Maternal Diabetes Mellitus and Infant Malformations

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OBJECTIVE: To investigate the effects of pregestational, as opposed to gestational, diabetes on infant malformations.

METHODS: All women delivering infants at Parkland Hospital between January 1, 1991, and December 31, 2000, were ascertained. Screening for gestational diabetes was methodically employed throughout the study period using National Diabetes Data Group criteria for diagnosis of pregestational and gestational diabetes. Standardized definitions of major infant malformations were specified before data analysis and subdivided according to the organ systems involved.

RESULTS: A total of 145,196 women were delivered during the study period, and 2687 (1.9%) were diagnosed to have diabetes mellitus. Gestational diabetes was diagnosed in 2277 (1.6%) of whom 230 (10%) had fasting hyperglycemia diagnosed, and the remainder consistently demonstrated fasting serum levels less than 105 mg/dL. Pregestational diabetes was diagnosed in 410 (0.3%) women. Infant malformations occurred in 1.5% of nondiabetic women compared with 1.2% of women with normal fasting glucose gestational diabetes, 4.8% in women with gestational diabetes plus fasting hyperglycemia, and 6.1% in those with pregestational diabetes ($P < .001$, for comparison of the latter two groups with the nondiabetic population).

CONCLUSION: Women with pregestational diabetes or gestational diabetes plus fasting hyperglycemia have a three- to four-fold increased risk of infant malformations, whereas women with mild gestational diabetes have malformation rates no different than the general nondiabetic obstetric population. (Obstet Gynecol 2002;100:925–30. © 2002 by The American College of Obstetricians and Gynecologists.)

Diabetes mellitus is the most common medical complication of pregnancy. Women with this complication can be separated into those who were known to have diabetes before pregnancy (pregestational) and those diagnosed during pregnancy (gestational). It is estimated that in 1999, approximately 106,000 American women had pregnancies complicated by diabetes mellitus, representing about 2.7% of all live births.[1] Ninety percent of all such pregnancies complicated by diabetes are estimated to be caused by gestational diabetes.[2] Thus, in 1999, approximately 10,000 American women with pregestational diabetes and 90,000 with gestational diabetes delivered live births.

Delivery of an infant with a major malformation has become the leading cause of perinatal mortality in pregnancies complicated by diabetes.[3] It is generally accepted that increased severe malformations are the consequence of poorly controlled diabetes both preconceptionally as well as early in pregnancy.[4–6] Schaefer-Graf et al[7] analyzed the pattern of congenital anomalies in pregnancies complicated by pregestational as well as gestational diabetes. The initial fasting glucose level was significantly higher in women whose pregnancies ended with the delivery of infants with malformations. The most common anomalies involved the cardiac, musculoskeletal, and central nervous systems. It is also generally believed that women with gestational diabetes are not at risk for infant malformations, whereas those with pregestational diabetes have a three- to five-fold increased risk compared with the general obstetric population.[3,8–10]

Using a computerized database that includes all women and their infants delivered at our hospital between 1991 and 2000, we sought to evaluate the rates of infant malformations in women with pregestational and gestational diabetes. Although other investigators have reported the prevalence of infant malformations in obstetric subpopulations of women with either gestational or pregestational diabetes,[7,11–14] our report describes these risks in a large population-based study of infant malformations in women with diabetes of any etiology.

MATERIALS AND METHODS

All women delivering infants at Parkland Hospital, Dallas, Texas, were entered into a computerized database containing selected obstetric and neonatal outcomes. Nurses attending each delivery completed an obstetric data sheet, and research nurses later assessed the data for consistency and completeness before electronic storage. The data sheet included the obstetric estimate of gesta-

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tional age that was used to manage the care of the women during the intrapartum period. Briefly, this estimate was based upon the date of the last menstrual period and the results of ultrasonography performed during the pregnancy. The reported date of the last menstrual period was accepted to be correct if the fundal height measured between 18 and 30 weeks' gestation corresponded to the predicted gestational age. Neonatal outcome information was abstracted from newborn discharge records. Antepartum data on all pregnancies complicated by diabetes was obtained through medical record review and entered into a separate but linked database. Ninety-five percent of the women who delivered at our hospital also received prenatal care in our hospital system. These women are almost exclusively medically indigent.

Parkland Hospital is a tax-supported institution serving Dallas County. The Obstetric Service is staffed by house officers and faculty members of the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical School.

