

Folate deficiency in early pregnancy increases the risk of low birth weight: survey of neonates in eastern China

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Research article

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Abstract

Background

Low birth weight (LBW) is a major cause of fetal mortality and morbidity. This study aims to assess the relationship between maternal serum folate levels and LBW in early pregnancy in eastern China.

Methods

We conducted a retrospective study including 124 newborns with LBW (born ≥ 1500 g to < 2500 g) and 393 normal birth weight neonates (NBW). The maternal methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism genotyping was performed by the gene chip hybrid method. The concentrations of serum homocysteine (hcy), folate, vitamin B12 and vitamin D were measured before 18 weeks of pregnancy. Multivariable logistic regression model was used to identify the predictors of LBW.

Results

After controlling the covariates, maternal underweight before pregnancy (AOR = 5.15: 95% CI 2.40, 11.05), folate deficiency in early pregnancy (AOR = 2.06: 95% CI 1.03, 4.09), preeclampsia during pregnancy (AOR = 6.02: 95% CI 2.83, 12.81), and premature delivery (AOR = 23.81: 95% CI 12.90, 43.95) were risk factors for LBW. However, multipara (AOR = 0.53:95% CI 0.31, 0.91) was a protective factor for LBW.

Conclusions

This study revealed different factors associated with LBW in eastern China. Sufficient folate before 18 weeks of pregnancy is a protective factor for LBW. Serum folate > 32.5 nmol/L can reduce the risk of LBW. Therefore, maternal screening of folate status in the first trimester of pregnancy could be helpful.

Background

Low birth weight (LBW, birth weighed < 2500 g) is a global public health problem. The incidence of LBW is reported around 10% worldwide(1). And there are more than one million infants with LBW annually in China(2). Growing evidence have shown that newborns with LBW along with preterm birth (PTB, deliver within 37 weeks of gestation) are associated with fetal growth and neuronal development, increasing the risk of mortality and morbidity(2).

Folate is a micronutrient involved in one-carbon (1C) metabolism and supplies with methyl donors required for the DNA synthesis, repair and methylation, which is essential for fetal and placental growth(3, 4). Therefore, folate plays an important role during pregnancy. 5,10- methylenetetrahydrofolate reductase (MTHFR) is an essential regulator enzyme in the folate metabolism, which converts 5,10-MTHF to 5-

MTHF irreversible(5). Its C677T variants make the amino acid changed from alanine to valine, which results in a reduced enzymatic activity. Evidence by Frosst et al(6). showed that compared with MTHFR 677CC genotype, MTHFR 677CT genotype retained nearly 65% of the enzymatic activity, and MTHFR 677TT genotype retained only approximately 30%. It was proved that the mutation of MTHFR C677T can lead to the decreasing of the folate utilization and hyper-homocysteinemia (HHcy)(7). Hcy is considered to damage the vascular endothelium, destroy the coagulation and fibrinolytic system, ultimately lead to adverse birth outcomes(8, 9). Statistics show folate deficiency is ubiquity in a quarter of pregnant women worldwide(10). Folate deficiency has been linked to neural tube defects (NTD)(11, 12), whereas its impact on other severe pregnancy outcomes is inconclusive. Some studies provide support to maternal MTHFR 677TT genotypes, together with maternal circulating folate and homocysteine (hcy) concentrations are independent risk factors for small gestational age (SGA)(13–15). Other observational studies found no direct association between low folate levels and pregnancy complications(16–18). To date, the role of folate intake to prevent NTD is verified(19, 20). Most relevant studies adopted self-statement of multivitamin supplementation, which may be imprecise, so serum folate concentration during pregnancy would be more ideal. Moreover, few studies focused on folate deficiency in early pregnancy in developing countries. In consideration of rural districts, folate deficiency was defined as < 6.8 nmol/ml and vitamin B12 deficiency as < 150 pmol/ml, which are recommended by WHO(21). As majority of the women have multivitamin supplement during the first three-months pregnancy in urban area of China, the cut-offs of micronutrient (Vitamin B12 and folate) are inappropriate.

