Do Multivitamin Supplements Attenuate the Risk for Diabetes-Associated Birth Defects?

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ABSTRACT. *Objective.* **To evaluate whether the risk for birth defects associated with maternal diabetes is attenuated by use of multivitamin supplements during the periconceptional period.**

Methods. **In the population-based Atlanta Birth Defects Case-Control Study, we identified case infants who had nonsyndromic birth defects that were reported to be associated with diabetes ($n = 3278$) and were born during 1968–1980 to residents of metropolitan Atlanta. Controls were infants without birth defects ($n = 3029$). Maternal diabetes was defined as reported diabetes with onset before the date of birth of the index infant, and periconceptional use of multivitamins was defined as reported regular use of multivitamin supplements from 3 months before pregnancy through the first 3 months of pregnancy.**

Results. **Offspring of mothers with diabetes had an increased risk for selected birth defects. However, the increased risk was limited to offspring of mothers who had diabetes and had not taken multivitamins during the periconceptional period (odds ratio: 3.93; 95% confidence interval: 1.79–8.63). Offspring of mothers who had diabetes and had taken multivitamins during the periconceptional period had no increased risk for birth defects (odds ratio: 0.15; 95% confidence interval: 0.00–1.99).**

Conclusions. **Periconceptional use of multivitamin supplements may reduce the risk for birth defects among offspring of mothers with diabetes.** ***Pediatrics*** **2003;111: 1146–1151;** ***birth defects, congenital heart defects, central nervous system defects, diabetes, multivitamin supplements, prevention.***

ABBREVIATIONS. OR, odds ratio; CI, confidence interval.

It is well established that offspring of mothers with diabetes are at increased risk for birth defects,[1–3] the most prevalent of which are heart and central nervous system defects.[4–7] Both human and animal studies have demonstrated that diabetic embryopathy is associated with hyperglycemia during the period of organogenesis.[8–12] However, the precise mechanism(s) by which hyperglycemia induces diabetic embryopathy remains unclear. A number of hypotheses have been proposed, such as alterations of fuels or fuel-related factors, arachidonic acid and myo-inositol deficiency, and an excess production of free oxygen radicals relative to the antioxidant reserve (ie, oxidative stress).[13] Recent studies have shown that administration of antioxidants to diabetic pregnant rodents can reduce the risk for diabetic-associated embryopathy,[14–17] suggesting that oxidative stress may be involved in the cause of malformations. Whether administration of antioxidants to pregnant women with diabetes reduces the risk for diabetic embryopathy remains to be determined. However, there is increasing evidence that the risk for birth defects may be reduced by the consumption of multivitamin supplements during the periconceptional period.[18–27] Although the underlying mechanism for this risk reduction with multivitamins is also unclear, such evidence suggests the possibility that the risk of birth defects among offspring of women with diabetes might also be attenuated by periconceptional consumption of multivitamin supplements. We used data from a case-control study of birth defects to examine whether maternal consumption of multivitamin supplements during the periconceptional period attenuates risk for birth defects associated with maternal diabetes.

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METHODS

Source Population and Data

We analyzed data from the Atlanta Birth Defects Case-Control Study, which has been described in detail elsewhere.[28,29] Eligible cases were singleton live and stillborn infants (born between January 1968 and December 1980) with birth defects ascertained within the first year of life by the Metropolitan Atlanta Congenital Defects Program, a population-based registry of infants with birth defects. Diagnostic information on cases was obtained from vital records, birthing hospitals, pediatric and specialty clinical facilities, and cytogenetic laboratories. Controls were a 1% stratified random sample of infants who did not have birth defects and were born in the same birth cohort and frequency matched to cases by race, calendar quarter of birth, and hospital of birth.

