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Objectives

After completing this article, the reader should be able to:

1. List the most important factors producing a normal neonate without untoward complications for the diabetic mother.
2. Explain the "mixed nutrient" hypothesis.
3. Describe the most probable cause of congenital malformations.
4. Describe the morbidities that have been reported in the infants of mothers who have uncontrolled diabetes.

Introduction

The infant of the diabetic mother (IDM) is the premier metabolic example of the morbidity that may exist in the neonate due to maternal disease (diabetes). From a developmental standpoint, the normal neonate is in a transitional state of glucose homeostasis. The fetus is completely dependent on the mother for glucose delivery, and the adult is considered to have control of glucose homeostasis because plasma glucose concentration is regulated precisely. (1) In contrast, maintenance of glucose homeostasis may be a major problem even for the normal neonate. (2) The precarious nature of this equilibrium is emphasized by the numerous morbidities producing or associated with neonatal hypo- and hyperglycemia. Although many IDMs have an uneventful perinatal course, there is still an increased risk of complications. Many of these can be minimized, but not eliminated, with appropriate obstetric and pediatric intervention. Because a recent analysis indicated that there is still much room for improvement due to the multiplicity of factors that affect any specific pregnancy, (3) the obstetrician and pediatrician must be knowledgeable about these potential problems. This discussion enumerates many of the difficulties that the IDM may encounter and evaluates the pathophysiologic basis of their occurrence.

Perinatal Mortality and Morbidity

Theoretically, closer metabolic control of the pregnant woman who has diabetes results in a greater potential for producing a normal neonate. The physician responsible for the care and delivery of the mother must inform the physician responsible for the care of the neonate of the mother's condition well in advance of delivery. Certainly, the pregnancy of the diabetic mother should be considered high risk. Knowledge of the character of the maternal diabetes, prior pregnancy history, and complications occurring during pregnancy allows the physician caring for the neonate to anticipate many potential fetal and neonatal complications and to be present at delivery (Table 1).

Studies of perinatal morbidity and mortality from diverse centers attest to the improving success of managing the pregnant diabetic woman with appreciation of the high-risk nature of the pregnancy. A number of years ago, Pedersen and associates (4) published a review of their experiences over a 26-year period with an analysis of 1,332 diabetic pregnancies. Perinatal mortality varied directly with maternal severity of diabetes, as judged by two commonly used maternal classification schema: White's original classification of diabetes in pregnancy and Pedersen's Prognostically Bad Signs in Pregnancy (PBSP) classification. White's revised classification (Table 2) is based on duration of diabetes and

Abbreviations

IDM: infant of the diabetic mother
PBSP: Prognostically Bad Signs in Pregnancy
RDS: respiratory distress syndrome
PTH: parathyroid hormone

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Table 1. Morbidities in the IDM

- Asphyxia
- Birth injury
- Caudal regression
- Congenital anomalies
- Double-outlet right ventricle
- Heart failure
- Hyperbilirubinemia
- Hypertrophic obstructive cardiomyopathy
- Hypocalcemia
- Hypoglycemia
- Hypomagnesemia
- Increased blood volume
- Macrosomia
- Neurologic instability (short- and long-term)
- Organomegaly
- Polycythemia and hyperviscosity
- Renal vein thrombosis
- Respiratory distress
- Respiratory distress syndrome
- Septal hypertrophy
- Shoulder dystocia
- Small left colon syndrome
- Transient hematuria
- Truncus arteriosus

the presence of late vascular complications; (5) the PBSP classification (Table 3) includes abnormalities of the current pregnancy.

A report from the Joslin Clinic supports the importance of these factors, especially preeclampsia (pretoxemia), as a significant morbidity in the pregnant diabetic woman. (6) Of 420 patients in the series who had type 1 diabetes, 110 (26.2%) delivered before 37 weeks' gestation compared with an incidence of 9.7% in the nondiabetic population. One third of the preterm deliveries were related to preeclampsia. The authors concluded that a major problem of the diabetic pregnancy relates to the problem of preeclampsia that produces prematurity. The risk to the fetus was increased when the PBSP classification was "added" to the White classification. The importance of preeclampsia recently was reiterated as a significant clinical issue in the care of the diabetic pregnancy. (7)

The relationship between PBSP and preeclampsia was emphasized by Diamond et al, (8) who studied 199 pregnancies. They noted that the presence of PBSP increased the perinatal mortality rate from 7.3% to 17.1% and was predictive of general pulmonary morbidity (31.6% versus 16.3%). The investigators concluded that the combination of the two classification systems remained as predictive as had been noted by Pedersen.

Table 2. White's Classification of Diabetes in Pregnancy (Modified)

Gestational diabetes	Abnormal glucose tolerance test, but euglycemia maintained by diet alone; if diet alone insufficient, insulin required
Class A	Diet alone, any duration or age of onset
Class B	Age of onset: ≥20 y; duration: <10 y
Class C	Age of onset: 10 to 19 y; duration: 10 to 19 y
Class D	Age of onset: <10 y; duration: >20 y; background retinopathy or hypertension (not preeclampsia)
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Nephropathy, with >500 mg/d proteinuria
Class RF	Criteria for both classes R and F coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal transplantation

Although these investigators noted an improvement in nondiabetic pregnancy outcome during this same period, they emphasized that the improved classification schema combined with increased experience were the major reasons for the improved results in the diabetic pregnancy. This improved perinatal mortality has been confirmed at many centers in the United States and in Europe. The frequency of macrosomia has decreased, but the rate remains higher than that in the neonate born to the woman who does not have diabetes. In a survey of macrosomic neonates (ie, large-for-gestational age, >95th percentile weight for gestational age), most were born to obese mothers, not all of whom had glucose intolerance. (9)(10) Nevertheless, the woman who has gestational diabetes with glucose intolerance during late pregnancy may remain undiagnosed and may deliver a neonate who has a greater risk for perinatal complications.

Table 3. Prognostically Bad Signs of Pregnancy (PBSP)

- Chemical pyelonephritis
- Precoma or severe acidosis
- Toxemia
- "Neglecters"

Maternal glucose variability has been studied in 154 pregnant diabetic patients who were hospitalized for 1 month prior to delivery. (11) There was a significant association between maternal glucose variability and enhanced neonatal outcome (ie, decreased incidence of complications) and no correlation between maternal glucose variability and the birthweight of the neonate. The authors acknowledged that absence of glucose variability would not ensure prevention of neonatal complications. A variation on this theme was reported by Mello et al, (12) who suggested that overall daily glucose concentrations of 95 mg/dL (5.3 mmol/L) or less were required in the second and third trimesters to avoid alterations (ie, excesses) in fetal growth.

Roberts and Pattison (13) reported on a 20-year experience involving 1,528 pregnancies of diabetic women of whom 571 had type 1 diabetes and 957 had gestational diabetes. The perinatal mortality rate decreased from 15.2% to 2% in those who had type 1 and from 6.7% to 0.5% for those who had gestational diabetes. The investigators related the improvement in mortality to improved glucose control. They reported, as noted by others, that the major outstanding problem was the persistent high incidence of congenital malformations.