Given above elements, we collected a cohort of hospital-delivered neonates to explore the relationship between maternal folate status and LBW in eastern Chinese pregnant women before 18 weeks of gestation.

Methods

Study population

Hospital-delivered newborns were enrolled between April 2018 and October 2020 in the Obstetrics and Gynecology Hospital of Fudan University, including a total of 124 newborns with LBW and 393 NBW. Epidemiological data were collected for pregnant women covered maternal age at delivery (<35, ≥35 years), pre-pregnancy body mass index (BMI), maternal education level (no education or primary education, secondary education, higher education), gravidity and parity.

The BMI was calculated by weight before pregnancy / (height²) and grouped into four categories according the China guidelines (underweight, <18.5, normal weight, 18.5-23.9, overweight, 24.0-27.9; obesity, ≥28.0). Preeclampsia was defined as PRH (SBP≥140 mmHg or DBP≥90 mmHg) with proteinuria (24h urinary protein level of >0.3 g or urine dipstick protein level≥+). GDM was diagnosed by oral glucose tolerance test (fasting plasma glucose≥5.1 mmol/L, 1h plasma glucose≥10.0 mmol/L, or 2h plasma glucose≥8.5 mmol/L). The PTB was defined to deliver within 37 weeks of gestation. Gestational age of serum sampling was determined by the result of ultrasound. Serum biochemical

parameters were measured within 18 weeks of gestation. Gestational age, delivery mode (eutocia vs. cesarean), gender and birth weight of newborns were obtained from medical records.

Pregnant women were excluded if they were under 18 years old, smoking or drinking, multiple pregnancy, embryo transfer, in vitro fertilization, and microbial infection. Neonates with birth defects, spontaneous abortion, birth weight <1500 g or gestational age <30 weeks were also excluded in this study.

Detection of MTHFR C677T polymorphism

Genomic DNA was extracted from the whole blood of the pregnant women using a column extraction kit. The MTHFR C677T polymorphism was detected by gene chip hybrid analysis following the manufacturer's instructions. The polymerase chain reaction (PCR), hybridization, gene array detection and analysis were conducted using the BaiO genotype detecting gene array kit and equipment (BaiO Technology Corp., Shanghai). The MTHFR C677T was genotyped as wild (CC), heterozygous (CT) and homozygous (TT) gene type, respectively.

Measurement of biochemical parameters

The biochemical parameters were measured before the 18th week of pregnancy. Plasma hcy was determined using Hitach 7600 automatic chemistry analyzer (Hitach Diagnostics Ltd.). Serum folate, vitamin B12 and vitamin D concentrations were measured using an Architect i2000 Analyzer (Abbott). The cut-off values for distribution of metabolic parameters considered in this study were hyper hcy $\geq 8\mu\text{mol/L}$, folate deficiency <32.5 nmol/L, vitamin B12 deficiency <280 pmol/L, and vitamin D deficiency <30 nmol/L, respectively.

Statistical analysis

Statistical analyses were performed using the SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Variable selection in multivariable modeling was based on clinical and statistical significance. Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were indicated as number and percent (n, %). Independent-sample t test or chi-square test was used to evaluate the difference in clinical characteristics. A two-sided *p*-value less than 0.05 was considered to be statistically significant. Multivariable logistic regression analysis was used to determine the adjusted odds ratios (AOR) with 95% confidence intervals (CI) for the associations between folate deficiency and LBW, adjusted for maternal age, pre-pregnancy BMI, MTHFR 677T, PE, delivery mode, parity, and gestational age.

Results

Socio-demographic Characteristics

A cord of 517 pregnant women with neonate were included. Of these, 23.98% (124/517) were LBW babies. The baseline characteristics are summarized in Table 1. There was a large difference in

birthweight between LBW (2164.90 ± 227.53 g) and NBW (3350.71 ± 415.75 g) neonates. Gestational ages were also lower in LBW newborns (249.72 ± 15.89) than NBW (274.06 ± 9.84). The proportion of underweight, MTHFR T allele, folate deficiency, primipara, cesarean and preeclampsia of LBW were higher than NBW group. No other differences in maternal or neonatal characteristics were observed, including maternal age ($p = 0.674$), education level ($p = 0.937$), GDM ($p = 0.352$) and gender ($p = 0.094$). Besides, there were no difference with the proportion of pregnant women being deficient in vitamin B12 (23.4% Vs 24.4%) and vitamin D (28.2% Vs 21.6%) and HHcy (29.8% Vs 25.7%).

