Diabetes Mellitus: Preventing Anomalies Through Maternal Metabolic Intervention

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The past decades have witnessed dramatic reductions of complications in diabetic pregnancies. Perinatal mortality rates among infants of diabetic mothers (IDM) decreased from 12.9% in the late 1960s to 4.6% in the mid-1970s.1 More recently in tertiary centers, perinatal mortality rates among IDM are about 2%.2-6 With improved obstetric and diabetic care, losses due to intrauterine death, intrapartum asphyxia and fetal injury (macrosomia), and respiratory distress syndromes have diminished. However, the same centers reporting reduced complications and perinatal mortality continue to report major malformation rates of 6–9%.1,7-11 This rate represents a three- to four-fold increase over the general population. Thus, in the 1980s major congenital malformations are the most important cause of mortality in IDM. The purpose of this article is to review the relationship between maternal diabetes mellitus (DM) and fetal anomalies, to discuss pathogenesis, and to suggest the direction that fetal treatment should take to decrease anomalies—rigid metabolic control at the time of conception or preferably earlier.

Frequency of Anomalies Among IDM

Pedersen and colleagues were among the first to present convincing evidence that IDM have an increased risk for congenital malformations.12 Those investigators reviewed records of 853 IDM birth weights of 1,000 g or more, born in Copenhagen between 1926 and 1963. Although frequently cited as a landmark study, this work is actually less than ideal in experimental design. Infants born before 1947 were examined by one consultant in pediatrics. However, control data were derived from a study by other investigators in the same department during a 6-month period in 1959–1960. In the latter investigation, pediatricians examined 1265 newborn infants for several purposes, only one of

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which was detection of congenital malformations. The control group thus differed temporally from the diabetic group and probably was analyzed according to different criteria. Nonetheless, 6.4% of the IDM showed a congenital abnormality, compared with only 2.1% of controls. Among infants who died, 19.5% were said to have an anomaly that could have caused the death (i.e., a "lethal" anomaly). Not surprisingly, the prevalence of anomalies was higher if maternal diabetes was more severe; 4.4% of infants born to mothers with class A, B, or C DM had anomalies, whereas 9.7% of infants of class D or F mothers had anomalies. Offspring of mothers with vascular complications (classes D and F) thus showed the highest frequencies of anomalous offspring.

Other retrospective studies of that era showed similar results, but again methodologic objections could be raised to all. Naeve observed a twofold increase in the frequency of anomalies in IDM, compared with controls matched for age, race, and gravidity. The incidence of 13 obvious anomalies (e.g., anencephaly) was twice as high (1.62% versus 0.85%) in IDM. Kucera reviewed many studies totaling 7,110 IDM; 4.79% of IDM were abnormal, compared with significantly fewer (0.65%) in a "control obtained from World Health Organization data." In a review of data gathered prospectively by the U.S. NICHD-Collaborative Perinatal Project, Chung and Myrianthopoulos calculated that offspring of white insulin-dependent pregnant diabetics had twice the incidence of anomalies as either control offspring or offspring of mothers with class A DM. The frequencies of anomalies in the U.S. Collaborative Perinatal Project were also significantly greater in whites than in blacks and significantly greater if mothers had been diabetic for 5 years or more. The frequency of malformations was not increased if the father, but not the mother, had DM. That infants of mothers with classes D and F DM were most likely to be malformed is the consensus of several studies. Farquhar failed to find a higher malformation rate among IDM, but he did observe more severe malformations among the diabetic group. More recent studies continue to show increased malformation rates among IDM. Using state and hospital records, Wheeler et al. identified 294 births associated with maternal diabetes in South Carolina in 1978. Congenital anomalies were documented in 15 infants (6.0%). Connell et al. examined records of Washington State residents' births during 1979 and 1980. Hospital records were reviewed for all diabetic women and their infants. Of 191 infants of insulin-dependent diabetic women, 11 (5.8%) had lethal malformations. Statewide anomaly frequencies were not reported in the Washington or the South Carolina study. However, the frequencies of anomalies among IDM were surely elevated compared with the accepted general population frequency of about 2.0%.

