

Early Sonographic Evaluation For Fetal Growth Delay and Congenital Malformations in Pregnancies Complicated by Insulin-Requiring Diabetes

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OBJECTIVE — It has been reported that early fetal growth retardation may be a useful marker for congenital malformations in diabetic pregnancies. To test this hypothesis, diabetic and nondiabetic women were sonographically evaluated during the first trimester.

RESEARCH DESIGN AND METHODS — Fetal crown-rump lengths were measured sonographically at least once during the first 15 wk of pregnancy in 329 nondiabetic and 312 diabetic women. Of these, 289 nondiabetic and 269 diabetic women had sonograms before 10 wk of gestation and 283 nondiabetic and 269 diabetic women had sonograms between 10 and 15 wk of gestation. Early fetal growth delay was defined as a sonographic gestational age of ≥ 6 days less than menstrual gestational age.

RESULTS — The mean crown-rump lengths at 8 wk were 17.9 ± 4.6 mm in the diabetic and 18.7 ± 4.9 mm in the nondiabetic groups ($P = 0.13$). At 12 wk, the mean fetal crown-rump length was 58.5 ± 8.8 mm for diabetic subjects and 60.6 ± 8.7 mm for nondiabetic subjects ($P = 0.04$). Between 5 and 9 wk, 28 of 289 (9.7%) fetuses of nondiabetic subjects, 34 of 259 (13.1%) normal fetuses of diabetic subjects, and 2 of 10 (20%) malformed fetuses of diabetic subjects demonstrated growth delay ($P = 0.31$, normal vs. malformed diabetic). Between 10 and 15 wk of gestation, 28 of 283 (9.9%) fetuses of nondiabetic subjects, 32 of 256 (12.5%) normal fetuses of diabetic subjects, and 4 of 13 (30.8%) malformed fetuses of diabetic subjects demonstrated growth delay ($P = 0.06$, normal vs. malformed diabetic). Early fetal growth delay did not predict a reduced birth weight at term.

CONCLUSIONS — Among insulin-dependent diabetic subjects who were moderately well controlled at conception, statistically significant but mild early fetal growth delay was present but did not appear to be useful clinically in predicting congenital malformations. Recommendations that growth delay demonstrated on early ultrasound be used as a predictor of congenital malformation require careful reexamination.

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An association between embryonic and early fetal growth retardation, congenital malformations, and an abnormal maternal diabetic metabolic milieu similar to that observed in animal and whole embryo models has been reported in human pregnancies (1). Pedersen and Molsted-Pedersen (2,3) demonstrated a sonographic association between elevated levels of maternal HbA_{1c}, early fetal growth delay, and an increased incidence of congenital malformations in some fetuses of diabetic mothers, observations which prompted these investigators to suggest that embryonic and early fetal growth delay could be of use in defining the risk of congenital malformations in diabetic pregnancies (2–5).

The National Institute of Child Health and Human Development (NICHD) Diabetes in Early Pregnancy Project has provided an opportunity to assess the severity and frequency of growth delay in pregnancies complicated by insulin-requiring diabetes and to relate these observations to their metabolic control. Relationships between glycemic control, congenital malformations, and spontaneous abortion in this population of mothers with insulin-requiring diabetes who were moderately well controlled from the immediate periconceptional period have been recently reported (6,7). In this study on the same population, we report our observations on the relationships between the ultrasound assessment of early fetal growth and congenital malformations.

RESEARCH DESIGN AND METHODS

The Diabetes in Early Pregnancy Project was a multicenter collaborative study designed to compare the incidence of congenital malformations and spontaneous abortion among the offspring of women with insulin-dependent diabetes with those of nondiabetic women and to identify the metabolic risk factors for congenital malformations. Cornell University, Brigham and Women's Hospital (Harvard Univ.), North-

