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Case Report

Correlation between folic acid supplement in different stage of pregnancy and wheezing in infants: a case-control study

Yanyan Yu, Guixiong Gu, Jing Yang, Yuhong Zhang, Yifen Wang, Qian Qian, Wei Li

Pediatric Asthma Department, Lianyungang Maternal and Child Healthcare Hospital in Jiangsu Province, Lianyungang 222006, Jiangsu Province, China

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Abstract: Objective: To investigate the relationship between folic acid supplement at different stage of pregnancy and wheezing in infants, so as to provide references for the choice of good timing of folic acid supplement during pregnancy. Methods: 1320 infants born in Lianyungang Maternal and Child Healthcare Center from April 201 1 to April 2012 were enrolled. By phone call and questionnaire survey in clinics, the data about the infants and their mothers were collected, including infants' gender, birth weight, first child or not, birth season and whether wheezing occurred within 2 years after birth, mother's education degree, smoking history, feeding method, whether vitamin A or vitamin D was supplemented during pregnancy, family-specific constitution or not, and timing of folic acid supplement during pregnancy. Based on whether wheezing occurred, the infants were divided into case group (n=397) and control group (n=923). Results: The two groups were not significantly different (P>0.05) in gender, birth weight, proportion of infants being first child, birth season, education levels of the mothers, smoking history, feeding method, proportion of mothers who had supplement of vitamin A and vitamin D during pregnancy. For infants, with or without wheezing, whose mothers had family-specific constitution, there was significant difference in the pregnancy stage of taking folic acid (P<0.05); for infants whose mothers began to take folic acid in middle and late stage of pregnancy, the risk of wheezing was 1.95 times greater than that of infants whose mothers did not take folic acid. Among infants, with or without wheezing, whose mothers did not have family-specific constitution, there was no significant difference in the pregnancy stage of taking folic acid (P>0.05). Conclusion: Folic acid supplement in mothers with family-specific constitution starting from middle and late stage of pregnancy may increase the risk of wheezing in infants.

Keywords: Folic acid, wheezing in infants, pregnancy, case-control studies

Introduction

Folic acid is a water-soluble B vitamin composed of pteridine, para-aminobenzoic acid and glutamate, and be considered as necessary nutrient for the cell growth and proliferation. Folic acid supplement during pregnancy can prevent neural tube defects during fetal development, low birth weight, premature birth and cleft plate [1]. It is important for all pregnant women to take folic acid and the US has mandated the addition of folic acid in food. Pregnant women in China are also advised of taking folic acid. But according to the latest research, supplement of folic acid as the methyl donor during pregnancy may have an impact on epigenetic mechanism of the infants, leading to a higher risk of some diseases, including allergic asthma phenotype [2, 3]. This study analyzed the correlation between the timing of folic acid supplement during pregnancy and occurrence of wheezing in infants from the perspective of epigenetics.

Materials and methods

Materials

A total of 1320 infants born in Lianyungang Maternal and Child Healthcare Center from April 2011 to April 2012 were enrolled. All of them satisfied the following criteria: No congenital heart disease; No severe liver and kidney dysfunction; No other congenital and metabolic

Table 1. Comparison of general data between the two groups

Group	Case	Gender (male/female)	Birth weight (g)	Proportion of being the first child [n (%)]	Season of birth [n (%)]			
					Spring	Summer	Autumn	Winter
Control group	923	476/447	3295±612	725 (78.5)	176 (19.1)	229 (24.8)	278 (30.1)	240 (26.0)
Case group	397	205/192	3280±737	314 (79.1)	71 (17.9)	82 (20.7)	138 (34.8)	106 (26.6)
X^2 (t) value		<0.01	0.38[a]	0.05			4.20	
P value		0.98	0.70	0.82			0.24	

Group	Mother's educational level[b] [n (%)]			Smoking history of the mother [n (%)]	Feeding method [n (%)]			Vitamin A and D supplement during pregnancy [n (%)]
	Low	Moderate	High		Breast feeding	Artificial breeding	Mixed	
Control group	216 (23.4)	405 (43.9)	302 (32.7)	5 (0.5)	458 (49.6)	217 (23.5)	248 (26.9)	209 (22.6)
Case group	96 (24.2)	187 (47.1)	114 (28.7)	1 (0.3)	198 (49.9)	103 (25.9)	96 (24.2)	82 (20.7)
X^2 (t) value		4.97		0.515		1.45		0.64
P value		0.083		0.47		0.48		0.42

Note: Subscript a denotes t value; subscript b denotes classification of mother's educational levels. Junior high school and below is defined as the primary educational level; senior high school or junior college education is defined as the secondary educational level; undergraduate education and above is defined as higher education.

diseases. Their mothers had no asthma, severe liver and kidney diseases, or mental and psychotic diseases.

Methods

By telephone call or questionnaire survey in clinic, the data of infants and mother were collected: gender of infants, birth weight, parity, season of birth and whether wheezing occurred infants within 2 years after birth; mothers' educational levels, smoking history, feeding method, with or without vitamin A or D supplement during pregnancy, timing of vitamin A or D supplement, and family-specific constitution or not. Wheezing in infants was diagnosed by physicians at the second-level hospital and above according to Zhu Futang Practice of Pediatrics [4]. Wheezing was classified into capillary bronchitis, asthmatoid bronchitis and asthmatoid bronchopneumonia according to the above diagnostic criteria. Family-specific constitution was evaluated based on the history of atopic dermatitis, urticaria and allergic rhinitis diagnosed at the second-level hospital and above. Infants were divided into two groups, wheezing group (397 cases) and non-wheezing group (923 cases).