Coustan et al. prospectively studied 73 diabetic women during pregnancy from 1975 to 1979. Of 74 IDM, six (8.1%) were anomalous. In another prospective study of 83 diabetic women, Tevaarwerk et al. observed only 4 of 110 IDM (3.6%) with anomalies. Like most other studies, neither of these prospective studies included a control group for which anomaly rates were reported. To address some of the shortcomings of these earlier studies, Simpson et al. prospectively investigated the frequency of malformations among IDM and a temporally matched control group. Infants of control and diabetic women were assessed in a systematic fashion by two independent examiners, one a geneticist and one a neonatologist. IDM and control infants were examined in as "blind" a fashion as possible. All control participants underwent a 3-hour glucose tolerance test to exclude undiagnosed diabetes. Between 1977 and 1982, 182 dia-
abetic women were delivered of 12 infants with major anomalies (6.6%). The frequency was 3/76 (3.9%) in class A diabetics and 9/106 (8.5%) in classes B to F. Although the control sample was unfortunately small, only 1 of 41 mothers was delivered of an anomalous infant (2.4%).

In summary, in IDM, congenital malformations occur three to four times more frequently than in infants of nondiabetic mothers. In general, the highest risk is for diabetic mothers with earliest onset, longest duration, and vascular complications.12,17,22

**Types of Anomalies**

Although most teratogens produce characteristic aggregates of anomalies, anomalies among IDM are nonspecific and include a wide spectrum of defects. Because the diabetic state persists throughout pregnancy, one could reason that nonspecific anomalies of all organ systems would be expected, in contrast with the specific group of anomalies characteristic of drug- or virus-induced teratogenesis.

Various anomalies have been said to occur commonly among offspring of diabetic mothers, but attention has focused especially on three: caudal regression syndrome, cardiac anomalies, and neural tube defects. Lenz and Maier were apparently the first to suggest that hypoplasia of the sacrum and lower extremities (caudal regression syndrome) was especially common in offspring of diabetic mothers.23 Similar observations were later made by others.14,24,25 The caudal regression syndrome is said to occur in about 0.2–0.5% of IDM, a 20- to 30-fold increase over the incidence in the general population. However, relatively few IDM have the caudal regression syndrome, and an infant with the anomaly is more likely to be born to a normal mother than to a diabetic mother because the former are so much more common. Only 2 of 576 offspring of diabetic moth-

ers in the Collaborative Perinatal Project15 and 0 of 182 infants in the Northwestern series had the caudal regression syndrome.11

Cardiac and other vascular anomalies occurred more often among diabetic offspring in the U.S. Collaborative Perinatal Project than would be expected by chance.15 The incidence of congenital heart disease in IDM was 25.4 per 1,000 compared with only 8.1 per 1,000 in infants of nondiabetic mothers.26 Likewise, Simpson et al. reported six cardiac defects among 182 IDM examined, perhaps a threefold increase over the incidence in the general population.11 Rowland et al. studied 571 pregnancies of 426 insulin-dependent women delivered between 1962 and 1968.27 Cardiac anomalies, usually transposition of great vessels or ventricular septal defect, occurred in 4% of IDM.

The incidence of neural tube defects is also increased among IDM. In his survey, Kucera tabulated a three- to fourfold increase of neural tube defects among IDM.14 Of 540 diabetic mothers, 33 (9.7%) were delivered of infants with neural tube defects. Of these, 17 had anencephaly, 12 had spina bifida, and 4 had both anencephaly and spina bifida. Among 546 diabetic women in the U.S. Collaborative Perinatal Project, 5 infants (1.1%) were affected (3 anencephaly, 1 spina bifida, 1 encephalocele). In a sample of women undergoing maternal serum alpha fetoprotein (AFP) screening, Milunsky et al. reported 8 of 411 (2.95%) IDM with neural tube defects (7 anencephaly, 1 spina bifida);28 this is significantly greater than the general population frequency of 0.1–0.2%.

Other anomalies have been said to be associated with maternal diabetes, but data are less substantiated than for the caudal regression syndrome, cardiac defects, and neural tube defects. Based on his literature review, Kucera concluded that the following anomalies were also likely to be present among offspring of diabetic mothers than
among controls: situs inversus, arthrogryposis (multiple fexion contractures), duplex ureter, "pseudohermaphroditism," "gross skeletal anomalies," hydronephrosis, and "gross skeletal and associated anomalies."14 Unfortunately, most of these categories are so general that meaningful inferences cannot be drawn.

