Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes

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OBJECTIVES: We sought to determine the types of congenital anomalies affecting infants of women with gestational diabetes mellitus or type 2 diabetes and to examine the relationship between those malformation types and measures of initial glycemia of women at entry into prenatal care with type 2 diabetes or at time of diagnosis in women with gestational diabetes mellitus.

STUDY DESIGN: A total of 4180 pregnancies complicated by gestational diabetes mellitus (n = 3764) or type 2 diabetes (n = 416) that were delivered after 20 weeks of gestation were reviewed for the presence of congenital malformations diagnosed before hospital discharge. Anomalies were categorized as being absent, minor, major, genetic syndromes, or aneuploidies. Major anomalies were further categorized by the number and type of affected organ systems. In addition to maternal clinical and historical parameters, the initial fasting serum glucose either from the diagnostic glucose tolerance test (gestational diabetes mellitus) or at entry to prenatal care (type 2 diabetes) and the initial glycosylated hemoglobin before insulin therapy were examined for a relationship to anomalies.

RESULTS: The initial fasting serum glucose and glycosylated hemoglobin levels were significantly higher in pregnancies with major (n = 143) and minor (n = 112) anomalies and genetic syndromes (n = 9) compared with pregnancies with no anomalies (n = 3895). Of those pregnancies with major anomalies, the most commonly affected organ systems were the cardiac (37.6%), musculoskeletal (14.7%), and central nervous systems (9.8%) and anomalies involving multiple organ systems (16%). There was no increased predominance of any specific organ system involvement seen with increasing fasting serum glucose levels in pregnancies with major congenital anomalies. Pregnancies with major anomalies affecting multiple organ systems had significantly higher initial fasting serum glucose levels (166 ± 64 mg/dL) compared with pregnancies in which one organ system was affected (141 ± 55 mg/dL, $P < .04$) or no organ systems were affected (115 ± 38 mg/dL, $P < .0001$).

CONCLUSION: Congenital anomalies in offspring of women with gestational and type 2 diabetes affect the same organ systems that have been previously described in pregnancies complicated by type 1 diabetes. Increasing hyperglycemia at diagnosis or presentation for care was associated with an increasing risk of anomalies in general and with anomalies involving multiple organ systems without a preferential increase in involvement of specific organ system. (Am J Obstet Gynecol 2000;182:313-20.)

Key words: Type 2 diabetes mellitus, gestational diabetes mellitus, congenital anomaly, fasting serum glucose, organ system

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Hyperglycemia during embryogenesis has been associated with birth defects in pregnancies complicated by diabetes mellitus. This association has been characterized best in women with type 1 diabetes, in whom the frequency of anomalies causing clinical morbidity and mortality has been related to the severity of metabolic disturbance during early pregnancy.[1-6] The anomalies most often affect the central nervous system, heart and great vessels, kidneys, and axial skeleton.[1, 7-9]

Recently, our group has found that offspring of women with type 2 diabetes[10] have rates of major anomalies that are similar to those of offspring of women with

type 1 diabetes. The risk of having a baby with a major anomaly was associated with maternal hyperglycemia at entry to prenatal care. Similarly, we demonstrated that women with hyperglycemia first detected during pregnancy (ie, gestational diabetes mellitus [GDM]) had an increased risk of major anomalies in their offspring when initial fasting glucose levels at diagnosis of GDM exceeded 120 mg/dL.[11] In this article we examined the patterns of congenital anomalies and the association of specific types of anomalies to maternal hyperglycemia in pregnancies complicated by GDM or type 2 diabetes.

Methods

Subjects. The study cohort comprised consecutive pregnancies complicated by GDM or type 2 diabetes that were delivered after 20 weeks of gestation at the Los Angeles County + University of Southern California Women and Children's Hospital from January 1987 to July 1995. The hospital serves as the major referral center for the care of indigent patients with pregnancies complicated by diabetes in Los Angeles County. During the period of study, type 2 diabetes was diagnosed in nonpregnant women by World Health Organization criteria, and GDM was diagnosed according to the recommendations of the Second International Workshop-Conference on GDM.[12] No subject with type 2 diabetes had a history of diabetic ketoacidosis during the index pregnancy or marked metabolic disturbances necessitating intravenous insulin or hydration therapy. Fewer than 5% of them had participated in preconception diabetes care.

