Periconceptional folate supplementation for the prevention of congenital heart diseases: A review of literatures

Mazin Mahmoud Fawzi
Department of Pediatrics, College of Medicine, University of Mosul, Mosul, Iraq
Correspondence: mmf@uomosul.edu.iq

(Ann Coll Med Mosul 2021; 43 (2):207-211).
Received: 12th July 2021; Accepted: 12th Sept. 2021.

ABSTRACT

Background: Folate is essential for metabolism and development. So, folate metabolism abnormalities are common in infants with some congenital defects. An infant born to mothers with normal folate status has more resistant to congenital heart diseases (CHDs). Evidence on risk factors for developmental defects resulting from drug use before conception and during pregnancy is still very limited. The relationship between folic acid for mothers before and throughout pregnancy and the incidence of fetal malformations and diseases have been recognized.

Aims: This article is a rapid review for assessment of the folic acid supplementation as a preventive measure of CHDs during fetal development, and what is already recognized about a policy of this subject, by using systematic review methods to search some of the existing researches.

Materials: publications related to determining and quantifying the use of folate by pregnant mothers to decrease the risk of congenital heart diseases were reviewed. Many studies have confirmed the reduction of congenital heart diseases by folic acid supplementation prior to pregnancy.

Conclusion: the protective effect of folic acid against congenital heart abnormalities has been established. Though, the dose and time of supplementation are not known; more researches are needed to explain the mechanisms.

Keywords: Pregnancy , Congenital heart defects , Folate , Supplements .
INTRODUCTION

Congenital heart diseases had been reported as a common disease of congenital malformations of newborns worldwide, leading to perinatal mortality. Although the survival rate of newborns with congenital heart defects have been increased due to an improvement in diagnosis and treatment over the past century, the cause of most congenital heart malformations remains obscured. From previous researches, the effect of folate on the incidence of neural tube defects throughout pregnancy was recognized by researchers. The supplement of folate decreases hazard of this defects, and many evidences suggest that it also be associated with decrease incidence of CHDs 1.

Folic acid is one of the B-complex vitamin. The vital biochemical reactions need the reduced forms of it as a necessary agent that give precursors for the synthesis of DNA 2. Folic acid is available as nutrient in foods e.g. fruits and leafy greens, also many countries fortify products of cereal and grain with synthetic folate 3.

Folic acid deficiency is relatively common condition that can be easily corrected by folic acid intake. Researchers have confirmed that folate plays a vital role in brain and nervous system development 4. Pregnant women are mainly liable to folate deficiency due to high rates of cellular division and rapid fetal growth. Since the 1950s, folate supplement for pregnant women has been recognized to inhibit megaloblastic anemia 5. Maternal status of folic acid has been connected with additional adverse pregnancy consequences such as cleft lip and palate, preeclampsia, growth retardation, fetal death, premature delivery and spontaneous abortion 6,7. Research’s data recommended a direct proportion between increased homocysteine serum level and vasoocclusive diseases. Clinically the folate supplementation has decreased the prevalence of hyperhomocysteinemia and improve in the folate status 8.

Folate-containing supplements are recommended during pregnancy, and also for those planning to be pregnant for the anticipation of CHDs, preterm and low weight birth. In addition to neural tube defects. Additionally, abnormal folate metabolism often found in newborns and children with CHDs. There is a relationship between hazard of having a new born with CHDs and maternal genotype for several genes of folate metabolism. Although effects of folic acid on this heart defects were clearly identified, there is no clear evidence whether the window of prevention time is similar to that for neural tube defects. It was suggested that high risk women including those with obesity or diabetes need a more folic acid to reduce incidence of or even prevent such heart defects 9.

Congenital Heart Defects and Folate Biomarkers in Children

Folate is of critical importance during human development at early stages and also throughout life. Pregnancy has been considered as a period of increased folate necessities due to fetal, placental, and maternal tissue demands for cell replication and rapid fetal growth, which are mainly depend on role of folate in protein DNA, and RNA synthesis. Therefore, maintenance of sufficient folate status during time of pregnancy is essential for both the mothers and the growing fetus because pregnant women with folate deficiency will be more susceptible for adversarial consequences including congenital heart defects and neural crest disorders 10.

The early diagnosis of abnormal fetal growth largely depends on ultrasound examination. A specific molecular marker for congenital malformation diagnosis is still lacking. Investigations that based on molecular biomarker testing is known to be a non-invasive and useful clinical method as a diagnostic tool of cancers, however they are not commonly applicable for fetal abnormalities and other high risk pregnancy complications.

