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Folic acid in pregnant women associated with reduced prevalence of severe congenital heart defects in their children: a national population-based case–control study

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ABSTRACT

Objective: Previous Hungarian intervention trials have shown an association between periconceptional folic-acid-containing multivitamin supplementation and significantly reduced risk of congenital heart defects (CHDs). These findings were confirmed in observational multivitamin studies in the USA, and studies in the Netherlands and China regarding folic acid. The objective of this observational population-based study was to estimate the possible preventive effect of folic acid supplementation for different CHDs during their critical period of development.

Study design: Evaluation of medically recorded use of folic acid (calculated daily average 5.6 mg) during the critical period of development of eight types of CHD (verified through autopsy reports or after catheter examination and/or surgical correction) in the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA), 1980–1996, containing 22,843 cases with congenital abnormalities and 38,151 population controls without any CHDs, including 5395 matched controls of 3567 live-born cases with various CHDs. A conditional logistic regression model was used to estimate the relative risk/protection [odds ratio (OR) with 95% confidence intervals (CI)] of folic acid in the mothers of cases with various types of CHD and their matched controls.

Results: There was a significant decrease in the prevalence of cases with ventricular septal defect (OR 0.57, 95% CI 0.45–0.73), tetralogy of Fallot (OR 0.53, 95% CI 0.17–0.94), d-transposition of great arteries (OR 0.47, 95% CI 0.26–0.86) and atrial septal defect secundum (OR 0.63, 95% CI 0.40–0.98) in infants born to mothers who had taken high doses of folic acid during the critical period of CHD development.

Conclusions: The risk of development of certain types of CHD was significantly reduced in pregnant women who were supplemented with folic acid. Thus, CHDs should be included as a secondary assessment in neural-tube-defect preventive programs.

Introduction

Congenital heart defects (CHDs) are the most prevalent and serious structural birth defects [i.e. congenital abnormalities (CAs)]. Of every 1000 live-births, 4–50 are affected by CHDs [1,2]. Pediatric cardiology examinations and evaluation of individual autopsy reports indicated a mean prevalence of CHDs of 10.2 [standard deviation (SD) 2.1] per 1000 live-births in a Hungarian population-based study [3].

There has been significant progress in the care of infants/children with CHDs over recent decades [4]; nevertheless, CHDs are responsible for a significant proportion of childhood deaths [5]. Recent progress in human genetics has improved understanding of the genetic background of CHDs [6]; however, the role of possible environmental factors in the origin of most CHDs is unclear [7].

Periconceptional folic-acid-containing multivitamins (0.8 mg folic acid) resulted in a significant reduction in the prevalence of CHDs in a Hungarian randomized controlled trial [relative risk 0.42, 95% confidence interval (CI) 0.19–0.98] [8,9] and a cohort controlled trial [odds ratio (OR) 0.60, 95% CI 0.38–0.96] [10]. Population-based observational studies in Atlanta, GA, USA [11–13] also showed that the use of periconceptional folic-acid-containing multivitamins reduced the risk of CHDs. These reductions were greatest for

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ventricular septal and conotruncal defects in the above reports. The meta-analyses of both observational case–control studies (OR 0.78, 95% CI 0.67–0.92) and randomized or cohort controlled trials (OR 0.61, 95% CI 0.40–0.92) confirmed the significant decrease in CHDs following the use of folic-acid-containing multivitamins [14].

A previous population-based Hungarian observational study showed an association between the use of high-dose (3–6 mg) folic acid by pregnant women and a significant decrease in the risk of total CHDs (OR 0.86, 95% CI 0.77–0.96) [15]. An observational Dutch study [16] reported a protective effect of folic acid intake in early pregnancy against CHDs (OR 0.82, 95% CI 0.68–0.98), and a recent Chinese study showed a decrease in the risk of CHDs of approximately 70% after periconceptional folic acid supplementation (OR 0.31, 95% CI 0.18–0.54) [17].

CHDs have heterogeneous manifestations and origins [18]. The objective of this study was to estimate the possible decrease in different types of CHD after the use of folic acid alone during the critical period of CHD development in the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) [19]. The classification of CHDs from the Baltimore-Washington Infant Study [20] was used in this study. Only those patients who underwent catheter examination or surgical correction, or had an autopsy diagnosis were included in this study.

Materials and methods

Cases and controls

Children born with CAs including CHDs in the HCCSCA were selected as cases from the Hungarian Congenital Abnormality Registry (HCAR) [21]. Autopsy was mandatory for all infant deaths.

Controls were defined as newborn infants without CAs. Controls were selected in each quarter of the year for the HCCSCA from the National Birth Registry of the Central Statistical Office including all Hungarian births. In general, two controls were matched to each case according to sex, birth year/week and district of parents' residence. If controls were twins, one twin was selected at random for the HCCSCA.

