

OBSTETRICS

Diabetes mellitus and birth defects

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OBJECTIVE: The purpose of this study was to examine associations between diabetes mellitus and 39 birth defects.

STUDY DESIGN: This was a multicenter case-control study of mothers of infants who were born with ($n = 13,030$) and without ($n = 4895$) birth defects in the National Birth Defects Prevention Study (1997-2003).

RESULTS: Pregestational diabetes mellitus (PGDM) was associated significantly with noncardiac defects (isolated, 7/23 defects; multiples, 13/23 defects) and cardiac defects (isolated, 11/16 defects; multiples, 8/16 defects). Adjusted odds ratios for PGDM and all isolated and multiple defects were 3.17 (95% CI, 2.20-4.99) and 8.62 (95% CI,

5.27-14.10), respectively. Gestational diabetes mellitus (GDM) was associated with fewer noncardiac defects (isolated, 3/23 defects; multiples, 3/23 defects) and cardiac defects (isolated, 3/16 defects; multiples, 2/16 defects). Odds ratios between GDM and all isolated and multiple defects were 1.42 (95% CI, 1.17-1.73) and 1.50 (95% CI, 1.13-2.00), respectively. These associations were limited generally to offspring of women with prepregnancy body mass index ≥ 25 kg/m².

CONCLUSION: PGDM was associated with a wide range of birth defects; GDM was associated with a limited group of birth defects.

Key words: birth defect, gestational diabetes mellitus, obesity, pregestational diabetes mellitus

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Birth defects affect 1 in 33 babies and are a leading cause of infant death in the United States.^{1,2} The causes of most birth defects remain unknown.^{3,4} Although pregestational diabetes (PGDM; ie, type 1 or type 2) is a known risk factor for defects of the cardiovascular, central nervous, and musculoskeletal systems,⁵⁻⁹ information

on the specific phenotypes within each 1 of these organ systems that are associated with diabetes mellitus remains unclear because most published studies have examined broad categories of birth defects. Moreover, the effect of diabetes mellitus on other organ systems (eg, gastrointestinal and genitourinary) remains poorly understood.

Although the mechanisms underlying the associations of diabetes mellitus with birth defects are not understood completely, it is clear that hyperglycemia plays a critical role. There is a positive correlation between hyperglycemia during embryogenesis and a risk for congenital malformations among infants of diabetic mothers^{10,11} and in animal models.¹² In addition, among diabetic women with good glycemic control, the prevalence of birth defects is similar to that in the general population.¹³ Accordingly, 1 of the proposed strategies to prevent birth defects that are associated with PGDM has been glycemic control during pregnancy.¹⁴ However, the increasing prevalence of diabetes mellitus¹⁵ and the challenges in achieving adequate glycemic control periconceptionally among women with diabetes mellitus¹⁶ raise concerns about the extent to which PGDM contributes to the burden of birth defects in the United States today.

Gestational diabetes mellitus (GDM) has also been reported as being associated with birth defects.^{5,17} Because some women diagnosed with GDM for the first time actually may have undiagnosed

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type 2 diabetes mellitus, the association of birth defects with GDM could well reflect an association with type 2 diabetes mellitus.^{5,9} This possibility and the observation that prepregnancy obesity, which is a risk factor for type 2 diabetes mellitus,¹⁸ has been found to be associated with birth defects¹⁹ raise the question about whether the association of GDM with birth defects is more likely to be evident among offspring of women with prepregnancy obesity.^{20,21}

We used data from the National Birth Defects Prevention Study (NBDPS)²² to examine the associations of PGDM (ie, types 1 or 2) and GDM with risk for a broader range of birth defect categories than has been examined before and to evaluate the extent to which maternal prepregnancy body mass index might modify such associations.

MATERIALS AND METHODS

NBDPS

Detailed methods of the NBDPS have been published previously.²² Briefly, the NBDPS is a population-based case control study that incorporates data from 10 birth defect surveillance systems in the United States (Arkansas, California, Georgia/Centers for Disease Control and Prevention, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Cases (live births, stillbirths, or terminations) had ≥ 1 of 30 eligible major birth defect groups. Cases with defects that are recognized to have a known cause (single-gene disorders and chromosome abnormalities) were excluded. Control subjects were liveborn infants without birth defects who were selected randomly either from birth certificates or from birth hospitals. Maternal interviews were conducted with a standardized questionnaire, in English or Spanish, between 6 weeks and 24 months after the estimated date of delivery. Interview participation rates were 71% among case mothers and 68% among control mothers. The NBDPS has been approved by the Institutional Review Boards of the CDC and the participating study centers.