Coustan and Imarah (14) first attempted to use prophylactic insulin in women who had gestational diabetes to reduce the incidence of macrosomia, operative delivery, and birth trauma. There was a partial decline of complications with tightened maternal metabolic control. Subsequently, the same investigators evaluated insulin pump or intensive conventional therapy by randomizing 22 pregnant diabetic women to the two treatments. (15) No significant differences were found with either regimen, and excellent glucose control was achieved with both. Howorka et al (16) reported the normalization of pregnancy outcome with the use of functional insulin treatment through individualization of insulin dosages during the day.

The use of insulin therapy was also reported in 108 women who had gestational diabetes and were randomized to receive diet plus insulin or diet alone to maintain glycemic control. (17) Among the patients treated for at least 6 weeks with diet plus insulin, the mean birthweight, the incidence of macrosomia, and the ponderal index were reduced. No patient who weighed less than 200 lb (90 kg) and maintained euglycemic control delivered a neonate who weighed more than 4,000 g. The investigators concluded that maternal obesity or failure to achieve glycemic control should alert the clinician to an increased risk of macrosomia.

Norlander and associates (18) found that perinatal morbidity was significantly more frequent in the women who had gestational diabetes (23%) than in the control group (13%). The occurrence of large-for-gestational age neonates did not differ between groups. Of those born to the women who had gestational diabetes, the neonates who presented with morbidities were of earlier gestational age at delivery, were delivered more frequently by cesarean section, and had mothers who had higher prepregnancy weights and greater area under the glucose tolerance curve. Gestational age at delivery and maternal prepregnancy weight were the most significant factors. The investigators concluded that factors beyond blood glucose control during pregnancy were critical to neonatal outcome in this population.

A population-based study compared 68 women who had diabetes requiring insulin treatment and 403 treated with diet alone with a random sample of 1 in 12 of 893 nondiabetic women who delivered in one regional hospital. (19) No relationship was noted between maternal glycosylated hemoglobin at delivery and the neonatal birthweight. At each week of gestation, the infants born to the diabetic women were heavier than the infants born to the nondiabetic women ($P<0.05$). No differences were noted in maternal glycosylated hemoglobin between the two groups throughout pregnancy. Factors affecting birthweight included diabetes, ethnic origin, and parity. The investigators concluded that substrates other than glucose, which induce hyperinsulinemia, may be related to the higher birthweight of the neonate.

Finally, Hod and colleagues (20) reported data evaluating the effect of patient compliance, fasting plasma glucose on the oral glucose tolerance test, maternal body constitution, and method of treatment on perinatal outcome of patients who had gestational diabetes mellitus. A total of 470 patients were compared with 250 control nondiabetics. Patient compliance reduced the rate of macrosomia (14.4%) and neonatal hypoglycemia (3.4%), but not to the level of the control population (5.2% and 1.2%, respectively). Intensified insulin treatment reduced the rate of perinatal complications in the obese parturients, but again, not to the level of the control group.

Although most investigators have agreed on the importance of maintaining euglycemia, the optimal clinical method has not been established. deVeciana et al (21) compared the efficacy of postprandial and preprandial monitoring to achieve glycemic control in the gestational diabetic woman. Sixty-six women who were at at least 30 weeks' gestation were treated with insulin therapy following either preprandial monitoring or postprandial monitoring 1 hour after a meal. The change in glycosy-

Table 4. Components for the Hypothesis of "Hyperinsulinism" in the IDM

- Islet hyperplasia and beta-cell hypertrophy
- Obesity and macrosomia
- Hypoglycemia with low free fatty acid concentration
- Rapid glucose disappearance rate
  —Higher plasma insulin-like activity after glucose
  —Umbilical vein reactive immunoinsulin increase
- Elevated C-peptide and proinsulin concentrations

lated hemoglobin was greater in the postprandial group, and the birthweights of the neonates were lower. Similarly, there was a lower rate of neonatal hypoglycemia in the large-for-gestational age neonates and a lower delivery rate by cesarean section.

Maintenance of a normal metabolic state, including euglycemia, should diminish, but will not completely eradicate the increased perinatal and neonatal mortalities and morbidities noted in the diabetic pregnancy.

Pathogenesis of the Effects of Maternal Diabetes on the Fetus

As yet, no single pathogenic mechanism has been clearly defined to explain the diverse problems observed in the IDM. Nevertheless, many of the effects can be attributed to maternal metabolic (ie, glucose) control. Pedersen originally emphasized the relationship between maternal glucose concentration and neonatal hypoglycemia (Table 4). (22) His simplified hypothesis recognized that maternal hyperglycemia resulted in fetal hyperglycemia, which stimulated the fetal pancreas, resulting in islet cell hypertrophy and beta cell hyperplasia with increased insulin availability. Following delivery, the neonate, who no longer was supported by placental glucose transfer, developed neonatal hypoglycemia.

Hyperinsulinemia in utero affects diverse organ systems, including the placenta. Insulin acts as the primary anabolic hormone of fetal growth and development, resulting in visceromegaly, especially of heart and liver, and macrosomia. In the presence of excess substrate, such as glucose, fat synthesis and deposition increases during the third trimester. Fetal macrosomia is reflected by increased body fat, muscle mass, and organomegaly, but not by an increased size of the brain or kidney. (23)(24) After delivery, there is a rapid fall in plasma glucose concentration, with persistently low concentrations of plasma free fatty acids, glycerol, and beta-hydroxybutyrate. In response to an intravenous glucose stimulus, plasma insulin-like activity is increased, as is plasma immunoreactive insulin, determined in the absence of maternal insulin antibodies and plasma C-peptide concentration. (25) The insulin response to intravenous arginine is also exaggerated in the infant of a woman who has gestational diabetes. (26)

In a follow-up study using the chronic hyperinsulinemic fetal rhesus monkey, Susa and associates (27) studied neonatal insulin secretion following delivery. Compared with controls, the experimental group evidenced a blunted insulin and C-peptide response to infusion of 300 mcg/kg glucagon to stimulate insulin secretion. The investigators suggested that fetal hyperinsulinemia inhibited insulin synthesis and secretion in utero and that these alterations persisted after birth.

MacFarlane and Tsakalakos (28) suggested that the initial increase in fetal size due to fetal hyperinsulinemia produced developing hypoxemia. The limitation in fetal oxygen availability altered differential utilization of glucose and increased alpha-glycerophosphate synthesis in the fetal adipocyte, which resulted in fetal adiposity.

Schwartz et al (29) evaluated whether macrosomia in the fetus of the diabetic mother is related to fetal hyperinsulinemia and whether hyperinsulinemia and macrosomia are related to maternal metabolic control. A total of 95 nondiabetic pregnant women were compared with 155 insulin-treated pregnant women who were subdivided according to the White classification, the presence of hypertension, the birthweight, and the mode of delivery. Optimal care was provided, and the neonates were evaluated. Macrosomia (≥97th percentile) was noted in 10% to 27% of the diabetic groups and was correlated with umbilical total insulin, free insulin, and C-peptide concentrations. Glycosylated hemoglobin was only a weak predictor of birthweight and fetal hyperinsulinemia. The investigators concluded that the cause of macrosomia essentially remains unexplained, but hyperinsulinemia is the major stimulus for excessive fetal growth.

