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Association of maternal folic acid consumption with preterm labor: Findings of a cohort study in Iran

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A B S T R A C T

Background and Objective: Nutritional factors are a matter of debate in the etiology of preterm labor. This study was conducted to assess the association of maternal folic acid consumption with preterm labor.

Materials and Methods: This cohort study was conducted on 191 healthy pregnant women in 2009, referring to two teaching hospitals in Tehran (Iran). The folic acid intake was measured and its correlation with preterm labor (premature rupture of membrane, newborn birth weight, and Apgar score) was assessed. Pearson and Spearman correlation tests were used for statistical analysis.

Results: The age range of the participants was 19 to 41 years with a mean and standard deviation of 27.8 and 4.4 years, respectively. Birth weight mean of newborns was 3228.64 (± 439.86) g with a gestational age mean of 38.7 (± 1.49) weeks. In 7 cases, 3.7% of the infants were born premature. In the second trimester of pregnancy, the average intake of folic acid was 1.16 (± 0.79) mg. The correlation of folic acid intake with the pregnancy outcomes was not significant.

Conclusion: Our findings did not indicate favorable association of folic acid intake with pregnancy outcomes neither for mothers nor for their neonates. We suggest conducting further studies on larger sample sizes and determining serum folate level.

Key Words:
Folic acid
Pregnancy outcome
Preterm labor
Prevention
Iran

1. Introduction

Pregnancy and childbirth have always been associated with complications. Preterm labor is the most common cause of morbidity and mortality near childbirth. The end of an untimely pregnancy represents one of the most important problems related to the delivery health care. The factors that trigger childbirth and subsequent pregnancy termination remain to be determined. Apart from survival rate, the quality of life in very premature infants with extremely low birth weight is also important. A considerable number of these newborns will have increased mortality rate in young adulthood (1) and will also suffer from physical and intellectual weaknesses in later life (2).

The expected survival rate of infants is primarily influenced by gestational age, and not only by birth weight. In fact, the infant survival rate increases from 20% in the 24th week of pregnancy to 50% at the 25th week. In other

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words, roughly a 4% increase in survival rate occurs per day. The serious forms of infections around childbirth showed a significant decrease every day from the 24th to the 26th week of pregnancy. The infant mortality rate based on gestational age reduces almost from 100% in the 23rd week of pregnancy to 10% at the 29th week. This rate will also have a slight improvement up to the 34th week (3).

Prevention of preterm labor may be possible with improved nutrition in pregnant women. Consumption of minerals and vitamins are among these essential actions. Folic acid is one of these types of vitamins, the low levels of which are associated with birth defects. Some studies have proposed a relationship between folate deficiency and premature childbirth, infant low birth weight, and intrauterine growth restriction (4,5). However, some studies did not confirm such association (6,7).

Folic acid is also called folate or vitamin B9. Folic acid is vital and fundamental for many bodily functions, as well as prevention and treatment of various disorders (8). Folic acid is destroyed in food products which have been boiled or heated. Keeping food at room temperature for long periods of time can also destroy the folic acid content. Folic acid is rarely toxic. Its excessive use (more than 15 milligrams) can cause stomach upset, sleep problems, skin reactions and seizures (9). This study for the first time in Iran aimed to assess the correlation of folic acid intake of pregnant mothers with premature birth.

2. Materials and Methods

This cohort study was conducted in 2009 on pregnant women admitted to the teaching hospitals of Mostafa Khomeini and Hazrat-e-Zeinab (SA) affiliated to Shahed University (Tehran). The study was approved by the Ethics Committee of Shahed University. Written informed consent was obtained from all participants. By considering a power of 80% and type 1 error (α) of 5%, the sample size was calculated as 170. Given the possible attrition from the study, 191 women were recruited by convenient sampling method. The inclusion criteria were as follows: having a live singleton pregnancy, being in the second trimester of pregnancy, i.e. 24th to 28th weeks, absence of known risk factors for preterm labor such as previous preterm childbirth, multiple pregnancies and cervical disorders. The exclusion criteria from the study consisted of fetal death of any reason, lack of mother's compliance to follow the study, preterm labor due to the termination of pregnancy for medical problems such as chorioamnionitis infection and preeclampsia.