Jia et al., 2021 showed that a circulating pi RNAs, which is isolated from plasma exosomes of pregnant women is a hopeful conservative biomarker for congenital deformity 11. Investigations of plasma folate and homocysteine in both mother and child with congenital heart defects. Increased levels of folate, hyperhomocysteinemia, methylenetetrahydrofolate reductase and the folate metabolizing enzyme polymorphisms were prevalent in the controls compared to patients. A case control study was carried out to estimate factors accompanied by the
incidence of birth defects. A studies were carried out to find the association between congenital heart defects and folate genetic polymorphisms. A single nucleotide polymorphism in methylenetetrahydrofolate reductase (MTHFR) gene has been revealed to be related with congenital heart defects. Also, multiple single nucleotide polymorphism in betaine-homocysteine methyltransferase found an association with congenital heart defects in relation with folic acid treatment. According to previous evidences, the following significance biomarkers had been selected: serum folate concentration; folate concentration of red blood cells; and concentration of plasma homocysteine. For long-term period, folate of red blood cells, usually debated as the strongest dependable biomarker.

**Previous Outcomes From Recent Studies of The Relationship Between Folic Acid and CHDs**

Evidence connecting mother folic acid supplementation to baby threat of CHDs is deficient. While it is recognized that folic acid during pregnancy can decreases the incidence of NTDs in newborns. Its connotation with less incidence of CHDs is only expressive. The exact action of folic acid on morphogenesis of cardiac tissues still vague, it may help in the cardiac neural cells migration that subsidize to the progress of the embryonic heart.

The comparative studies of tendencies before and after essential food fortification by folic acid, requesting a fundamental relationship between this vitamin and heart defect. Though, a discussion of causal inference need studies designed about mother's folic acid supplement use and infant's risk of heart defect. Many studies have such single level information of folic acid intake, most of them have contradictory findings correlated with different design, they could also be clarified by local differences in vitamin insufficiency.

Øyen et al., (2019) carried out a 2 large birth cohort studies to investigate whether folic acid ingestion in early time of pregnancy decreases new born threat of CHDs. They found that folic acid was not related with severe, or septal defects.

A birth cohort research was carried out at the Gansu Provincial Maternity & Child Care Hospital in Lanzhou, China. All stillbirths and multiple births are excluded, and only a total of 94 births were recognized with CHDs, while about 9,993 births without any birth defects. Statistical analysis was used to evaluate the associations recommended that folic acid given before pregnancy was related with a less risk of CHDs, reduced dietary folate provided throughout pregnancy was accompanying with higher risk. They found a relations diverse by CHD. A synergism between dietary folate and folic acid intake was also detected.

A study designed to assess the individual and joint effect of first-trimester maternal folic acid supplement and multivitamin use on CHDs in newborns, establish that first-trimester maternal FAS, but not multivitamin use, was substantially associated with lower risk of CHDs, and the association was strongest for the most severe CHD phenotypes. They recommend that mothers should supplemented with folic acid when she planned to be pregnant to ensure coverage of the dangerous window for fetal heart growth to inhibit CHDs.

Another study carried out on all live births and stillbirths at ≥20 weeks' gestation in Canada. Cases of CHD were identified at newborn and infants. They prevalence of CHDs subtypes were compared. Statistical analysis was used to measure the consequence of food fortification by folic acid on non-chromosomal CHD subtypes after adjusting the variations in mother age, multiple birth, pre pregnancy diabetes mellitus, preeclampsia, and termination of pregnancy. The relationship between food fortification with folic acid and a drop in the birth prevalence of specific CHDs gives modest evidence for additional benefit from this intermediation.

Recently, an interventional trials showed that about 90% of austere NTDs are avoidable by supplements of multivitamins before pregnancy, while about 70% are preventable by periconceptional folic acid supplementation. There are 3 probable uses of this novel preventive measure for NTDs and CHD: (i) folate rich diet alone although it is not enough for the prevention; (ii) folic acid supplementation before pregnancy; (iii) flour fortification.

One study results showed that multiple genetic variants in genes convoluted in the folate, homocysteine or glutathione/transsulfuration trails have modest effects on the risk of CHDs through either genetic main effects or relations with mother use of folic acid supplements, and pre pregnancy obesity. These results provide understandings of the genetic liability of CHDs. Among 877 single nucleotide polymorphisms involved in the folate, homocysteine, glutathione/transsulfuration pathways, multiple single nucleotide polymorphisms were identified to effect risk of obstructive CHD.

