Biotech Health Sci. 2018 February; 5(1):e12195.

Published online 2018 February 1. **Research Article**

Folic acid and prevention of congenital heart disease: Yes or No

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Received 2016 October 6; **Accepted** 2017 July 3.

Abstract

Background: Maternal nutrition during pregnancy may have profound effects on fetal cardiovascular formations. There are conflicting opinions about the effect of folic acid consumption during pregnancy on fetal cardiac morphogenesis.
Objective: This study was conducted to evaluate the protective effect of peri conceptional folic acid consumption during pregnancy on the genesis of congenital heart diseases.
Patients and methods: In this case- control study 56 children with congenital heart disease (case) were compared with 100 healthy children (control group), regarding maternal folic acid consumption during pregnancy. All data about taking folic acid supplement during pregnancy was obtained based on the in-person interview with mothers, parents or the maternal ambulatory history. Data were analyses and compared between groups.
Results: The most common congenital heart defect was ventricular septal defect (%23). There were no significant differences between two groups regarding folic acid supplements consumption before and during pregnancy (P>0.05).
Conclusion: Our results indicate that folate supplementation doesn't reduce the chance of congenital heart disease in newborns.

Key words: Congenital heart disease, Folic acid, Pregnancy

1. Background

Congenital Heart Disease (CHD) is an abnormal cardio-circulatory structure or function which presents at birth or appears much later in life. The incidence and pattern of this group of disorders varies among countries (1). According literature reports, the incidence of CHD is approximately 0.5-0.8% of live births whereas is higher in spontaneous abortuses (10-25%), stillborns (3-4%), and premature infants (2%) (2,3). Naturally leading causes of infant mortality associated with birth defects chronic are disability, morbidity, and increased healthcare costs (4,5). Although the etiology of the most CHD is unrevealed, some believe that a combination of genetic tendency and environmental factors may be involved (2). One of the issues discussed is the role of folic acid consumption during pregnancy in occurrence of CHD (6,7). Recent facts suggest that folic acid may reduce the incidence of CHD, however, the confirmations for an association between folic acid and CHD are still debatable (8-13). Folate which naturally exist in dark green vegetables and potatoes as a water-soluble B vitamin can be made artificially in dietary supplements and added to flour and grain products like breads. The liver has a significant role to convert folic acid to dihydrofolic acid and tetrahydrofolateis to be activated. Folate is necessary for human body to synthesize, repair and methylate DNA, as well as to do a vital function in certain biological processes as a cofactor. Also, it has a significant role to divide cells rapidly in order to grow human body (14-16). Given the importance of preventing congenital heart disease, this study was conducted to evaluate the protective effect of periconceptional folic acid consumption during pregnancy on the occurrence of CHD.

2. Materials and methods

2.1. Patient population

In this case–control and hospital-based study, 56 children with CHD (case group) were compared to 100 healthy children as control group in terms of maternal folic acid consumption during pregnancy. It should be noted that none of the control group suffered from CHD or the other diseases which were correlated by folic acid deficiency however they were referred to Qods clinic as they suffered from sepsis, neonatal icterus, diarrhea, and pneumonia. This study was conducted in pediatric heart clinic of Qods Children's Hospital affiliated to Qazvin University of Medical Sciences, (Qazvin, Iran) between 23 august to 29 February 2012. This hospital is the only educational medical center for children in Qazvin Province.

The children with abnormalities in cardio-circulatory structure or function in echocardiography are considered as having CHD (2). Children with genetic diseases or syndromes, isolated cardiomyopathies, single umbilical artery, and rhythm disorders (i.e. atrioventricular blocks, Wolff–Parkinson–White syndrome) were excluded.

2.2. Methodology

At first; the subject of the study was explained to children's parents in simple language. Once the written consent was adopted from the parents, the demographic information of children and their mothers and also results of echocardiography were recorded. The semi-structural interview was conducted with both parents. The interviewer was blind for two groups when obtaining all information about folic acid consumption with mothers, parents, and from the maternal ambulatory history. The date and dose of folic acid supplements (≥0.4 mg/day) were recorded. Also, preconceptional classification before the 30th and 90th day of gestation, or anytime during pregnancy were recorded. Taking multivitamin plus folic acid was also noted and included in study as folic acid. Echocardiography of neonates was performed by single pediatric cardiologist and parents of patients have paid costs of their diagnostic test while they were referred to Quds clinic from other clinician in outpatient clinics. The echocardiography was done with Sonosite apparatus (Micromaxx, USA). No one of infants had any evidence of Valve Heart Diseases (VHD). The conditions of echocardiography were standard for all children.