In conclusion, IDM show increased frequencies for a wide range of anomalies. However, the most common anomalies among IDM are those that are relatively common in the general population, namely cardiac defects and neural tube defects.

**Hyperglycemia, Ketosis, and Anomalies**

It has long been suspected that perturbations in the maternal metabolic milieu in diabetic gestations produce anomalies in offspring. This hypothesis is consistent with both the broad spectrum of anomalies in IDM as well as the increasing risk for anomalies with increasing diabetic class. An aberrant metabolic milieu could be teratogenic throughout organogenesis, affecting any organ system developing at the time of perturbation. Thus, any organ system could be affected.

Early studies of the effects of hyperglycemia on anomaly rates were retrospective, focusing on glucose levels in the second and third trimester of pregnancy. For example, Karlsson and Kjellmer examined the relationship between a) mean blood glucose values at 30 to 32 weeks' gestation and b) infant anomalies, studying 179 diabetic patients delivered between 1961 and 1970.15 Both mean blood glucose and anomaly rates increased with diabetic class, and all were significantly correlated with each other in pairwise comparisons. However, this study can be criticized not only for correlating malformation rates with blood glucose levels measured too late in gestation to reflect status during embryogenesis, but also for not excluding confounding effects of diabetic class (e.g., increased complications in higher classes).

More recently, hemoglobin A1c (HbA1c) levels have been favored as a measure of diabetic control. HbA1c represents an integrated measure of blood glucose levels during the preceding weeks. Thus, it has been assumed that HbA1c levels in the late first or early second trimester are a fair indication of maternal glycemic control during organogenesis; however, this remains unproved.

Miller et al. retrospectively studied 116 insulin-dependent diabetic women whose HbA1c levels were initially measured before 14 weeks' gestation and whose infants were examined at birth by a trained examiner.20 Fifteen women (13%) were delivered of an anomalous infant. The anomaly rates were 0/19 among women with an initial HbA1c of less than 7.0%, 2/37 (5.1%) among women whose initial value was 7.0–8.5%, 8/27 (22.9%) among women whose initial value was 8.6–9.9%, and 5/18 (21.7%) among women whose initial value was greater than 9.9%.20 There was no relationship between high or low initial HbA1c and diabetic class. Thus, a significantly higher prevalence of congenital malformations in women with elevated HbA1c before 14 weeks' gestation was found, independent of diabetic class. Yllinen et al. also reported significant associations between initial HbA1c levels and anomalies in IDM.30,31 They studied 142 insulin-dependent diabetic women whose initial HbA1c levels were measured between 6 and 15 weeks' gestation. Infants were examined by a neonatologist at birth, at 1 day of age, and on the day of discharge from the hospital. Additional diagnostic studies were performed if a congenital defect was found or suspected. Eleven women were delivered of an anomalous infant. Anomaly rates were 2/63 (3.2%) among women with initial HbA1c of less than 8.0%, 5/62 (8.1%) among women whose initial value was 8.0–9.9%, and 4/17
(23.5%) among women whose initial value was greater than 9.9%. The mean initial HbA1c value among women delivered of an anomalous infant was 9.6%, compared with 8.0% among women delivered of a normal infant (p < 0.001).

In a smaller study, Leslie et al. reported that three of five insulin-dependent diabetic mothers with elevated HbA1c levels at their initial prenatal visit had malformed infants. Of 18 infants born to women whose HbA1c was in the normal range at their initial visit, none were anomalous. Unfortunately, values measured at initial visits may provide little information on maternal metabolic status during organogenesis. For example, Simpson et al. also reported initial HbA1c values for diabetic mothers of 10 malformed infants. In contrast with results of Leslie and colleagues, normal values were observed among two mothers of anomalous infants whose initial values were measured before 14 weeks' gestation. Although these data are limited, they do suggest that metabolic disturbances other than hyperglycemia may be teratogenic in diabetic gestations.

