

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

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(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 .

مكملات حامض الفوليك قبل وأثناء الحمل للوقاية من أمراض القلب الخلقية : مراجعة مقالة

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الخلاصة

مقدمة: حمض الفوليك ضروري لعملية التمثيل الغذائي والنمو . لذلك ، تشوهات استقلاب حامض الفوليك شائعة عند الرضع المصابين بعيوب قلبية خلقية. يكون الطفل المولود لأمهات يتمتعن بحالة طبيعية من حمض الفوليك أكثر مقاومة لتشوهات القلب الخلقية. لا تزال الأدلة على عوامل الخطر لعيوب النمو الناتجة عن تعاطي الادوية قبل الحمل وأثناء الحمل محدودة للغاية. تم إثبات وجود علاقة ارتباط عالية بين مكملات حمض الفوليك الأم قبل وأثناء الحمل وانتشار التشوهات والأمراض التي تصيب الجنين. تهدف هذه الورقة إلى مراجعة آثار مكملات حمض الفوليك قبل وأثناء الحمل على الوقاية من أمراض القلب الخلقية أثناء نمو الجنين.

الطريقة: تمت مراجعة المنشورات المتعلقة بتحديد وقياس استخدام الأم لحمض الفوليك قبل الحمل كعوامل خطر لأمراض القلب الخلقية. أكدت العديد من الدراسات أن تناول مكملات حمض الفوليك قبل الحمل كان مرتبطاً بانخفاض خطر الإصابة بأمراض القلب الخلقية ، كما أن انخفاض تناول حمض الفوليك أثناء الحمل ارتبط بزيادة المخاطر.

الخلاصة: هناك دليل جيد على أن مكملات حامض الفوليك قد يكون لها تأثير وقائي ضد تشوهات القلب الخلقية. بالرغم من ذلك ، لم يتم تحديد جرعة حامض الفوليك ووقت تناول المكملات قبل الحمل أو أثناءه للوقاية من تشوهات القلب الخلقية ؛ هناك حاجة إلى مزيد من البحث لإلقاء الضوء على الآليات .

الكلمات المفتاحية : الحمل ، عيوب القلب الخلقية ، حامض الفوليك ، المكملات الغذائية .

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 CHDs¹.

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 DNA². 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 folate³.

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 development⁴. 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 anemia⁵. 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 status⁸.

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 defects⁹.

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 disorders¹⁰.

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 deformity¹¹.

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^{9,10}. 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 biomarker¹⁰.

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^{12,13}. Its connotation with less incidence of CHDs is only expressive^{14,15}. 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^{16,17}.

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^{18,19}.

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 defects²⁰.

A birth cohort research was carried out at the Gansu Provincial Maternity & Child Care Hospital in Lanzhou, China. All stillbirths and multiple births ae 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 detected²¹.

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 CHDs²².

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 intermediation²³.

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 fortification²⁴

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 CHD²⁵.

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 CHD²⁶

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.

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