Case Selection and Classification

We selected all liveborn and stillborn infants with a major birth defect reported to be associated with diabetes in population-based studies,[5–7] including selected defects of the central nervous system, cardiac defects, eye defects, respiratory tract defects, cleft palate, anal atresia/stenosis, hypospadias, urinary tract defects, and positional defects of the foot. Infants with >1 cardiac defect were assigned 1 anatomic diagnosis using a hierarchical classification approach.[7,30] Each case was classified as 1 of the following: isolated, if the birth defect was the only major anomaly present; multiple, if it was part of a pattern of multiple anomalies of unknown cause; or syndromic, if it was part of a pattern of a

genetic or teratogenic syndrome (eg, trisomy 13, 18, or 21; rubella syndrome). In this study, we evaluated nonsyndromic cases (ie, isolated and multiple). Distributions of these nonsyndromic cases by type of defect and overall clinical diagnosis are shown in Table 1.

Exposure Classification

Information on maternal diabetes and use of multivitamin supplements during pregnancy, as well as other factors, was obtained through telephone interviews of case and control parents.[29] We classified maternal diabetes status on the basis of the mothers' response to the question of whether at any time before the date of the index infant's birth she had ever received a diagnosis of having diabetes or sugar diabetes. For the index pregnancy, we classified mothers into 1 of 3 mutually exclusive categories: 1) "diabetic" when the mother reported having been diagnosed with diabetes before the birth of the index infant; 2) "nondiabetic" when the mother reported not having received a diagnosis of diabetes before the birth of the index infant; and 3) "unknown" when the response was missing or uncodable.

Classification of maternal use of multivitamin was based on the mothers' responses to 2 questions: 1) At any time during the period from 3 months before the pregnancy began through the first 3 months of the pregnancy, did you take any vitamins regularly, that is, at least 3 times a week? 2) In which months during this period did you take the vitamins? We used the answers to these questions and a definition of regular use of multivitamins as taking a multivitamin at least 3 times a week to group mothers into the following 4 mutually exclusive categories: 1) nonusers when they had reported no use of multivitamins; 2) periconceptional users when they reported regular use of multivitamins during the 6-month period, from 3 months before pregnancy through the third month of pregnancy; 3) other users when they reported other patterns of use of multivitamins; and 4) unknown or uncodable. Because the protective effect of multivitamin supplements against birth defects is reported to occur with supplements used regularly during the periconceptional period,[19–28] our evaluation of the protective effect of multivitamin supplements focused on the comparison of nonusers and regular users of multivitamin supplements during the periconceptional period.

Analysis

Frequency distributions of selected maternal characteristics were compared between all selected nonsyndromic cases and controls using χ^2 tests. We compared risk for nonsyndromic cases in the offspring of mothers with diabetes with that of mothers without diabetes by type of defect and, in the case of specific types of heart defects with a small number of cases, by broader anatomic groups (laterality or looping; outflow tract defects; left obstructive defects; right obstructive defects; and septal defects). For types of birth defects found to be associated with maternal diabetes, we then compared risk for birth defects among offspring of periconceptional users of multivitamin supplements (ie, from 3 months before pregnancy through the third month of pregnancy) with that among offspring of nonusers. We estimated relative risks with odds ratios (ORs) and 95% confidence intervals (CIs), using exact methods when the number of expected cases was <5.[31] We evaluated independent and joint effects of maternal diabetes and use of vitamin supplements by comparing risk for birth defects among offspring of women who used multivitamin supplements periconceptionally (users) with that among offspring of women who did not use multivitamin supplements periconceptionally (nonusers),

TABLE 1. Infants With Selected Nonsyndromic Birth Defects (Cases) by Type of Defect and Clinical Diagnosis, Atlanta Birth Defects Case-Control Study, 1968–1980