In an evaluation of specific material factors, adiposity in 119 term neonates born to women who had gestational diabetes (57 large for gestational age, 62 appropriate for gestational age) was compared with a control group of term neonates (74 large for gestational age, 69 appropriate for gestational age). (30) Multiple regression analyses suggested that pregnancy weight and weight gain were significant predictors of neonatal body mass index for both groups. Second and third trimester glucose concentrations were significant predictors for the body mass index of infants born to women who had

gestational diabetes; a significant glucose screen predicted body mass index in the control group. Increased adiposity in the IDMs was related to increased neonatal blood pressure.

Lipase activities were measured in the placentae of rats made diabetic by streptozotocin treatment and in the placentae of women identified as having type 2 diabetes (ie, impaired glucose tolerance) or type 1 diabetes with or without vascular complications. (31) Normals were evaluated for comparison. At pH 4, lipase activity increased in both the rat and the human placentae compared with controls. In the women, placental lipase activity at pH 4 correlated with birthweight in patients who had impaired glucose tolerance, suggesting that increased activity may contribute to increased fetal weight by adding to fat transfer across the placenta.

An interesting variation on the theme of the effects of maternal diabetes on the fetus was addressed by Homko et al, (32) who evaluated the relationship between ethnicity and gestational diabetes relative to macrosomia in an urban academic diabetes program. Between 1991 and 1994, gestational diabetes mellitus was diagnosed in 103 African-American women and 36 Latino women. All factors being equal, macrosomia developed in 50% of the neonates of the Latino women versus 19% of the neonates of the African-American women. The investigators suggested that, at least in this series, there may be an ethnic variation in fetal growth.

Finally, the cause of macrosomia in the IDM was further evaluated by the National Institute of Child Health and Human Development-Diabetes in Early Pregnancy Study, which recruited insulin-dependent diabetic and control women before conception and provided an opportunity to evaluate the relationship between maternal glycemia and percentile birthweight. (33) Data were analyzed from 323 diabetic and 361 control women. Fasting and nonfasting venous plasma glucose concentrations were measured on alternate weeks in the first trimester and monthly thereafter. Glycosylated hemoglobin was measured weekly in the first trimester and monthly thereafter. More infants of the diabetic women were at or above the 90th percentile for birthweight than infants of control women (28.5% versus 13.1%, $P<0.001$). The third-trimester nonfasting glucose concentration, adjusted for data in prior trimesters, was the stronger predictor of percentile birthweight ($P=0.001$). After adjusting for maternal hypertension, smoking, and ponderal index, the investigators concluded that monitoring of the nonfasting glucose concentration rather than the fasting concentration, which is more commonly monitored in clinical practice, is necessary to prevent macrosomia.

Metabolic Analyses

In vivo kinetic analysis has been used by numerous investigators to evaluate the IDM metabolically. An early study employing stable nonradioactive isotopes used [1-^{13}C]glucose and the prime constant infusion technique. (34) The investigators measured systemic glucose production rates in five infants of normal (nondiabetic) mothers and five infants of insulin-dependent diabetics at 2 hours of age. As expected, the IDMs had a lower glucose concentration during the study. For the first time, the investigators reported that the IDM had a lower systemic glucose production rate. They suggested that decreased glucose output was related to inhibited glycogenolysis and speculated that increased insulin and decreased glucagon concentrations and catecholamine responses resulted in decreased systemic output. For the time studied (late 1970s), the women who had diabetes were considered to be in excellent control. They had been hospitalized during the last 4 weeks of the pregnancy to achieve strict metabolic control, with maternal blood glucose levels maintained at 50 to 150 mg/dL (2.8 to 8.3 mmol/L). Yet, the systemic glucose production rates of these neonates were lower than that of the control neonates.

A further evaluation of the IDM was reported by the same group 5 years later. (35) Again focusing on the neonate of the mother in "strict control," the investigators evaluated systemic glucose production in five infants of insulin-dependent mothers, one neonate of a woman who had gestational diabetes, and five neonates born to women who did not have diabetes. The blood glucose data were in a more restrictive range of 36 to 104 mg/dL (2.0 to 5.8 mmol/L), and the glucose levels were controlled in the hospital setting for 3 to 4 weeks prior to delivery. In this series, the systemic glucose production rate was similar in all infants. However, these investigators, like other groups (36), carried their analysis a significant step further. They infused exogenous glucose, which can diminish endogenous glucose production, because of the precise control known to be the hallmark of the adult. The IDM did not evidence as great a suppression of endogenous glucose production as the adult. The investigators concluded that altered regulation of glucose production may be due to intermittent maternal hyperglycemia, even in the woman whose glucose levels are strictly controlled.

These studies paralleled the work of Cowett et al (37), who have studied glucose kinetics in the neonate. Using

78% enriched D[U-^{13}C] glucose, 16 infants of diabetic women (10 of whom were insulin-dependent and 6 of whom were chemical-dependent) were compared with five infants of nondiabetic women. Four infants of insulin-dependent mothers and five infants of chemical diabetic mothers received 0.45% saline as the stable isotopic tracer diluent to determine basal endogenous glucose production. All of the mothers were evaluated relative to control mothers by use of hemoglobin A_{1C} and maternal plasma glucose or cord vein glucose at delivery. None of the women were maintained in the hospital prior to study. There was a similarity between the basal glucose production rate in the neonates who received no exogenously infused glucose. The investigators concluded that good metabolic control of the maternal diabetic state would help maintain euglycemia. However, in a subsequent analysis in which neonates of nondiabetic mothers received glucose exogenously to maintain euglycemia, heterogeneity continued to exist in the ability of the neonate to depress endogenous glucose production. (38) These latter data parallel other work from the same group that reflect the transitional nature of glucose metabolism in the term and preterm infant, born to both diabetic and nondiabetic mothers. (36)(39)

Baarsma et al (40) followed 15 mother-infant pairs from the beginning of pregnancy until birth, measuring glucose kinetics on the first day after birth with stable isotopic dilution as well as plasma free fatty acids and ketones. The neonates received 3.4 ± 0.7 mg/kg^{-1} per minute^{-1} glucose during the study. No relationship existed between maternal control and glucose kinetics in the neonate. Total production was 5.2 ± 1.1 mg/kg^{-1} per minute^{-1}, and endogenous glucose production was 1.8 ± 1.1 mg/kg^{-1} per minute^{-1} following subtraction of the glucose infusion. Endogenous glucose production was significantly lower in the neonates studied at the end of the first day after birth. The lower production rate was associated with an increased concentration of ketone bodies, which suggested increased production. The investigators concluded that glucose kinetics in the infants of women whose diabetes is tightly controlled are probably normal.