2.3. Statistical analysis

The results of this research were analyzed by Chi-square test, Odds Ratio with the 95% confidence intervals. The software SPSS16 was used and $P<0.05$ was considered statistically significant.

2.4. Ethical Considerations

This study was approved by the ethics committee of the Research Department in the Qazvin University of Medical sciences, Qazvin, Iran. All parents have been given exact information about the research method. After parents agreed and signed the informed consent form, the neonates were included in the study.

3. Results

The most common congenital heart defect was ventricular septal defect (Table1).

Of the 56 children with CHD (case group), 32 (57.1%) were males and 24 (42.9%) females. In the control group, these values were 60(60%) and40 (40%), respectively (Table 2).

Table 1. Frequency of congenital heart disease types in case group

Type of CHD	Frequency
Ventricular septal defect	23
Ventricular septal defect & Atrial septal defect & Patent ductusarteriosus	11
Tetralogy of fallot	5
Atrial septal defect	4
Pulmonary stenosis	2
Atrial septal defect & Pulmonary stenosis	2
Coarctation of aorta & Aortic stenosis & Mitral stenosis	2
d-Transposition of great arteries	2
Hypoplastic left heart syndrome	2
Complete atrioventricular septal defect	1
Partial atrioventricular septal defect	1
Coarctation of aorta & Ventricular septal defect	1
Total	**54**

Table 2. Frequency of gender in case and control groups

Gender	Cases	Controls	X^2	P value	OR (CI 95%)
Male	32(20.5%)	60(38.5%)	0.12	0.73	1.13 (058-2.18)
Female	24(15.4%)	40(25.6)			

The odds Ratio of CHD occurrence in terms of gender was 1.13 (058-2.18). Therefore, there was no significant difference in the incidence of congenital heart disease by gender.

Frequency of infant ages at time of diagnosis was 121(77.6%) less than 3 months and 35(22.4%) more than 3 months.

The mean±SD of mother's age in the case and cons trol groups were 25.93±5.55 and 26.24±5.11, respectively (P>0.05). There were no significant differences between case and control groups regarding folic acid supplements consumption before and during pregnancy (Tables 3-5) (P>0.05).

Table 3. Odds Ratio of CHD occurrence with folic acid supplementation before pregnancy

Supplementation	cases	Controls	X^2	OR (CI 95%)	P
Folic acid supplementation before pregnancy	15(9.6%)	35(22.4%)	1.11	1.47(0.72-3.2)	0.29
No folic acid supplementation Before pregnancy	41(26.3%)	65(41.7%)			

Table 4. Odds Ratio of CHD occurrence with folic acid supplementation during pregnancy

Supplementation	cases	Controls	X^2	OR (CI 95%)	P
Folic acid supplementation during pregnancy	48(30.8%)	86(55.1%)	0.02	1.02 (0.4-2.62)	0.96
No folic acid supplementation during pregnancy	8(5.1%)	14(9%)			

Table 5. Odds Ratio of CHD occurrence with folic acid supplementation before or during pregnancy

Supplementation	cases	Controls	X^2	OR (CI 95%)	P
Folic acid supplementation before and during pregnancy	49(31.4%)	86(55.1%)	0.07	0.88 (0.33-2.32)	0.79
No folic acid supplementation before and during pregnancy	7(4.5%)	14(9%)			

4. Discussion

This study showed that folic acid supplementation during pregnancy does not reduce the risk of CHD. Women who stated taking folic acid in the advised period did not have lower risk of any type of heart defects in their infants. Both positive and negative associations have been shown in recent studies on the preventive effect of periconceptional folic acid and CHD risk in human offspring (17-22). Correlation between the use of periconceptional folic acid-containing multivitamins and the reduced risk of cardiovascular malformations have been showed in the population-based observational Atlanta study; OR 0.57 (95% CI 0.33–1.00)] (22). Another population-based study in Atlanta during 1982–1983 from infants born from 1968 to 1980 which based on Atlanta Birth Defects case–control study revealed that periconceptional multivitamin was associated with a reduced risk for any type of cardiac defect in the neonates [OR 0.76 (95% CI 0.60–0.97)], especially it is effective to decrease outflow tract defects [OR 0.46 (95% CI 0.24–0.86)], and VSD [OR 0.61 (95% CI 0.38–0.99)] (23). Possibility of recall errors in cases with more than one to two years old age had been high in these studies. Thus the results of these studies should be interpreted with caution (22, 23). Czeizel et al. in a randomized clinical trial study revealed that CHD (mainly VSD) were reduced by 58% [OR 0.42 (95% CI 0.19–0.98)] in the maternal care program with taking multivitamins containing 800 μg folic