For each pregnancy, historical and clinical variables were collected prospectively and entered in a database. Historical variables included any history of pregnancy complicated by gestational diabetes, stillbirth, macrosomia (>4000 g), or a newborn with a congenital anomaly. The duration and type of prior medical treatment were assessed in pregnancies complicated with type 2 diabetes. Clinical variables included maternal age, parity, prepregnancy body mass index (in kilograms per square meter), gestational age at entry to prenatal care, and gestational age at diagnosis of GDM or, for women with type 2 diabetes, the gestational age when the first measurement of glycemia was made. Glycemic variables included the initial fasting serum glucose level at the time of diagnosis of GDM or at the initial visit in patients with type 2 diabetes, the initial glycosylated hemoglobin concentration for all women with type 2 diabetes and women with GDM who had a fasting serum glucose level of >105 mg/dL while on diet, and the highest fasting serum glucose level before insulin therapy was started. Exposure to sulfonylurea drugs during the first 8 weeks of gestation and the use of alcohol, illicit drugs, or tobacco during pregnancy were also recorded.

Detection and classification of congenital anomalies. Before hospital discharge, all newborns underwent a detailed physical examination for anomalies performed under the supervision of a faculty neonatalogist. Infants with suspected anomalies had the diagnosis confirmed by a faculty geneticist or neonatologist. Additional tests, such as echocardiography, radiology studies, and chromosomal analyses, were performed as clinically indicated to confirm or exclude suspected anomalies. An autopsy or, if autopsy was declined by the parents, a detailed physical examination was performed on all stillborn infants or fetuses aborted after 20 weeks of gestation. Postnatal follow-up was limited to that abstracted from the infant's medical record if she or he continued care at Women & Children's Hospital.

Infants were assigned as follows to 1 of 5 categories with respect to anomaly status: no congenital anomaly, at least one major nongenetic malformation, minor nongenetic malformation only, a genetic syndrome, or a chromosomal aneuploidy. A detailed classification system for coding each minor and major anomaly was developed. Principles for classification of major malformations were based on the Congenital Malformations Surveillance Data from the Centers for Disease Control and Prevention.[13] The classification of minor malformations was based on work by Stevenson et al[14] and Jones.[15] Major anomalies were defined as those that caused significant functional or cosmetic impairment, required surgery, or were life-limiting. Minor anomalies were identifiable but met none of the 3 criteria of a major anomaly. Minor anomalies were differentiated from a variant of normal by having a frequency of occurrence in <1% of live births.[14] Malformations were classified as syndromes in which a pattern could be identified that was consistent with a defined congenital malformation syndrome complex.[15] Subjects with major anomalies that occurred in conjunction with syndromes previously reported to occur in pregnancies complicated with diabetes were included in the group with major anomalies. Subjects with syndromes with a presumed genetic cause were classified separately as having genetic syndromes. Infants with suspected chromosomal aneuploidy were classified as having aneuploidy after confirmation by chromosome analysis.

The infants with multiple anomalies were counted only once in the determination of the overall frequency of malformed infants. Infants with major anomalies, excluding genetic syndromes and aneuploidies, were further classified by the type of affected organ system. For infants with multiple major anomalies, individual affected systems were not counted for this analysis but were classified as a separate category, multiple organ system.