The realization that neonatal glucose homeostasis is in a transitional state and is not the only factor affecting neonatal birthweight is further supported by studies in which maternal control was evaluated in a group of women who had gestational diabetes relative to the birthweight of the neonate. (41) If the Pedersen hypothesis were correct, neonatal birthweight should correlate with the degree of diabetic control of the mother during the pregnancy. There was a lack of correlation between birthweight and mean maternal plasma glucose concentration during the third trimester of pregnancy in this group of women who had gestational diabetes (Fig. 1). This lack of correlation further supports the heterogeneity of the diabetic state and suggests that both control of glucose homeostasis and control of fetal growth are multifactorial. Similar conclusions led Freinkel (42) and others to decide that mixed nutrients (ie, amino acids, free fatty acids) other than glucose are important in fetal-neonatal metabolic control (Fig. 2). This concept is important for ongoing research.

Support for this concept has been provided by Kalkhoff and associates (43), who studied the relationship between neonatal birthweight and maternal plasma amino acid profiles in lean and obese nondiabetic woman and in women who had type 1 diabetes. HbA_{1c}, plasma glucose concentration, and total amino acid profiles were elevated in the diabetic patients compared with controls, but there were no differences between obese and lean control groups. Plasma glucose concentrations and profiles of HbA_{1c} did not correlate with relative weight of the neonate; average total plasma amino acid concentrations did. The investigators concluded that maternal plasma amino acid profiles may influence fetal weight generally and affect the development of neonatal macrosomia.

Some further investigation of protein metabolism in pregnancy was performed by Whittaker and associates. (44) They evaluated protein kinetics in six nondiabetic and five insulin-dependent diabetic women during and after pregnancy using stable isotopes and the hyperinsulinemic-euglycemic clamp and amino acid infusions. Evaluation of protein breakdown, as measured by leucine kinetics, was not higher than normal, and neither pregnancy nor type 1 diabetes altered insulin sensitivity to amino acid turnover. The data were interpreted to suggest that alterations may enable conservation of amino acids for protein synthesis and accretion in late pregnancy.

Other investigators evaluated the relationship between neonatal birthweight and plasma triglyceride concentrations. (45) They drew plasma samples for a number of metabolic parameters 1 hour after administration of a 50-g glucose load in 521 randomly selected negatively screened individuals, 264 positively screened individuals who had negative findings on glucose tolerance tests, and 96 positively screened individuals who had positive glucose tolerance test results at 24 to 28 weeks of gestation. Plasma triglyceride concentration was the only test elevated in the women who had gestational diabetes, but not in the negative glucose tolerance test group.

Only plasma triglyceride concentration was significantly related to birthweight ratio, with birthweight corrected for gestational age and to glucose intolerance besides glucose itself. The investigators concluded that plasma triglyceride may be a physiologic contributor to neonatal birthweight (Fig. 3).

This concept was further analyzed by Kitajima et al (46), who evaluated plasma triglyceride concentrations between 24 and 32 weeks' gestation in women who had positive diabetic screening results but negative glucose tolerance test results. Plasma triglyceride concentrations of more than 259 mg/dL (2.9 mmol/L) represented the significant factor related to the development of macrosomia rather than maternal obesity or maternal plasma glucose concentrations at these weeks of gestation. Clearly, metabolites rather than glucose contribute to the propensity of fetal/neonatal macrosomia and need to be evaluated prospectively.

Congenital Anomalies

Although most of the morbidity and mortality data for the IDM improve with time, congenital anomalies remain a significant unresolved problem. In a population-based study of 7,958 infants over 12 years, Becerra et al (47) documented differences in congenital malformation between the IDM and the nonIDM. The relative rate of major malformations in the neonate born to the mother who had insulin-dependent diabetes mellitus was 7.9 compared with the neonate of the nondiabetic mother. Similarly, the relative risks for central nervous system and cardiovascular system defects were 15.5 and 18.0, respectively. Interestingly, the neonate of the mother who had gestational diabetes and required insulin therapy was 20.6 times as likely to have a cardiovascular malformation as the neonate of the nondiabetic mother. This finding is from a time when centers were reporting no difference in perinatal mortalities among offspring of women who had insulin-dependent diabetes and women who did not have diabetes after correction for death due to congenital anomalies. (48)

These data were refined in a recent series reviewing the relationship between specific birthweight and the presence of major congenital malformations. (49) A total of 8,226 neonates in the Texas Birth Defects Monitoring files were compared with a control group of almost 1,000,000 neonates who did not have defects. Infants who had 45 specific defects were more likely to have birthweights greater than 4,500 g. In contrast, investigators in another series reported that the odds ratio of delivering a neonate who had congenital heart disease was higher in nondiabetic women if their prepregnancy weights indicated obesity. (50) Both of these data sets deserve further evaluation and confirmation.

The pathogenesis of the increase in congenital anomalies among IDMs has remained obscure, although several causes have been proposed, including hyperglycemia (either preconceptional or postconceptional), hypoglycemia, fetal hyperinsulinemia, uteroplacental vascular disease, and genetic predisposition. A review has cogently summarized the relevant data obtained from investigations during the 1980s. (51) There are data to support each of these proposed mechanisms, but current evidence seems strongest for postconceptional hyperglycemia.

If a preconceptional influence of hyperglycemia or hypoglycemia or a genetic predisposition for congenital anomalies were operative, the offspring of the diabetic father as well as of the diabetic mother would be expected to have an increased incidence of anomalies. This assumes that the sperm and egg are equally affected by the physiologic and biochemical permutations of maternal diabetes. In a careful hospital chart review by Neave (52) of 1,262 offspring of diabetic fathers, only a slight increase in anomalies of questionable significance was found compared with matched controls. In this same study, a marked increase in anomalies was found among the offspring of the diabetic mother compared with both the offspring of the diabetic father and an independent control group.

One of the first studies of normalization of blood glucose concentration before conception in the diabetic woman was reported from a large European diabetic population in Karlsburg, Germany, that included nonpregnant women. (53) These women were cared for in an ongoing diabetic outpatient program to normalize blood glucose concentration. The infants of the mothers in the study group had a markedly lower incidence of congenital anomalies compared with infants of a simultaneously studied group of women who received no prenatal therapeutic diabetic regimen.

These conclusions were confirmed in a group of 75 insulin-dependent diabetic women of whom 44 were followed preconceptually. (54) Glycemic control was obtained by intensified insulin therapy. There were no congenital malformations in the intensively followed group compared with a frequency of 9.6% in the control group, whose diabetes was not managed preconceptually.

In a series of women who had gestational diabetes, 136 underwent preconceptual counseling at least 2 months before the onset of pregnancy. (55) Evaluation included oral glucose tolerance testing, mean blood glu-

cose measurement, assessment of glycosylated hemoglobin, and management by self-monitoring as well as nutritional counseling. These women were compared with a group of 154 women who did not undergo this program. Those who participated in the preconceptual counseling delivered their neonates without congenital malformations.