western University, the University of Pittsburgh, and the University of Washington were the study centers, with NICHD serving as the data and coordinating center. The study design has been reported in detail elsewhere (8). Briefly, women with insulin-dependent diabetes antedating pregnancy ($N = 347$) and nondiabetic control subjects ($N = 389$) were enrolled either before conception (86%) or within 21 days of conception (14%). Patients with a first-degree relative who had a Mendelian disorder associated with congenital malformations or who were treated with anticonvulsants, warfarin, or corticosteroids were excluded from the study. Women with non-insulin dependent or gestational diabetes and potential control patients with a first-degree relative with insulin-dependent diabetes were excluded. All subjects kept careful menstrual records, and 55% monitored their basal body temperature. Pregnancy was confirmed with serum β -human chorionic gonadotropin (hCG) levels measured within 2 days of missed menses. If the level of β -hCG was equivocal, it was repeated every 3 days until either a positive result was obtained or a negative result was obtained and the patient began bleeding. A reference laboratory and the use of weighed samples of hCG confirmed that pregnancy was diagnosed accurately by each study center (9). The study design minimized the influences of irregular menses, aberrant oral contraceptive use, and uncertain menstrual dating.

After confirmation of pregnancy, patients with diabetes were hospitalized briefly for baseline laboratory observations and instruction in home glucose monitoring. Because this was an observational study and not an intervention trial, neither standard management protocols nor goals for glycemic control were imposed on the study centers. Patients with diabetes were then followed weekly as outpatients from 5 through 12 gestational wk. For the remainder of the pregnancy, the frequency of visits was dictated by the demands of clinical care

but was most commonly 2–4 times/month. At each visit, HbA_{1c}, β -hydroxybutyrate, and other biochemical measurements were obtained. A thiobarbituric acid colorimetric method was used for the HbA_{1c} analysis because that method permitted centralization of assays with frozen, washed erythrocytes (10). With a capillary blood glucose method (Ames, Dextrostix, Miles, Elkhart, IN) and a reflectance meter (Ames Dextrometer or Glucometer), patients recorded at least one fasting and three postprandial blood glucose levels daily in a glucose diary. In addition, many also measured capillary blood glucose levels before meals and at bedtime. Control patients were followed every other week during the same period to provide control laboratory data.

Sonograms were performed twice (as close as possible to 8 and 12 wk) in the first 15 wk of gestation with commercially available real-time sector and linear array systems with either 3.5- or 5.0-MHz transducers. To allow comparison with previously published series, sonographic age as determined by crown-rump length was compared with previously published tables of mean crown-rump lengths as a function of gestational age and analyzed with a delay of ≥ 6 days between the sonographic and menstrual ages as the definition of growth delay (3,11). After delivery, examinations of the neonate for malformations were performed by examiners blinded to the status of the mother with a standardized protocol with definitions of malformations and deformations accepted by all examiners (6,8). A major malformation was defined as one causing death or a significant handicap that required surgical correction or medical therapy. Major malformations were divided into three groups: 1) those that would prove fatal (severe-fatal), 2) those that could be repaired but would continue to cause disability (serious-handicapping), and 3) those that could be totally repaired (moderate-repairable). Intrauterine growth retardation was defined as weight < 10 th percentile for ges-

tational age, race, and sex. Information on known or suspected risk factors for malformation and spontaneous abortion was collected when pregnancy was diagnosed and periodically thereafter (at 6, 8, 10, 12, 20, 28, and 36 wk of gestation). Included was information on smoking (e.g., number of cigarettes/day), alcohol use (e.g., patterns of use and number of ounces of alcohol consumed per day and per week), drug use, infections, trauma, and exposure to radiation and chemicals.

Comparisons between groups were made by χ^2 analysis or Fisher's exact test for dichotomous outcomes. If the response variable was continuous, the t test was used, unless heterogeneity of variance was suspected, in which case the rank-sum Wilcoxon-Mann-Whitney test was applied. A logistic regression was used to model the presence or absence of major malformations as a function of growth retardation, White class, and mean of HbA_{1c} values obtained up to 1 wk before the first ultrasound examination. The effects of alcohol and smoking on fetal growth were examined by stratifying on levels of smoking and drinking (t test). We also examined the effects of smoking and drinking simultaneously by stratifying by both variables.

The end of the embryonic period and the beginning of the fetal period of human development is defined by most embryologists as 8 wk postovulation or 10 wk from last menstrual period. Because this study bridges both periods, we have arbitrarily used the term fetal rather than attempting to delineate embryonic from fetal periods in the text.