All pregnant women enrolled for prenatal care at Parkland Hospital between January 1, 1991, and December 31, 1996, with a family history of diabetes, prior 4000-g infant, prior stillbirth, or prior malformed infant were selectively screened for gestational diabetes between 24 and 28 weeks' gestation. Risk factors prompting screening regardless of gestational age included glucosuria, random serum glucose greater than or equal to 130 mg/dL (all antepartum women had a random serum glucose measured on presentation for prenatal care), or a history of prior gestational diabetes. Immediate screening was also performed for symptoms of overt diabetes or whenever macrosomia or hydramnios was diagnosed later in pregnancy. All women who underwent immediate screening and had a negative screen were again screened between 24 and 28 weeks. Between January 1, 1997, and December 31, 2000, all pregnant women were routinely tested for gestational diabetes at 24 to 28 weeks unless they had an indication for immediate testing as described above. Screening for gestational diabetes was performed after ingestion of 50 g of a commercially available glucose solution followed 1 hour later by measurement of serum glucose. Women whose serum glucose was 140 mg/dL or greater received a 3-hour 100-g oral glucose tolerance test after an overnight fast.

Results of the 100-g glucose tolerance tests were interpreted according to the National Diabetes Data Group,[15] and these women were referred to our Gestational Diabetes Clinic held weekly at Parkland Hospital. Ascertainment and management of women with diabetes during pregnancy was uniformly practiced throughout the Parkland Health and Hospital System using a written protocol. Diabetic and nutritional counseling was performed, and fasting serum glucose measurements were repeated at each visit. Women with fasting serum glucose values less than 105 mg/dL were treated with diet alone and diagnosed to have Class A_1 gestational diabetes. Those women with fasting hyperglycemia (greater than or equal to 105 mg/dL) were treated with insulin and diagnosed to have Class A_2 gestational diabetes. Women with the diagnosis of diabetes mellitus before conception were categorized using the White classification (Classes B-FR).[16] Daily fasting and preprandial self-monitoring of capillary glucose was routinely instituted in insulin-treated women.

Table 1. Categories of Major Infant Malformations

Category	Example(s)
Aneuploidy	Trisomy 21
Recognizable syndromes	VATER syndrome
Principal organ system	
Nervous	Neural tube defect; hydrocephaly; microcephaly
Cardiac	Ventricular septal defect; hypoplastic heart
Gastrointestinal	Intestinal atresia; ventral wall defects
Craniofacial	Clefts; choanal atresia
Renal	Agenesis; dysplasia
Skeletal	Limb defects; dysplasias
Other	Genital (eg, ambiguous genitalia); pulmonary (eg, congenital adenomatoid malformation); endocrine (eg, adrenal hyperplasia); muscular (eg, diaphragmatic hernia)

Information on malformations for all live births and stillbirths was abstracted from the newborn nursery hospital record at the time of discharge or death and from monthly committee reviews of all stillbirths delivered at our hospital. Malformations in live births were confirmed by neonatology fellows and faculty of the Department of Pediatrics, and all abnormal neonates were evaluated by board-certified clinical geneticists. Shown in Table 1 are the categories of major infant malformations used for analysis. Major malformations were categorized as those causing significant functional or cosmetic impairment or those which were life limiting. Infants with multiple anomalies were classified according to their principal organ system involvement and counted only once in the calculation of prevalence. The principal organ system allocation for infants with multiple anomalies was based on a judgment of the clinical significance of the malformations. For example, in the case of an infant with both a neural tube defect and hypoplastic left heart, the infant's principal organ system malformation

Table 2. Maternal Demographic Characteristics in Women With and Without Diabetes Mellitus During Pregnancy

Characteristic	No diabetes (n = 142,509)	Pregestational diabetes (n = 410)	Class A_1 gestational diabetes (n = 2047)	Class A_2 gestational diabetes (n = 230)
Maternal age (y)				
Mean ± SD	24 ± 6	28 ± 7*	29 ± 6*	30 ± 6*
≤ 15	3530 (2.5)	1 (0.2)*	6 (0.3)*	0*
≥ 35	6965 (5)	76 (19)*	365 (18)*	48 (21)*
Nulliparity	54,776 (38)	135 (33)*	584 (29)*	62 (27)*
Race				
Hispanic	94,025 (66)	234 (57)*	1606 (79)*	158 (69)
Black	31,938 (22)	121 (30)*	234 (11)*	51 (22)
White	12,556 (9)	46 (11)*	130 (6)	16 (7)
Other	3990 (3)	9 (2)	77 (4)	5 (2)

SD = standard deviation.
All data are shown as number (%) or mean ± SD.
Class A_1 includes women with fasting serum glucose <105 mg/dL. Class A_2 includes fasting values ≥105 mg/dL.
* $P < .001$ as compared with the nondiabetic referrent group.

was categorized as cardiac because hypoplastic left heart was the most life-threatening anomaly.