Defect Type	Isolated		Multiple		Total No.
	n	%	*n*	%	
Anencephaly	122	84.1	23	15.9	145
Spina bifida	154	76.2	48	23.8	202
Hydrocephaly	122	63.9	69	36.1	191
Eye defects	38	37.2	64	62.8	102
Heart defects					
Laterality/looping defects	4	22.2	14	77.8	18
Heterotaxia	1	6.7	14	93.3	15
Corrected (levo) transposition	3	100.0	0	0	3
Outflow tract defects	121	79.1	32	20.9	155
Tetralogy of Fallot	44	80.0	11	20.0	55
Dextro-transposition of the great vessels	59	85.5	10	14.5	69
Truncus arterious	11	57.9	8	42.1	19
Double outlet right ventricle	7	70.0	3	30.0	10
Atrioventricular septal defect	9	64.3	5	35.7	14
Total anomalous pulmonary venous return	12	70.6	5	29.4	17
Ebstein anomaly	7	77.8	2	22.2	9
Right obstructive defects	71	74.7	24	25.3	95
Tricuspid atresia	10	71.4	4	28.6	14
Pulmonary atresia, intact septum	4	57.1	3	42.9	7
Pulmonic stenosis or atresia	28	70.0	12	30.0	40
Pulmonic stenosis	18	81.8	4	18.8	22
Peripheral pulmonic stenosis	11	91.7	1	8.3	12
Left obstructive defects	88	73.3	32	26.7	120
Hypoplastic left heart	25	71.4	10	28.6	35
Coarctation of the aorta	39	67.2	19	32.8	58
Aortic arch atresia/hypoplasia	7	77.8	2	22.2	9
Aortic valve stenosis	17	94.4	1	5.6	18
Septal defects	163	74.1	57	25.9	220
Ventricular septal defects	147	74.2	51	25.8	198
Atrial septal defects	16	72.7	6	27.3	22
Respiratory tract defects	18	22.8	61	77.2	79
Cleft palate	56	59.6	38	40.4	94
Cleft lip ± cleft palate	172	76.8	52	23.2	224
Pyloric stenosis	284	91.6	26	8.4	310
Anal atresia/stenosis	32	36.4	56	63.6	88
Hypospadias	476	84.0	91	16.0	567
Urinary tract defects	128	49.8	129	50.2	257
Positional defects of the leg	667	80.2	165	19.8	832

stratifying by maternal diabetes status. We adjusted for several potential confounders, including infant's period of birth (January 1968–March 1972, April 1972–July 1976, August 1976–December 1980) and maternal race (white, nonwhite), age (<20, 20–29, 30+ years), education (elementary, high school, college), prenatal cigarette smoking (yes, no), and prenatal alcohol consumption (yes, no), using exact logistic regression methods.[32] Adjusted ORs and 95% CIs were calculated from maximum likelihood estimates for the regression coefficient and covariate matrix.

RESULTS

Study subjects consisted of 3278 nonsyndromic case infants and 3029 control infants with maternal interview data (participation rates of 71% and 68%, respectively). Case infants represented selected types of birth defects that have been associated with maternal diabetes in published reports (Table 1).

Compared with controls, slightly more cases were white and born to women who reported cigarette smoking during pregnancy (Table 2). Otherwise, case mothers were similar to control mothers with respect to all factors.

Prevalence of reported maternal diabetes was 1% among control infants and ranged from 0% to 17% among infants with 20 types of birth defects. Maternal diabetes was associated with a statistically significant increased risk for a birth defect (OR >1) among 6 types of birth defects (Table 3): hydrocephaly, outflow tract defects, septal defects, respiratory tract defects, pyloric stenosis, and anal atresia or stenosis. Maternal diabetes was not associated with a statistically significant decreased risk for any of these 20 types of birth defects.

We further evaluated the 6 types of defects associated with maternal diabetes above for possible protective effects of multivitamin supplement use during the periconceptional period (Table 4). Prevalence of reported use of multivitamin supplements periconceptionally was 38% among control infants and ranged from 13% to 38% among case infants. Maternal use of vitamin supplements was associated with a statistically significant decreased risk for birth defects (OR <1) among 2 types of defects: outflow tract defects and septal defects.

For the 6 types of defects associated with maternal diabetes, we then examined the independent and joint effects of maternal diabetes and use of multivitamin supplements during the periconceptional period on risk for birth defects. Because of small numbers, we grouped outflow tract defects and septal defects into 1 category of heart defects. We examined associations for each of these types of birth defects as well as for all of these types combined (Table 5). Among all birth defects types combined, the most prevalent group was that with no maternal diabetes and no use of multivitamins during the periconceptional period, so we used this as the reference group. Compared with infants whose mothers had no diabetes and had not used multivitamin supplements during the periconceptional period, infants whose mothers had no diabetes but had used multivitamin supplements during the periconceptional period had a lower risk for diabetes-associated birth defects (OR: 0.82; 95% CI: 0.65–1.03). Compared with the same reference group of infants, infants whose mothers had diabetes and had not used multivitamin supplements had an increased risk for diabetes-associated birth defects (OR: 3.93; 95% CI: 1.79–8.63). However, infants whose mothers had diabetes but used multivitamin supplements during the periconceptional period had no increased risk for diabetes-associated birth defects (OR: 0.15; 95% CI: 0.05–1.19). These findings remained essentially unchanged with adjustment for potential confounding by period of