Additionally, infants with major anomalies were classified into the following 3 subgroups according to the number of affected organ systems: no major anomalies, major anomalies affecting one organ system, or major

Table I. Maternal clinical and historical variables according to anomaly status of offspring (sample size) in a cohort of women with GDM and type 2 diabetes (reported as mean and SD or frequency)

	No anomaly	*Minor**	*Major†*	*Genetic syndrome*	*Aneuploidy*
Infants with anomalies (No. and rate)	3895 (93.2%)	112 (2.7%)	143 (3.4%)	9 (0.2%)	21 (0.5%)
Current pregnancy					
Maternal age (y)	31.7 ± 5.8	31.2 ± 5.9	31.5 ± 5.9	27.9 ± 7.03	38.6 ± 4.8‡
Parity	2.2 ± 1.8	2.3 ± 1.9	2.6 ± 2.1‡	2.6 ± 1.0‡	3.4 ± 2.6‡
Prepregnancy body mass index (kg/m^2)	29.5 ± 5.7	31.0 ± 6.0‡	31.4 ± 6.5‡	30.4 ± 3.8	31.4 ± 5.5
Gestational age at initial prenatal visit (wk)	17.3 ± 7.3	17.0 ± 8.0	17.6 ± 7.8	21.6 ± 6.9	18.8 ± 8.9
Gestational age at initial fasting serum glucose (wk)	24.5 ± 8.6	22.6 ± 9.2‡	22.2 ± 8.9‡	25.2 ± 8.7	22.6 ± 9.3
Substance abuse§ during pregnancy (% and No.)	1.5 (59)	0.9 (1)	1.4 (2)	0 (0)	0 (0)
First-trimester exposure to sulfonylurea agents‖ (% and No.)	3.7 (142)	9.1 (10)‡	12.9 (18)‡	22 (2)‡	5 (1)
Prior pregnancy					
GDM (%)	18.6	20.6	32.8‡	0	42.1‡
Anomalous infant (%)	2.8	3.7	3.0	0	0
Stillbirth	4.6	8.3	7.4	12.5	5.8
Macrosomia¶	28.5	31.5	34.1	0	41.2

*Minor anomalies not associated with major anomalies, a genetic syndrome, or aneuploidy.
†Anomalies not associated with a genetic syndrome or aneuploidy.
‡$P < .05$, compared with the no anomaly group.
§Alcohol, illicit drugs, or tobacco.
‖Exposure to sulfonylurea agents during first 8 weeks of pregnancy in 173 of the 416 pregnancies complicated by type 2 diabetes.
¶Birth weight >4000 g.

anomalies affecting more than one organ system (multiple anomalies). Each major anomaly was also identified as to whether that type of anomaly had been previously described in epidemiologic studies from Kucera,[9] Becerra et al,[1] and Martinez-Frias.[8] These studies have characterized the prevalence of specific anomalies in pregnancies of women with type 1 (insulin-dependent) and type 2 diabetes.

Laboratory analysis. Serum glucose concentrations were measured by glucose oxidase (Beckman Glucose Analyzer II; Beckman Instruments, Brea, Calif). Glycosylated hemoglobin levels was measured by boronate-affinity ion-exchange chromatography (Glycoglobin Kit; Endocrine Science, Tarzana, Calif).

Statistical analysis. Differences between study groups were tested for statistical significance by *t* tests or analysis of variance (continuous variables) or by χ^2 analysis (categoric variables). For the comparison of multiple groups, Bonferroni adjustment was performed. Normally distributed data are presented as mean and SD, and nonnormal data were log-transformed before analysis. Initial fasting serum glucose levels at the diagnosis of GDM or at entry into prenatal care in subjects with type 2 diabetes were analyzed as a continuous variable and as a categoric variable by dividing the fasting serum glucose level into 20- to 40-mg/dL increments. Over the study period 3 sequential laboratories performed the glycosylated hemoglobin measurements resulting in the following 3 different normal ranges for glycosylated hemoglobin: 4.9% to 7.5%, 4.0% to 6.8%, and 4.5% to 6.5%. For analysis, the glycosylated hemoglobin values were expressed as the number of standard deviations from the normal mean for the assay in which they were run.