Case infants were classified as having isolated or multiple defects by clinical

geneticists based on reviews of clinical information that were abstracted from medical records. Infants who were classified as having an isolated birth defect had (a) 1 major defect, (b) 1 major defect and ≥ 1 minor defects, (c) major defects that affect 1 organ system only, or (d) a major defect with a well-described sequence of related defects without any other unrelated major defects. Infants with multiple birth defects had either ≥ 2 major unrelated defects in different organ systems or multiple associated major defects.²³ All cases with heart defects were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy and were classified further about whether the heart defect was simple (ie, 1 well-recognized entity such as atrial septal defect [ASD] or tetralogy of Fallot with no other cardiac defects), complex (ie, heterotaxy and single ventricle malformations), or an association of ≥ 2 heart defects neither of which could be considered the primary defect for analysis (eg, ASD with ventricular septal defect [VSD]).²⁴

Inclusions and exclusions

For this analysis, the study population was restricted to mothers with known diabetes mellitus status and an estimated date of delivery between October 1, 1997, and December 31, 2003. Our final study population consisted of 4895 control subjects and 13,030 total cases. We analyzed case groups of ≥ 50 eligible infants. The exception was sacral agenesis ($n = 32$ infants), which remained in the analysis because of the previously reported strong association with PGDM.²⁵ Our analysis of heart defects was restricted to infants with simple heart defects, unless the infant had either a heart defect and heterotaxia or a heart defect association. We analyzed 3 categories of heart defect associations: (1) left ventricular outflow tract obstruction associations (coarctation of the aorta with aortic stenosis, coarctation of the aorta with VSD, and coarctation of the aorta with VSD and ASD), (2) right ventricular outflow tract obstruction associations (pulmonary valve stenosis with VSD and pulmonary valve stenosis with ASD), and (3) VSD with ASD. California cases with

pulmonary valve stenosis were excluded because the site did not ascertain these defects according to NBDPS protocol. A final restriction limited the control group for the hypospadias analysis to male infants.

Exposure and covariate definitions

In the interview, mothers reported whether a physician had diagnosed them previously with PGDM or GDM (Appendix). As in other case-control studies,^{26,27} we divided mothers into 1 of the following mutually exclusive categories: (1) PGDM, if the mother reported having been diagnosed with type 1 or type 2 diabetes mellitus before the birth of the index infant; (2) GDM, if the mother reported having been diagnosed with GDM during the index pregnancy; (3) nondiabetic, if the mother reported having never been diagnosed with either PGDM or GDM; and (4) unknown, if the response was missing, uncodable, or inconsistent (eg, maternal report of GDM diagnosed after delivery of index child).

Other covariates of interest, which were all self-reported, were maternal body mass index (BMI), age at delivery, education, race/ethnicity, household income, entry into prenatal care, history of fetal loss, periconceptional (from 1 month before pregnancy through the first trimester) maternal smoking, intake of folate antagonist medications and folic acid supplement intake, family history of a birth defect, and study center. Interview data on prepregnancy weight and height were used to calculate BMI, which was classified according to the National Heart, Lung and Blood Institute cutoff points: <18.5 kg/m² (underweight), ≥ 18.5 - <25.0 kg/m² (average-referent), ≥ 25.0 - <30.0 kg/m² (overweight), and ≥ 30.0 kg/m² (obese).²⁸

Statistical analysis

Crude and adjusted odds ratios (ORs) and 95% CIs were calculated with logistic regression. Multivariable analyses estimated effects from a "full" model that contained the diabetes mellitus variable (pregestational or gestational) and the covariates that are listed in Table 1. Backwards elimina-

TABLE 1

Frequency distributions of maternal characteristics among controls, cases of all birth defects, isolated birth defects, and multiple birth defects, National Birth Defects Prevention Study, 1997-2003.