TABLE 2. Characteristics of Mothers of Infants With Selected Nonsyndromic Birth Defects (Cases) and Mothers of Infants Without Birth Defects (Controls), Atlanta Birth Defects Case-Control Study, 1968–1980

	Cases (n = 3278)		Controls (n = 3029)	
	n	%	n	%
Characteristic				
Race*				
White	2590	79.0	2301	76.0
Nonwhite	688	21.0	728	24.0
Maternal age (y)				
<20	373	11.4	344	11.3
20–29	2200	67.1	1993	65.9
30 and older	705	21.5	689	22.8
Period of child's birth				
January 1968–March 1972	905	27.6	851	28.1
April 1972–July 1976	1127	34.4	1015	33.5
August 1976–December 1980	1246	38.0	1163	38.4
Education				
Elementary school	587	17.9	497	16.4
High school	2051	62.6	1956	64.6
College	639	19.5	576	19.0
Prenatal cigarette smoking*				
Yes	1134	34.6	973	32.1
No	2141	65.3	2056	67.9
Prenatal alcohol use				
Yes	1585	48.4	1517	50.2
No	1678	51.2	1504	49.8

Numbers and percentages may not add to totals as a result of missing values.
* $P < .01$.

TABLE 3. Frequency of Maternal Diabetes Among Mothers of Infants Without Birth Defects (Controls) and Mothers of Infants With Selected Nonsyndromic Birth Defects (Cases) and Associated Effect Estimates, by Type of Defect, Atlanta Birth Defects Case-Control Study, 1968–1980

	Diabetes*	No Diabetes†	OR	95% CI
Controls	33	2993	Reference	
Anencephaly	1	144	0.63	0.09–4.64
Spina bifida	4	198	1.83	0.64–5.22
Hydrocephaly	8	183	3.96	1.81–8.71
Eye defects	3	99	2.75	0.83–9.11
Heart defects				
Laterality/looping defects	1	17	5.32	0.12–36.05
Outflow tract defects	6	147	3.70	1.25–9.13
Atrioventricular septal defect	1	13	6.98	0.89–54.89
Total anomalous pulmonary venous return	0	17	0.00	0.00–18.12
Ebstein anomaly	0	9	0.00	0.00–37.12
Right obstructive defects	3	75	3.63	0.70–11.96
Left obstructive defects	0	119	0.00	0.0–3.02
Septal defects	7	212	2.99	1.10–6.99
Respiratory tract defects	5	74	6.13	2.33–16.14
Cleft palate	3	91	2.99	0.90–9.93
Cleft lip ± cleft palate	1	223	0.41	0.06–2.99
Pyloric stenosis	8	302	2.40	1.10–5.25
Anal atresia or stenosis	4	84	4.32	1.50–12.47
Hypospadias	9	558	1.46	0.70–3.07
Urinary tract defects	5	252	1.80	0.70–4.65
Positional defects of the leg	10	821	1.10	0.54–2.25

* Preexisting or gestational diabetes.
† No preexisting or gestational diabetes.

TABLE 4. Frequency of Periconceptional Multivitamin Supplement Use Among Mothers of Infants Without Birth Defects (Controls) and Mothers of Infants With Selected Nonsyndromic Birth Defects (Cases) Associated With Maternal Diabetes and Associated Effect Estimates, by Type of Defect, Atlanta Birth Defects Case-Control Study, 1968–1980

	Vitamins*	No Vitamins†	OR	95% CI
Controls	431	1179	Reference	
Hydrocephaly	21	82	0.70	0.43–1.15
Heart defects				
Outflow tract defects	12	73	0.45	0.24–0.84
Septal defects	22	100	0.60	0.37–0.97
Respiratory tract defects	11	33	0.91	0.46–1.82
Pyloric stenosis	48	109	1.20	0.84–1.72
Anal atresia/stenosis	12	38	0.86	0.45–1.67

* Periconceptional users of multivitamin supplements (ie, regular users from 3 months before conception through the first trimester of pregnancy).
† Nonusers of multivitamin supplements during the periconceptional period (ie, no use of multivitamin supplements at anytime, from 3 months before conception through the first trimester of pregnancy).

birth, maternal age, race, smoking, or alcohol use. Results for the individual defects were similar.