RESULTS— Among 347 diabetic women registered in the study, 269 had a sonogram performed before 10 wk of gestation, of which 165 were measured during the 8th gestational wk. Of the 269 that had a sonogram performed between 10 and 15 wk of gestation, 149 were measured during the 12th gestational wk. A sonogram was performed at least once during the first 15 wk of gestation on 312 diabetic women and dur-

Table 1—Demographic characteristics of mothers with (n = 312) and without (n = 329) diabetes

| | DIABETIC (%) | NONDIABETIC (%) | P* |
|------------------------------------|--------------|-----------------|--------|
| AGE <30 YR | 65.4 | 51.4 | <0.001 |
| INCOME <\$25,000/YR | 39.5 | 26.5 | 0.001 |
| EDUCATION <16 YR | 54.2 | 31.3 | <0.001 |
| NULLIPAROUS | 65.4 | 68.4 | NS |
| WHITE | 95.2 | 92.1 | NS |
| SMOKING >10 CIGARETTES | 9.9 | 4.6 | <0.008 |
| ALCOHOL ≥1 DRINK IN PRECEDING WEEK | 18.9 | 36.2 | <0.001 |

* χ^2 test.

ing both gestational periods (before 10 wk of gestation and between 10 and 15 wk of gestation) on 226 diabetic women. Among the 389 nondiabetic women, 289 had sonograms performed before 10 wk of gestation, of which 186 were measured during the 8th gestational wk. Of the 283 that had sonograms between 10 and 15 wk of gestation, 190 were measured during the 12 gestational wk. Sonograms were performed at least once during the first 15 wk of gestation on 329 nondiabetic women and during both gestational periods on 243 of the nondiabetic women.

Demographic comparisons of the 312 mothers with diabetes and 329 patients without diabetes showed that the patients with diabetes were younger and had lower annual incomes and less education than the nondiabetic patients (Table 1). Significantly more of the patients with diabetes smoked >10 cigarettes/day than nondiabetic patients ($P = 0.008$). In contrast, nondiabetic patients consumed more alcohol than patients with diabetes ($P < 0.001$). They were comparable for race and parity.

Major malformations were observed in the offspring of 17 patients with insulin-dependent diabetes, of whom 14 had at least one sonogram performed in the first 15 wk of pregnancy (Table 2); 10 had a sonogram between wk 5 and 10; 13 had a sonogram between wk 11 and 14. Of the 14 sonographically studied fetuses with major

malformations, 3 were severe-fatal, 3 were serious-handicapping, and 8 were moderate-repairable. Of the 14 malformed diabetic fetuses, 2 demonstrated a growth delay of ≥ 6 days at the 5- to 10-wk examination and 4 at the 11- to 14-wk examination. Of these 4 patients, 1 was from the 3 patients in the severe-fatal group and 3 were from the 8 patients in the moderate-repairable group. None of the 3 patients in the serious-handicapping group demonstrated a significant growth delay. One patient in the severe-fatal group (patient 2) demonstrated a significant growth delay at the 5- to 10-wk exam that did not persist at the 11- to 14-wk exam. Three of the patients with significant growth delays at the 11- to 14-wk examination had no earlier sonogram for comparison.

Of the 558 sonograms performed before the 10th wk on patients with and without diabetes, 351 (62.9%) were performed during the 8th gestational wk. Among the 552 sonograms performed between 10 and 15 wk, 339 (61.4%) were performed during the 12th gestational wk. Because this bimodal distribution of sonograms provided few observations at other gestational ages, we restricted the comparisons of crown-rump lengths between diabetic and nondiabetic women to measurements performed in the 8th and 12th gestational wk. Comparisons of crown-rump lengths at all other gestational ages between diabetic and nondiabetic women did not

produce significant differences. For the 165 fetuses of the mothers with diabetes measured during the 8th gestational wk, the mean crown-rump length was 17.9 ± 4.6 mm compared with 18.7 ± 4.9 mm for the 186 fetuses of the nondiabetic mothers ($P = 0.13$). For the 149 fetuses of mothers with diabetes measured during the 12th gestational wk, the mean crown-rump length was 58.5 ± 8.8 mm compared with 60.6 ± 8.7 mm for the 190 fetuses of the mothers without diabetes ($P = 0.04$; Table 3). Comparison of alcohol consumption in diabetic and nondiabetic women by subgroup analysis (t test) showed no significant difference in crown-rump length in either drinkers or nondrinkers. Likewise, diabetic women did not have significantly smaller fetuses than control women when the study population was divided into smokers and nonsmokers and the two groups were tested separately. Only the women with diabetes who both smoked cigarettes and drank alcohol demonstrated a mild but significant effect on fetal growth and then only at 12 wk.