A questionnaire including personal and medical information as well as supplements and medications used before and during pregnancy was completed through interviews with participants. Another questionnaire was also completed about the current dietary folic acid consumption. This 20-item questionnaire was adjusted based on foods with greatest amount of folic acid and highest rate of intake in the diet. Some questions were added to the questionnaire to assess the relationship of folic acid and iron intake before pregnancy with preterm labor. Participants were asked to indicate their food intake during the prior two to four weeks, and to return back the completed form. Then, in collaboration with nutrition experts, the average dietary intake of folic acid was calculated for each individual. Participants were followed until their labor. At the time of delivery, the infant weight, Apgar score, premature rupture of membrane (PROM) and the gestational age were recorded.

2.1 Statistical analysis

Folic acid intake was considered as an independent variable, and its association was determined with the following dependent variables including infant weight, Apgar score, and preterm labor. The significance of these associations was assessed using Pearson and Spearman correlation tests. Data analysis was conducted by SPSS software, version 13 (SPSS Inc., Chicago, Il., USA). The significance level was set at $p<0.05$.

3. Results

This study comprised 191 pregnant women. The age range was 19 to 41 years with a mean and standard deviation of 27.8 and 4.4 years, respectively. Most of the women (51.3%) were in their first pregnancy and very few (1%) had 5 pregnancies. Most of the subjects (53.4%) had not given birth up to that time. Overall, 12% of

them had given birth twice and 85.9% had no history of abortion. The mean birth weight of newborns was 3228.64 (±439.86) g with a mean gestational age of 38.7 (±1.49) weeks. In 7 (3.7%) out of cases, infants were born premature. Most preterm deliveries were due to pain (24.6%) and PROM (10.5%), and the lowest (2.1%) as a result of high blood pressure. In most of these cases (78%), the delivery mode was cesarean section.

Table 1 presents the consumption frequency of foods rich in folic acid in the phases before and during pregnancy. It shows that the maximum consumption was in the first trimester (90.6%) and the lowest was before pregnancy (39.7%).

The consumption frequency of folic acid and iron supplements is presented in Table 2. The highest rate of consumption was in the second trimester (47.1%) and lowest was before pregnancy (5.2%). Regarding iron, the maximum consumption was in the second trimester (93.2%) and the lowest was before pregnancy (6.8%). In total, the maximum consumption of iron was in the form of ferrous sulfate (48.7%) followed by compounds containing 1 mg of folic acid and 30 mg of iron (33%).

In the second trimester of pregnancy, the average intake of folic acid was 1.16 (±0.79) mg consisting of 0.44 (±0.23) mg from dietary intake, and 0.72 (±0.31) mg from supplement sources. The highest intake of folic acid by supplements was 5.4 mg and the lowest was zero. The highest daily dietary intake of folic acid was 0.807 mg and the lowest was 0.055 mg. The correlation tests revealed no significant correlation between the dosage of folic acid and the gestational age, Apgar score, birth weight, and PROM frequency (Table 3).

4. Discussion

In this cohort study of healthy pregnant women, 7 out of 191 participants (3.7%) had preterm labor. The average intake of folic acid was 1.16 mg per day, consisting of 0.44 mg by diet, and 0.72 mg by supplements. We did not document any statistically significant relationship between the dosage of folic acid consumption in the second trimester of pregnancy and the pregnancy outcomes in terms of the age of the termination of pregnancy, preterm labor, and the PROM frequency.

Our findings are in line with some previous studies, such as two studies conducted in 2003 (7) and 2005 (6) that did not document a significant association between folic acid consumption and preterm labor. Furthermore, our findings are consistent with a meta-analysis in 2009, which demonstrated that folic acid consumption during pregnancy has no effect on preterm labor (10).

Nonetheless, our findings are not consistent with some previous studies in which folate intake was associated with a lower risk for preterm labor. In a case-control study on 543 pregnant women, consumption of folic acid was associated with lower risk of preterm labor (11).

Table 1. Frequency of consumption of foods rich in folic acid before and during pregnancy.