DISCUSSION

We found that offspring of mothers with diabetes had increased risks for hydrocephaly, outflow tract defects, septal defects, respiratory tract defects, pyloric stenosis, and anal atresia or stenosis. However, the increased risk seemed to be limited to offspring of mothers who had diabetes and had not taken multivitamins during the periconceptional period. Offspring of mothers who had taken multivitamins during the periconceptional period had no increased risk for birth defects, regardless of whether they had diabetes.

Selection bias is not likely to explain these results. The control population in the original study (ie, Atlanta Birth Defects Case-Control Study) was a representative random sample of all liveborn infants without birth defects from a regional birth cohort,[29] and case infants were identified by a population-based surveillance system that ascertained cases on an active basis and from multiple sources. Study infants were born during 1968–1980, so the probability for their inclusion in this study was less likely to be affected by prenatal diagnosis, which did not become widely available and used until later. Maternal interview participation rates were comparable for case and control mothers.

In this study, assessments of diabetes status and of multivitamin supplement use were based on maternal reports. We were not able to verify this information or to obtain more detailed information, so we were not able to distinguish between type 1, type 2, and gestational diabetes and to evaluate whether the associations varied by the type of diabetes. The long recall period between the infant's birth and the time of the maternal interview (2–16 years) may have resulted in some reporting errors about the time of diagnosis of diabetes and the use of multivitamin

TABLE 5. Unadjusted Effect Estimates (ORs) for Maternal Diabetes, Use of Multivitamin Supplements During the Periconceptional Period, and Selected Nonsyndromic Birth Defects, Atlanta Birth Defects Case-Control Study, 1968–1980

Birth Defects*	Maternal Diabetes*	Use of Vitamins†	No. Cases/Controls	OR	95% CI
Hydrocephaly	Yes	Yes	0/7	0.00‖	0.00–3.71
	Yes	No	4/11	2.51‖	0.58–8.57
	No	Yes	21/424	0.74	0.45–1.21
	No	No	169/1165	Reference	
Heart‡	Yes	Yes	1/7	1.00‖	0.02–7.88
	Yes	No	7/11	4.47	1.71–11.68
	No	Yes	33/424	0.55	0.37–0.81
	No	No	166/1165	Reference	
Respiratory tract	Yes	Yes	0/7	0.00‖	0.00–20.88
	Yes	No	2/11	6.83‖	0.70–33.12
	No	Yes	11/424	0.97	0.49–1.96
	No	No	31/1165	Reference	
Pyloric stenosis	Yes	Yes	0/7	0.00‖	0.00–6.00
	Yes	No	4/11	4.03‖	0.92–13.89
	No	Yes	48/424	1.26	0.88–1.80
	No	No	105/1165	Reference	
Anal atresia/stenosis	Yes	Yes	0/7	0.00‖	0.00–16.87
	Yes	No	0/11	0.00‖	0.00–9.92
	No	Yes	12/424	0.87	0.45–1.68
	No	No	38/1165	Reference	
All defects§	Yes	Yes	1/7	0.15‖	0.00–1.19
	Yes	No	15/11	3.93	1.79–8.63
	No	Yes	120/424	0.82	0.65–1.03
	No	No	1095/1165	Reference	

* For maternal diabetes: Yes = preexisting or gestational; No = no preexisting or gestational diabetes.
† For use of vitamins: Yes = use of multivitamin supplements, from before conception through the first trimester of pregnancy; No = no use of multivitamins, from before conception through the first trimester of pregnancy.
‡ Outflow tract defects and septal defects.
§ Hydrocephaly, outflow tract defects, septal defects, respiratory tract defects, pyloric stenosis, and anal atresia or stenosis.
‖ORs and 95% CIs based on exact procedures.

supplements during the periconceptional period. However, differential misclassification is unlikely given that diabetes and multivitamin supplements were not generally regarded as factors associated with birth defects at the time the data were collected. Furthermore, similar associations between birth defects and diabetes and between birth defects and multivitamin supplements have been reported. Nondifferential exposure misclassification with respect to the onset of diabetes and periconceptional use of multivitamins probably occurred, so if the observed associations are real, then the effect estimates are probably underestimates.