P values ≤ 0.05 were considered significant. Statistical analysis was performed using the SAS system 8 (SAS Institute, Cary, NC). Comparisons among study groups were made using Pearson χ^2 test for categoric variables, analysis of variance for continuous variables, and Kruskal-Wallis test for ordinal variables. Logistic regression analysis was performed adjusting for maternal age.

RESULTS

A total of 145,196 women were delivered during the study period, and 2687 (1.9%) were diagnosed to have diabetes mellitus; 76% (n = 2047) of these were diagnosed to have Class A_1 gestational diabetes. Fasting hyperglycemia (mean serum glucose 124 ± 23 mg/dL at a mean gestational age of 23 ± 7 weeks) led to a diagnosis of Class A_2 diabetes in 230 (9%) women. White[16] Classes B-FR pregestational diabetes was diagnosed in 410 (15%) of the diabetic women.

Shown in Table 2 are maternal demographic characteristics for women with and without pregnancies complicated by diabetes. Women with diabetes tended to be older and parous. Hispanic women more often were diagnosed to have gestational diabetes, whereas black women were more likely to have pregestational diabetes.

Shown in Table 3 are the frequencies of major infant malformations in relation to maternal diabetes status. These results are also schematically depicted in Figure 1. The infant malformation rate in women without diabetes was 1.5% and was significantly increased in women with pregestational diabetes and Class A_2 gestational diabetes (6.1% and 4.8%, respectively, $P < .001$ when compared with women without diabetes). There was no difference in major infant malformations in women with A_2 and pregestational diabetes ($P = .6$). The infant malformation rate in women with Class A_1 gestational diabetes was similar to the referent group (1.2% and 1.5%, respectively, $P = .29$). Infants with malformations, according to maternal diabetes status, were then grouped into those with malformations caused by aneuploidy, those caused by recognizable syndromes, and those attributable to a principal organ system (Table 4). As maternal age is associated with aneuploidy risk, logistic regression adjusting for age was performed. The aneuploidy risk remained significantly higher in the Class A_2 women as compared with the other groups (odds ratio 3.63, 95% confidence interval 1.1, 11.5). Organ system malformations predominated in all maternal groups and were significantly increased in women with pregestational and Class A_2 diabetes when compared with women without diabetes (5.6% and 3.5% versus 1.2%, $P < .001$, respec-

Table 3. The Frequency of Major Infant Malformations in Women With and Without Pregnancies Complicated by Pregestational or Gestational Diabetes

Maternal diabetes status	Women at risk	Major infant malformation (%)
No diabetes	142,509	2075 (1.5)
Pregestational diabetes	410	25 (6.1)*
Gestational diabetes, normal fasting (Class A_1)	2047	24 (1.2)
Gestational diabetes, elevated fasting (Class A_2)	230	11 (4.8)*

* Indicates $P < .001$ when compared with women without diabetes.