Results

Study population. A total of 4180 infants were born to women with GDM (n = 3764) or known type 2 diabetes (n = 416) during the period of the study. Major anomalies were diagnosed before hospital discharge in 143 infants (3.4%, Table I), with a prevalence of 2.9% in the GDM group and 8.9% in women whose type 2 diabetes was known before pregnancy. Included in the major anomaly group were 2 infants with syndromes that have previously been associated with diabetes (caudal regression and VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia] association). Minor anomalies occurred in 112 (2.7%) infants, and aneuploidies occurred in 21 (0.5%) infants. Anomalies occurring in a pattern of syndromes with genetic causes were seen in 9 (0.2%) newborns and included 1 case each of Goldenhar, Holt-Oram, Treacher, Carpenter, Peters anomaly, Johanson-Blizzard, and cleido-cranial-dystosis syndromes and 2 cases of Jarcho-Levin syndrome.

Demographics describing the study groups are presented in Table I. Women who gave birth to infants with aneuploidy were significantly older and of higher parity than women with normal newborns. Women whose newborns had major or minor anomalies were significantly heavier than women with normal infants. They also had evaluation of their glycemic status at a slightly earlier gestational age. However, the mean gestational age in all groups for entry into prenatal care and initial evaluation of glycemia was in the late second trimester, well beyond the period of embryogenesis. Four hundred sixteen (41.6%) of the women with known type 2 diabetes used sulfonylurea agents during the first 8 weeks of pregnancy.

Table II. Glycemic parameters according to anomaly status of offspring in a cohort of women with gestational and type 2 diabetes (reported as mean ± SD)

Anomaly classification	*None*	*Minor**	*Major†*	*Genetic syndrome*	*Aneuploidy*
Initial fasting serum glucose level (mg/dL)‡	114.6 ± 37.2	132.1 ± 58.5§‖	144.6 ± 56.8§	152.2 ± 59.2§	115.2 ± 37.9
Highest fasting serum glucose level (mg/dL)¶	119.9 ± 40.0	138.4 ± 61.3§#	150.3 ± 58.7§	156.3 ± 60.9§	123.2 ± 41.4
Glycosylated hemoglobin level (SD)**	1.91 ± 3.64	3.35 ± 5.02§	3.60 ± 3.80§	3.92 ± 2.50§	3.65 ± 5.7

*Minor anomalies not associated with major anomalies, a genetic syndrome, or aneuploidy.
†At least one major anomaly not associated with a genetic syndrome or aneuploidy.
‡At time of the diagnosis of GDM or initial prenatal visit in women with type 2 diabetes.
§$P < .0001$, compared with the no anomaly group.
‖$P = .01$, compared with the major anomaly group.
¶Before initiation of insulin therapy only in women who required this therapy.
#$P = .03$, compared with the major anomaly group.
**Glycosylated hemoglobin available in 1705 subjects, all of whom required insulin, expressed as the number of standard deviations from the normal population mean for the assay.

Table III. Major anomalies and distribution of affected organ systems according to initial fasting serum glucose level

	Initial fasting serum glucose level			
	<120 mg/dL	*121-200 mg/dL*	*>200 mg/dL*	*Total*
Total No. of infants	3060	905	185	4151*
No. of infants with anomalies	64	53	26	143 (100%)
Rate of infants with anomalies (%)	2.1	5.9†	12.9†‡	3.3
Cardiac (total)§	22 (33.8%)	22 (40.7%)	10 (41.7%)	54 (37.6%)
Outflow–great vessels	2	6	0	8
Septal	13	9	5	27
Valves	1	2	0	3
Complex	6	5	5	16
Musculoskeletal (total)	15 (23.1%)	3 (5.6%)	3 (12.5%)	21 (14.7%)
Axial (spine and hemivertebrae)§	2	2	1	5
Apendicular–lower limbs§	3	1	1	5
Apendicular–upper limbs	0	0	0	0
Caudal regression syndrome§	0	0	1	1
Clubfoot	10	0	0	10
Central nervous system (total)	6 (9.2%)	5 (9.3%)	3 (12.5%)	14 (9.8%)
Neural tube defect§	2	2	1	5
Holoprosencephaly§	0	0	1	1
Microcephaly§	2	2	0	4
Others	2	1	1	4
Cranial-facial (total)	6 (9.2%)	3 (5.5%)	2 (8.3%)	11 (7.7%)
Eye	0	2	0	2
Midline defect	4	1	2	7
Others	2	0	0	2
Gastrointestinal (total)	4 (6.2%)	2 (3.7%)	0	6 (4.3%)
Atresia§	2	1	0	3
Other	2	1	0	3
Genitourinary (total)	3 (4.6%)	5 (9.3%)	1 (4.2%)	9 (6.4%)
Renal	2	4	1	7
Other	1	1	0	2
Others (total)	4 (6.2%)	1 (1.8%)	0	5 (3.5%)
Multiple organ system	5 (7.7%)	13 (24.1%)‖	5 (20.8%)¶#	23 (16%)