acid in comparison with the others who received trace elements(18). The study of Ionescu-Ittu et al on a large population in Canada showed that folic acid decreases the incidence of CHD more than 6%. This study was done following fortification of grain products with folic acid for preventing neural tube defect. Another large population-based case–control study in Netherlands found a 20% reduced risk of any type of CHD with maternal use of folic acid or any multivitamin supplement containing at least 400 μg daily compared with no maternal consumption. It should be noted that some studies declare that there is an odds ratio (OR) of 0.82 (95% CI 0.68–0.98) for all types of CHD relative to other malformations in women taking periconceptional folic acid tablet and the estimated relative risk for CHD in them in comparison with the general population was [OR 0.74 (95%CI 0.62–0.88)]. Also, an OR of 0.62 (95% CI 0.47–0.82) was detected in subgroup analysis for isolated septal defects (24). Since Shaw *et al* have stated a reduced risk of CHD associated with maternal use of any multivitamin supplement containing folic acid compared with no use [OR 0.53 (95% CI 0.34–0.85)], we can observe that only limited types of heart defects (essentially conotruncal heart defects) have been surveyed by most studies (7, 19-24). Indirect support for the importance of folate to reduce risk of congenital heart disease was provided by Hernandez-Diaz *et al*. which the periconceptional intake of medications acting as a folic acid antagonist has been doubled the risk of congenital heart disease such as conotruncal defects, VSD and others anomalies [OR 2.2 (95% CI 1.4–3.5)]. It should be noted that their study showed the folic acid component in multivitamins decrease the CHD risk associated with folic acid antagonists (25). Also, the experimental studies have been shown that folic acid administration can reduce the incidence of CHD (26, 27). In Serrano et al study, folate deficiency induced in pregnant mice by an intraperitoneal injection of ethanol and then treatment with high dose of folic acid has led to a reduction of CHD incidence. In another animal study, transient folate deficiency has led to increase of 29% to 58% congenital cardiovascular malformations in embryos (27). Although, the precise mechanism of protective effect of folic acid on CHD has not been established, but in recent years, the methylation hypothesis suggests that folic acid prevents congenital defects, in particular neural tube defects, by stimulating cellular methylation reactions (28). Unlike the before mentioned studies, no preventive effect on the risk of outflow tract defects from multivitamins containing folic acid administration before pregnancy [OR 0.97 (95% CI 0.6–1.6)] has been found by Scanlon (19). In addition, similar results are obtained by Werler *et al.* and Scanlon based on their hospital-based case–control study which show there is no folic acid effect on the risk of conotruncal [OR 1.0 (95% CI 0.7–1.5)] or VSD [$n = 186$; OR 1.2 (95% CI 0.8–1.8)] associated with periconceptional use of multivitamins containing folic acid (21). The findings of our study are consistent with their reports (19, 21). The difference in the results of studies might be as a result of variety in the study design or the types of heart defects. The results of present study should be interpreted in terms of its strengths and limitations. The main strength of our study is a relatively short time intervals between births and interviews with parents and use of infants with simple diseases as controls. Such measures are prevented parental recall bias relatively. Our limitations were small sample size and lack of measurement of serum folate. Serum folate measurement is not available in our area. In conclusion, our results do not establish that taken folic acid supplements in periconceptionally can prevent CHD. Considering the high prevalence of congenital heart diseases' worldwide, our interpretation of data might be important for public health policy makers especially in developing national policies to investigate for other possible causes of CHD and find appropriate strategies for women in their fertile period. We recommend further study with large population through multicenter collaborations in Iran.

Acknowledgements

Our special thanks for the mothers who worked and cooperated with interest in this study.

Conflict of interest

We declare no conflict of interest.

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