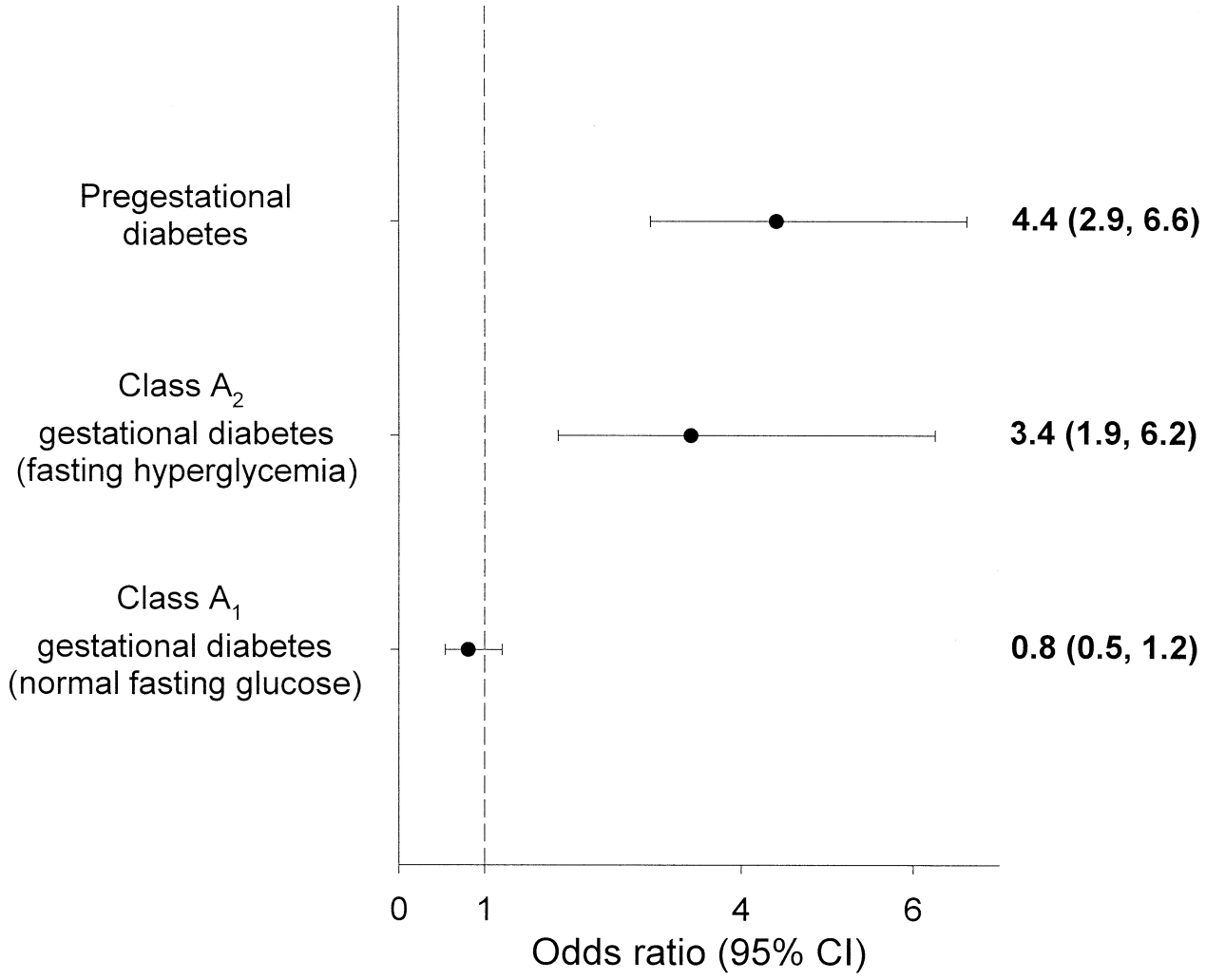

Figure 1. Relative risks (95% confidence intervals [CI]) for major fetal malformations in 2687 women with pregnancies complicated by pregestational or gestational diabetes compared with 142,509 women without diabetes.
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tively). Infants with principal organ system malformations were further subdivided into single organ system involvement (Table 5). Women with pregestational diabetes significantly more often delivered infants with nervous, cardiac, gastrointestinal, and renal malformations when compared with women without diabetes.

Infants with single organ system malformations and those with multiple system involvement were analyzed

Table 4. Grouped Infant Malformations According to Maternal Diabetes Status

Major malformation group	No diabetes (n = 142,509)	Pregestational diabetes (n = 410)	Class A_1 gestational diabetes (n = 2047)	Class A_2 gestational diabetes (n = 230)
Aneuploidy	267 (0.2)	1 (0.2)	2 (0.1)	3 (1.3)*
Recognizable syndrome	94 (0.1)	1 (0.2)	3 (0.2)	0
Principal organ system	1760 (1.2)	23 (5.6)*	19 (0.9)	8 (3.5)*

Percents are shown in parentheses.
* Indicates $P < .001$ compared with women without diabetes.

