



# Impact of Periconceptional Folic Acid Supplementation on Low Birth Weight and Small-for-Gestational-Age Infants in China: A Large Prospective Cohort Study

Nan Li, PhD<sup>1,2</sup>, Zhiwen Li, PhD<sup>1,2</sup>, Rongwei Ye, PhD<sup>1,2</sup>, Jianmeng Liu, PhD<sup>1,2</sup>, and Aiguo Ren, PhD<sup>1,2</sup>

**Objectives** To explore the effects of maternal folic acid supplementation alone during pregnancy on the incidence of low birth weight (LBW) and small-for-gestational-age (SGA) infant status.

**Study design** Data were derived from a large population-based cohort study performed in China to evaluate the prevention of neural tube defects with folic acid supplementation. The sample comprised 200 589 singleton live births registered in 2 southern Chinese provinces by mothers for whom detailed information on folic acid use was available. Gestational age was calculated from the first day of the last menstrual period. LBW was defined as a birth weight <2500 g. Infants were considered SGA when the age-adjusted birth weight was below the 10th percentile as defined by a national survey performed in 1998. Logistic regression was used to estimate the effects of folic acid after adjusting for the principal potential confounders.

**Results** The overall incidence of LBW and SGA status was 2.18% and 5.82%, respectively. The incidence of LBW and SGA status was 2.09% and 5.73% in women who took folic acid, and 2.27% and 5.90% in those who did not. The adjusted risk ratios associated with folic acid use were 0.85 (95% CI: 0.80-0.90) for LBW and 0.93 (95% CI: 0.89-0.96) for SGA status. Folic acid use during pregnancy appeared to be particularly important to prevent LBW and SGA status.

**Conclusions** A maternal daily intake of 400 µg folic acid alone significantly reduced the risks of infant LBW and SGA status. (*J Pediatr* 2017;187:105-10).

Low birth weight (LBW) is one of the most common adverse outcomes of pregnancy, causing substantial neonatal, infant, and childhood mortality and morbidity,<sup>1,2</sup> particularly in developing countries.<sup>3,4</sup> Globally, more than 20 million LBW infants are born annually, with a worldwide incidence of 16%; Asia accounts for 75% of all such infants.<sup>5</sup> The rates of LBW and small-for-gestational-age (SGA) infants have increased in recent years, and the current incidences in some Chinese regions are 5.2%<sup>6</sup> and 9.2%,<sup>7</sup> respectively. LBW infants delivered at term usually exhibit inadequate growth for gestational age, whereas those delivered pre-term include those with normal growth for gestational age and those with inadequate growth for gestational age. Maternal nutrition before and during pregnancy may play a vital role in pregnancy outcomes.<sup>8,9</sup>

It is widely believed that folic acid alone critically affects LBW and SGA status. Free folic acid supplementations with the dose of 400 µg/day have been given to rural women of child-bearing ages across China under a policy issued by the Ministry of Health since 2009. The prevalence of folic acid supplementation in the Chinese population increased thereafter.<sup>6</sup> However, the compliance did not reach expectations in rural China.<sup>10</sup>

A Cochrane review found that folic acid use during pregnancy had no significant effect on birth weight <2500 g<sup>11</sup> whereas the Generation R study showed that folic acid supplementation alone was associated with a reduced risk of LBW.<sup>12,13</sup> Differences in these findings may reflect that folic acid use was self-reported, rendering it impossible to record compliance, or the dose and timing of folic acid use, during pregnancy. In this study, we explored whether the use of folic acid alone during the periconceptional period reduced the risks of LBW and SGA status in China.

## Methods

The methods of the original study have been previously described.<sup>14,15</sup> Beginning in 1993, the Chinese Ministry of Health conducted a public health campaign to prevent neural tube defects in infants born in 21 counties of 2 southern Chinese provinces (Zhejiang and Jiangsu) and 1 northern province (Hebei). During this

|     |                           |
|-----|---------------------------|
| BMI | Body mass index           |
| LBW | Low birth weight          |
| RRs | Risk ratios               |
| SGA | Small-for-gestational-age |

From the <sup>1</sup>Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health; and <sup>2</sup>Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China

Supported by the National Natural Science Foundation of China (81373014 and 81673177). The original project was supported by a co-operative agreement between the United States Centers for Disease Control and Prevention and Peking University (U01 DD000293). The authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jpeds.2017.04.060>

campaign, all of the women who were preparing for marriage or who became pregnant were registered in a dedicated database that served as the principal record of prenatal care and the source of all of the demographic information. All of the women were advised to take a pill containing 400 µg folic acid alone every day, starting at the time of registration and continuing until completion of the first trimester of pregnancy. Those who consented received pills at the time of registration. At the end of each month, health workers recorded the dates of all of the menstrual periods and how many pills remained in the bottles. To evaluate the effects of folic acid on neural tube defects, we identified women registered between October 1993 and September 1995, who delivered by December 31, 1996 and whose fetuses or infants were confirmed to either have or not have neural tube defects, whose infants had been born live or stillborn, or who electively terminated their pregnancies because of prenatal diagnosis of a birth defect. Miscarriages and elective terminations occurring before 20 weeks of gestation were not included in this analysis. The original cohort included 247 831 women. The project was approved by the Institutional Review Boards of the United States Centers for Disease Control and Prevention and the Peking University Health Science Center. All of the women who took pills provided oral informed consent.