Characteristic	Controls (n=4895) %	All birth defects (n=13030) %	All isolated birth defects (n=10379) %	All multiple birth defects (n=1679) %
Diabetes type				
No diabetes	95.8	92.8	93.3	89.8
Pregestational	0.5	2.2	1.6	4.8
Gestational	3.7	5.1	5.1	5.4
Body mass index (kg/m ²)				
<18.5	5.7	5.8	5.7	5.4
18.5-<25.0	54.6	51.7	52.4	48.4
25.0-<30.0	21.1	21.5	21.6	22.0
≥30.0	14.6	17.3	16.7	19.3
Maternal age (years)				
<20	11.4	11.7	11.5	12.4
20-24	22.1	23.2	22.7	25.7
25-29	26.1	24.9	24.9	24.5
30-34	26.8	24.8	25.1	23.7
≥35	13.7	15.4	15.8	13.8
Maternal education				
<High school	16.8	18.1	17.3	21.0
High school	24.7	26.6	26.3	28.0
>High school	58.5	55.4	56.4	51.0
Race/ethnicity				
Non-Hispanic white	60.4	60.8	62.1	55.0
Non-Hispanic black	11.9	10.8	10.4	11.3
Hispanic	22.3	22.8	22.0	27.9
Other	5.4	5.6	5.5	5.8
Household income ≥40,000/year	44.0	41.6	43.0	34.6
Prenatal care in first trimester	88.1	87.1	87.4	85.1
History of fetal loss ^a	23.5	24.8	24.7	25.4
Maternal smoking ^b	19.2	21.8	21.7	23.0
Use of folate antagonist medications ^{b,c}	1.2	1.6	1.5	1.9
Folic acid supplement intake ^b	87.5	86.7	87.1	85.5
Family history of birth defect	2.5	3.3	3.1	2.8

Continued on page xxx.

tion removed other covariates that did not change the full model OR for the effect of diabetes mellitus by ≥10%. The most common confounders in these analyses (maternal BMI, age, race/ethnicity, entry into prenatal care, study center, and household income) were used as the final set of covariates.

We assessed effect modification by maternal BMI among all cases, all isolated cases, and all multiple cases using fully adjusted models with interaction terms between diabetes mellitus status and levels of BMI. All analyses were conducted with SAS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

From the original study population of 5008 control subjects and 13,586 cases, we excluded 113 control subjects and 401 cases with unknown or inconsistent diabetes mellitus status. An additional 155 cases were excluded during case clas-

TABLE 1

Frequency distributions of maternal characteristics among controls, cases of all birth defects, isolated birth defects, and multiple birth defects, National Birth Defects Prevention Study, 1997-2003.

Continued from page xxx.

Characteristic	Controls (n=4895) %	All birth defects (n=13030) %	All isolated birth defects (n=10379) %	All multiple birth defects (n=1679) %
Center				
Arkansas	11.9	13.4	13.7	12.0
California	13.8	13.2	12.4	17.1
CDC	11.1	12.5	12.6	12.0
Iowa	11.3	9.8	10.2	7.9
Massachusetts	12.9	14.0	14.3	11.6
New Jersey	11.7	12.1	12.3	11.3
New York	9.3	7.7	7.8	7.4
North Carolina	3.2	1.7	1.7	2.1
Texas	12.3	13.3	12.8	16.1
Utah	2.7	2.3	2.3	2.4

Totals may not add up to 100% because of missing data. All covariates missing less than 1% of data with exception of body mass index (4% among both cases and controls), income (13% among controls, 9% among cases), prenatal care (2% among controls, 3% among cases).

^a Fetal loss includes stillbirth and miscarriage

^b Exposure window is defined as month before conception through the third month of pregnancy

^c Folate antagonist medications include: aminopterin sodium, methotrexate, sulfasalazine, pyrimethamine, triamterene, trimethoprim, carbamazepine, phenytoin, phenobarbital, primidone, and cholestyramine resin.

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sification because all of the reported birth defects were determined to be ineligible for the study. The final analysis included 4895 control subjects and 13,030 cases. The prevalence of PGDM among control subjects was 0.5% (24/4895): 10 women had type 1 diabetes mellitus, and 14 women had type 2 diabetes mellitus. Among all cases combined, the prevalence was 2.2% (283/13,030): 138 women had type 1 diabetes mellitus, and 145 women had type 2 diabetes mellitus. The prevalence of GDM was 3.7% (182/4895) among control subjects and 5.1% (660/13,030) among cases (Table 1). The frequencies of both PGDM and GDM were higher in case mothers than in control mothers. The prevalence of each type of diabetes mellitus was highest among mothers of children with multiple defects. Compared with control mothers, case mothers were more likely to be obese; to have less education, lower family income, a history of fetal loss, and a family history of birth defects; and to have smoked (Table 1).