Data collection

A letter, structured questionnaire and informed consent form were posted to the mothers of cases and controls immediately after their selection for the HCCSCA, with the request to supply the prenatal maternity logbook and all medical records concerning their child's CA [19]. Prenatal care was mandatory for pregnant women in Hungary, so nearly 100% of pregnant women visited the prenatal care clinic an average of seven times during pregnancy. The mean time from the end of pregnancy until receipt of the logbook, discharge summary of delivery, questionnaire and informed consent was 3.5 (SD 2.1) and 5.2 (SD 2.9) months for cases and controls, respectively.

Regional district nurses were asked to visit the mothers of all cases who did not respond to help them to complete the questionnaire and evaluate the available medical documents. District nurses only visited 200 non-respondent and 600 respondent control mothers as part of two validation studies because the ethics committee considered this follow-up to be disturbing for the parents of healthy children [19].

Information regarding the use of folic acid was available for 96.3% of cases (84.4% from replies and 11.9% from visits) and 83.0% of controls (81.3% from replies and 1.7% from visits); in total, 22,843 cases and 38,151 controls were evaluated (the latter represented 1.8% of 2,134,714 live-births in Hungary). The informed consent form was signed and returned by 98% of cases; personal identifiers were deleted from the records of the remaining 2% [19]. This paper evaluates the data set of the HCCSCA from 1980 to 1996 because the method of data collection was changed in 1997; more recent data had not been validated at the time of this analysis.

Evaluation of cases with CHD

In the HCCSCA, approximately 70% of CHD cases had a specific diagnosis. The 30% of CHD cases with an unspecified diagnosis were assumed to have been cared for or received surgical intervention in a pediatric cardiology institution in Hungary. To obtain specific diagnoses for these 30% of cases, staff of the HCCSCA visited all cardiology clinics from 2008, and reviewed the medical records of patients. As such, only cases with specified and confirmed diagnoses of isolated CHDs were included in the study. Cases with syndromic CHDs due to major mutant genes (e.g. Holt–Oram) or chromosomal aberrations (e.g. Down's) were excluded from the HCCSCA [19], as were cases with unclassified multiple CAs including CHDs.

Some types of CHD have a wide spectrum of manifestations including spontaneous closure of ventricular or atrial septal defects, ductus arteriosus, etc. As such, only cases with lethal outcomes verified by autopsy report or with documented catheter examination and/or surgical correction were included in the study.

The main objective of this study was to investigate the possible association between folic acid supplementation during critical periods of embryonic development and a decrease in certain CHDs [22].

Statistical analysis

SAS Version 8.02 (SAS Institute, Cary, NC, USA) was used for statistical analysis of data. Three maternal confounders (age, birth order and employment status, as an indicator of socio-economic status [19]) were considered. A conditional logistic regression model was used to estimate the relative risk/protection [odds ratio (OR) with 95% confidence intervals (CI)] of folic acid use in the

Table 1
Sociodemographic characteristics of mothers of cases and matched controls with or without folic acid supplementation.

Variables	Cases				Controls			
	With folic acid (n = 1808)		Without folic acid (n = 1759)		Without folic acid (n = 2443)		With folic acid (n = 2952)	
Quantitative	n	%	n	%	n	%	n	%
Maternal age (years)								
≤19	180	10.8	161	9.2	212	8.7	240	8.1
20–29	1231	68.1	1215	69.1	1763	72.2	2193	74.3
≥30	397	22.0	383	21.8	468	19.2	519	17.6
Mean (SD)	25.8 (5.4)		25.7 (5.2)		25.5 (5.1)		25.3 (4.7)	
Birth order								
1	752	41.6	780	44.3	1105	45.2	1461	49.5
2	634	35.1	641	36.4	909	37.2	1110	37.6
≥3	422	23.3	338	19.2	429	17.6	381	12.9
Mean (SD)	2.0 (1.3)		1.9 (1.1)		1.8 (1.1)		1.7 (0.9)	
Unmarried	112	6.2	92	5.2	105	4.3	107	3.6
Employment status								
Professional	138	7.6	173	9.8	255	10.4	343	11.6
Managerial	355	19.6	385	21.9	597	24.4	809	27.4
Skilled worker	487	26.9	551	31.3	792	32.4	968	32.8
Semiskilled worker	325	18.0	280	15.9	372	15.2	462	15.7
Unskilled worker	159	8.8	122	6.9	158	6.5	136	4.6
Housewife	224	12.4	184	10.5	187	7.7	149	5.0
Others	120	6.6	64	3.6	82	3.4	85	2.9

Mothers of matched controls were somewhat younger with lower mean birth order compared with the mothers of cases with CHDs. Folic acid users appear to be the same age as non-users and to have similar birth order.