The percentage of fetuses demonstrating growth delay between 5 and 9 wk and 10 and 15 wk was next compared between the nondiabetic and the diabetic with either normal or malformed fetuses. Between 5 and 9 wk of gestation, 28 of 289 (9.7%) nondiabetic, 34 of 259 (13.1%) normal diabetic, and 2 of 10 (20%) malformed diabetic fetuses demonstrated early fetal growth delay ($P = 0.31$, normal vs. malformed diabetic). Between 10 and 15 wk of gestation, 28 of 283 (9.9%) of control, 32 of 256 (12.5%) normal diabetic, and 4 of 13 (30.8%) malformed diabetic fetuses demonstrated fetal growth delay ($P = 0.06$, normal vs. malformed diabetic) (Fig. 1).

Crude mean birthweights of infants demonstrating early growth delay (nondiabetic [3379 ± 787 g], normal diabetic [3340 ± 651 g], or malformed diabetic [2054 ± 1145 g]) were less than those of infants not demonstrating early

Table 2—Early fetal growth in malformed infants of mothers with diabetes

| NUMBER | STATUS | CONDITION | SONOGRAM 5–10 WK | | SONOGRAM 11–14 WK | |
|--------|--------|---|--|--|--|--|
| | | | GESTATIONAL AGE AT TIME OF SONOGRAM (DAYS) | SONOGRAPHIC AGE MINUS MENSTRUAL AGE (DAYS) | GESTATIONAL AGE AT TIME OF SONOGRAM (DAYS) | SONOGRAPHIC AGE MINUS MENSTRUAL AGE (DAYS) |
| 1 | SF | Anencephaly | NA | NA | 97 | -14 |
| 2 | SF | Arhinencephaly, holoprosencephaly, bilateral cleft lip, maxillary hypoplasia | 56 | -8 | 84 | -2 |
| 3 | SF | Ventricular septal defect, truncus arteriosus | 37 | +14 | 77 | +4 |
| 4 | SH | Microcephaly | 54 | +5 | 82 | +6 |
| 5 | SH | Transposition of great vessels, ventricular septal defect, pulmonic stenosis, patent ductus arteriosus | 56 | -2 | 84 | +8 |
| 6 | SH | Single ventricle, transposition of the great vessels, pulmonic stenosis, patent ductus arteriosus, mitral valve atresia | 56 | +1 | 84 | +4 |
| 7 | MR | Coarctation of the aorta | 69 | -12 | 96 | -8 |
| 8 | MR | Strawberry hemangioma | 60 | +3 | 81 | +1 |
| 9 | MR | Ventricular septal defect | NA | NA | 88 | -6 |
| 10 | MR | Ventricular septal defect | NA | NA | 89 | +4 |
| 11 | MR | Ventricular septal defect | 58 | +18 | 89 | 0 |
| 12 | MR | Paraurethral cyst | NA | NA | 86 | -9 |
| 13 | MR | Labial scrotal fusion | 55 | +7 | NA | NA |
| 14 | MR | Ventricular septal defect | 56 | -3 | 81 | +1 |

SF, severe-fatal; SH, serious-handicapping; MR, moderate-repairable; NA, not available.

growth delay (3541 ± 606 , 3398 ± 769 , or 2860 ± 1016 g, respectively). However, when adjusted for gestational age at delivery, these differences did not attain statistical significance. Among the neonates demonstrating early fetal growth delay, the differences in birthweight between normal and malformed fetuses when adjusted for gestational age also did not reach statistical significance. Among the neonates not demonstrating early growth delay, the differences in birthweight when adjusted for gestational age between normal and malformed fetuses was statistically different ($P = 0.04$). The number of subjects was too small to adjust the birthweight analyses for the effects of maternal use of alcohol and tobacco.

