supplementation in the association between a short IPI and adverse birth outcomes is contradictory. For instance, a recent study of 3,153 Dutch participants[6] found that folic acid supplementation attenuated the effect of a short IPI on the risk of preterm birth, LBW, and SGA. In comparison, a Canadian study[7] found that folic acid supplementation reduced the total number of preterm births. However, the decrease in preterm births between the short and normal IPI groups was similar. Several underlying differences may have contributed to these inconsistent results.

In China, nearly one-third of IPIs are less than 18 months[8]. The majority of short IPI pregnancies are unplanned, and folic acid supplementation is 22%–35% lower in unplanned pregnancies than in planned pregnancies[9]. To date, no study has addressed whether folic acid supplementation in the Chinese population has the same preventative effect on adverse birth outcomes for women conceiving shortly after a previous delivery. Thus, we conducted a retrospective cohort study in Changsha City to investigate whether folic acid supplementation modified the risk of adverse birth outcomes associated with a short IPI in the Chinese population. In doing so, we considered a different cultural background compared to previously published studies.

Changsha, a city in southern China, has six urban districts, one county, and two county-level cities. In 2016, Changsha recorded 116,336 live births. All multiparous women who had live births in the urban districts of Changsha in 2016 were eligible for enrolment. We excluded women who had multiple births, stillbirths, previous or current birth defect; or who suffered from chronic hypertension, diabetes, kidney disease, or cardiovascular disease before the current pregnancy; or who lacked information regarding previous or current birth outcomes or folic acid supplementation during this pregnancy. A total of 11,332 women were eligible for analysis (Supplementary Figure S1). The study protocol was reviewed and approved by the Ethical and Confidentiality Committee of Hunan Normal

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1. Department of Epidemiology, School of Public Health, Hunan Normal University, Changsha 410013, Hunan, China; 2. The First Hospital Affiliated with Hunan Normal University (Hunan Provincial People`s Hospital), Changsha 410005, Hunan, China; 3. Department of Epidemiology, Xiangya School of Public Health, Central South University, Changsha 410031, Hunan, China; 4. Health Bureau of Tianxin District, Changsha 410029, Hunan, China

University, which waived the need for further information. All data used in the present study were collected from antenatal care booklets, hospital maternal obstetric delivery, and newborn records, as previously described[10]. General information on maternal demographic characteristics, previous birth outcomes, and obstetric history, including folic acid supplementation, was reported by the participants themselves and obtained from antenatal care booklets. Information on current pregnancy outcomes, including maternal complications and neonatal outcomes, was extracted from the hospital records.

The IPI was defined as the period between the delivery date of the previous child and the current conception date. This was obtained by subtracting the gestational age of the current birth from the interval between the previous and current deliveries. Participants were categorized into three groups according to the length of their IPIs: very short (6 months ≤ IPI < 12 months), short (12 months ≤ IPI < 18 months), and normal (IPI ≥ 18 months), with normal IPI specified as the reference group. Patients with an IPI < 6 months were excluded because of the limited sample size.

Information on whether folic acid supplementation was initiated, when it was initiated, and whether it was continued until the 12th gestational age could be extracted from the antenatal care booklets. However, the specific supplement products and duration of supplementation after 12 weeks of gestation were not documented. Thus, this study could not measure the cumulative exposure dose of folic acid supplementation. For this reason, we divided participants' folic acid supplementation status into two categories: adequate and inadequate. The adequate category includes participants who started folic acid supplementation before conception and continued daily supplementation until 12 weeks of gestation. In the inadequate category, folic acid supplementation was either not initiated before conception, did not continue until 12 weeks of gestation, or was not initiated at all.

The adverse birth outcomes considered in this study included preterm delivery (delivered at less than 37 weeks of gestation), LBW (birth weight less than 2,500 g), and SGA (birth weight < 10^{th} percentile for gestational age and sex). Large-for-gestational-age (LGA) outcomes were excluded because of insufficient evidence as a mechanism with relevance to shorter IPIs.

Chi-square tests were used to compare the distributions of general characteristics among the very short, short, and normal IPI groups. Unconditional logistic regression models were used to estimate the odds ratios (*OR*s) for the associations between very short or short IPI and adverse birth outcomes. Dose-response relationships were confirmed using Cochran-Armitage trend tests. Potential confounding variables included in the multivariate analysis were maternal age (< 35 years, or ≥ 35 years), number of years of education (< 12 years, or ≥ 12 years), smoking during pregnancy (yes, or no), alcohol consumption during pregnancy (yes, or no), preterm birth history (yes, or no), and body mass index (BMI) before the current pregnancy (underweight, < 18.5; normal weight, 18.5 ≤ BMI< 24; overweight, 24 ≤ BMI < 28; or obese, BMI ≥ 28). To test whether adequate folic acid supplementation modified the association between a short IPI and adverse birth outcomes, a stratified analysis was performed. The relative excess risk due to interaction (RERI) and ratio of *OR*s were calculated to assess the modification effect under the additive and multiplicative models. The significance level for statistical tests was set at 5% (two-tailed). All analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA).