	Time	Frequency	Percentage
Before pregnancy	Every day	65	34
	Every other day	5	2.6
	Sometimes	6	3.1
	Never	115	60.2
First trimester of pregnancy	Every day	144	75.4
	Every other day	16	8.4
	Sometimes	13	6.8
	Never	18	9.4
Second trimester of pregnancy	Every day	124	64.9
	Every other day	8	4.2
	Sometimes	12	6.3
	Never	47	24.6

Table 2. Frequency of consuming supplements of multivitamin and iron.

	Time	Frequency	Percentage
Multivitamin			
Before pregnancy	Every day Every other day Sometimes Never	6 2 2 181	3.1 1 1 94.8
First trimester of pregnancy	Every day Every other day Sometimes Never	25 3 3 160	13.1 1.6 1.6 83.8
Second trimester of pregnancy	Every day Every other day Sometimes Never	78 7 5 101	40.8 3.7 2.6 52.9
Iron			
Before pregnancy	Every day Every other day Sometimes Never	6 2 5 178	3.1 1 2.6 93.2
First trimester of pregnancy	Every day Every other day Sometimes Never	33 3 4 151	17.3 1.6 2.1 79.1
Second trimester of pregnancy	Every day Every other day Sometimes Never	170 3 5 13	89 1.6 2.6 6.8

Table 3. Correlation of folic acid intake at different times with pregnancy outcomes.

Variables	r	p value
Before pregnancy		
Birth weight	-0.065	0.640
Pregnancy termination age	0.04	0.237
Apgar score	0.012	0.761
First pregnancy trimester		
Parameter	r value	p value
Birth weight	-0.057	0.453
Pregnancy termination age	-0.02	0.241
Apgar score	-0.045	0.890
Second pregnancy trimester		
Birth weight	-0.043	0.559
Pregnancy termination age	-0.059	0.190
Apgar score	0.01	0.925

Another study indicated that the serum level of folate in pregnant women declined in the fifth month of the pregnancy. This amount remained low up to 4 months after the delivery. This study suggested that folic acid consumption during pregnancy can reduce the risk of complications (12). In a case-control study on 871 pregnant women, consumption of folic acid was associated with increased birth weight and higher Apgar score, as well as decreased incidence of intrauterine growth restriction and maternal infections (13). Another study in 1999 revealed that folic acid consumption during pregnancy was associated with decreased incidence of preterm labor (5). Likewise, a case-control study in 2007 on 1823 American women reported that the consumption of folic acid significantly reduces the risk of preterm labor (14). In a large-scale study on 5000 pregnant American women, low folate level was associated with increased risk of preterm labor (15). In a study conducted in 2000, lack of folate consumption in pregnancy was associated with the increased risk of preterm labor (16). A large-scale cohort of 34480 pregnant women reported that the consumption of folic acid before pregnancy was associated with 50-70% reduction in preterm birth (17).

In terms of neonatal birth weight and Apgar score, our findings were not in agreement with some previous studies that reveal favorable results for neonates (5, 12, 13). The discrepancies between the findings of various studies might be because of differences in their sample size. Moreover, we had considered the dietary intake of folic acid, whereas some other studies did not. It should be acknowledged that most countries including Iran did not develop their own food composition table, thus estimation of the food folate content using tables from Western textbooks may not be precise. Moreover, some factors as zinc deficiency and excess intake of foods such as legumes, cabbages and oranges reduce folate absorption from foods, and in some countries foods are fortified with folate (18, 19). Moreover, some genetic polymorphisms influence folate metabolism and absorption (20). All these factors may have implications for folate intake at population level in general, and its association with pregnancy outcomes in particular. Moreover, the time of consuming foods and supplements containing folic acid before or during different trimesters of pregnancy differs in various studies and may have a significant impact on the associations reported in various studies.

The findings of this study did not indicate favorable association of folic acid intake with pregnancy outcomes for mothers and neonates. To reach more definite results, we suggest that future studies should be conducted on larger sample sizes by examining serum levels of folic acid. Declaration of Interest: None to declare

References

1. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. The Journal of American Medical Association 2011;306:1233-1240.

