The Infant of the Diabetic Mother

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The infant of the diabetic mother (IDM) is a prime example of the problems that may exist in the neonate secondary 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 its mother for glucose delivery, and the adult is considered to have precise control of glucose homeostasis, since plasma glucose concentration is regulated to a fine degree (1). In contrast, maintenance of glucose homeostasis may be a major problem even for the normal neonate (2). The precarious nature of this situation is emphasized by the numerous problems associated with neonatal hypoglycemia and hyperglycemia during this period of life. The IDM can be used to document not only how far we have come in understanding the pathophysiology of glucose disequilibrium, but also how far we need to go (3–5).

Although many infants of diabetic mothers have an uneventful perinatal course, there is still an increased risk of glucose disequilibrium. In this review, I shall enumerate the metabolic abnormalities that the IDM may encounter in relation to glucose metabolism and evaluate the pathophysiologic basis for their occurrence.

PERINATAL MORTALITY AND MORBIDITY

While the IDM may have greater morbidity than the neonate of the nondiabetic woman (Table 1), many infants of insulin-dependent diabetic women may experience an uneventful clinical course, and even more infants of gestational diabetic women do well (3–5). Theoretically, the better the metabolic control of the diabetic pregnant patient, the greater the potential for a normal neonate. Over the last decade or so, perinatal mortality, except for congenital anomalies, has approached that for neonates born to nondiabetic mothers (6,7).

Studies of perinatal morbidity and mortality from diverse centers attest to the increasing success of these principles. In 1974, Pedersen et al. published a review of their experiences over a 26-year period with an analysis of 1332 diabetic pregnancies (8). Perinatal mortality varied directly with the severity of maternal diabetes as judged by two commonly used maternal classification schemes: White's original
TABLE 1. Morbidity in the infant of the diabetic mother

<table>
<thead>
<tr>
<th>Morbidity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asphyxia</td>
<td>Macrosomia</td>
</tr>
<tr>
<td>Birth injury</td>
<td>Neurologic instability</td>
</tr>
<tr>
<td>Caudal regression</td>
<td>Organomegaly</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Polycythemia and hyperviscosity</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>Respiratory distress</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Septal hypertrophy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Small left colon syndrome</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Transient hematuria</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>Increased blood volume</td>
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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 the presence of late vascular complications (9), while the PBSP classification (Table 3) includes abnormalities of the current pregnancy.

An updated report from the Joslin Clinic service supports the importance of these factors, especially preeclampsia (pretoxemia) as a significant cause of morbidity in the pregnant diabetic. Of 420 patients in the series with insulin-dependent type 1 diabetes, 110, or 26.2%, delivered before 37 weeks, compared with an incidence of

TABLE 2. White's classification of diabetes in pregnancy (modified)

<table>
<thead>
<tr>
<th>Gestational diabetes</th>
<th>Abnormal glucose tolerance test, but euglycemia maintained by diet alone or, if diet alone insufficient, insulin required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Diet alone, any duration or onset age</td>
</tr>
<tr>
<td>Class B</td>
<td>Onset age 20 years or older and duration less than 10 years</td>
</tr>
<tr>
<td>Class C</td>
<td>Onset age 10–19 years or duration 10–19 years</td>
</tr>
<tr>
<td>Class D</td>
<td>Onset age under 10 years, duration over 20 years, background retinopathy, or hypertension (not preeclampsia)</td>
</tr>
<tr>
<td>Class R</td>
<td>Proliferative retinopathy or vitreous hemorrhage</td>
</tr>
<tr>
<td>Class F</td>
<td>Nephropathy with over 500 mg/day proteinuria</td>
</tr>
<tr>
<td>Class RF</td>
<td>Criteria for both R and F coexist</td>
</tr>
<tr>
<td>Class H</td>
<td>Arteriosclerotic heart disease clinically evident</td>
</tr>
<tr>
<td>Class T</td>
<td>Previous renal transplantation</td>
</tr>
</tbody>
</table>

TABLE 3. Prognostically Bad Signs of Pregnancy (PBSP)

<table>
<thead>
<tr>
<th>Chemical pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precoma or severe acidosis</td>
</tr>
<tr>
<td>Toxemia</td>
</tr>
<tr>
<td>&quot;Neglectors&quot;</td>
</tr>
</tbody>
</table>
9.7% in the nondiabetic population. One-third of the premature deliveries related to preeclampsia. They concluded that a major problem of the diabetic pregnancy was related to preeclampsia and its association with prematurity (10). The risk to the fetus was increased when the PBSP classification was added to the White classification.

