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The Correlation Between Infants' Congenital Heart Defects and Maternal Folic Acid Supplementation

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ABSTRACT

Background: Congenital heart defects (CHDs) are significant drivers of mortality and morbidity in children, folic acid supplementation for the pregnant month during or before delivery is said to influence risk reduction of congenital heart defects (CHDs). However, there are controversial claims and the hypothesis is concluded from limited epidemiologic studies. **Aim of the Study:** Conduct a systematic review and meta-analysis of published studies to reliably evaluate the correlation between Folic acid or multivitamins containing FA supplementation taken during pregnancy and the risk of CHDs. **Methods:** A systematic review and meta-analysis was conducted. PUBMED and EMBASE were searched to identify prospective cohort and case-control studies that had reported on the association between 1960 and 2017.Studies conducted in primarily high-risk populations (Case control and cohort studies) while participants in randomized controlled trials were excluded.

Results: The search yielded 10 studies published between 2000 and 2013 enrolling 13126 female participants. These studies included only one cohort study, and nine case-control studies. The overall results of this meta-analysis provide evidence that maternal folate supplementation is associated with a significantly decreased risk of CHDs (RR = 0.69, 95% CI: 0.54–0.84). Statistically significant heterogeneity was detected (Q = 79.43, P < 0.001, I2 = 70.2%).

Conclusion: FA supplementation during pregnancy significantly decreases the risk of CHDs in newborns.

Keywords: Folic acid, pregnancy, Congenital heart defects, Maternal Folic Acid Supplementation.

INTRODUCTION

Congenital heart disease (CHD) has been defined as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance. In the developed world, CHD is considered to be the most major congenital anomaly and a leading cause of mortality in the first year of life[1]. Congenital heart disease (CHD) is present in about 9 of every 1,000 live-born children[2]. Congenital heart defects (CHDs) are the most common structural abnormalities presenting at birth, and they are also one of the leading causes of perinatal and infant mortality[2].

It is reported that the prevalence of CHDs accounts for 6% of all neonatal death factors, and also accounts for 46% of all congenital lethal factors [3]. Recently, the survival of newborns with CHDs has increased due to massive breakthrough in cardiovascular diagnostics and cardiothoracic surgery [4].

Arious studies have shown the etiology of congenital heart disease (CHD) and its pattern of inheritance to be of multifactorial origin[5].A review of the literatures showed that consanguinity[6], and a variety of maternal ailments e.g., infections, maternal smoking, and gestational diabetes mellitus play a major role in the development of CHD. In addition, there are several fetal factors such as prematurity, low birth weight and stillbirth which are found to be associated with CHD.

THE CAUSE of congenital heart disease is unknown except for the recognition that it may occur in certain hereditary diseases, may be associated with chromosomal abnormalities, and may be related to an intrauterine viral disease such as rubella. This genetic and environmental interaction is most likely to be pathogenetic mechanism of congenital heart defects. Calculations based on this hypothesis predict the frequency of occurrence of the disease in first degree relatives to be square root of its frequency in the population; this fits the congenital heart disease figures[7]. Ventricular septal defect and coarctation of the aorta are typical examples of CHDs. Congenital heart defects are more common than well-known congenital anomalies such as congenital pyloric

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stenosis, cleft lip, Down syndrome and congenital dislocation of the hip[8].

Folic acid (FA) is an essential nutrient and plays an important role in the development of the cardiovascular system. The association of FA or multivitamins containing FA supplementation during the critical periods of organ formation with the risk of the occurrence of CHDs has been recognized in past decades[9].

Homocysteine levels have been directly associated with cardiovascular risk in observational studies[1]; and daily supplementation with folic acid, vitamin B_6, vitamin B_{12}, or a combination have been shown to reduce homocysteine levels to varying degrees in intervention studies.[2] Based on these data, several randomized trials were designed to test the hypothesis that supplementation with folic acid or B vitamins or both would prevent cardiovascular disease (CVD)[10].

Several studies have reported that FA or multivitamins containing FA supplementation taken during pregnancy could significantly reduce the risk of CHDs, particularly conotruncal defects and ventricular septal defects (VSDs) in newborns. However, the available data from epidemiological studies on the association between FA supplementation during pregnancy and CHDs are inconsistent and controversial[11].

In this systematic review, our purpose was to evaluate the correlation between FA or multivitamins containing FA supplementation taken during pregnancy and the risk of CHDs and provide more comprehensive and reliable evidence-based medicine.

MATERIALS AND METHODS

We performed a systematic review of the available literatures according to the PRISMA [12] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, systematically identifying and appraising peer-reviewed RCTs reporting on the correlation between Maternal folic acid level and CHD in offspring.