Indeed, most studies of the relationship between diabetic control and anomalies have focused solely on the relationship between glucose levels and malformations. The role of factors other than hyperglycemia is largely unknown. For example, the relationship between maternal ketone and free fatty acid levels during embryogenesis and anomalies in offspring is poorly explored. Moreover, synergistic effects of these metabolic fuels on embryotoxicty have yet to be studied in humans. Unfortunately, identifying the precise teratogen in diabetic gestations is complicated by DM's not being a simple disorder of carbohydrate metabolism. Numerous serum factors are altered in DM, not only glucose but free fatty acids and ketones. Furthermore, diabetic metabolic profiles must be examined during organogenesis in order to make meaningful correlations. Thus, studying multiple metabolic factors early in diabetic pregnancies will be necessary to define the relationship between diabetic control and fetal anomalies. In fact, these interactive effects will be clearer after analysis of the NICHD-Collaborative Study of Diabetes in Early Pregnancy (DIEP), an effort involving our group (Northwestern) and four other universities (Harvard, Cornell, University of Pittsburgh, University of Washington). A more detailed description of the DIEP is presented later in this article.

In the absence of definitive human studies, in-vitro studies of the effects of diabetic serum factors on embryogenesis have been attempted. Using embryo cultures, one can directly assess the teratogenic effects of altered serum factors on embryonic development. Sadler first demonstrated that serum from a diabetic animal used as culture medium produces exencephaly and growth retardation in cultured mouse embryos. Elevated glucose levels alone were also teratogenic to cultured rat embryos and cultured mouse embryos. Sadler and colleagues later demonstrated that ketone bodies and beta-hydroxybuterate (B-OHB) caused neural tube defects in early somite mouse embryos. This effect was age and dose related. Younger embryos were more frequently and more severely affected than older embryos, and the incidence of neural tube defects increased with increasing concentrations of B-OHB. Concentrations of B-OHB causing neural tube defects were in the range of ketone body levels observed in severe human ketosis. The teratogenic effects of B-OHB in embryo cultures are enhanced by media supplemented with subteratogenic levels of glucose. If culture media containing B-OHB levels causing minimal growth retardation and minor anomalies are supplemented by glucose levels that alone cause no developmental abnormalities, the new mixture now causes severe anomalies in rat embryos—neural tube, brain, and cardiac defects. Thus,
combinations of serum factors may be teratogenic, even if the individual components are not.

Overall, however, the precise mechanisms of action of these substrates remain unknown. Horton and Sadler hypothesize that elevated levels of glucose and/or B-OHB may inhibit glucose utilization in the early somite embryo. Because alternative metabolic pathways are only minimally operational at this developmental stage, the embryo relies almost exclusively on glycolysis for its energy production. Inhibition of glucose utilization at this stage could potentially result in growth retardation and, hence, developmental abnormalities. (Decreased cell number is the final teratogenesis.) This hypothesis is further supported by the embryotoxic effects of the glucose epimer D-mannose in rat embryo cultures. Freinkel and colleagues suggest that mannose teratogenicity is related to an impairment of glycolysis, further emphasizing the critical role of uninterrupted glycolysis during early embryogenesis.

In-vitro studies like those cited support the hypothesis that metabolic derangements in diabetic gestations cause anomalies in offspring. However, the obvious difficulties in systematically assessing metabolic control during the first ten weeks of pregnancy have meant that most human studies have been either retrospective entirely or have extrapolated from measures of diabetic control in the second and third trimesters to the first trimester. Despite these limitations, much indirect evidence has accumulated supporting the hypothesis that malformations in IDM result from aberrant maternal metabolic milieu during early pregnancy.

**Hypoglycemia**

Maternal hypoglycemia clearly causes birth defects in animals. Offspring of animals made hypoglycemic during pregnancy show increased malformations. Administration of insulin simultaneously to availability of adequate food to prevent hypoglycemia in pregnant rats reduced this malformation rate. Unfortunately, few data are available in humans, and those available appear conflicting. In humans, anomalies were reported in 2 of 8 infants whose mothers received insulin shock treatment before 14 weeks’ gestation. No anomalies were noted among 11 infants of mothers treated after 15 weeks. However, hypoglycemic reactions were noted more frequently among diabetic mothers delivered of normal offspring than among diabetic mothers delivered of an infant with congenital heart disease. Observing that only 8 of 55 mothers with anomalous offspring noted insulin reactions in the first trimester, Pedersen and colleagues concluded that hypoglycemia per se did not cause malformations. However, all these studies can be criticized on several grounds. Most important, recall biases are a serious potential problem. Furthermore, some insulin reactions may not have occurred during organogenesis, whereas others may have gone unnoticed. Thus, whether hypoglycemia causes anomalies in offspring in human pregnancies remains questionable.