The relationship between the two was emphasized by Diamond et al. (11) who studied 199 pregnancies from 1977 to 1983. They noted that the presence of PBSP increased the perinatal mortality rate from 7.3% to 17.1% and was predictive of pulmonary morbidity in general (31.6% versus 16.3%). The authors concluded that the combination of the two is still as predictive as had been found by Pedersen. While these investigators noted an improvement in nondiabetic pregnancy outcome during this same period, they emphasized that the improved classification scheme 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 Europe. While the frequency of macrosomia has decreased, the rate is still usually higher than that in neonates born to nondiabetic women. In a survey of macrosomic neonates (large for gestational age; >95 percentile weight for gestational age), most have been born to obese mothers, not all of whom have glucose intolerance as judged by postpartum glycohemoglobin studies (12,13). Nevertheless, the gestational diabetic with glucose intolerance during late pregnancy often remains undiagnosed and may have a neonate with a greater risk of perinatal complications.

Glycosylated hemoglobin (HbA1C) has been widely touted as a measure of long-term control of diabetic persons. However, recent reports reflect increasing disenchantment with its reliability. While higher HbA1 levels were noted in women diagnosed as having gestational diabetes, a relatively low sensitivity in detecting gestational diabetes was confirmed. HbA1 levels and oral glucose tolerance test (OGTT) indices did not correlate well, and delivery of large for gestation neonates was not associated with higher HbA1 levels (14).

In this same regard, Cano et al. studied the relationship of maternal glycosylated hemoglobin and fetal β cell activity with birth weight (15). A population of 40 maternal-neonatal pairs was studied, of whom 17 were diabetic pregnancies. Insulin and C-peptide were measured in cord blood and were compared with maternal HbA1 levels. HbA1 did not correlate with weight for gestational age at birth, while insulin and C-peptide concentrations did. The investigators suggested that, in populations with good diabetes control, blood glucose concentration, as monitored by HbA1 levels, is not the major determinant of fetal growth.

In contrast, Pollak et al. studied glucitollysine concentrations in umbilical cord extracts as a spin-off of the measurement of glycation processes in biologic samples (16). The results of 12 samples from the infants of diabetic mothers were compared with 14 control samples from infants with normal mothers. Using ion exchange chromatography followed by reverse-phase high-pressure liquid chromatography, these investigators noted higher glucitollysine levels in the IDM compared with controls.
The levels were even higher in the IDM with congenital malformations. The investigators suggested that nonenzymatic glycation of fetal tissue does occur as a result of in utero exposure to cumulative glycemia.

Teramo et al. have published data from Helsinki, Finland, relating to perinatal mortality (17). Their study focused on two time periods: 1970–1971 and 1975–1977. In 1974, the principles of obstetric monitoring and the treatment of pregnant diabetic women and their neonates were updated. The review focused on the differences resulting from those changes in management. Specifically, this involved increased monitoring and more frequent hospital admissions for metabolic control, especially in the third trimester. In 1975–1977, all diabetic patients were admitted to hospital from the 32nd week of pregnancy until delivery. Strict maintenance of normoglycemia (blood glucose <120 mg/dl) was the goal of management and, in the latter years, a permanent interdisciplinary team was in charge of the treatment of these patients. Gestational age of the neonates was increased significantly; however, mean birth weights were unchanged. The perinatal mortality rate fell markedly, as did neonatal morbidity. The authors concluded that, while advances were obvious, the final answers were far from apparent because of the significant neonatal morbidity still present.

Similar conclusions about strict metabolic control were mentioned by Jerwell et al., who evaluated their experience in Norway between 1967 and 1976 (18). A total of 1035 births to diabetic mothers were registered during the 10-year period. Not only did perinatal mortality fall by 30%, but the duration of gestation increased from 35.5 to 37 weeks over the same period. The number of neonates with appropriate weight for gestational age (AGA) increased from 53.3%–70.0%. The care of these pregnant diabetic women was more commonly carried out in university clinics and regional hospitals (from 38.7% in 1967–1968 to 77.1% in 1975–1976). The impact of these interventions did not affect malformation rates, which were still more common by a factor of 50% in infants born to these women compared with the general population.

More recently, maternal glucose variability was studied in 154 pregnant diabetic patients who were admitted to hospital for a month prior to delivery. It was found that reduced within-day plasma glucose variability was significantly correlated with enhanced neonatal outcome (that is, there was a decreased incidence of complications), but that there was no correlation between maternal glucose variability and the birth weight of the neonate. The investigators acknowledged that absence of glucose variability would not ensure prevention of neonatal complications (19).

Roberts and Patterson (20) reported on a 20-year experience involving 1528 pregnancies of diabetic women. Of these, 571 had type 1 diabetes and 957 had gestational diabetes. The perinatal mortality rate fell from 15.2%–2% in those with type 1 diabetes and from 6.7%–0.5% for those with gestational diabetes. The authors related the improvement in mortality to better glucose control. They reported, as have others, that the major outstanding problem related to the persistently high incidence of congenital malformations.

Another evaluation was performed in which normoglycemia was maintained in
diabetic women with evidence of vascular disease (21). While improvement was noted in many of the side effects of vascular compromise (proteinuria, retinopathy, etc.), a wide range in the birthweight of the infants (including macrosomia) was noted, in spite of normal hemoglobin A1 determinations.