*Major anomalies associated with genetic syndromes and aneuploidy were excluded.
†$P < .0001$, compared with initial fasting serum glucose level of ≤120 mg/dL.
‡$P < .0001$, compared with initial fasting serum glucose level of 121 to 200 mg/dL.
§Major anomalies previously described to occur more frequently in pregnancies in women with type 1 diabetes (Becerra et al,[1] Kucera et al,[9] and Martinez-Frias[8]).
‖$P = .001$, compared with initial fasting serum glucose level of ≤120 mg/dL.
¶$P = .008$, compared with initial fasting serum glucose level of ≤120 mg/dL.
#$P = .59$, compared with initial fasting serum glucose level of 121 to 200 mg/dL.

Exposure to sulfonylurea agents was significantly more frequent in the infants with major or minor anomalies and with genetic syndromes than in infants without anomalies. No woman reported exposure to other oral antidiabetic drugs. Women who used sulfonylurea agents during early pregnancy had significantly higher fasting serum glucose values than women without sulfonylurea agents (168 ± 58 vs 113 ± 35 mg/dL, $P = .0001$).

Glycemic parameters. All 3 glycemic parameters (initial fasting serum glucose level, highest fasting serum glu-

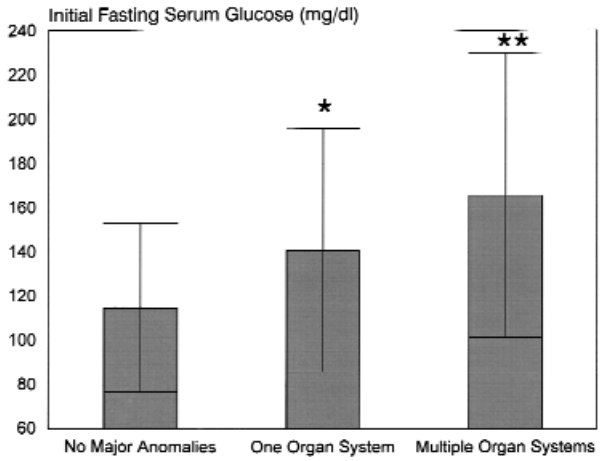

Fig 1. Mean and SD initial fasting serum glucose level (in milligrams per deciliter) according to number of organ systems involved. *1 Asterisk, P* = .0001, compared with no major anomalies; *1 asterisk, P* = .006, compared with anomaly involving one organ system; *2 asterisks, P* = .0001, compared with no major anomalies.

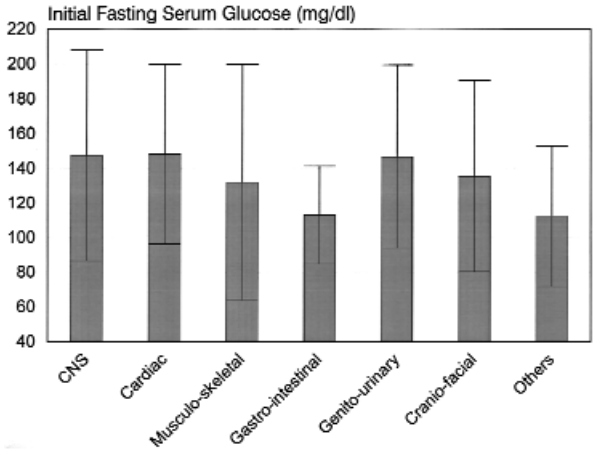

Fig 2. Mean and SD initial fasting serum glucose level (in milligrams per deciliter) according to type of involved organ system in infants with major anomalies born to women with GDM and type 2 diabetes. *P* > .5, for all comparisons. *CNS,* Central nervous system.