In recent years, a number of studies have reported the strong association of preconceptional testing and glycemic control with a marked diminution in the incidence of congenital anomalies. These data parallel other reports suggesting that control after the first trimester did not result in a decreased incidence of congenital malformations, although other morbidity did decrease. In fact, the neonatal malformation rate rose and was not influenced by maternal age or diabetic class. (56)

Hypoglycemia may play a teratogenic role in the diabetic pregnancy. Symptomatic hypoglycemia during the first trimester is a frequently observed morbidity in the insulin-dependent diabetic, although quantification has been difficult. The injection of insulin into the chick embryo has induced "rumplessness," (57) but data indicate that the primate placenta probably acts as a complete barrier to maternal insulin from midgestation onward. (58) The failure of insulin to cross the placenta in the rat during the critical period of organogenesis was noted by Widness and associates (59) using iodinated insulin.

One rare congenital defect that is increased in frequency in the IDM is the small left colon syndrome. (60) The cause of this deformity is obscure. With conservative medical management, the condition usually resolves spontaneously within the neonatal period.

The association of maternal diabetes and cardiovascular malformations was reported from the Baltimore Washington Infant study, a population-based case-control study of cardiovascular malformations. (61) The strongest associations with overt type 1 diabetes were for double-outlet right ventricle and truncus arteriosus. No associations were noted with gestational diabetes.

Weber and colleagues (62) suggested that hypertrophic cardiomyopathy and abnormal ventricular diastolic filling in the IDM is related to poor maternal glycemic control. These investigators evaluated the fetuses of well-controlled mothers and of nondiabetic women. Cardiac growth and ventricular diastolic filling were evaluated 20 to 26, 27 to 33, 34 to 40, and 48 to 72 hours after birth. No differences were noted between groups during any period, although progression of diastolic filling is abnormally delayed in the fetus of the diabetic woman and is presumably more likely in the poorly controlled diabetic.

Finally, a number of publications have raised the possibility that vitamin E may provide a protective effect against diabetic embryopathy through its well-known antioxidant effect. (63)(64)(65) Further research is required to determine the clinical applicability of these data.

Macrosomia, Birth Injury, and Asphyxia

At birth, the infant of the poorly controlled diabetic often appears macrosomic in contrast to the infant born to either the well-controlled diabetic or the nondiabetic, nonobese mother. One consequence of undetected fetal macrosomia may be a difficult vaginal delivery due to shoulder dystocia, with resultant birth injury or asphyxia. These potential birth injuries include cephalhematoma, subdural hemorrhage, facial palsy, ocular hemorrhage, brachial plexus injuries, and clavicular fracture. Injury to the brachial plexus may have a variety of presentations because the nerves of the brachial plexus may be variably damaged. In addition to the obvious injury to the nerves of the arm, diaphragmatic paralysis occurs when the phrenic nerve is injured. Because of associated organomegaly in the IDM, hemorrhage in the abdominal organs is possible, specifically the liver and the adrenal gland. Hemorrhage into the external genitalia of the large neonate has been reported.

In a study of the incidence and predisposing factors for clavicular fracture in the neonate, 46 of 3,030 neonates were diagnosed as having clavicular fracture. (66) When compared with a control group of 52 neonates who did not have a fracture, the affected neonates had higher birthweights, older mothers, longer second stage of labor, and higher rates of instrumented delivery and shoulder dystocia. Eighty percent of the neonates weighed less than 4,000 g. Multivariate analysis revealed two significant predisposing variables: birthweight more than 3,500 g and maternal age older than 29 years.

Because IDMs are at high risk, intrapartum monitoring is essential to minimize potential complications. Clearly, early identification of macrosomia is critical. Mintz et al (67) suggested that shoulder soft tissue measurements and abdominal circumstance may be the best individual predictors of the potential for macrosomia. The combination of the abdominal circumference greater than the 90th percentile and the shoulder soft tissue width greater than 12 mm was the best predictor, with a sensitivity of 96%, specificity of 89%, and accuracy of 93%.

Although the specific cause of asphyxia is unclear, it may be due to difficulty in the intrapartum period because of relative macrosomia. Asphyxia may have diverse

consequences for the neonate. Acutely, it may affect respiratory, renal, and central nervous system function. Decreased fluid intake usually is recommended until the degree of injury to the renal and central nervous systems can be ascertained. An important complication of asphyxia in the neonate may be later respiratory difficulty. For infants of women who have insulin-dependent diabetes, investigators have suggested that poor glycemic control in the third trimester, diabetic vascular disease, preeclampia, and smoking are significant risk factors for perinatal asphyxia. (68) In this prospective study of 162 infants born to 149 diabetic mothers of White class B-R-T, 44 neonates (27.2%) had evidence of asphyxia. Its presence did not correlate with third trimester control or the other factors listed, but it did correlate with nephropathy occurring in pregnancy, maternal hyperglycemia before delivery, and prematurity. The investigators concluded that in the pregnant diabetic woman, maternal and subsequently fetal hyperglycemia before delivery leads to fetal hypoxemia.

A rare occurrence of gangrene in an upper extremity of an IDM with massive muscle necrosis of the forearm requiring debridement was noted in one report. (69) It was postulated that gangrene developed from a propensity for thrombosis in the IDM. Another case was reported of an IDM who was diagnosed in utero as having a brachial artery thrombosis. (70) Of 32 neonates reported in the literature, seven who had peripartum limb gangrene were IDMs. The investigators speculated that the IDM may be at increased risk for thrombosis if an umbilical artery catheter was placed.

Identification of maternal diabetes and maintenance of good metabolic control in the pregnant diabetic should diminish the frequency and magnitude of macrosomia and its attendant complications. Careful obstetric management should prevent birth injury and asphyxia. Ogata et al (71) reported data that seem to confirm this concept. Serial studies to estimate fetal biparietal diameter and abdominal circumference were used as differential inducers of intrauterine growth in fetuses of mothers who were White class A through C compared with fetuses of nondiabetic mothers. Biparietal diameter was similar in fetuses of both groups, but abdominal circumference was normal or enhanced in the fetuses of diabetic mothers. The group that had enhanced abdominal circumference had an increased insulin concentration, weighed more at birth, and had more subcutaneous fat. The investigators concluded that ultrasonography was useful in the preliminary detection of macrosomia.

A recent study evaluated whether macrosomia is associated with increased perinatal morbidity and mortality by assessing whether the birth of a previous macrosomic neonate heralded the risk for a subsequent macrosomic neonate. (72) A population-based cohort study using birth data from Washington state between 1984 and 1990 identified a 7.0 times risk in this clinical situation. The overall prevalence of macrosomia was 22% and was interpreted to suggest that a mother who has one macrosomic neonate is at markedly increased risk to deliver a second in a subsequent pregnancy.

Respiratory Distress Syndrome

Respiratory distress, including respiratory distress syndrome (RDS), may be a relatively frequent and potentially severe complication in the IDM. Although the increased susceptibility to RDS has been suspected in the IDM, a definitive retrospective analysis evaluated the relative risk in a large series of diabetic pregnancies from the Joslin Clinic and the Boston Hospital for Women a number of years ago. (73) The relative risk of RDS in the IDM was higher compared with infants of nondiabetic mothers. If specific confounding variables were excluded, including gestational age, delivery by cesarean section, presence of labor, birthweight, gender, Apgar score at 5 minutes, hemorrhage, presence of hydramnios, maternal anemia, and maternal age, the relative risk was 5.6 times higher in the IDM. This effect was primarily confined to the neonate whose gestational age was 38 weeks or less. Present obstetric management has markedly reduced the frequency of RDS.