Coustan and Imarah attempted to use prophylactic insulin treatment in women with gestational diabetes to reduce the incidence of macrosomia, operative delivery, and birth trauma. The results showed a partial decline in complications with tightened maternal metabolic control (22). Subsequently, the same group evaluated a randomized clinical trial of insulin pump or intensive conventional therapy. Twenty-two pregnant diabetic women were randomized to conventional therapy or insulin pump therapy. No significant differences were found with either regimen. Excellent therapy was achieved with both (23).

A more recent review of the use of insulin therapy was reported by Thompson et al. (24). One-hundred-eight gestational diabetic women were randomized to receive diet plus insulin or diet alone to maintain glycemic control. The investigators reported that if the patients were treated for at least 6 weeks with diet plus insulin, the mean birth weight, incidence of macrosomia, and ponderal index were reduced. No patient who weighed less than 90 kg and maintained euglycemic control delivered a neonate who weighed more than 4000 g. The authors concluded that maternal obesity or failure to achieve glycemic control should alert the clinician to an increased risk of macrosomia.

The same conclusion was reached by Larsen et al., who found that maternal obesity (>95%) was associated with an odds ratio of 2.2 of macrosomia (BW >4000 g) compared with 1.0 for women who weighed between the 25th and the 75th percentile (25).

An extension of the above was reported by Nordlander et al., who evaluated factors that influence neonatal morbidity in gestational diabetes (26). Perinatal morbidity was significantly more frequent in women with gestational diabetes (23%) than in a control group (13%). The occurrence of large for gestational age neonates was not different between the groups. Of infants born to gestational diabetic women, those who presented with morbidity were of shorter gestational age at delivery, were delivered more frequently by cesarean section, and had mothers who had a higher prepregnancy weight and a 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 besides blood glucose control during pregnancy were critical in determining neonatal outcome in gestational diabetic pregnancies.

Hanson et al. (27) evaluated factors influencing neonatal morbidity in diabetic pregnancies. They evaluated maternal duration of diabetes, third-trimester blood glucose control, gestational age at delivery, mode of delivery, and hypertension in 92 consecutive pregnancies of White’s classes B through F. Morbidity was classified as none, minor, or severe, and no differences were noted in the former two groups. Those with severe morbidity had longer duration of maternal diabetes, shorter gestational age at birth, higher rates of cesarean section, and higher frequency of toxemia.
The most significant single factor was the gestational age of the pregnancy. Glucose control between 70 and 153 mg/dl did not influence morbidity.

Hunter et al. (28) compared neonatal mortality rates among infants of women with insulin-dependent diabetes and infants of women without diabetes using an historical cohort analysis between 1980 and 1989. There were 230 infants in the former group and 460 infants in the latter group. The infants born to diabetic mothers had higher incidences of glucose infusions, birth weight ≥90th percentile, and neonatal jaundice, but no differences in the incidence of respiratory distress, polycythemia, or hypocalcemia. Glycosylated hemoglobin levels were not related to birth weight. Nearly 25% of the infants were delivered before 37 weeks’ gestation, nearly half because of maternal hypertension. The investigators suggested that neonatal morbidity is more likely to be determined by the gestational age at delivery than by the maternal diabetes.

In contrast, Persson and Hanson evaluated the outcome in a population with strictly individualized glucose control from their own institution and from a multicenter network (29). They noted a normal premature delivery rate of 8.9% and a low rate of maternal hypoglycemia and concluded that strictly individualized management programs offer the optimum neonatal outcome.

Finally, a recent evaluation known as the Diabetes in Early Pregnancy Study considered maternal postprandial glucose levels and infant birth weight. Recruited before conceiving, 323 diabetic and 361 control women were evaluated for fasting and non-fasting venous plasma glucose concentrations measured on alternate weeks during the first trimester and monthly thereafter. A greater percentage of infants of diabetic mothers were ≥90th percentile for birthweight compared with the control group (28.5% versus 13.1%, p < 0.0001). After adjusting for specific maternal indications, monitoring of nonfasting glucose concentrations was thought to be necessary to prevent macrosomia (30).

A conclusion from many of the studies that have been cited might be that the maintenance of a normal metabolic state, including euglycemia, should diminish, but will not completely eradicate, the increased perinatal and neonatal mortality and morbidity 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 infants of diabetic mothers. Nevertheless, many of the effects can be attributed to maternal metabolic (glucose) control. Pedersen and his colleagues originally emphasized the relationship between maternal glucose concentration and neonatal hypoglycemia (31) (Table 4). His simplified hypothesis recognized that maternal hyperglycemia was paralleled by fetal hyperglycemia, which stimulated the fetal pancreas, resulting in islet cell hypertrophy and β-cell hyperplasia with increased insulin content. Following separation of the fetus from the mother,
the former was no longer supported by placental glucose transfer, with the result that neonatal hypoglycemia occurred.