Table 1

Maternal clinical characteristics and neonatal birth data in LBW (n = 124) and NBW(n = 393) groups

Predictor variables	Category of variables	LBW (n/%)	NBW (n/%)	p value
Maternal age (years)	< 35	92 (74.2)	284(72.3)	0.674
	≥ 35	32(25.8)	109(27.7)	
Pre-pregnancy BMI (kg/m ²)	underweight (< 18.5)	23(18.5)	33(8.4)	0.013
	normal weight (18.5–23.9)	73(58.9)	253(64.4)	
	overweight (24-27.9)	22(17.7)	76(19.3)	
	obesity (≥ 28)	6(4.8)	31(7.9)	
Parity	primipara	67(54.0)	158(40.2)	0.007
	multipara	57(46.0)	235(59.8)	
Education level	no education or primary education	7(5.6%)	19(4.8%)	0.937
	secondary education	33(26.6%)	106(27.0%)	
	higher education	84(67.7%)	268(68.2%)	
GDM	yes	22(17.7%)	85(21.6%)	0.352
	no	102(82.3)	308(78.4)	
Preeclampsia	yes	37(29.8%)	28(7.1%)	0.000
	no	87(70.2)	365(92.9)	
Gestational age (weeks)	< 37	75(60.5)	28(7.1)	0.000
	≥ 37	49(39.5)	365(92.9)	
MTHFR C677T	CC	29(23.4)	115(29.3)	0.045
	CT	62(50.0)	212(53.9)	
	TT	33(26.6)	66(16.8)	
Hcy (μmol/L)	< 8	87(70.2)	292(74.3)	0.364
	≥ 8	37(29.8)	101(25.7)	
Folic acid (nmol/L)	< 32.5	29(23.4)	50(12.7)	0.004

BMI, body mass index; Hcy, homocysteine; MTHFR, methylenetetrahydrofolic acid reductase

Predictor variables	Category of variables	LBW (n/%)	NBW (n/%)	<i>p</i> value
	≥ 32.5	95(76.6)	343(87.3)	
Vitamin B12 (µmol/L)	< 280	29(23.4)	96(24.4)	0.814
	≥ 280	95(76.6)	297(75.6)	
Vitamin D (pmol/L)	< 30	35(28.2)	85(21.6)	0.129
	≥ 30	89(71.8)	308(78.4)	
Sex of the newborn	boys	54(43.5)	205(52.2)	0.094
	girls	70(56.5)	188(47.8)	
Mode of delivery	eutocia	49(39.5)	219(56.0)	0.001
	cesarean	75(60.5)	174(44)	
Gestational age (weeks)	preterm (< 37)	75(60.5)	28(7.1)	0.000
	term (≥ 37)	49(39.5)	365(92.9)	
BMI, body mass index; Hcy, homocysteine; MTHFR, methylenetetrahydrofolic acid reductase				

Interaction of MTHFR C677T genotypes with serum parameter levels

Table 2 shows the interaction of MTHFR C677T gene polymorphism with serum hcy, folate, vitamin B12 and vitamin D concentrations. Hcy concentrations were significantly higher in individuals having 677T allele of MTHFR (7.0 µmol/L (TT) vs 6.28 µmol/L (CC), $p = 0.004$), while folate levels were lower (36.56 nmol/L vs 38.62 nmol/L, $p = 0.023$). However, MTHFR 677 genotypes did not show impact on Vitamin B12 or D levels. This result showed certain genotypes have a close relationship with serum hcy or folate levels.