Warburton et al (74) provided a biochemical correlation of the association between RDS and diabetes in a fetal lamb model. Infusion of 14 mg/kg^{-1} per $minute^{-1}$ glucose before 113 days' gestation resulted in 1.5-fold higher pulmonary desaturated phosphatidyl choline compared with controls. After this point in gestation, it increased in the controls but not in the glucose-infused fetuses. Lung stability to air inflation was 2.0-fold greater in the control. The investigators concluded that desaturated phosphatidyl choline and lung stability were comparable following chronic glucose infusion in fetal lamb lung, with a predisposition of the fetus to develop RDS.

Surfactant production increases near term from activation of the pathway for dipalmitoyl lecithin, which may be mediated through increases in fetal plasma cortisol concentration. Although plasma cortisol production rates are normal in the IDM, insulin can interfere with incorporation of choline into lecithin, even when cortisol is present. (75) Neufeld and associates (76) has reported that incorporation of labeled glucose and fatty acid residues into saturated phosphatidyl choline was reduced in fetal rabbit lung slices in the presence of insulin. Endog-

enous insulin, known to be increased in the fetus of the poorly controlled pregnant diabetic woman, may play a significant role in delaying pulmonary maturation. The specific biochemical mechanisms are not completely understood, but these data correlate with the clinical situation in which pulmonary maturation is not only delayed in the IDM, but RDS may be noted with lecithin/sphingomyelin ratios of at least 2.0.

A extension of these concepts was reported by Curet et al, (77) who analyzed samples of amniotic fluid for phospholipid content and correlated them with the incidence of RDS. The incidence of RDS was 4.5% in IDMs and 5.3% in infants of nondiabetic mothers. If phosphatidyl glycerol was present, no neonate developed RDS, but RDS occurred in 16.7% and 14.4% of infants of diabetic and nondiabetic women, respectively, if phosphatidyl glycerol was absent. After 37 weeks' gestation, RDS did not occur in IDMs and only in 0.6% in infants of nondiabetic mothers. The investigators suggested that dating of the pregnancy decreases the need for phospholipid analysis.

Hypoglycemia

A decline in plasma glucose concentration following delivery is characteristic of the IDM, especially among neonates who are either large- or small-for-gestational age or whose mothers had poor glycemic control during their pregnancies. Other factors, besides hyperinsulinemia, that may contribute to the development of hypoglycemia include defective counterregulation by catecholamines or glucagon.

The neonate exhibits transitional control of glucose metabolism, which suggests that a multiplicity of factors affect homeostasis. Many of the factors are similar to those that influence homeostasis in the adult. What differs in the neonate are the various stages of maturation. Prior work in conjunction with glucose infusion studies suggest that there is blunted splanchnic (hepatic) responsiveness to insulin both in the IDM and in the preterm and term neonate of the nondiabetic mother compared with the adult. (38) What have not been studied, but are of particular interest, are the many contrainsulin hormones that influence metabolism. If insulin is the primary glucoregulatory hormone, contrainsulin hormones assist in balancing the effect of insulin and other factors.

The contrainsulin hormones that have been of particular interest in the IDM are those of the sympathoadrenal neural axis. Results of evaluations of epinephrine and norepinephrine concentrations in the IDM are variable. A very early study involved 11 infants of diabetic mothers, only two of whom had gestational diabetes. (78) Urinary excretion of catecholamines was measured and compared with excretion from 10 infants of nondiabetic mothers. Urinary norepinephrine and epinephrine concentrations did not increase in the infants of diabetic women who had severe hypoglycemia, but they did increase in the neonates whose mothers had mild hypoglycemia. Other investigators have corroborated this report. (79)(80)(81)

Other factors related to sympathoadrenal activity in the neonate may be of importance. In a continuing evaluation of the transitional nature of neonatal glucose metabolism, both of insulin and contrainsulin factors, epinephrine was infused in two doses (50 mg or 500 mg/kg^{-1} per $minute^{-1}$ in a newborn lamb model), and glucose kinetics (turnover) were measured with [6-^{3}H]glucose. (82)(83) The newborn lamb showed a blunted response to the lower dose of epinephrine. The investigators speculated that the newborn lamb evidenced blunted responsiveness to this important contrainsulin stimulus. This tendency was reaffirmed by recent data from the same laboratory. (84) If this occurs in the diabetic state, this would partially account for the clinical presence of hypoglycemia.

Thus, the IDM is a prime example of the potential of glucose disequilibrium in the neonate. Because of the transitional nature of glucose homeostasis in the neonatal period, accentuation of the disequilibrium may be enhanced in the IDM due to metabolic alterations in the diabetic mother. Substantial work is necessary to appreciate fully the operative physiology.

The IDM is generally asymptomatic, with a relatively low plasma glucose concentration. This may be due to the initial brain stores of glycogen, although the exact biochemistry is undefined. Signs and symptoms that may be observed in the asymptomatic neonate are nonspecific and include tachypnea, apnea, tremulousness, sweating, irritability, and seizures. The asymptomatic neonate generally does not require parenteral treatment to maintain carbohydrate homeostasis.

Glucagon has been administered within 15 minutes after delivery to prevent hypoglycemia, but because the majority of neonates are asymptomatic, this is probably not warranted in most patients. Furthermore, glucagon may stimulate insulin release, which may exaggerate the tendency to hypoglycemia.

Prompt recognition and treatment of symptomatic neonates has minimized sequelae. To date, there is no consensus about the potential for long-term sequelae due to hypoglycemia in the neonate. (85)

Hypocalcemia and Hypomagnesemia

Hypocalcemia ranks as one of the important metabolic derangements observed in the IDM. (86) Serum calcium concentration is elevated following an increase in parathyroid hormone (PTH) concentration by three mechanisms: mobilization of bone calcium, reabsorption of calcium in the kidney, and increased absorption of calcium in the intestine through the action of vitamin D. In contrast, serum calcium concentration is decreased following an increase in calcitonin, which antagonizes the action of PTH. Serum calcium concentration may be increased by vitamin D (1,25 dihydroxy vitamin D), which improves both absorption of calcium in the intestine after feeding and reabsorption from bone.

During pregnancy, calcium is transferred from mother to fetus, concomitant with an increasing hyperparathyroid state in the mother. Calcium concentration is higher in the fetus than in the mother. This hyperparathyroid state functions as homeostatic compensation to restore the maternal calcium that is diverted to the fetus. Neither calcitonin nor parathyroid hormone crosses the placenta.

At birth, because of the concentration of calcitonin and 1,25 dihydroxy vitamin D, serum calcium concentration declines following interruption of maternal-fetal calcium transfer. Increases in PTH and 1,25 dihydroxy vitamin D as early as 24 hours after birth ensure correction of the low serum calcium concentration.