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 the heart and liver) and macrosomia. In the presence of excess substrate (glucose), increased fat synthesis and deposition occur 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 kidneys (32,33). After delivery there is a rapid fall in plasma glucose with persistently low concentrations of plasma free fatty acids (FFA), glycerol, and β-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 (34). The insulin response to intravenous arginine is also exaggerated in infants of gestationally diabetic mothers (35).

In a follow-up study using the chronic hyperinsulinemic fetal rhesus monkey, Susa and coworkers studied neonatal insulin secretion following delivery (36). They gave 300 μg/kg of glucagon to stimulate insulin secretion. Compared with controls, the experimental group had a blunted insulin and C-peptide response to the glucagon infusion. The investigators suggested that fetal hyperinsulinemia resulted in inhibition of insulin synthesis and secretion in extrauterine life.

MacFarlane and Tsakalakos suggested that the initial increase in fetal size due to fetal hyperinsulinemia was implicated in the development of hypoxemia. The limitation in fetal oxygen availability altered differential utilization of glucose and increased α-glycerophosphate synthesis in the fetal adipocyte, which resulted in fetal adiposity (37).

The response to an oral glucose load results in an earlier plasma insulin rise than in normal neonates, although the area under the insulin curve is similar (38). During the initial hours after birth, the response to an acute intravenous bolus of glucose in infants of diabetic mothers compared with normal controls is a rapid rate of glucose disappearance from the plasma (39). In contrast, the rise in plasma glucose concentration following stepwise hourly increases in the rate of infused glucose, occurs even at normal rates of infusion, that is, 4–6 mg/kg/min (40,41). The latter may be attributed to a persistence of hepatic glucose output, which is similar to that of the normal infant.

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**TABLE 4. Components for the hypothesis of hyperinsulinism in the infant of the diabetic mother**

| 1. Islet hyperplasia and β cell hypertrophy |
| 2. Obesity and macrosomia                  |
| 3. Hypoglycemia with low free fatty acids concentration |
| 4. Rapid glucose disappearance rate        |
| 5. (a) Higher plasma insulin-like activity after glucose infusion |
| (b) Umbilical vein reactive immunoinsulin increase |
| 6. C-peptide and proinsulin concentrations increased |
Alterations of plasma glucocorticoids and growth hormone have not been significant in infants of diabetic mothers. Definitive studies of the somatomedins (IGF-1, IGF-2) are currently being reported. As an example, Hill et al. studied insulin-like growth factors in fetal macrosomia in neonates whose mothers did or did not have diabetes (42). Cord blood concentrations of IGF-I, total IGF, and IGF binding protein were determined in 15 term infants of diabetic mothers and 29 term neonates of nondiabetic mothers. Although there was a relationship between cord IGF and total IGF concentration in large for gestational age versus appropriate for gestational age neonates of nondiabetic mothers, there was no such relationship in infants of diabetic mothers. IGF binding proteins were not different in any group. The authors concluded that the absence of increased IGF concentration in infants of diabetic mothers suggested that these growth factors are not involved in the development of macrosomia in such infants. In contrast, urinary excretion of catecholamines was diminished, especially in neonates with low plasma glucose concentrations (43). In addition, plasma glucagon levels were less raised after delivery than in normal neonates (44).

Recent studies of insulin receptors on fetal monocytes isolated from placental blood of infants of gestationally diabetic mothers (IGDM) at delivery indicated that these infants had more receptor sites per monocyte than normal adults or normal neonates (45). Monocytes from both normal neonates and IGDM showed greater affinity for insulin than did those from adults. Furthermore, in the presence of increased ambient levels of plasma insulin, monocytes from the IGDM seemed to develop increased (not decreased) concentrations of insulin receptors, as well as an increased affinity for the hormone. The significance of these observations in relation to the physiologic effects of insulin are unclear. However, there are implications for competition of insulin and its antibodies for receptor sites and for the resulting insulin-sensitive tissues.

In a more recent evaluation, the role of insulin receptors in macrosomia and the tendency to hypoglycemia was studied in infants of diabetic mothers and control infants at between 3 and 14 days of age. The infants of diabetic mothers were macrosomic. Plasma-free insulin concentrations in cord blood were 15-fold higher in these infants compared with controls, and threefold higher in peripheral venous blood. Hypoglycemia was noted in 12 of 17 IDMs but in none of the control neonates. In umbilical blood, insulin binding to erythrocytes was not different between groups but decreased during the first weeks at a more rapid rate in IDM, because of decreased receptor affinity and receptor concentration in these infants. Thus insulin binding was similar in spite of gross hyperinsulinemia in the IDM, the latter resulting in macrosomia and hypoglycemia that decreased early on in the neonatal period (46).