### Selection of Study Subjects

We selected women from the large cohort study described above who resided in 2 neighboring southern provinces (Jiangsu and Zhejiang provinces). Of the 215 871 women, 15 282 were excluded for 1 or more of the following reasons: major external birth defects in the infant, neonatal death, or stillbirth ( $n = 3247$ ), unknown gestational age ( $n = 105$ ), gestational age <28 weeks or >45 weeks ( $n = 2050$ )<sup>16</sup>; multiple births ( $n = 8749$ ), missing data on parity, ethnicity, education, and/or occupation ( $n = 7057$ ); missing data for infant birth weight or birth weight <1500g or >6000 g ( $n = 9052$ ). The final study population included 200 589 women (92.92% of all those in the database).

### Definition of Folic Acid Use

We evaluated folic acid consumption according to the method by Berry et al.<sup>14</sup> Women who took folic acid pills at any time from registration until the end of the first trimester were classified as folic acid users. Folic acid usage was divided into 4 patterns based on usage period: (1) periconceptional use, defined as initiation of folic acid supplementation before the last menstrual period and termination at the end of the first trimester; (2) preconceptional use, defined as the initiation and termination of folic acid use before the last menstrual period; (3) postconceptional use, defined as initiation of folic acid supplementation after the last menstrual period but within the first trimester; and (4) no use, defined as no supplementation at all. Women for whom relevant dates were missing were considered unclassifiable and were not assigned to any folic acid usage subgroup. Women who refused to take folic acid or who became registered during the second trimester of pregnancy (ie, who did not have the opportunity to start taking

folic acid by the end of the first trimester) were considered nonusers. Compliance was calculated by dividing the total number of pills taken by the total number of days between initiation and termination of supplementation.

### Definition of Low Birth Weight and SGA Status

Calculation of gestational age was based on the first day of the last menstrual period. LBW was defined as a birth weight <2500 g.<sup>17</sup> Infants were considered SGA when the age-adjusted birth weight was <10th percentile based on results of a 1998 national survey.<sup>18</sup>

### Statistical Analyses

The basic characteristics of pregnant women in different groups were compared using the Student *t* test for quantitative variables and the  $\chi^2$  test for categorical variables. We used logistic regression to evaluate the risk ratios (RRs) of LBW by folic acid supplementation, adjusted for potential confounders (Table I). The mean body mass index (BMI) was used if individual data were missing. All of the analyses employed SPSS v 20.0 software (SPSS, Inc, Chicago, Illinois).

## Results

The final study population included 200 589 women. The maternal characteristics are shown in Table I. Women who took folic acid averaged 1.27 years younger and 0.52 kg/m<sup>2</sup> less in terms of BMI than those who did not. Women who took folic acid were more likely to be primiparous, of Han ethnicity, factory workers, and better educated.

The overall incidence of LBW and SGA status was 2.18% and 5.82%, respectively. The incidence of LBW and SGA status was 2.09% and 5.73% in women who took folic acid, and 2.27% and 5.90% in those who did not. Compared with women who did not take folic acid, those who did were less likely to bear infants of LBW (RR: 0.92 [95% CI: 0.86, 0.97]), but SGA status

**Table I. Characteristics of women who enrolled in the pregnancy monitoring system according to their folic acid use in China between 1993-1996**

| Characteristics                    | Folic acid user<br>(n = 105 238) |       | Nonusers<br>(n = 95 351) |       | P     |
|------------------------------------|----------------------------------|-------|--------------------------|-------|-------|
|                                    | n*                               | %†    | n*                       | %†    |       |
| Age at pregnancy, (y, mean, SD)    | 24.27 (2.45)                     |       | 25.54 (3.76)             |       | <.001 |
| BMI (kg/m <sup>2</sup> , mean, SD) | 20.32 (2.16)                     |       | 20.84 (2.41)             |       | <.001 |
| Primiparous                        | 96919                            | 92.10 | 69 887                   | 73.29 | <.001 |
| Han ethnic group                   | 104 673                          | 99.46 | 94 707                   | 99.32 | <.001 |
| Education                          |                                  |       |                          |       | <.001 |
| High school or higher              | 12 233                           | 11.62 | 9812                     | 1.29  |       |
| Junior high school                 | 66 389                           | 63.08 | 52 802                   | 55.38 |       |
| Primary school or lower            | 26 616                           | 25.29 | 32 737                   | 34.33 |       |
| Occupation                         |                                  |       |                          |       | <.001 |
| Farmer                             | 55 772                           | 53.00 | 62 696                   | 65.75 |       |
| Factory worker                     | 34 179                           | 32.48 | 20 806                   | 21.82 |       |
| Other occupation                   | 15 287                           | 14.53 | 11 849                   | 12.43 |       |

\*Values for some characteristics may not be equal to total numbers of folic-acid or nonfolic acid groups because of missing values.

†Values for some characteristics may not be equal to 100 because of rounding.

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