Issues of sample size and potential confounding are limitations of this study. The small number of cases with reports of both maternal diabetes and use of multivitamin supplements limited our ability to evaluate possible effect modification of multivitamins on risks for specific types of birth defects associated with diabetes and to obtain more precise effect estimates. Consistency of the findings for 5 categories of birth defects that we evaluated (Table 5), however, suggests that chance is not a likely explanation. Associations among birth defects, diabetes, and use of multivitamin supplements, including attenuation of risk for diabetes-associated birth defects by use of multivitamin supplements, exhibited little change with adjustment for potential confounding by period of birth, maternal age, race, smoking, or alcohol use. However, 1 potential confounder for which we had no information and could not take into account was the level of control of diabetes early in pregnancy. Meticulous control of diabetes during organogenesis reduces the risk for malformations in animals,[33] and timely institution of intensive therapy for pregnant women with insulin-dependent diabetes has been associated with rates of congenital malformations similar to those among nondiabetic pregnant women.[34] If in our study, use of multivitamin supplements among mothers with preexisting diabetes happened to be a surrogate for such type of diabetic control early in pregnancy, then the reduced risk for diabetes-associated birth defects with use of multivitamin supplements might be explained by differences in the level of control of diabetes between users and nonusers of multivitamins. We did not have information on type or severity of diabetes among mothers of study subjects, on the level of glycemic control, or on a possible surrogate measure for level of glycemic control. However, during the study period, the level of such control probably varied, even among women who took multivitamin supplements.

If the observed attenuation risk for diabetes-associated birth defects with multivitamin supplements is not attributable to chance or confounding, then questions arise about possible factor(s) in multivitamin supplements and mechanism(s) underlying this attenuation. Use of multivitamin supplements that may or may not contain folic acid has been associated with decreased risk for various birth defects, including neural tube defects,[18,20,21] heart defects,[24,25,27] urinary tract defects, limb defects, and pyloric stenosis.[27] Furthermore, use of folic acid supplements has also been associated with reduced risk for neural tube defects[19] and imperforate anus.[35] An-

imal studies have shown that the teratogenic effects of diabetes can be prevented by consumption of the antioxidant vitamin E.[14–17] We had no information on the actual composition and dosage of individual vitamins in the multivitamin supplements used by mothers of study subjects, and so determining which ingredient(s) in the multivitamin supplements may account for the observed protective effects is not possible.

Although congenital anomalies associated with maternal diabetes are thought to be related to abnormalities in maternal metabolic fuels essential for embryogenesis,[13] precise pathogenetic mechanisms remain unclear. One hypothesis is that abnormal glucose levels characteristic of diabetes disrupt expression of a regulatory gene in the embryo, leading to embryotoxic apoptotic cellular changes.[36] The prevention of diabetic embryopathy by antioxidants in animal studies might suggest that oxidative stress resulting from metabolic abnormalities and generation of free radicals is another possible mechanism.[14–17,37,38] Because our study had no information on the type of diabetes, level of diabetic control, or composition of the multivitamin supplements used by the women in our study, we are unable to shed light on either of these hypotheses.

Randomized clinical trials in women with diabetes have demonstrated that the prevention of malformations among offspring is possible with "tight" glycemic control early in pregnancy.[34] The 1992 US Public Health Service recommendation that all women who are capable of becoming pregnant consume 400 μg of folic acid daily[39] may be particularly important for women with diabetes, because two thirds of pregnancies are unplanned.[40] This study presents results with potentially important prevention implications for women with diabetes during pregnancy.

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