Tsang and associates (87)(88)(89) have shown that the neonate is prone to hypocalcemia, particularly the preterm neonate, the one who is asphyxiated, and the IDM. Noguchi et al (90) evaluated parathyroid function in the hypocalcemic versus the normocalcemic IDM. In the hypocalcemic IDM, serum PTH concentration did not increase in response to low serum calcium concentration, but PTH concentration did increase in the normocalcemic IDM in response to a slight decline in serum calcium concentration. These data in the IDM are interpreted to suggest that maternal diabetes may be an independent factor related to suppressed neonatal parathyroid function.

Martinez et al (91) measured osteocalcin and PTH serum concentrations in 41 insulin-dependent diabetic pregnant women throughout pregnancy, in the umbilical cord, and in infants during the first days after birth. The data suggested that diabetes decreases bone turnover during pregnancy in the mother and during the perinatal period in the offspring.

More recently, Namgung and Tsang (92) reported that several factors have a significant impact on newborn bone mineral content. The IDM whose mother had poor glycemic control in the first trimester evidenced decreased bone mineral content at birth. They suggested that the poor bone mineral content was related to decreased transplacental mineral transfer.

Hypomagnesemia (<1.5 mg/dL [0.6 mmol/L]) has been found in as many as 33% of IDMs. As with hypocalcemia, the frequency and severity of clinical symptoms are correlated with the maternal status. Noguchi et al (90) have correlated neonatal magnesium concentration with that of the mother as well as with the maternal insulin requirement and concentration of intravenous glucose administered to the neonate. They speculated that hypocalcemia in the IDM may be due to decreased hypoparathyroid function resulting from the hypomagnesemia. In a subsequent evaluation, these investigators correlated decreased maternal serum magnesium concentration with adverse fetal outcome in the insulin-dependent diabetic woman. They speculated that decreased magnesium concentration may contribute to the high spontaneous abortion and malformation rate seen in such women. (93)

Hyperbilirubinemia and Polycythemia

Hyperbilirubinemia is observed more frequently in the IDM than in the normal neonate. Although a number of hypotheses have been suggested, the pathogenesis remains uncertain. Red blood cell lifespan, osmotic fragility, and deformability have not been found to be appreciably different in the IDM, and an increased umbilical cord bilirubin concentration or an increased postnatal rate of hemoglobin decline has not been demonstrated. Results of one evaluation suggested that only the macrosomic IDM was at risk for hyperbilirubinemia and that increased hemoglobin turnover was a significant factor in its pathogenesis. (94) However, Stevenson et al (95)(96) initially suggested that delayed clearance of the bilirubin load was a factor, as measured by pulmonary excretion of carbon monoxide, which served as an index of bilirubin production.

The polycythemia frequently observed in the IDM may be the most important factor associated with hyperbilirubinemia. Indirect evidence for fetal hypoxia in the IDM may explain the neonatal preponderence for polycythemia and hyperbilirubinemia. Umbilical cord erythropoietin concentration, measured at birth using a highly sensitive and specific radioimmunoassay, which is stimulated by hypoxia, was found to be above the narrow range for the control neonate in one third of a group of 61 IDMs. (97) There was an association with relative hyperinsulinemia at birth. The fetal monkey that is hyperinsulinemic in the last third of gestation in the absence of

maternal diabetes has been shown to have markedly elevated plasma erythropoietin concentrations as well as other evidence of increased fetal erythropoiesis, such as an elevated reticulocyte count. (98) In addition, chronically catheterized fetal sheep that have been made hyperglycemic have been found to have increased oxygen consumption and decreased distal aortic arterial oxygen content. (99) Similar speculation was suggested by Mimouni et al (100) following their finding of a 29.4% incidence of polycythemia in the IDM versus 5.9% in the control neonate.

Another consideration is potential ineffective erythropoiesis in the IDM, which is suggested by findings from a study of gestational age-matched controls and IDMs in whom increased carbon monoxide excretion, derived from heme metabolism, was observed. (95)(96) Hemoglobin concentration was not significantly higher in the IDM. Hemolysis was not present, as confirmed by the absence of Coombs-positive blood group incompatibility. Increased ineffective erythropoiesis, defined as erythroid precursors harbored in body organs such as the liver and spleen and not released into the peripheral circulation, was postulated as a cause for the observed increased bilirubin concentration in the IDM. In related data, Perrine and associates (101) reported delay in the fetal globin switch in the IDM. The mechanism of this delay is unknown.

In a study of 32 mother-infant pairs, Green and colleagues (102) showed a correlation between maternal total glycosylated hemoglobin at delivery and neonatal hematocrit. They concluded that improved maternal glycemic control during late gestation may decrease the incidence of neonatal polycythemia.

In a study of the mechanisms involving neonatal polycythemia in the IDM, a complete blood count, serum iron, transferrin, and ferritin concentrations were evaluated in samples from the umbilical cords of neonates born to 9 mothers who had gestational diabetes, 21 mothers who had type 2 diabetes, and 8 mothers who had type 1 diabetes. (103) There were no differences in serum iron concentration, but transferrin concentration was higher and ferritin concentration was significantly lower in the IDMs compared with the control population. The investigators concluded that iron storage is reduced in the fetus of the diabetic mother.

Renal Vein Thrombosis

Renal vein thrombosis is a severe, life-threatening, but rare occurrence in the perinatal period. (104) Its occurs more frequently in association with maternal diabetes mellitus. Although Pedersen failed to mention this condition in his monograph, (22) in one postmortem survey of 16 cases of neonatal renal vein thrombosis, five were found in IDMs. (105) Seven other affected neonates were born to mothers without known diabetes, but the infants had fetal macrosomia and pancreatic beta-cell hypertrophy and hyperplasia. Another center reported a case of an IDM who had nearly a totally occlusive thrombosis in the umbilical vein. (106)

The pathogenesis of this lesion remains obscure, although most of the speculation has centered around the possible role of polycythemia. Sludging of red blood cells, combined with a further reduction in cardiac output as a result of diabetic cardiomyopathy, may be a contributing factor. Stuart and colleagues (107) have suggested that because platelet endoperoxides are increased in the IDM, the normal balance between proaggregatory platelets and antiaggregatory vascular prostaglandins is disrupted, favoring the development of thrombosis. In a subsequent evaluation, this group evaluated abnormalities in vascular arachidonic acid metabolism in the IDM, noting that decreased prostacyclin formation has been suggested as a cause of an atherothrombotic tendency in the adult. (108) The level of 6-ketoprostaglandin F_1 was normal in umbilical cord samples from IDMs if the mothers were in good glycemic control. Inhibition of 6-keto F_1 alpha was noted if the mother's glycosylated hemoglobin was elevated, indicating poor diabetic control. The investigators suggested that the correlation observed between plasma 6-keto F_1 alpha prostaglandin formation and endogenous vascular prostaglandin formation in the IDM indicated an in vitro deficiency of prostacyclin formation that reflected a concomitant in vivo abnormality. Why this lesion shows selectivity for the kidney is not known. Birth trauma is an unlikely initiating factor because this lesion has been observed in both the stillborn infant and the IDM delivered by cesarean section. Another case has been reported in a stillborn IDM whose mother received oxytocin induction. (109)

Long-Term Prognosis and Follow-up

Of equal concern to problems primarily encountered during the neonatal period and perhaps of greater ultimate importance to the IDM are the long-term effects on growth and development, psychosocial intellectual capabilities, and the risk of subsequently developing diabetes. One of the most important factors influencing long-term prognosis is the improvement in management of the pregnant diabetic patient and her neonate. Assuming that many of the deleterious effects of the diabetic pregnancy are being modified by normalization of metabolic

status in both the pregnant woman and her conceptus, the poor prognoses that have been reported in previous retrospective studies should be ameliorated in future prospective evaluations.