KINETIC ANALYSIS OF THE IDM

Application of in vivo kinetic analysis has been used by numerous investigators to evaluate the infant of the diabetic mother metabolically. An early study using stable nonradioactive isotopes was reported by Kalhan et al. (using [1-13C]glucose and the
prime constant infusion technique) (47). These investigators measured systemic glucose production rates in five normal (nondiabetic) and five infants of insulin-dependent diabetics at 2 hours of age. As expected, the infant of the diabetic mother had a lower glucose concentration during the study compared with the infant of the nondiabetic mother. For the first time, the authors reported that the IDM had a lower systemic glucose production rate. They suggested that decreased glucose output was related to inhibited glycogenolysis. They speculated that increased insulin and decreased glucagon and catecholamine responses resulted in decreased systemic output. What was fascinating about this report was that for the time studied (the late 1970s) the diabetic women were considered to be in excellent control, having been admitted to hospital during the last four weeks of the pregnancy to achieve strict metabolic control (maternal blood glucose between 50 and 150 mg/dl). Yet the systemic glucose production rates of these neonates were lower than those of the control neonates.

A further evaluation of the infant of the diabetic mother was reported by the same group five years later in 1982 (48). Again focusing on neonates of mothers in “strict control” the authors evaluated systemic glucose production in five infants of insulin-dependent mothers, one infant of a gestational diabetic mother, and five infants born to normal mothers. The blood glucose measurements were in a more restricted range (36–104 mg/dl) than in the previous series, and the mothers were controlled in a hospital setting for 3–4 weeks before delivery. In this series, systemic glucose production rates were similar in the diabetic women and the controls. However, the investigators, like other groups (49), carried their analyses 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 infants of diabetic mothers did not show as great a suppression of endogenous glucose production as the adults. The investigators concluded that altered regulation of glucose production may be secondary to intermittent maternal hyperglycemia, even in women whose diabetes was strictly controlled.

These studies parallel the work of the Brown University group that studied glucose kinetics in the neonate. Using 78% enriched D[U-13C] glucose, 16 infants of diabetic women (10 insulin-dependent and six chemical dependent) were compared with five infants of normal nondiabetic women. Four 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 (Fig. 1). All of the mothers were evaluated relative to control mothers by hemoglobin A_{1C} and maternal plasma glucose and/or cord vein glucose determinations at delivery. None of the women was maintained in the hospital before study. There was a similarity between basal glucose production rates in the neonates studied with no exogenous glucose infused. The investigators concluded that good metabolic control of the maternal diabetic state would help maintain euglycemia (50). However, in a subsequent analysis in which neonates of nondiabetic mothers received glucose exogenously to maintain euglycemia, a heterogeneity continued to exist in the ability of the neonates to depress endogenous glucose production (51). These latter data parallel other work from the
same group that reflects the transitional nature of glucose metabolism in the term and preterm infant, born both to diabetic and to nondiabetic mothers (47,52).

Another recent evaluation of postnatal glucose kinetics in neonates born to tightly controlled, insulin-dependent diabetic mothers was reported from Groningen, The Netherlands, by Baarsma et al. (53). These investigators studied 15 mother-infant pairs from the beginning of pregnancy until birth and then measured glucose kinetics on the first day. Alternate substrates, free fatty acids, and ketone bodies were also measured. There was no relationship between diabetic control in the mothers and glucose kinetics in the neonates. Glucose production was significantly lower in neonates studied at the end of the first day (Fig. 2) and the lower rate of production
The realization that neonatal glucose homeostasis is in a transitional state is further supported by studies in which maternal control was evaluated in a group of gestationally diabetic women in relation to the birthweights of their infants (54). If the Pedersen hypothesis were correct, birthweights of the neonates should correlate with the degree of 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 gestational diabetics (Fig. 3). This lack of correlation further supports the heterogeneity of the diabetic state and suggests
that, as control of glucose is multifactorial, control of fetal growth is likewise multifactorial. Similar conclusions led Freinkel and others to conclude that mixed nutrients (amino acids, free fatty acids, etc.) other than glucose are important in fetal-neonatal metabolic control (55,56), as shown schematically in Fig. 4. This concept is an important one for ongoing research.

Support for the concept has recently been provided by Kalkhoff et al. (57), who studied the relationship between neonatal birthweight and maternal plasma amino acid profiles in lean and obese, nondiabetic women and in type 1 diabetic pregnant women. HbA₁, plasma glucose, and total amino acid profiles were increased in diabetic subjects compared with controls. No differences were present between obese
and lean control groups. Plasma glucose concentrations and profiles of HbA₁c did not correlate with relative weights of the neonates, while average total plasma amino acid concentrations did. The authors concluded that maternal plasma amino acid profiles may influence fetal weight generally and affect the development of neonatal macrosomia.

Patel and Kalhan have evaluated glycerol kinetics in infants of diabetic mothers (58). They noted the possibility of intermittent hyperglycemia and hyperinsulinemia in utero and suggested that lower concentrations of plasma FFA concomitant with lower plasma glucose concentrations were secondary to decreased mobilization of fatty acids from adipose tissue. Since glycerol is released in a 1:3 molar ratio with fatty acids, they measured glycerol turnover using [2-¹³C]glycerol. Unexpectedly in the macrosomic infants that were studied, a normal adaptive response to fasting was noted that could assist in maintaining euglycemia.