cose levels, and initial glycosylated hemoglobin level before insulin) were significantly increased in women whose infants had minor anomalies compared with the women with newborns without anomaly (132 vs 114 mg/dL, 138 vs 119 mg/dL, and 3.3 vs 1.9 SD from the normal population mean; *P* < .0001 for all of the following comparisons with the no anomaly group; Table II). The initial fasting serum glucose level and the highest fasting serum glucose level in the minor anomaly group were significantly lower than the values in the major anomaly group, but the initial glycosylated hemoglobin level was not significantly lower (*P* = .01, *P* = .03, and *P* = .3, respectively). The glycemic values in the nongenetic major anomaly group were also significantly higher than in the no anomaly group (144 mg/dL, 150 mg/dL, and 3.6 SD from the normal population mean; *P* < .0001). Genetic syndromes were associated with significantly higher glycemic values than were found in the group without anomalies (152 mg/dL, 156 mg/dL, and 3.9 SD from the normal population mean) and even slightly higher values than were found in major anomalies not associated with a genetic syndrome. There was no association between hyperglycemia and the risk of aneuploidy.

Major anomalies. The distribution of organ systems affected by major anomalies is shown in Table III. Cardiovascular defects were the most common type of major anomalies, accounting for 37.6% of the anomalies in this category. Musculoskeletal anomalies were second, accounting for 14.7% of major anomalies, followed by central nervous system anomalies (9.8% of major). In 16% of the infants with major anomalies, multiple organ systems were affected.

Anomalies that involved multiple organ systems were associated with significantly higher maternal glycemic indexes compared with anomalies involving one organ system or with the lack of anomalies. The mean initial fasting serum glucose level for pregnancies in which offspring had multiple anomalies was significantly higher (166 ± 64 mg/dL) than when anomalies involved only one organ system (141 ± 55 mg/dL, *P* = .006) or were absent (115 ± 38 mg/dL, *P* = .0001; Fig 1). Similarly, the highest fasting serum glucose level recorded before insulin therapy was significantly higher (168 ± 64 mg/dL) when offspring had multiple anomalies than when anomalies involved only one organ system (147 ± 57 mg/dL, *P* = .04) or were absent (120 ± 41 mg/dL, *P* = .0001).

The distribution of the mean entry fasting serum glucose level and involved organ systems are shown in Fig 2. Plots of initial fasting serum glucose concentrations according to organ system did not reveal any significant difference among the 8 categories of organ systems with major anomalies. There was also no significant difference in the mean highest fasting serum glucose or initial glycosylated hemoglobin level.

When major anomaly rates were calculated for each 20-mg/dL increase in the initial fasting glucose level, 3 stepwise increases in malformation rates were observed. Initial fasting glucose levels of <120 mg/dL were associated with a 2.1% rate of major anomalies. When initial fasting serum glucose levels were 121 to 200 mg/dL, the malformation rate was 5.9% (*P* < .0001, vs rate with fasting serum glucose level of <120 mg/dL). When the fasting serum glucose level exceeded 200 mg/dL, the rate further increased to 12.9% (*P* < .0001, compared with initial fasting serum glucose level of <120 mg/dL; *P* < .0001, compared with initial fasting serum glucose level of 121 to 200 mg/dL). These cutoff values were used to divide the study cohort into 3 groups for analysis and calculation of the anomaly rates of specific types of major anomalies (Table III). There was no difference in the fre-

quency of distribution of the specific types of anomalies between the subgroups of increasing initial fasting serum glucose concentration. The exception occurred with musculoskeletal lesions, where talipes equinovarus (clubfoot) was found in 10 infants with initial fasting serum glucose levels of <120 mg/dL. When talipes equinovarus is excluded, the rate of musculoskeletal anomalies was 7.6% for this category of glycemia.