Significant positive associations were observed between PGDM and isolated cases of 7 noncardiac defects (Table 2): anencephaly and craniorachischisis, hydrocephaly, anotia/microtia, cleft lip with or without cleft palate, anorectal atresia, bilateral renal agenesis/hypoplasia, and longitudinal limb deficiencies. For each of these defects, with the exception of anencephaly, the effects were stronger among the cases with multiple defects. For several additional defects, associations were seen among multiples. Three noncardiac defects were associated with GDM: cleft palate, cleft lip with or without cleft palate, and anorectal atresia.

Eleven of 16 isolated cardiac defects were associated positively with PGDM (Table 3): tetralogy of Fallot, dextrotransposition of the great arteries, atrial VSD, total anomalous pulmonary venous return, aortic stenosis, left ventricular outflow tract obstruction associations, right ventricular outflow tract obstruction associations, perimembranous VSD, ASD secundum, ASD not otherwise specified, and

VSD with ASD. Cardiac defects did not show a systematic variation of the association with PGDM between isolated and multiple defect phenotypes. Many cardiac defects that were associated with PGDM were not associated with GDM; only 3 cardiac defects (tetralogy of Fallot, pulmonary valve stenosis, and ASD secundum) were associated with GDM.

Analyses that explored the independent and joint effects of prepregnancy BMI and diabetes mellitus (Table 4) showed that the association between PGDM and birth defects is consistent, irrespective of maternal BMI, for both isolated and multiple defects. GDM confers no additional risk of isolated or multiple birth defects among mothers with average prepregnancy BMI; however, a prepregnancy BMI ≥ 25 kg/m² combined with GDM confers an increased risk of both isolated and multiple defects.

COMMENT

PGDM was associated with approximately 50% of the birth defect categories

TABLE 2
Adjusted ORs^a and 95% CIs for associations between diabetes mellitus and selected noncardiac birth defects: NBDPS, 1997-2003

