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Do multivitamin supplements reduce the risk for congenital heart defects? Evidence and gaps

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Abstract

Progress in the primary prevention of heart defects has been slow. Some findings suggest that multivitamin supplementation might reduce the risk for some heart defects. This review of the literature shows that two studies, one of which is a randomized clinical trial, provide data supporting a possible protective effect of multivitamins for all heart defects combined (a 25 to 50% reduction). Three of five studies support a protective effect for outflow tract defects, whereas two studies do not.

More studies are clearly needed to elucidate the relation between multivitamin use and occurrence of heart defects. Such studies must take into account intake from multiple sources (diet and supplements), as well as genetic background and potential confounders. From a practical perspective, all health-care providers, including pediatric cardiologists, should ensure that women of childbearing age, regardless of whether they had a previous child with a heart defect, take a multivitamin containing 400 micrograms of folic acid, to reduce their risk of having a baby with a neural tube defect. Should such supplements eventually be proven to reduce the risk also for heart defects, this would be an important additional benefit of such supplement use.

MeSH: Vitamins, Folic acid, Heart defects, congenital, Prevention, Epidemiology

The quest for primary prevention

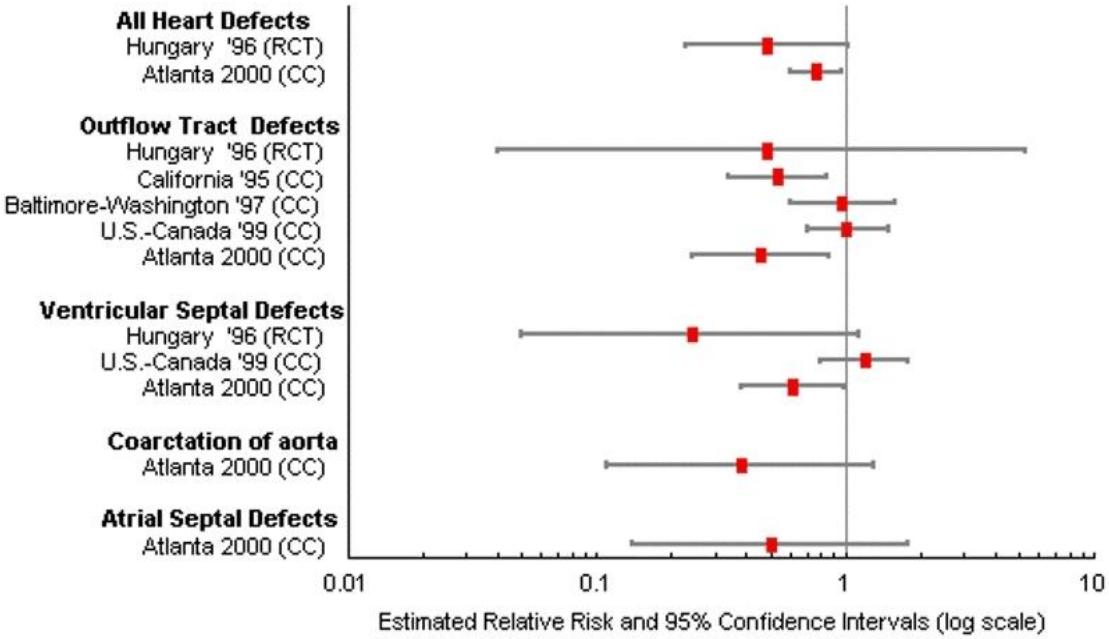
No congenital anomaly causes more deaths than heart defects.[1,2] In the United States, for example, heart defects have recently surpassed anencephaly and spina bifida as the leading cause of infant death.[1] Because of the impact of heart defects, even in the face of improved diagnostic methods and treatment opportunities, the prevailing goal among medical and public health professionals is to find effective means for primary prevention. Progress towards this goal, however, has been slow.

A landmark series of papers from the Hungarian randomized clinical trial, published from 1992 through 1998,[3–5] sparked hope that such primary prevention might be feasible, at least for a proportion of heart defects. That series of papers showed that multivitamin supplements containing folic acid could prevent a proportion of neural tube defects[3] and probably of other birth defects, including some heart defects.[5] In the wake of that first report, four other research groups reported findings on the relation between the use of multivitamin supplements and heart defects in the offspring.[6–10] Such findings are mixed but encouraging. The purpose of this paper is to review such findings, to highlight current gaps in knowledge, and to suggest ways to fill such gaps.

