Infants of diabetic mothers

Joan L. Nold, MD, Michael K. Georgieff, MD*

Department of Pediatrics and Child Development, University of Minnesota, MMC 39, 420 Delaware Street SE, Minneapolis, MN 55455, USA

Historically, infants born to mothers with diabetes have been at significantly greater risk for spontaneous abortion, stillbirth, congenital malformations, and perinatal morbidity and mortality. Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal and neonatal care. Over the past three decades, practitioners have sought to improve the outcome of diabetic pregnancies so that the results approach those of nondiabetic pregnancies [1]. Subsequently, advances in maternal and fetal care have improved the outlook of the infant of a diabetic mother (IDM) to the point at which most pregnant women with diabetes can expect to deliver a healthy child when they have received appropriate prenatal care. Currently, 3% to 10% of pregnancies are complicated by abnormal glycemic control. Of these, 80% are caused by gestational diabetes mellitus as opposed to pregestational diabetes mellitus. This number may rise significantly in the next decade as the current significantly overweight pediatric population heads into their child-bearing years.

The IDM is at increased risk for periconceptional, fetal, neonatal, and long-term morbidities [1,2]. The causes of the fetal and neonatal sequelae of maternal diabetes are likely multifactorial; however, many of the perinatal complications can be traced to the effect of maternal glycemic control on the fetus [2] and can be prevented by appropriate periconceptional and prenatal care.

This article focuses on the complications associated with diabetes in pregnancy as they occur in the periconceptional, fetal, neonatal, and postnatal time period. Obstetric and pediatric management strategies to prevent morbidity in IDM are discussed at the end of the article.

The Pedersen hypothesis and diabetic fetopathy

Most, but not all, of the fetal and neonatal sequelae of diabetes during gestation are a function of maternal glycemic control (Fig. 1). This concept had its
ontogeny in the Pedersen hypothesis, which states that maternal hyperglycemia results in fetal hyperglycemia because glucose readily traverses the placenta [3]. Before 20 weeks’ gestation, the fetal islet cells are not capable of responsive insulin secretion, and the main pathologic condition to which the embryo and early fetus are subjected is hyperglycemia. After 20 weeks’ gestation, the fetus has a functioning pancreas and is responsible for its own glucose homeostasis, because maternal insulin does not cross the placenta in appreciable amounts. Unchecked fetal hyperglycemia results in hypertrophy of fetal pancreatic islets and hyperinsulinemia. The pathologic conditions in the late gestation fetus and newborn IDM are the result of fetal hyperglycemia, hyperinsulinemia, or the combined effects of the two (Fig. 1).

**Diabetes during the periconceptional period**

Several well-done epidemiologic studies have demonstrated a strong association between maternal glycemic control at the time of conception and during early
gestation and the incidence of congenital anomalies [1,4,5]. These studies demonstrated a fourfold higher rate of congenital anomalies of the brain, heart, kidneys, intestine, and skeleton in IDM [4]. The rate of major congenital anomalies for IDM can be predicted from maternal hemoglobin A1c values at 14 weeks’ gestation. Mothers with values of less than 7% have no greater risk of having an infant with congenital anomalies than mothers without diabetes. For mothers with values between 7% and 8.5%, the risk is 5%; the risk rises to 22% for mothers with hemoglobin A1c values of more than 10% [1].

By definition, these structural anomalies occur between the periconceptional period and 2 months’ gestation, during organogenesis. More than 50% of these anomalies affect the central nervous or cardiovascular systems. The most common neurologic structural abnormalities are related to failure of neural tube closure, including meningomyelocele, encephalocele, and anencephaly [4]. Anomalies of the cardiovascular system include transposition of the great vessels, ventricular septal defects, atrial septal defects, and left-sided obstructive lesions, such as hypoplastic left heart syndrome, aortic stenosis, and coarctation of the aorta.

Periconceptional hyperglycemia also seems to increase the risk of skeletal anomalies [1,4,5]. Anomalies include the caudal regression syndrome, which is almost synonymous with IDM, spinal anomalies, and syringomyelia. Renal anomalies include hydronephrosis, renal agenesis, and cystic kidneys [1,5]. The most common intestinal anomalies include atresias of the duodenum and rectum, although atretic sections may occur anywhere along the length of the gastrointestinal tract.

Most significant congenital anomalies are identified on prenatal ultrasound or initial physical examination. One must have a high index of suspicion when evaluating newborn IDM. A thorough physical examination of the newborn IDM is essential. It is not cost effective to perform routine screening of all newborn IDM for congenital anomalies. Rather, further studies should be ordered based on clinical suspicion. Postnatal caregivers should be aware that not all anomalies are clinically present at birth, however. A careful gestation and birth history may provide clues about the presence of hydronephrosis or ventricular septal defects.