CHD is considered a folic acid-sensitive birth defect because female who consumes folic acid-containing multivitamins early in pregnancy have a 30-40% lower risk of having offspring with these CHD. Folic acid is an vital B vitamin that the
human body cannot produce; it can only be obtained from the diet. Studies have shown that folic acid has a vital role in embryonic development, including the heart. If folic acid is metabolically disordered, it will cause the methionine cycle to be blocked. On the one hand, it affects the methylation reaction in the body, which in turn affects the metabolic growth of cells. On the other hand, it causes the metabolic disorder of homocysteine in the blood, which leads to an increase in homocysteine levels. Elevated homocysteine is an autonomous risk factor for cardiovascular disease, which can damage or interfere with early cardiovascular growth and progress. If the metabolism of folate is affected, deoxyribonucleic acid synthesis and repair will be reduced, and the development of the neural crest in the embryo will be abnormal, which will eventually lead to the occurrence of CHD.

CONCLUSION
The link between folate supplementation and congenital heart abnormalities has been proven in several researches. Folate supplementation appears to have a prophylaxis against severe forms of congenital heart abnormalities. Though, the optimal folate dose and timing for prevention of congenital heart abnormalities before or during pregnancy remain unknown. If folate is shown to prevent congenital heart abnormalities, its universally predicted to outweigh that of neural tube defects prevention. The hunt for other supplements that might help prevent congenital cardiac abnormalities is still ongoing. More study is needed, however, to fully understand the processes.

ACKNOWLEDGMENTS
The author is very grateful to the University of Mosul/ College of Medicine for their support to progress of this work.

REFERENCES
1. Feng Y, Wang S, Chen R, Tong X, Wu Z, Mo X. Maternal Folic Acid Supplementation and the Risk of Congenital Heart Defects in Offspring: A Meta-Analysis of Epidemiological Observational Studies. Scientific Reports, 2015, 5(1). doi:10.1038/srep08506
2. Zhao M, Chen Y, H, Chen X, Dong X, T. Folic acid supplementation during pregnancy protects against lipopolysaccharide-induced neural tube defects in mice. Toxicology Letters, 2014, 224 (2): 201-208. doi: 10.1016/j.toxlet.2013.10.021.
3. LaVerne B, Cohen Barbara E, Emmeline E, Gustin Courtney E, CNM RN, Zara Noreen BA. Physiological Need for Calcium, Iron, and Folic Acid for Women of Various Subpopulations During Pregnancy and Beyond. JOURNAL OF WOMEN'S HEALTH. 2021, 30(2), Mary Ann Liebert, Inc. DOI: 10.1089/jwh.2020.8873
4. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartlala J, Allayee H, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr. 2012, 96: 80–9.
5. Li Z, Ye R, Zhang L, Li H, Liu J, Ren A. Periconceptional folic acid supplementation and the risk of preterm births in China: a large prospective cohort study. Int J Epidemiol. 2014;43(4):1132-9. doi: 10.1093/ije/dyu020.
6. Sengpiel V, Bacelis J, Myhre R, Myking S, Pay AD, Haugen M, et al. Folic acid supplementation, dietary folate intake during pregnancy and risk for spontaneous preterm delivery: a prospective observational cohort study. BMC Pregnancy Childbirth. 2013, 12;13:160. doi: 10.1186/1471-2393-13-160. Retraction in: Sengpiel V, Bacelis J, Myhre R, Myking S, Pay AD, Haugen M, Brantsæter AL, Meltzer HM, Nilsen RM, Magnus P, Vollset SE, Nilsson S, Jacobsson B. BMC Pregnancy Childbirth. 2014;14:202. PMID: 23937678; PMCID: PMC3751653.
7. Melissa van der Windt, Sam Schoenmakers, Bas van Rijn, Sander Galjaard, Régine Steegers-Theunissen, Lenie van Rossem. Epidemiology and (Patho)Physiology of Folic Acid Supplement Use in Obese Women before and during Pregnancy. Nutrients, 2021, 13, 331. https://doi.org/10.3390/nu13020331
8. Veeranki SP, Gebretsadik T, Dorris SL, Mitchel EF, Hartert TV, Cooper WO, et al. Association of folic Acid supplementation during pregnancy and infant bronchiolitis. Am J Epidemiol. 2014; 15; 179 (8): 938-46.
9. Obeid R, Holzgreve W, Pietrzik K. Folate supplementation for prevention of congenital heart defects and low birth weight: an update. Cardiovasc Diagn Ther. 2019 ;9(Suppl 2):S424-S433. doi: 10.21037/cdt.2019.02.03.
10. Bailey LB, Stover PJ, McNulty H, Fenech MF, Gregory JF 3rd, Mills JL, et al. Biomarkers of Nutrition for Development-Folate Review. J Nutr. 2015 Jul;145(7):1636S-1680S. doi: 10.3945/jn.114.206599.
11. Jia S, Zhang Q, Wang Y, Wang Y, Liu D, He Y, et al. PIWI-interacting RNA sequencing profiles in maternal plasma-derived exosomes reveal novel non-invasive prenatal biomarkers for the early diagnosis of nonsyndromic cleft lip and palate. EBioMedicine. 2021; 65:103253. doi:
10.1016/j.ebiom.2021.103253. Epub 2021 Feb 24. PMID: 33639402; PMCID: PMC7921467.