Statistical methods

Statistical analyses were conducted using SPSS 15.0 software. Measurements were reported as mean ± standard deviation. *t*-test was used to compare means of the two groups. Counts were reported as relative numbers. X^2 test was used for intergroup comparison and P<0.05 was considered significant difference.

Results

General information comparison

There was no significant difference in infant gender, birth weight, proportion of being the first child, season of birth, mother's educational levels, smoking history of the mother, feeding method and taking supplement of vitamin A and D or not during pregnancy (P>0.05, **Table 1**).

Hierarchical analysis

Stratified analysis was performed between mothers with or without family-specific constitution. For infants, with or without wheezing, whose mothers had family-specific constitution, there was significant difference in the pregnancy stage of taking folic acid (P<0.05); for infants whose mothers began to take folic acid in middle and late stage of pregnancy, the risk of wheezing was 1.95 times greater than that of infants whose mothers did not take folic acid (**Table 2**). Among infants, with or without wheezing, whose mothers did not have family-specific constitution, there was no significant difference in the pregnancy stage of taking folic acid (P>0.05) (**Table 3**).

Discussion

Wheezing is the most common type of respiratory tract disease in infancy and considered the primary cause of hospitalization of infants. Recurrent wheezing may evolve into asthma. The pathogenesis of wheezing in infants and the increasing prevalence may be hardly ex-

Table 2. Correlation between pregnancy stage of taking folic acid among women with family-specific constitution and wheezing in infants

Group	Case	Not taking folic acid	1 month before pregnancy	Early stage of pregnancy	Middle and later stage of pregnancy
Control group	273	61 (22.3)	71 (26.0)	85 (31.1)	56 (20.6)
Case group	125	24 (19.2)	26 (20.8)	32 (25.6)	43 (34.4)
OR (95% CI)		1	0.93 (0.49, 1.79)	0.96 (0.51, 1.78)	1.95 (1.05, 3.62)
X^2 value			8.89		
P value			0.03		

Table 3. Correlation between pregnancy stage of taking folic acid among mothers without family-specific constitution and wheezing of infants

Group	Case	Not taking vitamin A and D supplement	1 month before pregnancy	Early stage of pregnancy	Middle and later stage of pregnancy
Control group	652	184 (28.3)	132 (20.3)	191 (29.4)	143 (22.0)
Case group	272	79 (29.0)	53 (19.5)	77 (28.3)	63 (23.2)
OR (95% CI)		1	0.94 (0.62, 1.41)	0.94 (0.65, 1.36)	1.03 (0.69, 1.53)
X^2 value			0.29		
P value			0.96		

plained by genomics. Human and animal experiments indicate that exposure to microbial risks, dietary changes and environmental pollution in the key pregnancy stage may lead to an altered pattern of gene expression or even permanent injury [5, 6]. And this is mainly mediated by epigenetic mechanism [7].

Epigenetics consists of several regulatory mechanisms, including DNA methylation, histone modification, chromatic remodeling and non-encoding RNA, all of which are independent from changes in DNA sequences. DNA methylation is the most common type of epigenetic modification. A latest research indicates that supplement of folic acid as the methyl donor during pregnancy may lead to epigenetic changes in infants and hence a higher risk of allergic diseases such as asthma phenotypes [8].

We found that the infants with and without wheezing did not differ significantly in gender, birth weight, proportion of being the first child, season of birth, educational background of the mother, feeding method, and taking vitamin A and D supplement or not during pregnancy. Wheezing in infants was correlated to whether taking folic acid supplement or not during middle and later stage of pregnancy for mothers with family-specific constitution [OR=1.95, 95% CI (1.05, 3.62)], but not correlated to the timing of taking folic acid supplement for mothers without family-specific constitution. Haberg *et al*. [9] showed that high levels of folic acid during middle stage of pregnancy led to a higher risk of asthma for infants aged 3 years. Hollingsworth *et al*. [3] built the allergic asthma model in mice, which were fed with diet with high folic acid during pregnancy. As a result, the infant mice suffered from hyperreactive airway and the level of eosinophil granulocytes and interleukin (IL) in bronchoalveolar lavage fluid increased dramatically. Moreover, the total serum IgE was increased by 13%, CD4+/CD8+ ratio was increased and a large amount of IL-4 and chemotactic ligands CCIA and CCL5 were produced with Th2 predominance. These all led to a higher risk of severe allergic diseases. Hollingsworth et al. [3] believed that the above changes were related to increased protein methylation levels and downregulation of RUNX3, Nfactl, JAK2, RCOR3 and UBE2J1 gene. Runt-related transcription factor 3 (RUNX3) is inhibitory of the production of CD4+/CD8+ cells. Hliberg et al. [10] studied 32077 mothers who took 400 μg/d folic acid daily and the results showed that folic acid supplement 3 months before pregnancy could lead to a higher risk of wheezing in infants [OR=1.06, 95% CI (1.03, 1.10)], lower respiratory tract infection [OR=1.09, 95% CI (1.02, 1.15)] and hospitalization related to lower respiratory tract infection [OR=1.24, 95% CI (1.09, 1.41)].

To conclude, folic acid supplement in middle and later pregnancy stage for mothers with family-specific constitution is associated with the risk of asthma in infants. Therefore determining the key stage of folic acid supplement and appropriate amount of folic acid is important for optimizing the neuroprotective effect of folic acid without increasing the risk of wheezing and asthma in infants.

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Disclosure of conflict of interest

None.

Address correspondence to: Yanyan Yu, Pediatric Asthma Department, Lianyungang Maternal and Child Healthcare Hospital in Jiangsu Province, 10 Cangwu Road, Haizhou Area, Lianyungang 222002, Jiangsu Province, China. Tel: +86-0518-85810035; Fax: +86-0518-85810035; E-mail: yayuyan@126.com

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