Table 2
Interaction of MTHFR 677 genotypes with hcy, folate, vitamin B12 and D biomarkers

MTHFR C677 T genotype	Hcy ($\mu\text{mol/L}$)	Folate (nmol/L)	Vitamin B12 (pmol/L)	Vitamin D (nmol/L)
CC	6.28 \pm 1.51	38.62 \pm 5.19	405 \pm 159.52	43.62 \pm 16.86
CT	6.70 \pm 1.86	37.63 \pm 5.93	385.88 \pm 145.02	46.10 \pm 18.76
TT	7.00 \pm 1.53	36.56 \pm 6.02	364.76 \pm 149.01	46.69 \pm 18.33
<i>p</i> value	0.004	0.023	0.119	0.326

Hcy, homocysteine; MTHFR, methylenetetrahydrofolic acid reductase

Multivariable logistic regression analysis for the risk factors associated with LBW

After controlling the covariates, women with folate deficiency in early pregnancy had twice-higher odds of newborns with LBW compared to women with sufficient serum folate (AOR = 2.06: 95% CI 1.03, 4.09). The likelihood of LBW was 5-folds higher odds among newborns who had underweight mothers before pregnancy compared to those normal weight mothers (AOR = 5.15: 95% CI 2.40, 11.05). As was expected, preterm births had 23-folds higher odds of LBW compared to full-term neonates (AOR = 23.81: 95% CI 12.9,43.95). Moreover, women who were diagnosed with preeclampsia during pregnancy had 6-greater odds of newborns with LBW (AOR = 6.02: 95% CI 2.83, 12.81). While the odds of delivery with LBW babies were less by 47% among multipara women compared with primipara women (AOR = 0.53: 95% CI 0.31, 0.91). Besides, maternal age, education level, GDM, hyper hcy, vitamin B12 or D deficiency, and gender were not associated with neonatal LBW in this study (Table 3).

Table 3
Multivariable logistic regression analysis for the risk factors associated with LBW

LBW	β	SE	Wald	df	P	AOR (95% CI)
BMI						
underweight	1.64	0.39	17.65	1	0.000	5.15(2.40-11.05)
normal weight						1(reference)
overweight	-0.47	0.39	1.46	1	0.23	0.62(0.29–1.34)
obesity	-1.14	0.61	3.46	1	0.06	0.32(0.10–1.06)
MTHFR C677T						
CC			2.56	2	0.28	1(reference)
CT	-0.06	0.33	0.04	1	0.85	0.94(0.49–1.79)
TT	0.50	0.40	1.55	1	0.21	1.65(0.75–3.62)
Folate deficiency	0.72	0.35	4.21	1	0.04	2.06(1.03–4.09)
Mode of delivery	-0.33	0.29	1.28	1	0.26	0.72(0.41–1.27)
Preeclampsia	1.80	0.39	21.67	1	0.000	6.02(2.83–12.81)
Preterm	3.17	0.31	102.78	1	0.000	23.81(12.90-43.95)
Multipara	-0.64	0.28	5.25	1	0.022	0.53(0.31–0.91)
AOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; MTHFR, methylenetetrahydrofolic acid reductase						

Discussion

According to epidemiological observations, LBW along with PTB remains the main cause of neonatal mortality and morbidity. Despite intervention efforts, the rate of LBW newborns remained high and varies across regions within countries(22–30), 9.8% in USA and 13-17.3% in Zimbabwe and Ethiopia(30–32). This study was conducted in eastern China where owned several Obstetrics and Gynecology Hospitals. The proportion of LBW was about 23.98% because we oversampled LBW at enrolment. As a result, the likelihood of delivering a LBW newborn would be less as compared to pregnant women in rural areas(26, 28).

A majority of studies principally emphasized the association of maternal folic acid supplementation and fetal birth weight(33–35). Our study focused on serum folate levels before 18 weeks of pregnancy and evaluated the relationship with LBW. In our individuals, serum folate concentrations were generally high, with a mean value of 37.71 nmol/l. Beside the previously known factors (prematurity, preeclampsia)(36, 37), the results showed that folate deficiency (< 32.5 nmol/l) before 18 weeks gestation was an

independent risk factor for LBW in eastern Chinese pregnant women. This is more accurate than studying the relationship between folic acid supplementation and LBW. Similarly, our result indicated that the maternal preeclampsia in late pregnancy was found to be an independent factor contributing to LBW. The probability of LBW was 6-folds higher among mothers having preeclampsia than those not having PE. This finding is in line with studies conducted in Ethiopia and Nepal(29, 38). This might due to the decreased oxygen and nutrient perfusion to the placenta(30).