Birth defect	Pregestational (type 1 or type 2) diabetes mellitus				GDM			
	Isolated defects		Multiple defects		Isolated defects		Multiple defects	
	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)
Control subjects	24/4689		24/4689		182/4689		182/4689	
All noncardiac defects	75/6162	2.34 (1.44-3.81)	62/1233	7.80 (4.66-13.05)	299/6162	1.30 (1.05-1.60)	68/1233	1.31 (0.95-1.80)
Anencephaly and craniorachischisis	4/216	3.39 (1.11-10.31)	0/20	NE	10/216	1.33 (0.68-2.61)	1/20	1.63 (0.20-13.11)
Spina bifida	2/444	0.75 (0.17-3.24)	2/43	7.99 (1.61-39.70)	28/444	1.21 (0.74-1.96)	1/43	0.70 (0.09-5.22)
Encephalocele	3/73	2.09 (0.26-16.56)	0/25	NE	5/73	1.82 (0.70-4.71)	0/25	NE
Holoprosencephaly	1/41	6.00 (0.72-49.76)	1/18	16.16 (1.59-163.88)	1/41	0.76 (0.10-5.75)	0/18	NE
Hydrocephaly	6/146	8.80 (3.39-22.84)	6/53	12.13 (3.68-39.98)	10/146	1.97 (0.96-4.03)	4/53	1.86 (0.63-5.47)
Anotia/microtia	5/193	3.75 (1.04-13.51)	7/66	18.50 (6.95-49.24)	13/193	1.31 (0.65-2.61)	2/66	0.43 (0.06-3.20)
Choanal atresia	1/35	5.43 (0.63-47.09)	0/29	NE	3/35	1.67 (0.38-7.28)	2/29	2.20 (0.49-9.92)
Cleft palate	5/535	1.80 (0.67-4.87)	6/119	10.73 (3.99-28.86)	29/535	1.54 (1.01-2.37)	5/119	1.26 (0.50-3.20)
Cleft lip with or without cleft palate	14/1066	2.92 (1.45-5.87)	8/139	8.07 (3.05-21.39)	54/1066	1.45 (1.03-2.04)	8/139	1.22 (0.52-2.86)
Small intestinal atresia	0/165	NE	0/25	NE	5/165	0.45 (0.14-1.46)	4/25	3.59 (0.99-12.98)
Duodenal atresia	0/54	NE	0/30	NE	1/54	0.51 (0.07-3.79)	5/30	4.19 (1.40-12.59)
Esophageal atresia	0/127	NE	6/188	7.04 (2.69-18.45)	9/127	1.57 (0.67-3.69)	6/188	1.05 (0.45-2.43)
Anorectal atresia	4/200	4.70 (1.55-14.26)	11/230	8.22 (3.62-18.66)	14/200	1.91 (1.02-3.56)	14/230	1.41 (0.74-2.69)
Biliary atresia	1/65	3.14 (0.40-24.62)	1/14	18.40 (1.84-183.79)	5/65	2.21 (0.85-5.75)	0/14	NE
Hypospadias	8/806	1.89 (0.70-5.14)	6/70	18.73 (5.59-62.76)	38/806	1.49 (0.94-2.37)	8/70	2.94 (1.14-7.61)
Bilateral renal agenesis/hypoplasia	3/47	11.91 (3.10-45.72)	1/20	NE	1/47	0.58 (0.08-4.32)	0/20	NE
Longitudinal limb deficiency	3/109	6.47 (1.83-22.90)	4/86	7.01 (1.91-25.68)	7/109	1.82 (0.77-4.29)	3/86	0.94 (0.29-3.09)
Transverse limb deficiency	3/260	2.63 (0.76-9.13)	1/44	4.42 (0.54-36.11)	6/260	0.60 (0.24-1.49)	3/44	1.18 (0.27-5.03)
Craniosynostosis	4/443	1.66 (0.55-5.00)	1/46	4.31 (0.52-35.66)	20/443	1.21 (0.74-1.98)	5/46	3.51 (1.31-9.40)
Diaphragmatic hernia	2/280	0.77 (0.10-5.78)	2/63	4.70 (1.02-21.60)	12/280	1.07 (0.55-2.09)	3/63	1.12 (0.33-3.73)
Omphalocele	1/108	1.45 (0.19-11.33)	3/72	7.14 (1.93-26.40)	4/108	1.10 (0.40-3.11)	4/72	1.25 (0.44-3.55)
Gastroschisis	1/462	0.52 (0.06-4.45)	0/41	NE	7/462	0.48 (0.19-1.24)	0/41	NE
Sacral agenesis/caudal dysplasia	1/3	NE	10/18	130.17 (33.80-501.40)	0/3	NE	0/18	NE

NE, not estimable from the logistic regression model.

^a Models adjusted for maternal age, race/ethnicity, entry into prenatal care, BMI, study center, and household income.

^b Ratio of number of cases (or control subjects) with diabetes mellitus to the number of cases (or control subjects) without diabetes mellitus of any type.

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analyzed: 7 of 23 isolated noncardiac defects and 11 of 16 isolated cardiac defects; 13 of 23 multiple noncardiac defects and 8 of 16 multiple cardiac defects. These associations tended to be stronger when the defect that was studied occurred with other defects (multiple) rather than as an isolated defect. GDM was

associated with 3 of 23 isolated noncardiac defects and 3 of 16 isolated cardiac defects and with 3 of 23 multiple noncardiac defects and 2 of 16 multiple cardiac defects. The associations with GDM were weaker and generally limited to offspring of women with a prepregnancy BMI ≥ 25.0 kg/m².

Strengths of this study include the large sample size and standardized procedures for case definition and classification of birth defects, which allowed for examination of more specific categories of birth defects than has been possible in previous studies. The study's ability to characterize the current impact of

TABLE 3
Adjusted ORs^a and 95% CIs for associations between diabetes mellitus and selected cardiac defects: NBDPS, 1997-2003