A recent study has focused on the concept of alternate substrates in relation to the morbidity of macrosomia (59). The investigators measured plasma glucose, glycosylated hemoglobin, glycosylated protein, insulin, and triglyceride concentrations in gestational diabetes to determine their relationship to glucose intolerance and macrosomia. Plasma triglyceride concentration was the only estimation that was significantly associated with birth weight corrected for gestational age (birthweight ratio) \( p < 0.05 < 0.01 \). Using multivariate analysis, triglyceride concentration was associated with birthweight ratio even when maternal prepregnancy weight gain and the
correlations between prepregnancy weight gain and triglyceride and birthweight ratio were controlled ($p < 0.019$). The investigators concluded that triglyceride concentration may be a physiological contributor to infant birthweight.

In contrast, we performed a lipid tolerance test in women with gestational diabetes, both on and off insulin, and compared the results to control groups who were pregnant nondiabetic or not pregnant. Figure 5 shows the plasma total triglyceride concentration over time in these groups. Although pregnancy appeared to be associated with a decreased rate of triglyceride lipolysis compared with the nonpregnant state, no differences were noted in lipid metabolism among normal pregnant and relatively well-controlled gestational diabetic patients (60).

Further work is necessary to understand the glucose kinetics and the relationships between glucose and lipid kinetics in neonates, especially infants born to well-controlled as well as poorly controlled diabetic women.

**HYPOGLYCEMIA**

A rapid fall in plasma glucose concentration following delivery is characteristic of the infant of the diabetic mother. Values less than 35 mg/dl in term neonates and
less than 25 mg/dl in preterm neonates are abnormal and may occur within 30 minutes of clamping the umbilical vessels. Factors that are known to influence the degree of hypoglycemia include prior maternal glucose homeostasis and maternal glycemia during delivery (2). In inadequately controlled pregnancy diabetes, the fetal pancreas will have been stimulated to synthesize excessive insulin, which may readily be released. Administration of intravenous dextrose during the intrapartum period, which results in maternal hyperglycemia (>125 mg/dl) will be reflected in the fetus and will exaggerate the infant's normal postdelivery fall in plasma glucose concentration. In addition, hypoglycemia may persist for 48 hours or may develop after 24 hours.

As noted previously, fetal hyperinsulinemia is associated with suppressed concentrations of plasma free fatty acids and/or with variably diminished hepatic glucose production in the neonate. Other factors that may contribute to the development of hypoglycemia include defective counterregulation by catecholamines and/or glucagon.

The neonate shows 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 is different in the neonate is that various stages of maturation exist for each factor. Prior work, in conjunction with glucose infusion studies, can be summarized to suggest that there is blunted splanchnic (hepatic) responsiveness to insulin in the neonate, both in infants of diabetic mothers and in preterm and term infants of nondiabetic mothers, compared with the adult (51). What have not been studied, but are of particular interest, are the many counter-insulin hormones that influence metabolism. If insulin is the primary glucoregulatory hormone, then counter-insulin hormones assist in balancing the effect of insulin and other factors.

One should probably evaluate all of the counter-insulin hormones but those that have been studied and are of particular interest in the infant of the diabetic mother have been of the sympat-ho-adrenal neural axis. There are many studies that have looked at epinephrine and norepinephrine concentrations in infants of diabetic mothers. The results are quite variable. An early study involved 11 infants of diabetic mothers, only two of whom were gestational. Urinary excretion of catecholamines was measured and compared with 10 infants of normal mothers. Urinary norepinephrine and epinephrine levels did not increase in the infants of diabetic women who were severely hypoglycemic but did rise in infants whose mothers were mildly hypoglycemic (43).

These results parallel investigations of Stern et al. who suggested that hypoglycemia may be secondary to an adrenal medullary exhaustion phenomenon (61). This would itself be secondary to longstanding hypoglycemia in the infant of the diabetic mother (presumably from the fetal period and related to poor control of maternal diabetes). In further studies, however, Keenan et al. noted normal increases in plasma glucose and free fatty acids and normal falls in plasma insulin in response to exogenous administration of epinephrine (62). This confirmed the exhaustion theory. A
parallel explanation was given by Young et al. to explain the high plasma norepinephrine concentrations in the infant of the diabetic mother, whose degree of euglycemic control was not reported except that some of the neonates were borderline large for gestational age (63). These investigators speculated that the infant of the diabetic mother exposed to excessive quantities of glucose may be subject to chronic sympathoadrenal stimulation.