The effect of maternal diabetes on the developing fetus

Uncontrolled maternal diabetes has an effect on fetal growth, glucose metabolism, oxygenation, iron metabolism, and preparation for extrauterine life.

Growth

The fetal growth effects of excess glucose and the combination of glucose and insulin are shown in Fig. 1. In the first half of pregnancy, the fetus is exposed primarily to hyperglycemia, which, without secondary hyperinsulinemia, results
in slowing of fetal growth [6]. During the second half of pregnancy, hypertrophic islet cells respond to hyperglycemia with an increase in insulin production. This potent combination of hyperinsulinemia, a major anabolic hormone, and hyperglycemia, a major anabolic fuel, results in a cascade of third-trimester events that culminate in a striking increase in fat stores [7] and a modest 12% increase in protein stores. Much of the consequent weight accretion occurs after 32 weeks’ gestation. Hepatomegaly, splenomegaly, and cardiomegaly (caused by intraventricular septal hypertrophy) are particularly prominent. Head circumferences are not typically increased. In the past, up to 60% of IDMs have been reported to be macrosomic, as defined by a weight more than the ninety-fifth percentile, although this rate has declined to 20% to 35% [1], most likely secondary to aggressive diagnosis and treatment of diabetes during pregnancy.

Macrosomia places the IDM at greater risk for birth trauma because of cephalopelvic disproportion. Appropriate evaluation before delivery includes a review of maternal glycemic control, estimated fetal weight and size, and biophysical profile assessments. Not surprisingly, cesarean delivery rates remain higher in IDMs with fetal macrosomia documented on prenatal ultrasound [8].

A small (<5%) subgroup of fetuses, usually carried by mothers with advanced diabetic vascular disease, is at risk for fetal growth deceleration, defined as birth weight less than the fifth percentile for gestational age [5,6]. The placental vascular insufficiency frequently is accompanied by maternal hypertension and results in protein-energy malnutrition (manifested as fetal growth deceleration) and restricted oxygen delivery (manifested as secondary polycythemia). Their tenuous fetal physiology places them at increased risk of being compromised at delivery. These pathologic conditions may be independent of maternal glycemic control. As with the macrosomic fetus, appropriate evaluation includes biophysical profile assessment and estimation of fetal weight.

Aside from the impact of maternal diabetes on overall growth patterns, the growth of specific organ systems also can be impaired. Although rare, neonatal small left colon syndrome is well described in the IDM. The syndrome is defined by a uniformly small diameter of the descending and sigmoid colon and rectum. Whereas most other congenital anomalies in IDM occur early in gestation, this anomaly is believed to occur during the second half of gestation, after organogenesis is complete. The cause may be related to wide swings in maternal and, consequently, fetal glycemic status. Fetal hyperglucagonemia in response to rapid reductions in fetal glucose concentration may cause intestinal hypomotility. Fetal intestinal motility is an important factor for stimulating intestinal growth, differentiation, and motility [5]. Fetal hypoglycemia can occur either in the setting of maternal hypoglycemia or with profound fetal hyperinsulinemia. The IDM with small left colon syndrome typically presents with signs of intestinal hypomotility, including feeding intolerance, vomiting, and abdominal distention. The signs and symptoms may mimic meconium plug syndrome. Newborn IDMs frequently are poor feeders and have signs of intestinal hypomotility (without necessarily having small left colon syndrome), which suggests a common fetal etiology among these intestinal disorders.
Glucose metabolism

Maternal diabetes mellitus during pregnancy is characterized by glucose intolerance and insulin absence or resistance. Mothers with glucose intolerance are frequently treated with exogenous insulin to maintain normoglycemia. Whereas maternal glucose traverses the human placenta relatively easily, maternally derived or exogenously given insulin does not [1,6]. The fetus becomes hyperglycemic and stimulates islet cell proliferation and insulin production. As long as maternal glycemic status is controlled and transplacental glucose delivery remains steady, fetal glucose metabolism remains stable. Fetal glucose metabolism is most likely to be compromised by wide swings in maternal serum glucose concentrations caused by inconsistent maternal glycemic control. Periods of chronic maternal (and fetal) hyperglycemia result in accelerated fetal growth, whereas sudden reductions in maternal glucose concentrations place fetuses with islet cell hyperplasia at an increased risk for hypoglycemic episodes. Both events have been implicated in the increased fetal mortality rate seen in diabetic pregnancies [9].