Cardiac defect	Pregestational (ie, type 1 or type 2) diabetes mellitus				GDM			
	Isolated defects		Multiple defects		Isolated defects		Multiple defects	
	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)	Exposure odds ^b	OR (95% CI)
Controls	24/4689		24/4689		182/4689		182/4689	
All cardiac defects	91/3519	4.64 (2.87-7.51)	44/689	10.77 (6.23-18.62)	233/3519	1.59 (1.27-1.99)	45/689	1.65 (1.14-2.39)
Heterotaxia ^c	1/31	7.48 (0.90-62.31)	3/33	19.51 (4.82-79.0)	1/31	1.13 (0.15-8.59)	3/33	1.64 (0.37-7.22)
Tetralogy of Fallot	10/351	4.89 (2.18-10.95)	5/90	6.00 (1.67-21.58)	28/351	1.80 (1.12-2.87)	5/90	1.58 (0.62-4.05)
Dextro-transposition of the great arteries	4/254	3.34 (1.11-10.07)	2/11	71.97 (7.43-696.81)	13/254	1.11 (0.55-2.22)	0/11	NE
Atrial VSD	4/66	12.36 (3.68-41.49)	2/11	25.28 (4.20-152.11)	2/66	0.99 (0.23-4.18)	0/11	NE
Total anomalous pulmonary venous return	3/102	7.12 (1.99-25.42)	0/7	NE	2/102	0.33 (0.04-2.38)	0/7	NE
Hypoplastic left heart syndrome	4/203	2.52 (0.73-8.75)	0/16	NE	15/203	1.81 (0.99-3.30)	2/16	4.01 (0.84-19.13)
Coarctation of the aorta	2/196	2.14 (0.48-9.45)	0/29	NE	15/196	1.31 (0.65-2.65)	3/29	3.15 (0.89-11.22)
Aortic stenosis	2/113	5.01 (1.09-22.90)	0/8	NE	2/113	0.58 (0.14-2.43)	0/8	NE
Left ventricular outflow tract associations ^d	3/148	4.58 (1.30-16.10)	0/30	NE	5/148	0.98 (0.39-2.47)	3/30	1.25 (0.28-5.65)
Pulmonary valve stenosis	4/368	1.44 (0.41-5.06)	0/18	NE	35/368	2.41 (1.59-3.64)	4/18	5.96 (1.86-19.11)
Pulmonary atresia	0/72	NE	1/3	0.50 (0.07-3.69)	1/72	NE	1/3	5.64 (0.44-72.97)
Right ventricular outflow tract associations ^d	6/118	9.61 (3.53-26.15)	2/16	9.83 (1.05-91.85)	4/118	0.87 (0.31-2.43)	2/16	3.14 (0.64-15.28)
VSD: perimembranous	12/571	2.89 (1.27-6.56)	5/75	7.70 (2.37-25.04)	33/571	1.45 (0.95-2.20)	3/75	1.14 (0.35-3.76)
ASD: secundum	22/419	8.47 (4.37-16.42)	7/127	13.46 (5.23-34.60)	40/419	2.16 (1.46-3.21)	11/127	2.40 (1.19-4.82)
ASD: not otherwise specified	3/120	5.32 (1.44-19.68)	1/39	4.17 (0.50-34.96)	7/120	1.39 (0.59-3.30)	2/39	1.40 (0.32-6.05)
VSD + ASD ^d	9/242	5.83 (2.48-13.70)	5/72	9.62 (2.95-31.35)	16/242	1.10 (0.58-2.10)	2/72	0.66 (0.16-2.78)

NE, not estimable from the logistic regression model.

^a Models adjusted for maternal age, race/ethnicity, entry into prenatal care, BMI, study center, and household income.

^b Ratio of number of cases (or control subjects) with diabetes mellitus to the number of cases (or control subjects) without diabetes mellitus of any type.

^c All heterotaxia cases with congenital heart defects are included in this analysis.

^d Heart defect associations: left ventricular outflow tract associations: aortic stenosis with coarctation of the aorta, coarctation of the aorta with VSD, and coarctation of the aorta with both VSD and ASD; right ventricular outflow tract associations: pulmonary valve stenosis with VSD and pulmonary valve stenosis with ASD.

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PGDM on birth defects with the use of population-based data from several US regions was an additional strength. In this study, approximately 70% (95% CI, 54-80%) of the isolated birth defects among infants who were born to mothers with PGDM may be attributable to her diabetes mellitus (etiologic fraction among the exposed = $[OR-1]/OR$; OR for all isolated defects, 3.35 [95% CI, 2.18-5.14]). This increases to 90% (95% CI, 85-94%) for multiple defects. The attributable risks because of PGDM in the total population are 1.18% (95% CI, 0.85-1.51%) and 4.53% (95% CI, 3.45-

5.65%) for isolated and multiple defects, respectively. We were able to identify overweight and obese women with GDM as a subgroup who may be at increased risk of having offspring with birth defects and in need of closer follow-up examination and evaluation.