**Teratogenic Mechanisms Not Involving Metabolism**

A number of pathogenic factors other than maternal metabolism could influence the increased malformation rate among IDM. Postulated mechanisms include genetic influences, insulin teratogenicity, and maternal vascular disease.

**Fetal Genotype**

That fetal genotypes per se influence susceptibility to anomalous offspring is unlikely because the frequency of anomalies is not increased if the father but not the mother is diabetic. If combinations of genes predisposing to diabetes (e.g., cer-
tain HLA haplotypes) also predispose to developmental defects, infants of diabetic fathers would be expected to show the same increased frequency of anomalies. The failure of this to occur does not, however, exclude the possibility that a maternal diabetes-associated haplotype might predispose toward maternal susceptibility to teratogenic metabolic derangement.

**Chromosomal Abnormalities**

A testable pathogenic possibility is that of chromosomal abnormalities. Aberrant metabolism could interfere with maternal meiosis to produce aneuploid oocytes or act on the embryo to produce mosaicism through mitotic nondisjunction. Occurrence of chromosomal abnormalities could explain not only the increased frequency of anomalies among IDM, but also the failure to observe a specific pattern of anomalies. (Involvement of different chromosomes in different infants would produce various anomalies rather than a specific pattern of anomalies.) Using a case-control design, Milunsky showed that mothers of trisomy 21 infants were more likely to have diabetes than controls. Others have shown that the frequency of DM is increased in relatives of probands with 45,X Turner syndrome. However, prospective studies of 247 IDM did not show an increased frequency of chromosomal abnormalities. Only 1 of 247 IDM (0.4%) had a cytogenetic abnormality (45,XY, +mar), a rate comparable with that in the general population. Thus, it seems unlikely that maternal DM increases the risk of cytogenetic abnormalities.

**Insulin Teratogenicity**

Insulin teratogenicity has been proposed but can be excluded readily. Administering insulin to pregnant diabetic mice decreases, rather than increases, the frequency of congenital malformations. Furthermore, insulin is not transferred across the placenta.

**Vascular Disease and Fetal Hypoxia**

Vascular disease secondary to maternal DM could influence occurrence of fetal anomalies. Indeed, anomalies occurred more commonly among offspring of mother with class D or F DM and more commonly among mother who had diabetes for at least 5 years at the time of delivery. If maternal–fetal exchange is compromised by decreased blood flow or by impaired exchange among diabetic mothers with vascular disease, fetal hypoxia could occur or delivery of nutrients and vital substrates to the fetus could be diminished. Furthermore, impaired renal function secondary to vascular disease could result in a teratogenic environment for the developing fetus. Thus, maternal vascular abnormalities might play a role in fetal anomalies, but whether or not maternal vascular disease acts independent of other factors, such as maternal metabolic status, remains to be clarified.

**Prevention of Anomalies in Diabetic Gestations**

If perturbations in the maternal metabolic milieu in diabetic pregnancies cause anomalies in offspring, then strict diabetic control should lower anomaly rates in IDM. However, in tertiary centers where diabetic patients are managed aggressively to achieve euglycemia during pregnancy, anomaly rates have remained comparable with those observed among diabetic patients managed less rigorously. However, patients in these studies were not routinely identified until the late first or early second trimester of pregnancy, long after embryogenesis is completed. Thus, aggressive metabolic management after the first trimester of pregnancy does not decrease the frequency of anomalies in IDM. This is actually not surprising because most congenital malformations in IDM are completed by 7 weeks' gestation. Therefore, identification of diabetic women before conception and aggressive management of
diabetes in early pregnancy may be necessary to reduce the increased risk of anomalies in these infants.