Data Sources: Literature searches of Pubmed, Embase , CENTRAL and SCOPUS Cochrane Library between January 1960 until July 2017 were performed. The search terms were used in combinations and together with the Boolean operators OR and AND; Search terms used were: ("Folic Acid", "Folate", "Multivitamins") AND ("Heart Abnormality","congenital malformations", "CHD","Heart Abnormality") AND ("maternal" OR "mother" OR "periconceptional" OR "pregnant" OR "gestation")

Data extraction was performed by two independent reviewers and consisted of analysis of critical appraisal criteria per included study. Very few differences in rating were settled by consensus agreement after a discussion. If consensus could not be reached, a third review author was consulted for adjudication. The critical appraisal criteria were rated as 'yes', 'no' or as 'unknown' when insufficient information are provided and summarized.

Study Selection and Criteria

Search results were screened by scanning abstracts for the following

Inclusion criteria

- Publications in English, German, French or Spanish language articles
- Publications investigated the association between periconceptional folic acid use any one of the CHD subtypes in infants.
- Only RCTs , Cohort or case-control studies were accepted
- Publications which clearly defined CHDs or one of the CHD subtypes as an outcome.
- Publications reported RRs (i.e., risk ratios or odds ratios) and associated 95% confidence intervals (CIs) or provided raw data from which these measures could be calculated.

Exclusion criteria

- *In vitro* laboratory studies in experimental set-up
- Non-peer-reviewed articles
- Studies involving experiments on animals

Studies including patients with DBS since dysphagia has often been described as a side-effect of DBS

Decision-Making

Relevant publications were identified from title, abstract and study descriptors by one researcher; the decision to include was independently validated by a second and disagreements were referred to third for an independent ruling.

Study Quality Assessment

The quality of included trials was assessed by R.O. and J.B. using the Newcastle-Ottawa Scale (NOS) [13], which was modified to fit our study design: 0-3 stars indicate poor study quality, 4-6 stars indicate acceptable study quality, and 7-9 stars indicate good study quality. In the event of disagreements, consensus was reached by discussion.

Statistical Analysis

Summary estimates were obtained using a random-effects model to account for between-study heterogeneity. Overall and cohort estimates are presented as relative risks (RR) with 95% CI, and case-control estimates are presented as odds ratios (OR) with 95% CI. For those studies that had reported both multiple risk estimates, only the most-adjusted estimated contributed to the summary estimates. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I2 statistic[14]. p-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed with STATA, version 11.1 (Stata, College Station, Texas).**The study was done after approval of ethical board of King Abdulaziz university**.

RESULTS

The initial search was broad; accepting any article related to the attribution of Vitamin D to PCOS so as to ensure a fully comprehensive view of available work, and generated 819 articles. Preliminary application of study criteria identified 532 potential studies for inclusion that met one or more criteria. Further review of these investigations by independent reviewers yielded 131studies that fully met all inclusion criteria. No individual authors were contacted for information. No further review of methodological quality of the studies was conducted beyond that it appeared in a peer review journal and comprised an RCT. The 131 eligible articles were again closely examined and data extracted using a standard protocol regarding target population, sample size, program provider, program content, intervention components, processes, and outcomes. Another 121 publications were excluded (57 of which were publications of the same cohort and 45 did not meet the current study endpoints/outcomes). Comparison among provider type was computation of differences between percent of successful program to number attempted.

Finally, 10 studies were included and detailed as the focus for the present study.