We were not able to ascertain the extent to which pregnancies that were complicated by PGDM and defects likely to lead to termination (eg, anencephaly/craniorachischisis and hypoplastic left heart syndrome) actually resulted in terminations in our target population. Although we did observe an association

with anencephaly, we could not exclude selection bias as a possible explanation for the lack of association of PGDM with hypoplastic left heart syndrome or for an attenuation of associations with other defects. Our definition of diabetes mellitus was based on maternal self-reports of diagnosed diabetes mellitus that were similar to approaches used in previous population-based case-control studies of birth defects.^{26,27} This is subject to misclassification for 2 reasons. First, some women who reported having GDM or no diabetes mellitus may have had undiagnosed type 2 diabetes mellitus. Second,

among individuals with a previous diagnosis of diabetes mellitus in North America, self-reports of diabetes mellitus tend to vary in sensitivity (72-98%).^{29,30} However, there is no reason to believe that the resultant misclassification of diabetes mellitus status occurred differently for case and control mothers in this study, so the net effect was probably of an attenuation of associations of diabetes mellitus with birth defects. Of interest is that the prevalence of PGDM among control subjects in this study (0.5%) is similar to that reported in earlier case-control studies of diabetes mellitus and birth defects.^{26,27} The low prevalence of PGDM resulted in imprecise risk estimates for some birth defects and did not allow for evaluation of possible associations with others. However, the large number of cases and systematic classification of defects in this study allowed for more detailed evaluations of associations of maternal diabetes mellitus with a wider spectrum of birth defects than has been published to date. Because of multiple comparisons, some of the observed associations probably reflect chance.

It is unlikely that our findings about the associations of diabetes mellitus with a wide spectrum of birth defects are the result of bias. First, the control population was a representative sample of infants without defects from the delivery cohorts that gave rise to the infants with birth defects.²² Also, case infants were identified by population-based surveillance systems that ascertained cases from multiple sources. In addition, interview participation rates were comparable for case and control mothers, and our findings changed little with adjustment for potential confounders.

Our findings of moderate-to-strong ORs for PGDM and a wide range of birth defects are consistent with and expand on previous reports that examined all birth defects as a group or broad categories of birth defects.^{26,31} In particular, our findings of associations of PGDM with central nervous system defects, limb deficiencies, renal agenesis, hypospadias, orofacial clefts, and heart defects are consistent with those reported previously.^{5,26,27,31-34} These findings support

TABLE 4

Adjusted ORs^a and 95% CIs for independent and joint associations of diabetes mellitus and maternal prepregnancy BMI with all birth defects, all isolated birth defects, and all multiple birth defects: NBDPS, 1997-2003

Diabetes mellitus status	Prepregnancy weight status ^b	OR (95% CI)
All birth defects		
None	Average weight	Reference
	Overweight	1.07 (0.98-1.18)
	Obese	1.16 (1.04-1.29)
Pregestational	Average weight	3.50 (1.68-7.30)
	Overweight	5.44 (1.97-15.05)
	Obese	5.28 (2.76-10.10)
Gestational	Average weight	1.07 (0.79-1.44)
	Overweight	1.81 (1.23-2.67)
	Obese	1.95 (1.43-2.67)
All isolated birth defects		
None	Average weight	Reference
	Overweight	1.07 (0.97-1.18)
	Obese	1.13 (1.01-1.26)
Pregestational	Average weight	2.61 (1.22-5.58)
	Overweight	3.53 (1.24-10.08)
	Obese	3.92 (2.02-7.62)
Gestational	Average weight	1.07 (0.78-1.45)
	Overweight	1.90 (1.28-2.82)
	Obese	1.90 (1.38-2.63)
All multiple birth defects		
None	Average weight	Reference
	Overweight	1.10 (0.94-1.29)
	Obese	1.28 (1.07-1.53)
Pregestational	Average weight	7.25 (3.12-16.81)
	Overweight	14.99 (5.01-44.84)
	Obese	9.94 (4.82-20.47)
Gestational	Average weight	1.17 (0.71-1.91)
	Overweight	1.80 (0.99-3.29)
	Obese	2.45 (1.57-3.81)

^a Separate models for gestational and PGDM mellitus and for the 3 groupings of birth defects. Models include 3 terms to represent interaction between levels of BMI and diabetes mellitus. Models were adjusted for maternal age, race/ethnicity, entry into prenatal care, study center, household income.