The Evidence

Five studies have evaluated the relation between maternal use of multivitamin supplements and risk for congenital heart defects in the offspring: one was a randomized clinical trial,[5] three were population-based case-control studies,[6,8,9] and one was a hospital-based case-control study[10] (Table 1). Two of these studies (the Hungarian randomized trial[5] and the Atlanta case-control study[8] evaluated a broad range of heart anomalies, whereas the others focused on one or two major groups of heart defects (Figure 1).

Figure 1 Multivitamins/folic acid and congenital heart defects: summary of studies published as of December 2000 (modified from Am J Epidemiol 2000:51;878-84)



In the two studies of a broad range of heart defects, mothers who used the multivitamin supplement were less likely to have children with heart defects than women who did not take the supplement. Specifically, in the randomized clinical trial,[5] the risk was cut by half (from 8.4 per 1000 to 4.0 per 1,000), whereas in the Atlanta case-control study[8] the risk was cut by one quarter (odds ratio 0.76, 95% CI 0.60-0.97). These findings suggest that at least 1 in 4 heart defects could be prevented by periconceptional use of multivitamin supplements.

The Hungarian randomized trial and the Atlanta case-control study also suggested that the risk reduction might vary by heart defect, and that it might be strongest for septal defects and some outflow tract defects (mainly tetralogy of Fallot and transposition of the great arteries). The data from the Hungarian randomized trial, summarized in Table 1, are presented in greater detail in Table 2. In the Atlanta case-control study (Table 1), the risk reduction was 54 percent for outflow tract defects; predominantly tetralogy of Fallot and transposition of the great arteries; and 39 percent for ventricular septal defects.[8]

Table 1 Studies on multivitamin supplements or folic acid and congenital heart defects, 1992-2000

									Estimated Relative Risk (95% CL)	Estimated Relative Risk (95% CL)	Estimated Relative Risk (95% CL)
Study type	**Year Pub.**	**Authors**	**Pop. based**	**Years**	**Location**	**Study Participants (1)**	**Exposure (2)**	**Heart defects evaluated**	**Heart Defects (overall)**	**Outflow Tract defects**	**Ventricular Septal Defect**
Rand. Clin trial	1998	Czeizel et al.	NA	1985-1993	Hungary	2,471 women on MV supplements; 2,391 on trace elements	MV pill with 0.8 mg folic acid (Elevit Pronatal)	Heart defects and major subgroups	0.42 (0.19-0.98)	0.48 (0.04-5.34)	0.24 (0.05-1.14)
Case-control	1995	Shaw et al.	Yes	1987-1988	California	207 with OTD, 481 controls	MV supplements	Outflow tract defects	-	0.70 (0.46-1.1)	-
Case-control	1997	Scanlon et al.	Yes	1981-1989	Baltimore Washington	126 with OTD, 679 controls	Folic acid in supplements	Outflow tract defects	-	0.97 (0.6-1.6)	-
Case-control	2000	Botto et al.	Yes	1968-1980	Atlanta	958 with heart defects, 3,029 controls	MV supplements	Heart defects and major subgroups	0.76 (0.60-0.97)	0.46 (0.24-0.86)	0.61 (0.38-0.99)
Case-control	1999	Werler et al.	No	1993-1996	Boston, Philadelphia, Toronto	157 with OTD, 186 with VSD, 521 controls	MV supplements	Outflow tract defects, ventricular septal defects	-	1.00 (0.70-1.50)	1.20 (0.80-1.80)

(1) MV, multivitamin; OTD, outflow tract defects, VSD, ventricular septal defects
(2) MV, multivitamin

Table 2 Occurrence of cardiovascular defects among the offspring of women who participated in the Hungarian randomized clinical trial of periconceptional multivitamin supplements (MV) and trace element supplements (Trace). [Data from reference 5]