Fetal oxygenation

Chronic fetal hyperglycemia and hyperinsulinemia affect the fetal basal metabolic rate, with secondary effects on fetal oxygenation [10,11] and erythropoiesis [12–14]. Fetal hyperglycemia and fetal hyperinsulinemia increase fetal total body oxygen consumption by as much as 30% in a relatively oxygen-limited environment [10,11]. Although the fetus increases its rate of substrate uptake and oxidation, the human placenta has limited ability to increase oxygen delivery in the face of increased demand. Oxygen transport may be further complicated by placental vascular disease, particularly in women with more advanced diabetes. The resultant relative fetal hypoxemia likely contributes to the increased incidence of fetal death, metabolic acidosis, erythropoiesis, and alterations in fetal iron distribution. The fetus responds to the relative hypoxemia by increasing oxygen-carrying capacity [12–15]. IDMs have elevated cord serum erythropoietin concentrations that indicate fetal hypoxemia [12]. Primate and sheep models demonstrate that this effect is chronic and results in polycythemia and altered iron distribution [12–14]. In humans, the severity of polycythemia is directly related to lack of maternal glycemic control [16].

Iron metabolism

As the fetal red cell mass expands by up to 30%, the need for fetal iron expands in parallel, because each gram of hemoglobin requires 3.46 mg of iron. The diabetic placenta responds to this increased iron need by expressing more transferrin receptor on its apical (maternal facing) surface [17]. This compensation is incomplete, potentially because of the decreased transferrin binding affinity of the hyperglycosylated receptor [18]. The result is only an 11% increase in potential iron transport [17]. The fetus must draw on fetal iron stores primarily in the liver and prioritize available transplacental iron. The resultant redistribution of iron
supports the red cell mass, which becomes polycythemic, at the expense of other developing organs, including the heart and brain, which become iron deficient [19]. An autopsy study of newborn IDMs with severe islet cell hyperplasia demonstrated a 55% reduction in heart iron concentration and a 40% reduction in brain iron concentration [19]. Low cord serum ferritin concentrations, which indicate reduced fetal hepatic iron stores, are found in 65% of live-born IDMs at birth [20].

The functional consequences of fetal iron redistribution and organ iron deficiency are being investigated. Iron is an important factor in cell growth and energetics. Early postnatal iron deficiency results in myopathies and altered neurodevelopment. It is plausible that iron deficiency compromises fetal well-being, which makes the fetus of the mother with diabetes at higher risk for morbidity and mortality.

Cardiac abnormalities

Chronic fetal hyperglycemia and hyperinsulinemia can result in glycogen loading of the intraventricular septum. Although usually diagnosed in the neonatal IDM, a fetal cardiomyopathy can be visualized on prenatal ultrasound and can be reversed slowly with normalization of maternal glycemic control.

Preparation for extrauterine life

Fetal hyperinsulinemia is also likely responsible for delayed functional maturation of many fetal organs. Researchers have hypothesized that insulin inhibits the normal maturational effect of cortisol on the lung [21]. This blunting of the “cortisol surge” before delivery may contribute to the higher incidence of respiratory distress syndrome (RDS) and immature bilirubin metabolism.

Neonatal complications in infants of mothers with diabetes

Abnormal fetal metabolism during pregnancy complicated by maternal diabetes mellitus results in multiple neonatal sequelae, including abnormalities of neonatal body habitus, glucose, calcium and magnesium metabolism, hematologic status, cardiorespiratory function, bilirubin metabolism, and neurologic functioning [5]. A general approach to screening for common derangements is outlined in Table 1 [5,22,23].

Growth

Poor maternal glycemic control predicts neonatal macrosomia, particularly in gestational and early White class women with diabetes. After birth, each infant should be plotted for weight, length, and head circumference on appropriate growth curves. Classically, birth weights more than the ninety-fifth percentile are considered abnormal. Many infants born to mothers with normal glycemic status
can be large for dates, however. Their body habitus, however, is distinctly different than that of the IDM in that they are proportionately large (eg, similar weight, length, and head circumference percentiles). IDMs, because of their increased fat mass [7], have higher weight than length and head circumference percentiles. These differences can be detected through body proportion measurements, such as the Ponderal Index or the mid-arm-circumference-to-head-circumference ratio, which have a better predictive accuracy for identifying infants at risk for metabolic abnormalities in the newborn period [24]. Macrosomia at birth is an excellent marker for detecting the IDM at risk for subsequent neonatal morbidity, including hypoglycemia, hypocalcemia, intraventricular cardiac septal hypertrophy, polycythemia, and iron abnormalities [1,4,16,19,20,24]. Intrauterine growth-restricted IDMs should be plotted on appropriate growth curves to assess degree of growth restriction. Clinical findings of growth restriction include wasted body habitus and decreased body fat and protein mass. Infants with an abnormal Ponderal Index or mid-arm-circumference-to-head-circumference ratio are at increased risk of metabolic sequelae, and their progress should be followed closely.