^b BMI for average weight was 18.5-<25.0 kg/m², for overweight was 25.0-<30.0 kg/m², and for obese was ≥30.0 kg/m²

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the hypothesis that the embryopathy that is associated with PGDM is nonspecific and that complex underlying metabolic disorders that are associated with diabetes mellitus increase the likelihood that different signal transduction path-

ways and morphogenetic processes might be disturbed.^{12,35,36} A possible model for the association of maternal hyperglycemia and neural tube defects has been proposed recently on the basis of animal studies.³⁷ According to this

model, maternal hyperglycemia results in increased glucose levels in the embryo and, consequently, biochemical abnormalities that increase oxidative stress. Oxidative stress results in inhibition of the *Pax3* gene, which is a gene that is required for neural crest development. Inhibition of expressions of the *Pax3* gene leads to derepression of p53-dependent cell death, which results in impaired normal neural tube closure.^{12,37} The extent to which such a model applies to associations of PGDM with defects of other organ systems is unclear. Although the variation in magnitude of the ORs for different types of birth defects that we observed could reflect, in part, a variation in tissue-selective sensitivity to the effects of underlying metabolic disturbances, it is also possible that all or part of such variation could reflect random variation because of small numbers of exposed cases. Our findings of stronger associations of PGDM with multiple defects than with isolated defects are also consistent with earlier reports.^{5,6} Possible reasons for the stronger associations with multiple defects include an increased underlying susceptibility and/or exposure to a more adverse metabolic environment in utero. Further work is warranted to elucidate the basis for the variation in the ORs by birth defect phenotype and to identify the reasons for the stronger associations of PGDM with multiple defects.

It has been hypothesized that associations of birth defects with GDM may reflect associations with undiagnosed type 2 diabetes mellitus.^{5,9} That the associations with GDM in our study were weak and limited to offspring of mothers with GDM and who were overweight or obese, both of which are risk factors for diabetes mellitus,¹⁸ is consistent with this possibility. The associations of birth defects with GDM highlight the importance of follow-up evaluation and counseling of women who are diagnosed with GDM during and subsequent to the index pregnancy. Pregnancies that are complicated by GDM among women with a history of above average weight before pregnancy might warrant consideration for prenatal screening for malformations with ultrasound scans and fetal echocardiogram, even though the

quality of such examinations might be rendered less than optimal by the presence of abdominal adiposity.³⁸ Because a diagnosis of GDM actually may represent undiagnosed type 2 diabetes mellitus and because GDM is associated with an increased risk of GDM in subsequent pregnancies and with type 2 diabetes mellitus later in life,^{39,40} women who are diagnosed with GDM might benefit from follow-up evaluations, family planning, and counseling regarding diabetes mellitus management if they are found to have type 2 diabetes mellitus and of diabetes mellitus prevention education otherwise.

Our findings expand on the body of literature of birth defects among infants of women with diabetes mellitus and highlight some of the challenges in the control of diabetes mellitus before and during pregnancy. Given the increasing prevalence of diabetes mellitus among women of childbearing age,¹⁵ the increased risk for type 2 diabetes mellitus after the onset of GDM,⁴¹ and the morbidity and mortality rates that are associated with birth defects, the importance of identifying and implementing effective detection, control, and prevention strategies for impaired glucose tolerance among women of childbearing age cannot be overstated. ■

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APPENDIX

Question 1 was asked of all participants; questions 2 and 3 were asked of participants who responded affirmatively to question 1.

Question 1: Were you ever told by a doctor that you had diabetes mellitus (including GDM), sometimes called sugar diabetes or diabetes mellitus? *Response options:* Yes/No/Don't know

Question 2: What type of diabetes mellitus did you have?

Response options: Gestational (only during pregnancy)/insulin-dependent diabetes mellitus (also called type 1 or juvenile diabetes mellitus)/non-insulin-dependent diabetes mellitus (also called type 2 or adult onset diabetes mellitus)/Don't know

Question 3: What month and year did you receive this diagnosis?

000 Diabetes mellitus and birth defects

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Pregestational diabetes mellitus is associated with a wide variety of birth defects; gestational diabetes mellitus is associated with a smaller group of defects, but only if the mother was overweight or obese before pregnancy.