Trace	MV	Trace	MV	Rate	Ratio	Percent reduction
Birth Cohort	2391	2471				
Total babies with congenital heart defects	20	10	83.6	40.5	0.48	52
Septal	11	4	46.0	16.2	0.35	65
Ventricular septal defect	8	2	33.5	8.1	0.24	76
Secundum atrial septal defect	3	2	12.5	8.1	0.65	35
Left Obstructions	5	3	20.9	12.1	0.58	42
Hypoplastic left heart	2	1	8.4	4.0	0.48	52
Aortic stenosis	3	2	12.5	8.1	0.65	35
Right Obstructions						
Pulmonic stenosis	0	1	0.0	4.0	-	-
Outflow tract defects	2	1	8.4	4.0	0.48	
Tetralogy of Fallot	1	0	4.2	0.0	0.00	100
Transposition of the great arteries	1	0	4.2	0.0	0.00	100
Double onset pulmonary artery (*)	0	1	0.0	4.0	-	-
Other	2	1	8.4	4.0	0.48	
ASD primum, VSD	0	1	0.0	4.0	-	-
Unspecified heart defect	1	0	4.2	0.0	0.00	100
Patent ductus arteriosus	1	0	4.2	0.0	0.00	100

(*) term used in original report

Although the double-blind randomized clinical trial had many strengths, it did not elucidate definitively the relation between multivitamin use and risk for heart defects. The major limitation was its size: the trial was relatively small and thus was limited in its ability to assess the risk for most groups of heart defects.

Several research groups have evaluated one specific subgroup of heart defects, the outflow tract defects, mainly tetralogy of Fallot and transposition of the great arteries. Three studies provide data supporting a protective effect for multivitamin use,[5,6,8] whereas two studies showed no effect.[9,10]

The three studies supporting a protective effect are the Hungarian clinical trial[5] and case-control studies from California[6] and Atlanta.[8] In the Hungarian trial, the cohort that consumed multivitamin supplements experienced no cases of Fallot or transposition of the great arteries, whereas the control group experienced two such cases (one each of tetralogy of Fallot and transposition of the great arteries). The population-based case-control studies from California (the first to be published) and Atlanta (discussed above) reported a 30 and 54%reduction of outflow tract defects, respectively.

The two studies that did not show a protective effect were a population-based case-control study from Baltimore[9] and a hospital-based study coordinated in Boston[10] (odds ratios of 1.0 and 0.9, respectively).
The scant data on truncus arteriosus does not suggest a strong protective effect of multivitamin use for this lesion.
Finally, three studies had information on ventricular septal defects.[5,8,10] The hospital-based study from Boston found no risk reduction.[10] However, the Hungarian randomized trial[5] and population-based study from Atlanta[8] reported a marked risk reduction associated with multivitamin use (85 and 40 percent reduction, respectively).
In summary, the evidence of a protective effect of multivitamins is mixed but encouraging. That three well-designed studies; a double blind randomized clinical trial and two population-based case-control studies; suggest that a multivitamin supplement might reduce the risk for certain heart defects is a finding that deserves careful and prompt study.

Knowledge and gaps

The following questions need resolution.
Do multivitamins definitively reduce the risk for heart defects? It will be important to evaluate if the association is consistent across studies, areas, and races, if it is causal, and if it holds for all or, as it now appears, for selected types of heart defects. Pediatric cardiologists will be critically important for such studies for their ability to distinguish specific groups of heart defects (e.g., the different types of ventricular septal defects) and specific clinical presentations (e.g., genetic syndromes, patterns of multiple congenital anomalies).
How much do multivitamins reduce the risk for heart defects? Precisely measuring the effect will require careful study and large patient populations, and therefore collaboration and common protocols.
Do multivitamin supplements reduce the risk for heart defects from other exposures? Some exposures, such as some febrile infections or diabetes, are known to increase the risk for certain heart defects. Whether such risk is reduced by multivitamin supplementation is not known, but the question is of clinical and public health importance.
What component(s) of the multivitamin supplement account for the effect? Folic acid is effective even alone for preventing spina bifida.[11,12] Whether it is effective in preventing other birth defects, including heart defects, is unclear.
What dose of supplement(s) is most effective for prevention? For preventing spina bifida, 400 micrograms (0.4 milligrams) are effective alone[11,12] or as part of a multivitamin supplement. Similar data are lacking for other births heart defects.
Do gene-environment interactions play a role in the risk reduction? For example, the effect of vitamins might reflect a complex interaction between use of supplements, dietary intake, and genotype. Because such complex interactions have been noted in relation to neural tube defects,[13] a similar approach for heart defects might prove rewarding.
If multivitamins prevent heart defects, what is the mechanism? Elucidating the mechanisms of action of multivitamins might provide insights into the pathogenesis of cardiac defects, which is not well known.