In another series, Artel et al. measured plasma epinephrine and norepinephrine concentrations in infants of diabetic mothers (64). Increased levels of both hormones were found, although the variation was markedly increased in the IDM. The investigators speculated that hypoglycemia after birth may be secondary to adrenal exhaustion producing temporary depletion later in the neonatal period. This temporary depletion might account for the appearance of hypoglycemia noted clinically by others. In a follow-up to evaluate whether the neonatal changes were related to maternal metabolic control, plasma glucose, catecholamines, and glucagon were measured in the neonatal period in 10 neonates of well-controlled class B diabetic women. Good control resulted in appropriate counterregulatory hormone responses comparable with those neonates of normal mothers. The investigators concluded that epinephrine and glucagon levels, which paralleled the development of euglycemia, were significant factors in perinatal glucose homeostasis (65).

A series by Broberger et al. (66) evaluated sympathoadrenal activity in the first 12 hours after birth in infants of diabetic mothers (nine from women with type 1 diabetes and 13 from women with insulin-treated gestational diabetes). Failure to observe differences in plasma epinephrine and norepinephrine levels between the IDM and control neonates was believed to be secondary to good metabolic control of the diabetic mother.

However, 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, relating both to insulin and to counter-insulin factors, we infused epinephrine in two doses (50 or 500 mg/kg/min) in a newborn lamb model and glucose kinetics (turnover) were measured with [6-\(^3\)H]glucose. The newborn lamb showed a blunted response to the lower dose of epinephrine infused. We speculated that the neonate has blunted responsiveness to this important counter-insulin stimulus. If this occurs in the diabetic state, it could partially account for the hypoglycemia that is found clinically (67,68).

Thus the infant of the diabetic mother is a prime example of the potential for glucose disequilibrium in the neonate. Because of the transitional state of glucose homeostasis in the neonatal period, accentuation of disequilibrium may be enhanced in such infants secondary to metabolic alterations present in the diabetic mother. A great deal of work is necessary to fully appreciate the pathophysiology.

CONCLUSION

Although there has been continuing improvement in the outcome of neonates born to diabetic mothers, they remain a high-risk population. Optimal results are obtained
when meticulous, medical-obstetric care throughout pregnancy is combined with expert neonatal supervision following delivery. Many of the risks previously identified now occur less often, however, further investigations are necessary to clarify the specific pathology of the metabolic abnormalities.

ACKNOWLEDGMENTS

We wish to express our appreciation to Ms. Patricia Knight for her expert secretarial assistance.

REFERENCES


THE INFANT OF THE DIABETIC MOTHER


DISCUSSION

Dr. Bartsokas: Although you did not touch on the subject, would you speculate on the cause of the cardiomyopathy in infants of diabetic mothers?

Dr. Cowett: It has been shown that there is increased glycogen in the heart in cases of cardiomyopathy but I do not know the origin of the congenital cardiac malformations that occur.

Dr. Nattrass: What changes do you find in the catecholamines? What effect would such changes have upon the delivery of substrates, for example fatty acids and also gluconeogenic substrates, in view of the changes that you find in glucose production?

Dr. Cowett: We know there are increases in catecholamine production but the stresses
responsible for this are not well understood. The fact is that the pregnancies that are considered to be under stress produce the biggest infants, so there seems to be a positive correlation between increased catecholamines and the size of the infant.

Dr. Catalano: I have a question regarding the timing of your kinetic studies in the newborn. How important is it to time when you do the measurements and to ensure that the timing is equal between groups? Is there a delay of enzyme maturation in the liver that may affect the time when you study an infant of a diabetic mother as compared with an infant of a woman who has normal glucose metabolism?

Dr. Cowett: Kalhan's studies were done at 2 hours, ours tended to be done between 24 and 72 hours. Until now we have not studied newborns before 24 hours of age, and we have no studies after 72 hours. Early on, in the first hours, glycogenolysis is likely to be predominant. From alanine studies, Bier and colleagues have suggested that gluconeogenesis probably begins at around 6 hours of age, but it has not been looked at earlier than that. The response that Kalhan showed was not only a response of glucagon but also of catecholamines, and it has been suggested that this occurs in the infant of the diabetic mother as well.

Dr. Schwartz: Many years ago, Drash and I independently studied glucagon responses in babies. When we gave glucagon to a normal newborn infant, the hyperglycemic response was slow and delayed and very different from what one sees in an older infant or an adult, where you get a prompt response with a rise of glucose in 30 minutes. In the newborn, the rise occurs over 120 minutes. I believe that the insulin response that you showed was initially low and also delayed, in contrast to the adult, and I wonder whether you can reconcile that with your hypothesis about catecholamines and glucose and insulin effectiveness.

Dr. Cowett: The concern in the infant of the diabetic mother has always been that there is a blunted catecholamine response. Paul Wu showed that the response was blunted compared with normal when glucagon was given to the infant of the diabetic mother.

Dr. Bergman: I don't know whether Dr. Schwartz is going to cover this, but I was interested in his insulin-infused rhesus monkey model. I was very curious about the blood sugar, for example, and what effect this may have on the developing brain. I assume that blood sugar would have been very low in the fetus. This could also have an impact on the metabolism of the mother, who has to deliver large amounts of glucose to the fetus.