Our finding indicated that MTHFR 677T and folate deficiency were associated with LBW, not including vitamin B12 and D deficiency or elevated Hcy. Seemingly our findings were in disagreement with other results, which show that elevated Hcy and lowered folate levels during pregnancy are associated with LBW(39, 40). In fact, Hcy levels were significantly higher in individuals having 677T allele of MTHFR, while folate level was distinctly lower. However, following the binary logistic regression analysis, it turns out that folate deficiency but not MTHFR 677T was independent risk factor. This result might due to the different cut-off value of serum parameter levels. Here we define it as lower range of the parameter spectrum. Besides, no statistically significant difference was found in the education level of our individuals. However, a retrospective analysis of the Nigeria population found maternal characteristic (education) was a predictor of LBW, including a cohort of 9,244 live births(41). Another case-control study in Blacks and Whites reported maternal educational attainment was inversely associated with LBW overall, including 2,922 births to Black (n = 2,146) and White (n = 776) mothers)(42). In this study, the rate of secondary school and higher education graduates were 94.97%. We thought that the increased awareness of adequate multivitamin nutrition intake was associated with increased education levels. These two findings were contrary to our results, which may be due to the overall high level of education and low sample size of low education level pregnant women in our area.

It was reported that the risk of LBW in women with pre-pregnancy low BMI was significantly increased. One birth cohort survey of 3401 neonates in Pomerania found that compared to women with normal pre-pregnancy BMI, underweight women had an increased chance of premature labour and low birth weight (AOR = 1.73; 95% CI: 1.29–2.31)(43). Our result was consistent with this phenomenon (AOR = 5.15; 95% CI: 2.40-11.05). In this research, we also found another interesting phenomenon. The likelihood of LBW was higher in primipara compared with multipara, suggesting multipara as a protective impact on LBW. This might be due to the fact that multipara women might have a better preparation folic acid supplementation and timely detection and treatment of folate statue. As a result, the likelihood of having a low birth weight baby would be less as compared to primipara. This finding supports that timely supervision, multivitamin supplement, and folate determination are important during early pregnancy.

There were several certain strengths and limitations in this study. We did not recruit babies with birth asphyxia or antenatal infection, delivery before 30 weeks gestation and/or < 1500 g birthweight. It allows us to confidently exclude any clinically severe conditions. In additions, the data were collected from medical records and avoided recall bias of self-report. In view of the fact that almost all mothers of our cases added folic acid or multivitamins, supplementation before pregnancy was not investigated, which

could modify the level of plasma parameters. Further studies are warranted to examine other factors. The data was collected in eastern China so the results cannot be generalizable to other zones.

Conclusions

Our study confirms a positive association between adequate serum folate concentrations before 18th pregnancy and increased birth weight. Based on our findings, maternal adequate folate status (> 32.5 nmol/L) can reduce the risk of LBW. Further investigations with high-quality prospective data are required to explore the mechanisms. Clinicians should pay more attention to folate deficiency pregnant women and strengthen the supervision of early pregnancy, which has importance for newborn health.

Abbreviations

LBW: Low birth weight; NBW: normal birth weight neonates; MTHFR: methylenetetrahydrofolate reductase; Hcy: homocysteine; PTB: preterm birth; SGA: small gestational age; NTD: neural tube defects; BMI: body mass index; PCR: polymerase chain reaction; AOR: adjusted odds ratios; CI: confidence interval

Declarations

Ethics approval and consent to participate

The current retrospective study protocol was approved by the Medicine Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University (No. 2020-54). All women written informed consent in this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

YC analyzed and interpreted the data and was a major contributor in writing the manuscript. CY critically reviewed and modified the manuscript. All authors read and approved the final manuscript.

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