Neither an increased duration of diabetes nor the presence of vascular complications increased the likelihood of fetal growth delay. When the 312 mothers with diabetes were stratified by the

White classification (12), 117 were classes D and R/F and 195 were classes B and C. Growth delay was demonstrated in 20 of 117 (17.1%) fetuses of diabetic mothers in White class D or R/F; 1 of the 20 (5%) had an infant that was malformed. Of the remaining 195 mothers in White classes B and C, 43 (22.1%) demonstrated fetal growth delay; 4 of these 43 mothers (9.3%) delivered fe-

tuses with major malformations ($P = 0.07$ for comparison between diabetic groups for fetal growth delay, Fisher's exact test).

Finally, to determine whether the level of HbA_{1c} in early pregnancy predicted fetal growth delay, a mean HbA_{1c} for each patient was calculated from the values obtained during the interval from last menstrual period to 1 wk before the

Table 3—Crown-rump length of fetuses of diabetic and nondiabetic mothers at 8 and 12 wk

| | N | CROWN-RUMP LENGTH (MM) | P* |
|--------------------|-----|------------------------|------|
| 8 WK OF GESTATION | | | |
| DIABETIC | 165 | 17.9 ± 4.6 | 0.13 |
| NONDIABETIC | 186 | 18.7 ± 4.9 | |
| 12 WK OF GESTATION | | | |
| DIABETIC | 149 | 58.5 ± 8.8 | 0.04 |
| NONDIABETIC | 190 | 60.6 ± 8.7 | |

*Two-sided *t* test.

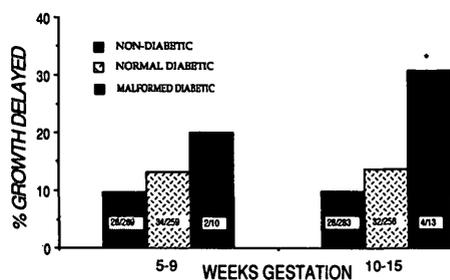


Figure 1—Percentage of growth-delayed fetuses among nondiabetic and diabetic subjects with normal or malformed fetuses. * $P = 0.06$, normal vs. malformed fetuses of diabetic mothers.

ultrasound examination in the 10- to 15-wk interval. The mean HbA_{1c} value for the 205 diabetic women with normal fetuses not showing fetal growth delay was 51.1 ± 10.7 nmol fructose compared with 53.6 ± 11.2 nmol fructose for the 46 diabetic women with normal fetuses demonstrating growth delay on sonograms obtained between 10 and 15 wk of gestation ($P = 0.15$, 2-sided t test). Similarly, the mean HbA_{1c} value for the 4 diabetic women whose fetuses had malformations and early fetal growth delay was 51.8 ± 7.5 nmol fructose compared with 54.0 ± 11.4 nmol fructose for the 8 diabetic women whose malformed fetuses failed to demonstrate early fetal growth delay ($P = 0.73$, 2-sided t test).

CONCLUSIONS— We were unable to demonstrate significant differences in rates of fetal growth between diabetic and nondiabetic fetuses at 8 wk of gestation. At 12 wk of gestation, however, small but significant differences were evident. Although there was an increased incidence of growth delay among fetuses with malformations compared to those without malformations, the differences never attained statistical significance. Therefore, although we were able to demonstrate a mild fetal growth delay in the fetus of the insulin-requiring diabetic woman, the association between the fetal growth delay and congenital malforma-

tion was weak, approaching statistical significance at the 0.05 level only in the 10- to 15-wk interval.

Our cohort of patients with diabetes consumed more alcohol and tobacco than the patients without diabetes. When we tested for the effects of these agents on early fetal growth, we were unable to demonstrate an effect for the individual agents. Those diabetic subjects who both smoked and drank showed mild growth delay by 12 wk. However, the few numbers of these patients did not perturb our observations on the entire cohort.

We confined our comparisons of fetal growth between diabetics and nondiabetics to ultrasounds obtained at 8 and 12 wks. Although we analyzed the data by week of gestation from wk 5 through wk 15, most of the observations were aggregated at wk 8 and 12 (as per the study design). Including all of the observations at all weeks did not alter the interpretation or the strength of the conclusions.