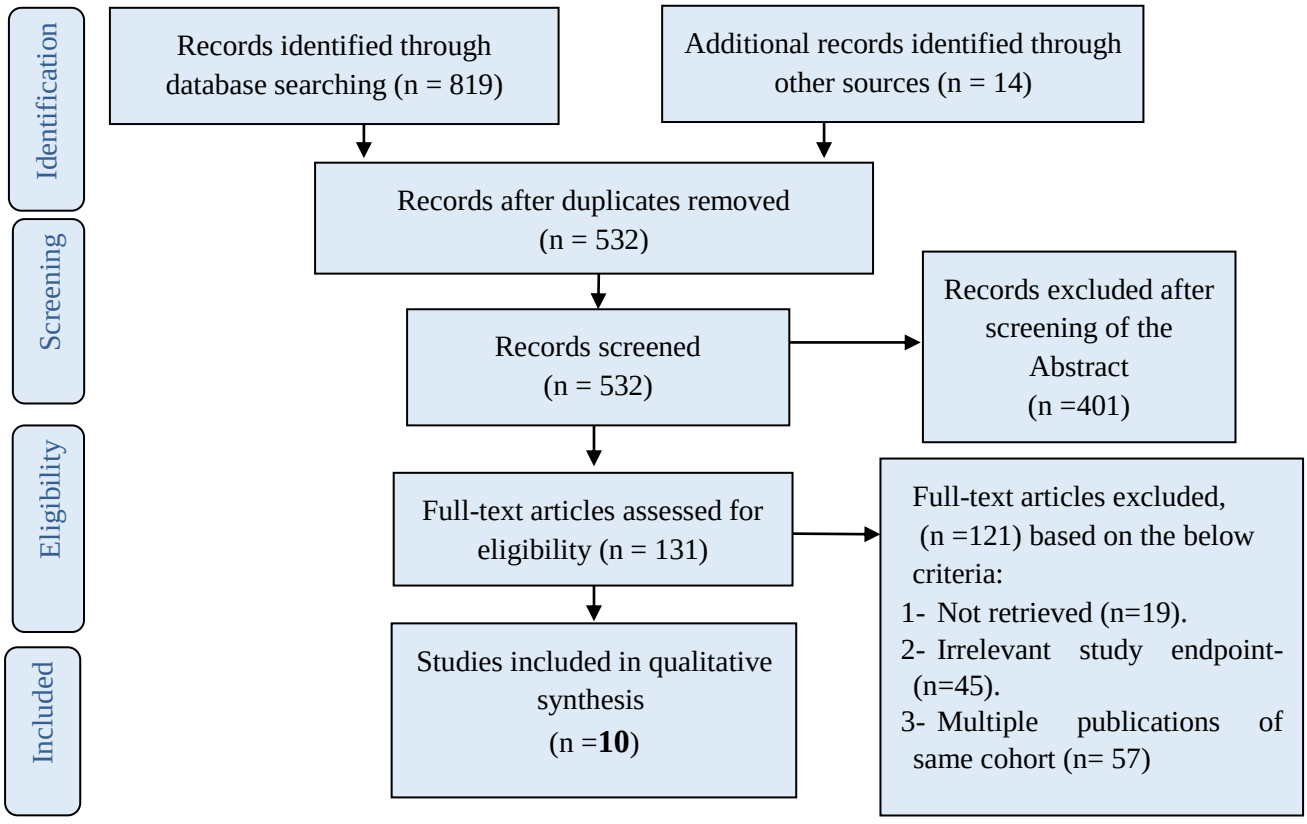

Figure 1: PRISMA flow diagram showing the selection criteria of assessed the studies[12].

All studies were published between 2000 and 2013 enrolling 13126 female participants. These studies included only one cohort study[16], and nine case-control studies[15,17-24]. The key characteristics of the included studies are presented in Table 1.

Table 1: baseline characteristics of patients enrolled in the included studies

Authors	Year of publication	Location	Study design	Sample Size		
				cases	control	Total
Botto*et al.*[15]	2000	USA	Case Control	958	3029	3987
Czeizel *et al.*[16]	2004	Hungary	Cohort	3056	3056	6112
Malik *et al.*[17]	2008	USA	Case Control	3067	3947	7014
Van Beynum *et al.*[18]	2010	Netherlands	Case Control	611	2401	3012
Obermann-Borst *et al.*[19]	2011	Netherlands	Case Control	282	308	590
Bean *et al.*[20]	2011	USA	Case Control	566	552	1118
Hobbs *et al.*[21]	2011	USA	Case Control	417	250	667
Csaky-Szunyogy *et al.*[22]	2013	Hungary	Case Control	302	469	771
Li *et al.*[23]	2013	China	Case Control	358	422	780
Vereczkey *et al.*[24]	2013	Hungary	Case Control	77	38151	38228

CC: case-control study; CHDs: congenital heart defects; VSD: ventricular septal defect; ASD: atrial septal defect; TOF: tetralogy of Fallot; TGA: D-transposition of the great arteries; HLHS: hypoplastic left heart syndrome; COA: coarctation of the aorta; AVSD: atrioventricular septal defect.

Table 2: Summary of the relative risks (RR) and 95% CI estimates for the association between maternal folate supplementation and the risk of CHDs in neonates