2. Baron IS, Rey-Casserly C. Extremely preterm birth outcome: a review of four decades of cognitive research. Neuropsychology Review 2010;20:430-452.

3. Berek JS, Adashi EY, Hillard PA. Novak's Gynecology. 14th Baltimore, MD: Lippincott Williams & Wilkins; 2006.

4. Martí-Carvajal A, Peña-Martí G, Comunián-Carrasco G, Muñoz-Navarro S, Luco M, Martí-Peña A, Medina-Laurentín C. Prematurity and maternal folate deficiency: anemia during pregnancy study group results in Valencia, Venezuela. Archivos Latino-americanos de Nutrición 2004;54:45-9.

5. Rolschau J, Kristoffersen K, Ulrich M, Grinsted P, Schaumburg E, Foged N. The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part I. European Journal of Obstetrics, Gynecology and Reproductive Biology 1999 ;87:105-114.

6. Charles DH, Ness AR, Campbell D, Smith GD, Whitley E, Hall MH. Folic acid supplements in pregnancy and birth outcome: re-analysis of a large randomised controlled trial and update of Cochrane review. Paediatric and Perinatal Epidemiology 2005;19:112-124.

7. Vahartian A, Siega-Riz Am, Savitz DA, Thorp JM Jr. Multivitamin use and the risk of preterm birth. American Journal of Epidemiology 2004;160:886-892.

8. Varela-Moreiras G, Murphy MM, Scott JM. Cobalamin, folic acid, and homocysteine. Nutrition Reviews 2009;67:69-72.

9. Lindenbaum J, Allen RH. Clinical Spectrum and Diagnosis of Folate Deficiency. In: Bailey LB, ed. Folate in Health and Disease. New York, NY: Marcel Dekker, Inc; 1995. pp 43-73.

10. Shah PS, Ohlsson A, Shah V, Murphy KE, McDonald SD, Hutton E, Newburn-Cook C, Frick C, Scott F, Allen V, Beyene J. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. Canadian Medical Association Journal 2009;180:99-108.

11. Martí-Carvajal A, Peña-Martí G, Comunián-Carrasco G, Muñoz-Navarro S, Luco M, Martí-Peña A, Medina-Laurentín C. Prematurity and maternal folate deficiency: anemia during pregnancy study group results in Valencia, Venezuela. Arch Latinoam Nutr. 2004;54:45-49.

12. Smits LJ, Essed GG. Short interpregnancy intervals and unfavourable pregnancy outcome: role of folate depletion. Lancet. 2001;358:2074-2077.

13. Hundson T. Pregnancy and the use of nutritional supplements (women's health update). Thousand letter for doctors and patients. 2002;78:213.

14. Catov JM, Bodnar LM, Ness RB, Markovic N, Roberts JM. Association of periconceptional multivitamin use and risk of preterm or small for gestational age births. American Journal of Epidemiology 2007;166:296-303.

15. Siega-Riz Am, Savitz DA, Zeisel SH, Thorp JM, Herring A. Second trimester folate status and preterm birth. American Journal of Obstetrics and Gynecology. 2004;191:1851-1857.

16. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy.The American Journal of Clinical Nutrition 2000;71:1295-1303.

17. Bukowski R, Malone FD, Porter FT, Nyberg DA, Comstock CH, Hankins GD, Eddleman K, Gross SJ, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, D'Alton ME. Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study. Public Library of Science Medicine 2009;6:e1000061.

18. Baraka MA, Steurbaut S, Leemans L, Foulon W, Laubach M, Coomans D, Jansen E, Dupont AG. Determinants of folic acid use in a multi-ethnic population of pregnant women: a cross-sectional study. Journal of Perinatal Medicine 2011;39:685-692.

19. Colapinto CK, O'Connor DL, Tremblay MS. Folate status of the population in the Canadian Health Measures Survey. Canadian Medical Association Journal 2011;183:100-106.

20. Ubeda N, Reyes L, González-Medina A, Alonso-Aperte E, Varela-Moreiras G. Physiologic changes in homocysteine metabolism in pregnancy: a longitudinal study in Spain. Nutrition 2011;27:925-930.