This retrospective study included 11,332 multiparous women (Supplementary Figure S1). One-third of the participants were over 35 years of age, 90% had given birth to their second child, and 32% had taken adequate folic acid supplements during their current pregnancy.

Table 1 presents the distribution of the enrolled participants' sociodemographic characteristics according to their IPI category. There were no significant differences in maternal age, education level, smoking, or alcohol consumption during pregnancy, pre-pregnancy BMI category, preterm birth history, or folic acid supplementation category between the different IPI groups. This indicated a low risk of selection bias.

Table 2 presents the associations between a short IPI and adverse birth outcomes. A shorter IPI was significantly associated with an increased risk of preterm birth, LBW, and SGA in a dose-response manner (P < 0.01 for the trend). Compared with a normal IPI, a short IPI had a slightly, but not statistically significant, increased risk of LBW (*OR* = 1.11, 95% *CI*: 0.90, 1.36). On the other hand, a very short IPI was associated with a significantly higher risk of LBW (*OR* = 1.45, 95% *CI*: 1.17, 1.78). Compared with a normal IPI, a short IPI was associated with a 0.41-fold increased risk of preterm

birth (*OR* = 1.41, 95% *CI*: 1.17, 1.70), and a 0.26-fold increased risk of SGA (*OR* = 1.26, 95% *CI*: 1.11, 1.44). The associations between a very short IPI and preterm birth and SGA were even stronger, with adjusted *OR*s of 1.51 (95% *CI*: 1.24, 1.85) and 1.52 (95% *CI*: 1.32, 1.74), respectively. This dose-response pattern aligns with the biological gradient observed in nutritional depletion syndromes, where women with closely spaced pregnancies are at an increased risk of entering the reproductive cycle with reduced folate reserves[4].

After stratification by folic acid supplementation category, a significant modification effect of inadequate folic acid supplementation was found in the association between a short IPI and SGA. A short IPI was significantly associated with an increased risk of SGA (*OR* = 1.39, 95% *CI*: 1.19, 1.63). This association was positive on both the multiplicative (*P* = 0.02) and additive scales (*P* = 0.01) (Figure 1 and Supplementary Table S1). However, this association was statistically insignificant when folic acid was adequately supplemented (*OR* = 1.00; 95% *CI*: 0.78, 1.28). A similar effect was observed for preterm births. There was a lower risk of preterm birth associated with short IPIs and very short IPIs in the adequate supplementation stratum than in the inadequate stratum, although there was no statistically significant between these two strata (*P* > 0.05, Supplementary Table S2). Similar results were observed for very short IPI and LBW (Supplementary Table S3). This aligns with the Dutch study findings[6] but diverges from Canadian data showing uniform folate benefits across IPI groups[7]. This discrepancy may be attributable to the mitigation of baseline folate deficiency by mandatory fortification[11]. Conversely, despite the existence of a nationally subsidized pre-conception program, voluntary supplementation presents persistent systemic

Table 1. Participant characteristics by IPI category (*N* = 11,332)

Characteristics	Normal IPI, *n* (%)	Short IPI, *n* (%)	Very short IPI, *n* (%)	*P*
Maternal age (years)				0.60
< 35	5,210 (68.91)	1,472 (69.60)	1,160 (70.05)	
≥ 35	2,351 (31.09)	643 (30.40)	496 (29.95)	
Years of education				0.10
≤ 12	5,667 (74.95)	1,633 (77.21)	1,255 (75.79)	
> 12	1,894 (25.05)	482 (22.79)	401 (24.21)	
Smoking during pregnancy				0.98
No	7,312 (96.71)	2,045 (96.69)	1,603 (96.80)	
Yes	249 (3.29)	70 (3.31)	53 (3.20)	
Alcohol consumption				0.58
No	7,343 (97.12)	2,048 (96.83)	1,613 (97.40)	
Yes	218 (2.88)	67 (3.17)	43 (2.60)	
Pre-pregnancy BMI category				0.14
Underweight	1,745 (23.08)	450 (21.28)	377 (22.77)	
Normal weight	4,942 (65.36)	1,409 (66.62)	1,103 (66.61)	
Overweight	466 (6.16)	117 (5.53)	94 (5.68)	
Obese	408 (5.40)	139 (6.57)	82 (4.95)	
Preterm birth history				0.94
No	7,166 (94.78)	2,006 (94.85)	1,573 (94.99)	
Yes	395 (5.22)	109 (5.15)	83 (5.01)	
Folic acid supplementation				0.44
Adequate	2,417 (31.97)	688 (32.53)	556 (33.57)	
Inadequate	5,144 (68.03)	1,427 (67.47)	1,100 (66.43)	

Note. IPI, inter-pregnancy interval; BMI, Body Mass Index.

challenges in China.