Our study demonstrates less-striking fetal growth-retarding effects of maternal diabetes than suggested by the data of Pedersen and Molstead-Pedersen (2). However, among diabetic fetuses that were growth delayed, the incidence of major malformations in the two studies was comparable. Pedersen and colleagues followed 135 diabetic women with regular 28- to 30-day menstrual cycles. On sonograms performed between 7 and 14 wks of gestation, 53 (39%) of the fetuses were ≥ 6 days below expected size for gestational dates predicted by menstrual history. These 53 women delivered 7 (13.2%) infants with major malformations (2). The positive predictive value for detecting fetal malformation by sonographically demonstrating early fetal growth delay was 0.13. With the same definition of fetal growth delay, only 36 (13.4%) of our 269 diabetic women who had sonograms between 10 and 15 wk of gestation demonstrated fetal growth delay. These 36 women delivered 4 (11.1%) infants with

malformations. The positive predictive value for detecting fetal malformation by sonographically demonstrating early fetal growth delay was 0.11.

Unlike Pedersen et al., we did not find that vascular disease (White classes D, F, and R) or elevated HbA_{1c} levels early in the pregnancy of a mother with diabetes predicted an increased risk for fetal growth delay or malformation (4). We were also unable to confirm their observations that fetal growth delay predicted decreased birthweights in either nondiabetic control, normal diabetic, or malformed diabetic offspring (5).

These differences between our results and those of Pedersen et al. (2-4) may be partly due to improved preconceptional diabetic control in our population and socioeconomic differences between the patient populations. Because of the nature of our recruiting process, our patients were self-selected, highly motivated, and in better glycemic control before conception than patients reported in the Danish studies (8). Ninety-three percent of our patients with diabetes had initial HbA_{1c} levels in early pregnancy $< 7SD$ from the mean (i.e., $< 8.5\%$), a level considered by Miller et al. (13) and Greene et al. (14) to be at low risk for congenital malformations. In addition, differences may be attributable to the multi-institutional nature of our study, which necessitated the use of various ultrasound laboratories, equipment, and ultrasonographers. In contrast, the sonographic measurements in the Danish studies were performed by a single investigator. Our inability to confirm the relationships between vascular disease, the level of maternal HbA_{1c}, early fetal growth delay, and major malformations probably reflects differences in the two populations and the improved degree of preconceptional glycemic control in our population. Because the early fetus luxuriates in an abundant environment, vascular insufficiency would have to be marked to affect early fetal growth.

Other investigators have demonstrated a variable relationship between

early fetal growth delay and fetal malformations in patients with diabetes (15,16). More recently, Cousins et al., (17) in a prospective study of 20 women with diabetes and 20 nondiabetic control subjects followed from the first 8 wks of pregnancy were unable to demonstrate significant early fetal growth delay.

Studies of experimental diabetes in rodents or in vitro culture of rodent embryos have demonstrated that early growth delay and malformation occur in proportion to the degree of metabolic disturbance in the diabetic test system (18–24). However, in these test systems, fetal growth delay was a relatively consistent observation, whereas malformation was far more variable; a circumstance suggested by this study and that of Pedersen and Molsted-Pedersen (2). The exact mechanism by which this abnormal metabolic environment causes fetal growth retardation and malformations is uncertain. Microangiopathically induced tissue hypoxia resulting in a hypocellular embryo, the involvement of the arachidonic prostaglandin pathway, the non-enzymatic glycosylation of embryonic and yolk sac proteins with the inhibition of yolk sac function, the deposition of sorbital in fetal tissues, and perturbations in glucose, ketones, glucagon, somatomedin inhibitors, osmolarity, HbA_{1c}, 2,3-diphosphoglycerate, and trace metals have been proposed as possible mechanisms (18,24–30).

Because the meticulous menstrual dating and sonographic measurement of crown-rump lengths characteristic of study protocols is unlikely to be duplicated in clinical practice, inaccuracies in menstrual dating and sonographic measurements will probably obscure and confound the interpretation of subtle delays in fetal growth. Therefore, although our studies support the concept that a fetus growing in an abnormal metabolic milieu has an increased risk of growth delay and malformations, the sonographic differences in growth are unlikely to be of clinical use in predicting the fetus with major malformations. Par-

enthetically, the demonstration of presumed early fetal delay in a diabetic patient should not result in counseling regarding the advisability of continuing the pregnancy.

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