12. Group MVSR. Prevention of neural tube defects. Results of the Medical Research Council Vitamin Study. Lancet.1991, 338:131–137.

13. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992 Dec 24;327(26):1832-5. doi: 10.1056/NEJM199212243272602. PMID: 1307234.

14. Shaw GM, O'Malley CD, Wasserman CR, Tolarova MM, Lammer EJ. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. Am J Med Genet. 1995 Dec 4;59(4):536-45. doi: 10.1002/ajmg.1320590428. PMID: 8585581.

15. Van Beynum, I. M., Kapusta, L., Bakker, M. K., den Heijer, M., Blom, H. J., & de Walle, H. E. K. Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands. European Heart Journal. (2009), 31(4), 464–471. doi:10.1093/eurheartj/ehp479

16. Tang LS, Wlodarczyk BJ, Santilliano DR, Miranda RC, Finnell RH. Developmental consequences of abnormal folate transport during murine heart morphogenesis. Birth Defects Res A Clin Mol Teratol. 2004 Jul;70(7):449-58. doi: 10.1002/bdra.20043. PMID: 15259034.

17. van Beynum IM, Kapusta L, den Heijer M, Vermeulen SH, Kowuenberg M, Daniëls O, et al. Maternal MTHFR 677C>T is a risk factor for congenital heart defects: effect modification by periconceptional folate supplementation. Eur Heart J. 2006 Apr;27(8):981-7. doi:10.1093/eurheartj/ehi815. Epub 2006 Mar 7. PMID: 16524890.

18. Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. BMJ. 2009;338:b1673.

19. Liu S, Joseph KS, Luo W, Leon JA, Lisonkova S, Van den Hof M, et al. Canadian Perinatal Surveillance System (Public Health Agency of Canada). Effect of folic acid food fortification in Canada on congenital heart disease subtypes. Circulation. 2016, 134:647–655.

20. Øyen N, Olsen SF, Basit S, Leirgul E, Strem M, Carstensen L , et al. Association Between Maternal Folic Acid Supplementation and Congenital Heart Defects in Offspring in Birth Cohorts From Denmark and Norway. Journal of the American Heart Association. 2019, 8(6). doi:10.1161/ jaha.118.011615

21. Mao B, Qiu J, Zhao N, Shao Y, Dai W, He X, et al . Maternal folic acid supplementation and dietary folate intake and congenital heart defects. PLOS ONE. 2017, 12(11), e0187996. doi:10.1371/journal.pone.0187996

22. Qu Y, Lin S, Zhuang J, Bloom MS, Smith M, Nie Z, et al. First-Trimester Maternal Folic Acid Supplementation Reduced Risks of Severe and Most Congenital Heart Diseases in Offspring: A Large Case-Control Study. Journal of the American Heart Association. J Am Heart Assoc. 2020;9:e015652. DOI: 10.1161/JAHA.119.015652.

23. Liu S, Joseph KS, Luo W, León JA, Lisonkova S, Van den Hof M, et al. Effect of Folic Acid Food Fortification in Canada on Congenital Heart Disease SubtypesClinical Perspective. Circulation, 2016, 134(9), 647–655. doi: 10.1161/circulationaha.116.011611

24. Czeizel A, Dudás I, Vereczkey A, Bánhidy F. Folate Deficiency and Folic Acid Supplementation: The Prevention of Neural-Tube Defects and Congenital Heart Defects. Nutrients, (2013). 5(11), 4760–4775. doi:10.3390/nu5114760

25. Tang X, Cleves MA, Nick TG, Li M, MacLeod SL, Erickson SW, et al. Obstructive heart defects associated with candidate genes, maternal obesity, and folic acid supplementation. Am J Med Genet Part A. 2015,167A:1231–1242. doi:10.1002/ajmg.a.36867

26. Kang Yi, Yu-Hu Ma, Wei Wang, Xin Zhang, Jie Gao, Shao-E He, et al. The Roles of Reduced Folate Carrier-1 (RFC1) A80G (rs1051266) Polymorphism in Congenital Heart Disease: A Meta-Analysis. Med Sci Monit. 2021, 27: e929911 DOI: 10.12659/MSM.929911.