Dr. Schwartz: May I answer this? Our first study was of in utero hyperinsulinemia that had no effect on maternal glucose or any other variable that we could measure and that caused a slight decrease in umbilical artery glucose in the fetus, but no decrease in umbilical vein glucose because of maternal-fetal transfer. The other study was to take this model and to produce neonatal hypoglycemia deliberately. We delivered the fetuses with the insulin infusion pump intact, put a catheter in the umbilical vein, and followed blood glucose serially for 12-14 hours while inducing severe hypoglycemia. We also had a control group. These two groups were then put in the monkey baby nursery and reared. When the monkeys were growing and stabilized they were transferred to the university and went through an elaborate 2-year blinded analysis. This analysis could not discriminate between the two groups of monkeys. So severe neonatal hypoglycemia in the monkey apparently has no consequences as far as development is considered. These results have been published (1).

Dr. Girard: The fetal and neonatal brain is relatively well protected against hypoglycemia since the brain can take up lactate to a very large extent and this is capable of covering its energy needs. This has been very well demonstrated (2).

Dr. Bergman: What is the enzymatic mechanism of this, compared with the normal adult brain?

Dr. Girard: It is probably the capacity of the blood-brain barrier to transfer dicarboxylic
acid very efficiently. There is also glucose transporter expression that allows the brain to take up glucose even in the presence of hypoglycemia.

_Dr. Cowett:_ Does that persist, or when does it diminish?

_Dr. Girard:_ It seems to decrease with development, but it is very particularly efficient during the neonatal period. It has been demonstrated recently (3) in the adult that lactate is capable of replacing glucose as a fuel for the brain during hypoglycemia.

_Dr. Schwartz:_ The classical example of that is type 1 glycogen storage disease where you get severe hypoglycemia, blood sugars at zero for example, and lactate that are 12–15 mM, extraordinarily high. Lactate uptake by the brain has been shown in older children (2).

_Dr. Drash:_ Are you willing to extrapolate to the human situation? Should we have no concern about the effect of maternal hypoglycemia on the fetus?

_Dr. Schwartz:_ No, I would not say that at all.

_Dr. Swift:_ This is a very worrying discussion for pediatricians involved in neonatal care. Infants of diabetic mothers who have in the past became hypoglycemic seem to be normal mentally on long-term follow up, but Alan Lucas’s data from Cambridge published in recent years suggests that the one identifiable variable relating to poor outcome in children who were preterm is hypoglycemia in the preterm nursery. Of course that might relate to overall nutrition rather than just to hypoglycemia, but perhaps you would like to comment.

_Dr. Cowett:_ We are familiar with Lucas’ data. It does not really equate with work in the monkey, and I am concerned that their data have not been confirmed by others. Many different components are usually operative when the infant becomes hypoglycemic, so it is hard to tease out one variable. However, we should be cautious in suggesting that this model shows that hypoglycemia does not have any effect on the human; it simply says that in this model the monkeys grew up seemingly normal.

_Dr. Marliss:_ Along the same lines, I was very impressed by the rates of endogenous glucose production in the small-for-gestational age subjects you showed. If I remember correctly, it was in the neighborhood of 6 or even more mg per kg per minute. Is that because those individuals have disproportionately large brains and if you were to look at glucose production with some other denominator it might be somewhat less impressive?

_Dr. Cowett:_ The infants were all appropriate for gestational age and their head circumferences were over the 10th and under the 90th percentile. We would agree, however, that there is an increased glucose production based on an increased brain size relative to body size in small-for-dates infants. It has been shown by others that there is a correlation between glucose turnover and brain size indirectly measured by head circumference in a heterogeneous age group of infants.

_Dr. Drash:_ I would like to ask Girard about the time course of lactate adaptation. Type 1 glycogen storage disease is a very interesting model in this regard. Years ago we treated some of these children with diazoxide and they ran around the house with blood sugars of 5 or 10 mg/dl (0.3–0.6 mM) and were absolutely asymptomatic. However, when we put them on diazoxide and maintained their blood sugars around 50 or 60 mg/dl (2.7–3.3 mM) they then developed severe hypoglycemic symptoms with very mild falls in blood sugar so we had to abandon diazoxide therapy. I did not think in terms of lactate at the time. I thought we were probably dealing with ketone bodies. But I felt that what we had done was to remove a very important metabolic adaptation, and once they had lost it they could not regain it quickly. I wonder if there are any data on the time course of this adaptation?

_Dr. Girard:_ From the data obtained in the rat, the adaptation seems to be rapid, but in order for lactate to replace glucose as a fuel you must have a high plasma-lactate concentration. So
in a situation in which you have an infusion of insulin, you probably stimulate glucose metabolism in peripheral tissue and provide more lactate. In a situation in which you have a very low lactate concentration in the blood the brain is not protected at all.

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