Authors	Period	OR/RR	95% CI	Types of CHDs	Adjustment variables
Botto *et al.*[15]	3 months before through 3 months after conception	0.76	0.60–0.97	CHDs	Infant's period of birth, race, chronic diseases
		0.46	0.24–0.86	CTD	
		1.09	0.21–5.66	AVSD	
		0.59	0.38–0.94	Septal	
		0.5	0.14–1.79	ASD	
		0.61	0.38–0.99	VSD	
Czeizel *et al.*[16]	1 month before through 3 months after conception	0.6	0.38–0.96	CHDs	Parity, chronic diseases, history of previous unsuccessful pregnancies
		0.26	0.09–0.72	VSD	
Malik *et al.*[17]	1 month before through 2 months after conception	1	0.90–1.12	CHDs	Residence
Van Beynum *et al.*[18]	4 weeks before conception to 8 weeks after conception	0.82	0.68–1.00	CHDs	Age, BMI, education, smoking, alcohol use
		0.62	0.47–0.82	Septal	No
		0.58	0.31–1.07	VSD	
		0.54	0.31–0.94	ASD	
		0.77	0.52–1.15	CTD	
		1.42	0.37–5.49	AVSD	
Obermann-Borst *et al.*[19]	4 weeks before conception to 8 weeks thereafter	0.79	0.57–1.10	CHDs	No
Bean *et al.*[20]	Before pregnancy or within the first 4 weeks of pregnancy	0.59	0.38–0.93	AVSD	Race, sex, alcohol use, smoking
		0.59	0.39–0.90	ASD	
		0.79	0.53–1.17	VSD	
Hobbs *et al.*[21]	During pregnancy	1.03	0.96–1.12	CHDs	BMI, age, smoking, alcohol
Csaky-Szunyogy *et al.*[22]	First trimester	0.53	0.38–0.75	LOVT	Age, parity, maternal employment status
Li *et al.*[23]	3 months before through 2 months after conception	0.47	0.32–0.70	CHDs	Residence, age, education family history, planned pregnancy
		0.39	0.25–0.61	VSD	
		0.55	0.33–0.89	CTD	
Vereczkey *et al.*[24]	First trimester	0.51	0.30–0.87	AVSD	Age, parity

Meta-analysis outcome for the correlation between Maternal folate supplementation and CHDs.

The overall results of this meta-analysis provided evidence for a significant decrease in the risk of CHDs with maternal folate supplementation (RR = 0.69, 95% CI: 0.54–0.84). Statistically significant heterogeneity was detected (Q = 79.43, P < 0.001, I^2 = 70.2%), In stratified analyses, the corresponding pooled RRs were not materially altered in any stratification.

DISCUSSION

The present systematic review and meta-analysis aimed mainly at investigating the relationship between maternal low folate level and infants' CHDs.

Even though the exact biological mechanisms explaining the relationship between maternal folate supplementation and the risk of CHDs remain to be explored, some relevant evidence has been published. Since FA is a cofactor for the remethylation of homocysteine metabolism, and FA deficiency can result in hyperhomocysteinemia, which is frequently associated with congenital defects of the heart and neural tube[25], there is a hypothesis stating that impaired folate and/or homocysteine metabolism interferes with the development of the heart, possibly by affecting neural crest cells. Methylenetetrahydrofolate reductase (MTHFR), which is a critical folate-metabolizing enzyme, plays an important role in processing amino acids. A C→T substitution is commonly found at position 677 in the MTHFR enzyme and results in a substitution of valine for alanine; this substitution causes impaired folate binding and reduced activity of the MTHFR enzyme[26].The effect of the MTHFR 677TT genotype on homocysteine levels is more pronounced with low folate status[27].

Additionally, daily supplementation with folic acid, vitamin B6, vitamin B12, or a combination have been shown to reduce homocysteine levels to varying degrees in intervention studies[10].

Initially, epidemiologic studies, which were primarily retrospective and cross-sectional, suggested that reducing plasma homocysteine by 5 μmol/L would decrease vascular risk by one-third[28].However, a more recent meta-analysis of prospective observational studies suggested that risk reductions associated with homocysteine lowering would be much more modest.1 In these studies, a 25%-lower homocysteine level, approximately 3 μmol/L, was associated with 11% reduction in coronary heart disease risk and a 19% lower stroke risk[10]. The expected reductions in cardiovascular events may have been even lower in this trial where the reduction in homocysteine levels was only 18.5% (2.3 μmol/L) among adherent patients. Although this trial was not initially powered to detect such modest reductions in cardiovascular events, the 95% CIs for the primary end point excludes with reasonable certainty reductions as low as 10% in the combined end point of total cardiovascular events. However, such modest plausible reductions in the individual secondary end points of stroke, MI, and cardiovascular death cannot be excluded even in a trial of this size

Overall, the findings of our meta-analysis suggest that maternal folate supplementation is significantly associated with a decreased risk of CHDs (RR = 0.69, 95% CI: 0.54–0.84).

CONCLUSION

The present meta-analysis demonstrates that maternal FA supplementation significantly decreases the risk of CHDs in newborns. Therefore, this will provide evidence for the reduction of CHD incidence by FA supplementation and play an important role in minimizing adverse pregnancy outcomes.

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