Gerlini et al (110) evaluated infant body weight, length, and head circumference from birth through 48 months of age. In the IDM, no specific differences were related to the White classification. Children of mothers exhibiting poor glycemic control during pregnancy showed higher values for weight and the weight-to-height ratio in infancy compared with neonates of well-controlled diabetic mothers. Female offspring contributed most to the observed differences.

Silverman et al (111) tested the hypothesis that long-term postnatal development may be modified by the in utero metabolic experience. They enrolled the offspring of women who had type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes in a prospective study from 1977 through 1983. Fetal beta-cell function was assessed by measuring amniotic fluid insulin at 32 to 38 weeks' gestation. Postnatally, plasma glucose and insulin concentrations were measured yearly from 1.5 years of age after fasting and 2 hours after a 1.75 g/kg oral glucose tolerance test. Control subjects had a single oral glucose challenge at 10 to 16 years of age. In the offspring of diabetic mothers, the prevalence of impaired glucose tolerance was 1.2% at less than 5 years of age, 5.4% at 5 to 9 years, and 19.3% at 10 to 16 years. The 88 offspring of diabetic mothers (12.3±1.7 y), when compared with 80 control subjects of the same age and pubertal stage, had higher 2-hour glucose and insulin concentrations. Impaired glucose tolerance was not associated with the cause of the mother's diabetes or macrosomia at birth. Impaired glucose tolerance was recorded in only 3.7% of adolescents whose amniotic fluid insulin was normal and 33.3% of those who had elevated concentrations. The investigators concluded that impaired glucose tolerance in the offspring is a long-term complication of maternal diabetes. Excessive insulin secretion in utero, as assessed by amniotic fluid insulin concentration, is a strong predictor of impaired glucose tolerance in childhood. These investigators subsequently restated the significance of these data. (112)

The outcome of children at 1, 3, and 5 years of age was evaluated by Stehbens and associates. (113) Psychological evaluations suggested that at 3 and 5 years of age, the IDM was more vulnerable to intellectual impairment, especially if the neonate was born small-for-gestational age or if the pregnancy was complicated by acetonuria. This concept was reinforced by the work of Petersen et al, (114) who studied early growth delay in diabetic pregnancies related to psychomotor development at age 4 years. Their studies of 99 consecutive insulin-dependent and 101 nondiabetic pregnant women led them to conclude that children who have a history of growth delay in early diabetic pregnancy should be screened at 4 to 5 years of age by the Denver Developmental Screening Test for possible developmental impairment.

The presence of hypoglycemia per se has not been related to later neuropsychological defects. Persson and colleagues (115) found no evidence that asymptomatic hypoglycemia leads to intellectual impairment by 5 years of age. No obvious relationship was found between maternal acetonuria during pregnancy, infant birthweight, blood glucose levels during the first hours after birth, or neonatal complications and the intellectual quotient (IQ) of the children. There was a correlation between maternal and child IQ. Hadden et al (116) studied 123 children of mothers who had type 1 diabetes and 124 children of nondiabetic mothers. No differences were found following pediatric assessment or by a psychologically based maternal and teacher questionnaire of the emotional states or academic achievements of the children.

Questioning the extent to which maternal metabolism during pregnancy affects cognitive and behavioral function of the offspring by altering brain development, Rizzo et al (117) correlated measures of metabolism in pregnant diabetic and nondiabetic woman with intellectual development of their offspring. Of 223 pregnant women, 89 had pregestational diabetes mellitus, 99 had gestational diabetes, and 35 had normal carbohydrate metabolism. Carbohydrate and lipid metabolism were evaluated with respect to two measures of infant development: the Bayley Scale administered at age 2 years and the Stanford-Binet administered at ages 3, 4, and 5 years. Bayley scale results at 2 years of age correlated inversely with the mother's third trimester plasma beta hydroxyl butyrate concentration, and the Stanford-Binet results correlated inversely with third trimester plasma beta hydroxybutyrale and free fatty acid concentrations. The investigators concluded that ketoacidosis and accelerated starvation should be avoided in pregnancy because of potential long-term adverse consequences.

More recently, Ornoy et al (118) studied the neurobehavorial effects that maternal pregestational and gestational diabetes might have on offspring studied at school age compared with children of control mothers. Pregestational and gestational diabetes were reported to affect attention span and motor functions adversely, but not cognitive ability. The effects were negatively correlated with the degree of maternal glycemic control and

were more pronounced when observed in the younger child.

After documenting the decline in perinatal mortality from 23% prior to 1961 to 14% from 1961 to 1975 and subsequently to about 4%, Warram and associates (119) evaluated the number of neonates who subsequently developed diabetes in a cohort of 1,391. Type 1 diabetes had developed in 21 of the children, a risk of 2.1±0.5%, by 20 years of age. The risk of diabetes in offspring of the diabetic mother was increased in the young mother and was independent of the risk factors for perinatal mortality. This is one third of the risk previously reported for offspring of fathers who have type 1 diabetes. The investigators speculated that exposure in utero to an affected mother may protect the fetus from developing type 1 diabetes later in life.

It is apparent that both immediate and potentially long-term effects are seen in the offspring of women who have type 1 or gestational diabetes. Further research clearly is required to refine the operative pathophysiology, thereby allowing the development and study of enhanced treatment modalities. Clearly, the goal is to afford the pregnant women who has diabetes either before or during her pregnancy the opportunity to deliver as normal and unaffected a neonate as possible.

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NeoReviews Quiz

3. A 26-year-old primigravida is seen at a prenatal clinic. Her history is significant for type 1 diabetes mellitus initially detected at 21 years of age. She has no complications related to diabetes. Of the following, the class of diabetes in pregnancy according to the White classification *most* consistent with this patient is:

   A. Class A.
   B. Class B.
   C. Class C.
   D. Class D.
   E. Class R.

4. Pregnancy in a patient who has diabetes mellitus often is complicated because of perturbations of glucose homeostasis. Of the following, the *most* significant morbidity associated with diabetes during pregnancy is:

   A. Metabolic acidosis.
   B. Obesity.
   C. Preeclampsia.
   D. Pyelonephritis.
   E. Sepsis.

5. Infants born to diabetic mothers are at a substantially greater risk for major malformations than those born to nondiabetic mothers. Of the following, the mechanism *most likely* implicated in the pathogenesis of malformations in a diabetic pregnancy is:

   A. Antioxidant deficiency.
   B. Fetal hyperinsulinism.
   C. Genetic predisposition.
   D. Postconceptional hyperglycemia.
   E. Uteroplacental vascular disease.

The Infant of the Diabetic Mother

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