Multivitamin Supplements and Congenital Heart Defects

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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 the hope that such primary prevention might be feasible at least for a proportion of heart defects. That series of papers, in addition to demonstrating that multivitamin supplements containing folic acid prevented a proportion of neural tube defects (3), also suggested that these same supplements might have an effect on some heart defects (5). In the wake of that first report, 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. Animal models are beyond the scope of the review and will not be covered.

THE EVIDENCE

So far, five studies have evaluated the relation between maternal use of multivitamin supplements and risk for congenital heart defects in the offspring. Of these, 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 limited their scope to some specific types of heart defects (Figure 1).

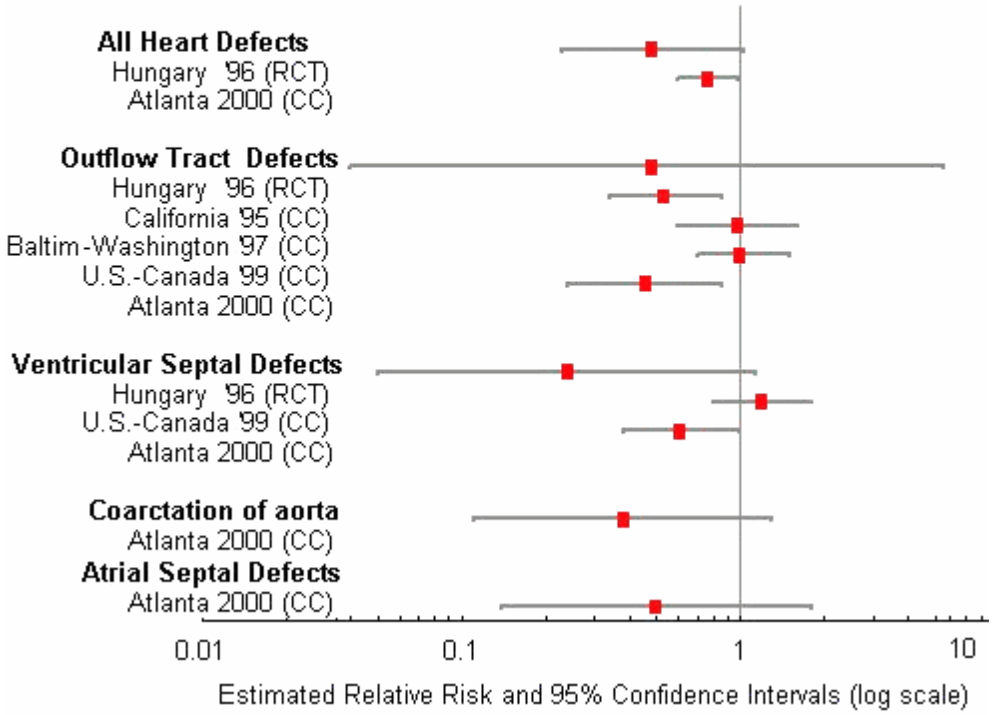
Table 1. Studies on multivitamin supplements and congenital heart defects, 1992-2000.

Type of Study	Authors and Year	Population-based?	Study participants (1)	Exposure (2)	Relative Risk (95% Confidence Interval)		
					Heart Defects (overall)	Outflow tract defects	Ventricular Septal Defect
Randomized clinical trial	Czeizel et al. 1999	--	2,471 women on MV supplements; 2,391 on trace elements	MV pill with 0.8 mg folic acid	0.42 (0.19-0.98)	0.48 (0.04-5.34)	0.24 (0.05-1.14)
Case-control	Shaw et al. 1995	Yes	207 with OTD, 491 controls	MV supplements	-	0.70 (0.46-1.1)	-
Case-control	Scanlon et al. 1997	Yes	126 with OTD, 679 controls	MV supplements with folic acid	-	0.97 (0.6-1.6)	-
Case-control	Botto et al. 1996 & 2000	Yes	958 with heart defects, 3,029 controls	MV supplements	0.76 (0.60-0.97)	0.46 (0.24-0.86)	0.61 (0.38-0.99)
Case-control	Werler et al. 1999	No	157 with OTD, 186 with VSD, 521 controls	MV supplements	-	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

Figure 1. Multivitamins/folic acid and congenital heart defects: summary of studies (case-control -- CC, and randomized clinical trials -- RCT)

(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 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 A. Czeizel "Periconceptional folic acid containing multivitamin supplementation: Eur J Obst Gynecol Repr Biol 78 (1998) 151-161.]

Study Group	Number of pregnancies		Rate per 10,000		Rate Ratio	Percent Reduction
	Trace	MV	Trace	MV		
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 (VSD)	8	2	33.5	8.1	0.24	76
Atrial septal defect (ASD) secundum	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 type of heart defects, the outflow tract defects, which include tetralogy of Fallot and D-Transposition of the great arteries. Three studies provide data supporting a protective effect for multivitamin use (5, 6, 8), whereas two studies showed no such 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 percent 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).

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).

Ancillary evidence supporting a protective effect of folic-acid containing supplements on heart defects comes from a recent study of the effects of folic acid antagonists on birth defects in humans (11). In that

study, women who used such antagonists during pregnancy had a two-fold increased risk for having babies with heart defects. Of note, that risk was reduced among those who also took a multivitamin supplement containing folic acid.

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 immediate study.

KNOWLEDGE AND GAPS

The following questions need resolution.

1. *Do multivitamins definitively reduce the risk for heart defects?* It will be important to evaluate if the association is consistent, if it is likely to be causal, and if it holds for all or, as it now appears, for only some major groups 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).
2. *How much do multivitamins reduce the risk for heart defects?* Precisely measuring the effect will require careful study and large sample sizes. Such studies will require collaboration and common protocols but will be indispensable to estimate the preventable fraction of heart defects.
3. *Do multivitamin supplements reduce the risk for heart defects from other exposures?* Some exposures, such as some febrile infections, diabetes, and use of folic acid antagonists, are known to increase the risk for certain heart defects. Whether such risk is reduced by multivitamin supplementation has not been extensively studied though some results support the notion that such risk reduction might indeed occur (11, 12). This question is of substantial practical importance from both a clinical and public health perspective and deserves further study.
4. *What component(s) of the multivitamin supplement account for the effect?* Folic acid is effective even alone for preventing spina bifida (13, 14). It is unclear whether it is effective alone in preventing heart defects.
5. *What dose of supplement(s) is most effective for prevention?* For preventing spina bifida, it appears that effective supplements contain 400 micrograms (0.4 milligrams) of folic acid (13, 14). Similar data are lacking for heart defects. An open question is whether higher doses might have a greater preventive effect.
6. *Do gene-environment interactions play a role in the risk reduction?* For example, the effect of micronutrients such as vitamins might reflect a complex interaction between use of supplements, dietary intake, and genotype. Such complex interactions have been noted in relation to neural tube defects (reviewed in reference 15), for example in relation to polymorphisms of folate related genes such as MTHFR or cysthathione-beta-synthase. A similar approach for heart defects might prove rewarding.
7. *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. For ethical reasons, each participant ought to receive at least 400 micrograms of folic acid. 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.

CONCLUDING REMARKS

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(16-19) 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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