Table 5. Single Organ System Infant Malformations According to Maternal Diabetes

Single organ system malformation	No diabetes (n = 142,509)	Pregestational diabetes (n = 410)	Class A_1 gestational diabetes (n = 2047)	Class A_2 gestational diabetes (n = 230)
Nervous	290 (0.2)	7 (1.7)*	5 (0.2)	1 (0.4)
Cardiac	206 (0.1)	5 (1.2)*	2 (0.1)	1 (0.4)
Gastrointestinal	226 (0.2)	4 (1.0)*	0	0
Craniofacial	43 (0)	0	0	0
Renal	110 (0.1)	3 (0.7)*	1 (0.1)	0
Skeletal	446 (0.3)	1 (0.2)	6 (0.3)	1 (0.4)
Other	439 (0.3)	3 (0.7)	5 (0.2)	5 (2.2)

Percents are shown in parentheses.
* Indicates $P < .001$ compared with women without diabetes.

in relation to maternal diabetes, and the results are shown in Table 6. The malformed infants were also analyzed based on the presence of at least one of the four organ system malformations reported to be characteristically associated with maternal diabetes.[17]

DISCUSSION

Prior reports on the prevalence of infant malformations associated with different types of maternal diabetes during pregnancy have been limited to analyses of subpopulations where women with either gestational or pregestational diabetes but not both types of diabetes were ascertained. Our primary purpose was to compare infant malformation rates in women with gestational versus pregestational diabetes in a single general obstetric population where ascertainment of diabetes as well as infant malformations were systematically employed. Such a population-based study minimizes ascertainment bias in the selection of women at risk and also permits standardized definitions for the outcomes of interest to be applied uniformly to all the subpopulations studied. Using this analytic method, women with gestational diabetes and without fasting hyperglycemia were shown to have infant malformation rates no different than the general nondiabetic obstetric population. In contrast, those women with pregestational diabetes or fasting hyperglycemia diagnosed by midpregnancy experienced a three- to four-fold increased rate of delivery of infants with major malformations. The specific organ system malformations characteristic of maternal diabetes, as opposed to aneuploidy or recognizable syndromes, predominated in the malformed infants delivered of diabetic women.

The prevalence of the various types of maternal diabetes as well as associated infant malformations observed in our study are similar to those published by others who also used the National Diabetes Data Group[15] definitions of diabetes in pregnancy. For example, Wen et al[18] analyzed 1,729,225 Canadian women and found that the prevalence of gestational and pregestational diabetes in 1996 was 2.7% and 0.4%, respectively. Our rates of gestational diabetes (Class A_1 combined with Class A_2) and pregestational diabetes were very similar to these results from Canada (2.0% and 0.3%, respectively). Others[6,19–23] reported rates of gestational diabetes to vary between 2.0% and 3.5% depending on the racial background of the women studied. The rate of pregestational diabetes, although there are more limited data available, is reported to be between 0.2 and 0.5%.[8]

It is generally considered that the risk of delivering an

Table 6. Analysis of Grouped Infant Malformations According to Maternal Diabetes Status

Malformation group	No diabetes (n = 142,509)	Pregestational diabetes (n = 410)	Class A_1 gestational diabetes (n = 2047)	Class A_2 gestational diabetes (n = 230)
Single organ system	1452 (1)	12 (2.9)*	15 (0.7)	6 (2.6)†
Multiple organ system	308 (0.2)	11 (2.7)*	4 (0.2)	2 (0.9)†
At least one of CNS, cardiac, renal, or skeletal systems involved	1052 (0.7)	16 (4.0)*	14 (0.7)	3 (1.3)

CNS = central nervous system.
Percents are shown in parentheses.
* Indicates $P < .001$ compared with women without diabetes.
† Indicates $P < .05$ compared with women without diabetes.

infant with a major malformation is 1–3% in the general obstetric population and that this risk is increased three- to eight-fold in women with pregestational diabetes.[24] Our results are very similar to these rates. Specifically, malformed infants were delivered of 1.5% of nondiabetic women, and this risk was increased four-fold in women with pregestational diabetes. A similar increase (3.2-fold) was also observed in women with fasting hyperglycemia associated with gestational diabetes. Our results suggest that women with pregestational diabetes and a small subset of gestational diabetics (Class A_2, fasting hyperglycemia) are at a distinct risk for delivery of infants with malformations. Preconceptual screening for diabetes in high-risk women and aggressive diabetic management may be able to prevent some of these anomalies. Importantly, women with milder gestational diabetes (Class A_1, normal fasting glucose) do not experience an increased risk of delivering a malformed infant.

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