The rate of multiple anomalies did appear to increase with increasing initial glycemia (Table III). Multiple anomalies affected 7.7% of infants when the initial maternal fasting serum glucose level was ≤120 mg/dL, 24% of infants when the initial maternal fasting serum glucose level was 121 to 200 mg/dL (P = .001), and 20% when the initial maternal fasting serum glucose level was >200 mg/dL (P = .008). There was no significant difference in the rate of multiple anomalies between the two highest groups of fasting serum glucose levels (P = .59).

Offspring with major anomalies that have been described to occur more frequently in pregnancies complicated with type 1 diabetes (n = 106) had significantly elevated initial fasting serum glucose and glycosylated hemoglobin levels compared with those in offspring without major anomalies (151 ± 56 vs 115 mg/dL and 3.87 ± 4.07 vs 1.90 ± 3.7 SD from the normal population mean; P = .0001 for each comparison). The glycemic parameters were slightly (122 ± 55 mg/dL and 2.48 ± 2.46 SD from the normal population mean) but not significantly elevated in women whose infants had major anomalies that were not previously described in pregnancies complicated with diabetes (n = 37) compared with offspring without anomalies.

Comment

To our knowledge, this is the first large-scale study examining the pattern of major anomalies in relationship to the initial maternal glycemic indexes in infants born to women with GDM or known type 2 diabetes. Our investigation revealed 3 important findings. First, cardiovascular defects were the most frequently occurring anomalies, followed by musculoskeletal and central nervous system anomalies. Thus the pattern of anomalies found in infants of women with type 2 diabetes and GDM appeared to be similar in distribution and type compared with those documented in offspring of women with type 1 diabetes.[1, 6-9] Second, increased maternal hyperglycemia was associated with minor anomalies and genetic syndromes, which have not traditionally been associated with poor glycemic control. Third, there was no apparent increased risk for a specific type of anomaly with increasing maternal glycemia, but there was an increased risk of anomalies affecting more than one organ system.

Evidence from epidemiologic studies examining the occurrence of congenital anomalies in pregnancies complicated with type 1 diabetes has led to the postulation that certain types of anomalies are characteristic for offspring of women with type 1 diabetes.[1, 2, 7-9] In our cohort of women with gestational or type 2 diabetes, the majority (74%) of major anomalies had been described previously in studies of women with type 1 diabetes. Cardiovascular defects were clearly the most frequent type of major anomaly, affecting more than one third of the infants with major anomalies, a finding that is similar to findings in previous studies. Anomalies involving the musculoskeletal and the central nervous systems constituted the majority of the remaining major anomalies. The similar pattern of anomalies between this study and pregnancies complicated with type 1 diabetes suggests that metabolic abnormalities shared among type 1 and type 2 diabetes and GDM may contribute to the excess of anomalies. Existing data from clinical[1, 2, 7-9] and animal studies[16, 17] suggest that the deranged maternal glucose metabolism at the critical time during embryogenesis is a major determinant of the risk of anomalies in pregnancies complicated by diabetes. Although in most of our patients we had no direct measures of fasting hyperglycemia or glycosylated hemoglobin during early pregnancy, we did demonstrate a relationship between increasing hyperglycemia later in pregnancy and the risk of malformations. We do not have measures of blood or urine ketones in our subjects, and therefore we cannot exclude the possibility that maternal ketonemia contributed to the high rates of malformations in the most severely decompensated patients. However, the low frequency of ketosis in patients with type 2 diabetes suggests that any such contribution would be small. Hypoglycemia is likewise unlikely because 83% of women whose infants had birth defects were not receiving glucose-lowering agents at initial presentation. Thus we conclude that maternal hyperglycemia or some closely related metabolic disturbance was most likely the cause of the high malformation rates in our cohort.

We recognize that our actual prevalence of anomalies may be undercounted because we do not have follow-up examination in those infants discharged without recognized anomalies. However, it is least likely that major anomalies, defined as those that cause significant functional or cosmetic impairment, require surgery, or are life-limiting, would be missed.