Our study found that concurrent folate deficiency and a shorter IPI could synergistically disrupt fetal growth. In particular, these features were found to impact the risk of SGA, which is a metric integrating gestational age and weight.

Table 2. Associations between a short IPI and adverse birth outcomes (*N* = 11,332)

Exposure	Outcome		*OR* (95% *CI*)	OR_{adj} (95% *CI*)[+]	*P* for trend
	Preterm birth, *N* (%)				
	No	Yes			
Normal IPI	7,134 (94.35)	427 (5.65)	1.00	1.00	< 0.01
Short IPI	1,951 (92.25)	164 (7.75)	1.40 (1.17, 1.69)	1.41 (1.17, 1.70)	
Very Short IPI	1,520 (91.79)	136 (8.21)	1.50 (1.22, 1.83)	1.51 (1.24, 1.85)	
	Low birth weight, *N* (%)				
	No	Yes			
Normal IPI	7,153 (94.60)	408 (5.40)	1.00	1.00	< 0.01
Short IPI	1,990 (94.09)	125 (5.91)	1.10 (0.90, 1.35)	1.11 (0.90, 1.36)	
Very Short IPI	1,531 (92.45).	125 (7.55)	1.43 (1.16, 1.76)	1.45 (1.17, 1.78)	
	Small for gestational age, *N* (%)				
	No	Yes			
Normal IPI	6,507 (86.06)	1,054 (13.94)	1.00	1.00	< 0.01
Short IPI	1,758 (83.12)	357 (16.88)	1.25 (1.10, 1.43)	1.26 (1.11, 1.44)	
Very Short IPI	1,333 (80.50)	323 (19.50)	1.50 (1.30, 1.72)	1.52 (1.32, 1.74)	

Note. [+]Adjustment variables included maternal age, education, smoking, alcohol consumption, pre-pregnancy BMI category and preterm birth history. IPI, inter-pregnancy interval; *OR*, odds ratio; *CI*, confidence interval.

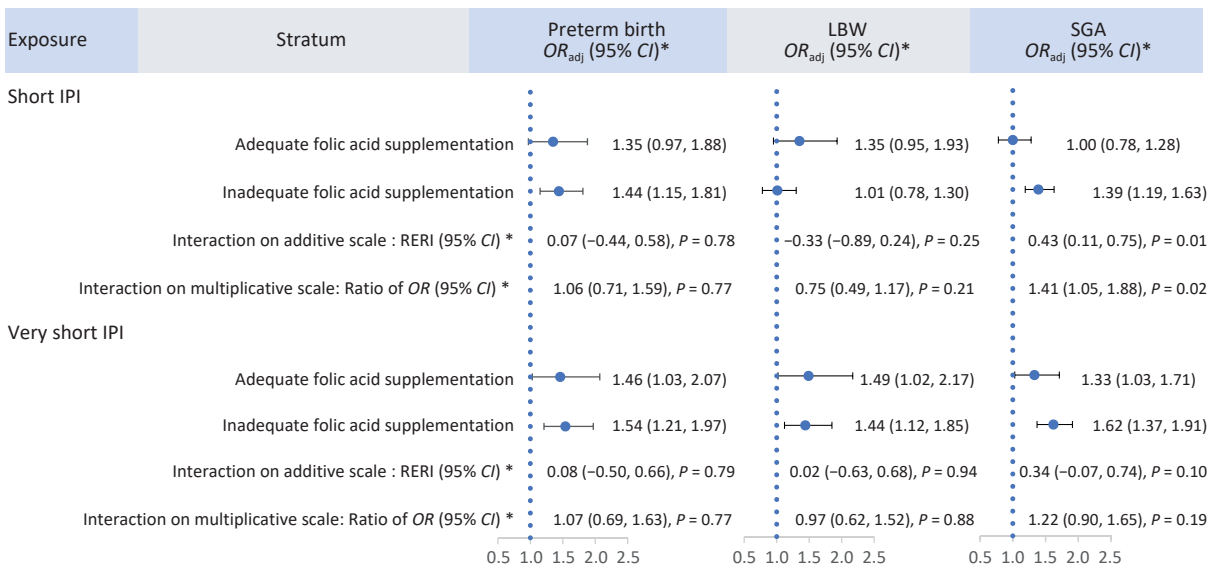

Figure 1. Stratification analysis on the association between short IPI and adverse birth outcomes by folic acid supplementation category. [*]Adjustment variables included maternal age, education, smoking, alcohol consumption, pre-pregnancy BMI category and preterm birth history. IPI, inter-pregnancy interval; LBW, low birth weight; SGA, small for gestational age; *OR*, odds ratio; RERI, relative excess risk of interaction; *CI*, confidence interval.