To evaluate the effect of a euglycemic program initiated before the 12th week of gestation, Jovanovic et al. studied 52 insulin-dependent diabetic women. All women in the study presented for their first clinic visit before 12 weeks, and all received intensive diabetic care throughout pregnancy. The mean HbA1c value on entry into the study was 10%. HbA1c values for all women decreased to the normal range within 6 weeks and remained there throughout pregnancy. However, for many subjects, tight metabolic control was probably not achieved until after organogenesis was completed. Still, no anomalous infants (0/52) were born. These exemplary results could, however, reflect small sample size effects or factors other than hyperglycemia in diabetic gestations.

In a larger investigation, Furlhmann et al. studied 420 insulin-dependent diabetic women delivered between 1977 and 1981. Of 420 women studied, 128 were educated before pregnancy and hospitalized during gestational weeks 5 to 8 to achieve optimal metabolic control. The remaining 292 began intensive metabolic control after 8 weeks' gestation. The 128 women educated before pregnancy were delivered of only 1 anomalous infant (0.8%), whereas the 929 women hospitalized after 8 weeks were delivered of 22 anomalous infants (7.5%). Anomaly rates were not associated with diabetic class. The authors concluded that instituting strict metabolic control of maternal diabetes before conception and continuing it throughout organogenesis can normalize malformation rates. Unfortunately, metabolic status before 8 weeks' gestation was not known for women with anomalous offspring. Thus, these data provide little information on either specific teratogens or the degree to which rigid control must be exerted to reduce anomaly rates.

As already noted, NICHD has just completed a 5-year collaborative investigation of the relationships between diabetic control before and during organogenesis and anomalies in offspring. Using an innovative study design, the DIEP study recruited diabetic and control subjects before conception. Pregnancy was diagnosed by serum B-HCG measurements within 21 days of conception. From the time of pregnancy diagnosis through the 12th week of gestation, metabolic control was assessed weekly in diabetic women and biweekly in control women. In addition, diabetic women monitored their blood sugars four times daily with a dextrometer (Ames Company, Elkhart, Ind). Metabolic surveillance continued throughout pregnancy. Anomalies were assessed in newborns by only one or two examiners per participating center, using a standardized protocol with a malformation checklist. To minimize potential confounding variables, the DIEP study obtained information on potential risk factors for malformations throughout pregnancy. Analysis of these data should help identify specific teratogens in diabetic gestations and elucidate the relationship between early diagnosis of pregnancy, diabetic control, and anomalies in IDM.

Monitoring Anomalies in Diabetic Pregnancies

Maintaining euglycemia during organogenesis may well reduce anomalies in IDM. Of course, control cannot be restored over-night. To facilitate management, diabetic women should thus be counseled to defer pregnancy until a satisfactory degree of metabolic control has been achieved. If this is not possible (some unintended pregnancies will always occur), aggressive management and education should at least begin as early as possible in gestation.

Until the risk of fetal anomalies in diabetic pregnancies is reduced to that of the general population, consideration should also be given to aggressive monitoring of
anomalies in diabetic pregnancies. Fetal ultrasound in the first or early second trimester is already standard to confirm fetal viability and determine gestational age. In addition, detection of growth retardation in the first trimester may presage anomalous infants, and warrant closer surveillance during pregnancy. In the second trimester, level-II ultrasound for diagnosis of structural defects (caudal regression syndrome, some cardiac and skeletal anomalies, renal anomalies, some neural tube defects) has been proposed. If it is used, the patient should be aware that many serious defects pass undetected. Whether level-II ultrasound should be performed later in gestation (on the grounds of altering mode of delivery) is arguable.

One defect that should be readily sought is neural tube defects. Maternal serum alpha-fetoprotein screening between 15 and 18 weeks, now recommended in all pregnancies, allows prenatal detection of 80–90% of neural tube defects. Elevated serum values may warrant amniocentesis for definitive confirmation of neural tube defects. Given the small but finite risks of amniocentesis, this procedure should be offered for detection of neural tube defects only after maternal serum alpha-fetoprotein levels are found to be elevated.

Amniocentesis or chorionic villus sampling solely for prenatal cytogenetic diagnosis is not recommended on the basis of maternal diabetes. However, if amniocentesis is performed for assessment of amniotic fluid alpha fetoprotein, chromosomal analysis is recommended. The converse is also true.

References

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