The road ahead

Many of the questions can and should be answered by carefully conducted population-based studies, including case-control studies, clinical trials, and focused birth defects monitoring.

Population-based case-control studies must be large enough to provide precise estimates of the effect for specific types of heart defects. They should also examine the composition and intake of micronutrients from diet and supplements, and include genetic data to examine the relative role of genes, environmental factors, and their interactions.

Randomized clinical trials could also be used to answer many of the same questions. However, for ethical reasons, each participant must receive at least 400 micrograms of folic acid. In addition, the cost, organizational burden, and ethical issues related to a clinical trial require careful consideration.

Birth defect monitoring in areas where folic acid intake is changing can provide powerful complementary information. For example, the addition of folic acid in fortified flour, begun in the United states in 1997-1998, will increase the average intake of folic acid among women of childbearing age. A decrease in the prevalence of heart defects in such areas might provide important supporting information on the relation between folic acid intake and occurrence of heart defects.

In these studies diagnostic criteria and anatomic definitions must be clearly defined. This critical step can be best accomplished by close collaboration between pediatric cardiologists and epidemiologists. For example, transposition of the great arteries can be defined differently in different studies; in some it may have included only people with concordant atrioventricular and discordant ventriculo-arterial connections, whereas in others it might include all those in which the ventriculo-arterial connections are discordant (e.g., those with double inlet left ventricle and transposition, or tricuspid atresia and transposition). Similarly, tetralogy of Fallot can be defined according to antero-cephalad deviation of the muscular outlet septum in the setting of muscular subpulmonary obstruction. However, some authors might not always have followed this strict definition. Others may or may not include extreme forms of tetralogy -- tetralogy with pulmonary atresia. Thus case definitions should be clearly stated and justified for all groupings. This may also help identify and avoid potential pitfalls such as lumping primum atrial septal defects with secundum defects. In our analysis,[8] for example, we used a hierarchical classification scheme, and we included in the transposition of the great arteries group not only isolated ventriculo-arterial discordance but also cases where such discordance occurred with other heart anomalies such as tricuspid atresia and double inlet left ventricle; we included in the tetralogy of Fallot group also the extreme form with pulmonary atresia; and we separated primum atrial septal defects from secundum defects, lumping the former with the atrio-ventricular septal defects. In our original reports[7,8] the case definitions may have not been always clear; moreover, we cannot say whether the same case definitions (or which case definitions] were used in some of the other reports cited here.[3–6,9,10]

In summary, researchers need to define clearly the phenotypic features of cases to be included within their groupings and comment on how they decide such groupings. Pediatric cardiologists, embryologists, and morphologists can provide critical advice in this important phase.

Conclusions

The possibility suggested by recent findings that multivitamin supplements containing folic acid might effectively prevent a proportion of heart defects is of major clinical and public health import. A concerted effort of the medical and public health community is needed to examine this question systematically, efficiently, and

conclusively. If such quest for the primary prevention of heart defects is successful, it will represent a major breakthrough in pediatric cardiology, as heart defects now cause more infant deaths than any other birth defect.

In the meantime, however, what should pediatric cardiologists do? The answer, fortunately, is simple: they should ensure that all women of childbearing age consume a daily multivitamin containing 400 micrograms (0.4 milligrams) of folic acid, in addition to a healthy diet. This has been recommended by many professional organizations and public health authorities worldwide[14–17] to reduce a woman's risk of having a pregnancy affected by a neural tube defect. Should future research confirm that such supplementation reduces also the risk for heart defects, it would be an added benefit to an already effective way to prevent much unnecessary death and disability.

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