Notably, although folate supplementation attenuated SGA risk in short IPI pregnancies, this effect was absent for preterm birth and LBW. This finding suggests divergent pathways, in which SGA infants may be more responsive to nutritional intervention. Folate, an essential nutrient for DNA synthesis and cellular replication, is progressively depleted during pregnancy and lactation. Postpartum replenishment occurs gradually, and maternal folate levels remain suboptimal for up to six months following delivery[3,5]. This sustained nutritional deficit likely contributes to the folate deficiency observed among women with a short IPI, thereby adversely affecting fetal growth and pregnancy maintenance[4].

In addition to these established mechanisms, breastfeeding emerged as a dual mediator of this association. Prolonged breastfeeding extends the IPI *via* lactational amenorrhea while conserving iron and folate through reduced menstrual loss[12]. Abrupt weaning before a short IPI may exacerbate micronutrient deficits, suggesting that combined supplementation and lactation education may be a synergistic intervention to reduce the risk of adverse birth outcomes.

Humans are entirely dependent on dietary sources or supplements to maintain their folate supplies. Mean folate intake of Chinese women of childbearing age was estimated as 211.0 μg/d in the South and 189.2 μg/d in the North. These intakes are approximately equivalent to the recommended dietary allowance (RDA) for women who are not pregnant (180 μg/d). Respectively, 65.9% of Northern Chinese women and 12.0% of Southern Chinese women did not achieve the required serum folate levels (≥ 15.9 nmol/L)[13]. Thus, folic acid supplementation before pregnancy is necessary for Chinese women. However, our study showed that 68% of mothers received inadequate folic acid supplementation, and most did not initiate supplementation before pregnancy. Although China has a free folic acid program for women who are planning to conceive[14], increasing the rate of preconception folic acid supplementation is essential. Methods to improve folic acid supplementation should be explored. We recommend extending routine folic acid supplementation for a minimum of six months postpartum. Counseling interventions for women at elevated risk of folate deficiency should be prioritized, including those experiencing unplanned pregnancies or with IPIs under 12 months.

To our knowledge, this is the first population-based cohort study conducted in China to discuss the role of folic acid supplementation in the association between a short IPI and adverse birth outcomes. Information on maternal demographics, health habits, and first pregnancy allowed the analysis to adjust for several confounding factors. Medical records were used to obtain birth outcome information in a robust manner.

However, the limitations of this study should be considered. Although the analysis considered a number of confounders, residual confounders may still exist in our study results. Information on folic acid supplementation was based on self-report. However, self-report questionnaires have been shown to provide valid measures of folic acid use. However, the specific cumulative exposure dose of folic acid supplementation could not be measured in our study, making it difficult to analyze the dose-response effect of folic acid supplementation on the risk of adverse birth outcomes associated with a short IPI. Our study was conducted in Changsha, a region of central China. It remains to be determined whether the findings are generalizable to other regions, especially to populations with different dietary habits.

This population-based study found that 33% of multiparous Chinese women had an IPI of less than 18 months, and a shorter IPI was significantly associated with an increased risk of preterm birth, LBW, and SGA in a dose-response relationship. Adequate folic acid supplementation may significantly reduce the risk of SGA associated with a shorter IPI to 12–18 months among Chinese multiparous women. Thus, our results support prolonging postpartum folic acid supplementation to six months and implementing risk-stratified counseling programs targeting populations with unplanned pregnancies or short IPIs (< 12 months). In doing so, maternal nutrient depletion will be addressed within these high-risk categories.

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Competing Interests The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate This study had a retrospective design, and all data were collected solely from medical records. All personal information was recorded with initials or numbers,

which guaranteed that no participant information could be identified in the data analysis. This study was reviewed by the Ethical and Confidentiality Committee of Hunan Normal University (2019-002, approved on Mar 1, 2019), which waived the need for information.

Authors' Contributions Investigation and writing of the original draft preparation: Zhiqing Zhao; Data management and formal analysis: Wenbin Ouyang; Supervision and methodology: Ling Chen; Methodology and interpretation of results: Jing Deng; Data management and investigation: Xiaohui Chen; Supervision, funding acquisition, methodology, writing, reviewing, and interpretation of results: Xin Huang. All the authors have read and approved the manuscript.

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Data Sharing The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request. The supplementary materials will be available in www.besjournal.com.

[&]These authors contributed equally to this work.

[#]Correspondence should be addressed to Xin Huang, PhD, E-mail: xin.huang@hunnu.edu.cn

Biographical notes of the first authors: Zhiqing Zhao, Master of Public Health, majoring in epidemiology and statistics; E-mail: zhao1310492162@163.com; Ling Chen, Associate Chief Physician, majoring in obstetrics and gynecology, E-mail: ling_chen929@163.com

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