An unexpected finding was the association between minor anomalies and anomalies attributed to genetic syndromes and initial hyperglycemia. In pregnancies with minor anomalies, the mean glycemic indexes were significantly higher than in pregnancies without anomalies, but they did not reach the level of pregnancies with major anomalies. Syndromes are defined as a recognizable constellation of anomalies, which may affect different organ systems, and not all of them need to be expressed to define the syndrome. In the case of the 9

syndromes classified as genetic, the exact inheritance pattern or genes have not been completely elucidated. The mean glycemic indexes of the genetic syndrome group were slightly higher than those of the major anomaly group and comparable with the multiple organ system group. This observation leads to the speculation that hyperglycemia may somehow influence the penetrance or expression of these defects. Such a mechanism might explain some of the variable penetrance and expression of traits seen with several syndromes.

We could not find evidence that any specific organ system was more susceptible to malformations at increasing glucose ranges. Instead, the overall rate of anomalies of all organ systems appeared to increase without any predominance of specific lesions or organ systems. This lack of an association with specific lesions or organ systems with increasing hyperglycemia may be related to (1) limited power to detect differences in the number of anomalies in the many subsets of organ systems and categories of glycemia despite a relatively large cohort and (2) categorization of anomalies on the basis of postnatal anatomy rather than on the mechanisms of embryologic development that may be shared by different organ systems in utero. The most significant finding was the association of increased hyperglycemia with an increased risk for multiple organ system involvement, suggesting that increasing degrees of maternal metabolic derangement may increase the probability of a sufficient disturbance to disrupt development in more than one organ system, perhaps through a shared biochemical abnormality. Thus the degree of maternal hyperglycemia appears to have a greater influence on the extent of organ system involvement rather than on which organ systems are specifically involved.

Our study is limited in that we do not have information about the maternal glycemic control at the time of embryogenesis in the vast majority of our subjects. GDM is generally diagnosed well after embryogenesis, and our subjects with type 2 diabetes generally sought care during or after the second trimester. In our prior study[10] examining malformations in offspring of women with type 2 diabetes, entry glycosylated hemoglobin measured before 14 weeks of gestation was as predictive of anomalies as glycosylated hemoglobin measured after 14 weeks of gestation in association with later entry into care. This observation, along with our current findings, suggests that moderate-to-marked hyperglycemia at the time of entry into prenatal care after the first trimester is indicative of hyperglycemia during early pregnancy. We found that increased glycosylated hemoglobin levels at entry to care were associated with increased rates of anomalies; this is similar to findings in pregnancies complicated with type 1 diabetes.[5, 18, 19] The initial fasting glucose level was a stronger predictor than glycosylated hemoglobin level for the risk of malformations, a finding that may be attributed in part to the fact that only 41% of our cohort had an entry determination of glycosylated hemoglobin. The threshold of an initial fasting glucose level of >120 mg/dL for increased risk of major anomalies was identical to that in our prior study of women with GDM[11] and to the threshold reported by Rosenn et al[18] during the first trimester in women with type 1 diabetes. Thus, pending prospective studies to document directly the association between maternal glycemia during early pregnancy and the rate of malformations in women without established diabetes or with known type 2 diabetes, we propose fasting serum or plasma glucose concentrations of >120 mg/dL as an important threshold for assessment of clinical risks to embryogenesis.

In summary, in a large cohort of offspring born to women with GDM or type 2 diabetes, we found that the organ systems most frequently affected with congenital anomalies were similar to those described in reports from studies involving pregnancies with type 1 diabetes. Initial maternal glucose levels were higher when offspring had minor anomalies and genetic syndromes, as well as when offspring had major anomalies. There was no clear trend for a predominance of any particular organ system involvement to increase disproportionately with increasing maternal glycemia. There was, however, an increased risk of anomalies involving multiple organ systems as maternal glucose levels increased in the cohort. Thus the level of entry maternal hyperglycemia in women with GDM and type 2 diabetes appears to influence both the risk of and the degree of the anomaly involvement rather than the specific organ system involved. The initial fasting serum glucose concentration provides important information for counseling of women with GDM or type 2 diabetes regarding the risk of giving birth to an infant with anomalies.

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