Glucose metabolism

The newborn IDM undergoes a sudden interruption of glucose delivery in the postpartum period, which, when accompanied by high neonatal insulin levels, results in neonatal hypoglycemia (Fig. 1). Up to 50% of IDMs experience significant hypoglycemia after birth [1]. Hypoglycemia is more common in macrosomic or growth-retarded IDMs than in IDMs who are of appropriate size for gestational age [1]. The nadir in the IDM’s blood sugar usually occurs between 1 and 3 hours of life. The definition of hypoglycemia remains controversial, with

### Table 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>Ultrasound for size and anomalies</td>
</tr>
<tr>
<td></td>
<td>Biophysical profile</td>
</tr>
<tr>
<td></td>
<td>Maternal hemoglobin A1c</td>
</tr>
<tr>
<td>Delivery room</td>
<td>Physical examination for:</td>
</tr>
<tr>
<td></td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Size for dates</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
</tr>
<tr>
<td>Evaluation at postnatal age (h)</td>
<td></td>
</tr>
<tr>
<td>Serum glucose</td>
<td>0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48</td>
</tr>
<tr>
<td>Calcium</td>
<td>6, 24, 48</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Check if calcium low</td>
</tr>
<tr>
<td>Hgb/Hct</td>
<td>4, 24</td>
</tr>
<tr>
<td>Platelet count</td>
<td>24</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Based on clinical jaundice</td>
</tr>
<tr>
<td>Ferritin</td>
<td>24</td>
</tr>
</tbody>
</table>

These guidelines represent initial, minimal assessments. Abnormal parameters must be followed more closely. Adapted from references [5,22,23].
limited outcome data available for symptomatic or asymptomatic hypoglycemia. Because of the lack of consensus, it has been recommended that practitioners aggressively screen at-risk infants and treat those with values less than 40 mg/dL [25].

Neonatal hypoglycemia in the macrosomic IDM primarily is caused by a combination of hyperinsulinemia secondary to pancreatic islet cell hyperplasia and removal of the exogenous (maternal) glucose source at the time of delivery. During pregnancy, elevated maternal serum glucose results in elevated fetal serum glucose. Because insulin does not cross the placenta [1,6], fetal hyperglycemia results in pancreatic stimulation and subsequent hyperplasia of the fetal islet cells. Perinatal stress may have an additive effect on hypoglycemia secondary to catecholamine and glucocorticoid release and glycogen depletion [26]. Reactive hypoglycemia in the IDM tends to occur within 2 hours of birth, persists up to 72 hours, and may even last up to 1 week. Hypoglycemia in the macrosomic IDM is an exaggeration of the normal decrease in serum glucose observed after delivery. Neonatal hypoglycemia also can be seen in growth-retarded IDM with advanced vascular disease. Hypoglycemia in the growth-retarded IDM may be caused by decreased hepatic glycogen stores typically seen in intrauterine growth-retarded infants rather than hyperinsulinemia. Symptoms of hypoglycemia include jitteriness, sweating, tachypnea or apnea, seizures, agitation, and respiratory distress.

The primary goal should be to prevent neonatal hypoglycemia by maintaining tight glucose control throughout pregnancy, thus reducing islet cell hyperplasia. Newborn IDMs should be watched closely for hypoglycemia, particularly infants who are macrosomic or growth retarded. The use of body proportion anthropometric studies, such as the Ponderal Index and the mid-arm-circumference-to-head-circumference ratio, are more sensitive and specific than weight for dates alone for identifying infants who will have hypoglycemia [24]. Universal screening of IDMs is not indicated, nor should they all be admitted for observation to special care nurseries. An assessment of their risk based on maternal history and fetal anthropometrics can narrow the search substantially [24]. For the higher risk infants, serum glucose levels should be checked hourly until feedings are initiated and then checked preprandially for the next several feeds. Early initiation of feedings is highly recommended. Asymptomatic infants with normal serum glucose levels who are stable and able to tolerate feeds do not require intravenous dextrose administration.

Calcium and magnesium metabolism

Hypocalcemia and hypomagnesemia occur within the first 72 hours of birth in up to 50% of IDMs. IDMs who are ill with respiratory distress or have been asphyxiated are at higher risk. Abnormalities in calcium metabolism most likely represent a delayed transition from fetal to neonatal parathyroid control. In utero, the fetal parathyroids are relatively inactive because of the high transplacental flux of calcium. Maternal parathyroid hormone and vitamin D do not cross the placenta in appreciable amounts. During neonatal transition, calcium delivery
decreases. Low fetal parathyroid hormone levels at the end of gestation and persistently high levels of calcitonin and possible alterations in vitamin D metabolism may complicate neonatal calcium homeostasis [4]. These effects may occur for the first 24 to 72 hours, which leaves the newborn vulnerable to early neonatal hypocalcemia [4]. The parathyroid hormone system becomes more reactive after 72 hours. IDMs demonstrate a delay in this postnatal parathyroid hormone response, the pathophysiology of which is not well established. The delay of parathyroid hormone regulation in IDMs is independent of the presence or absence of birth asphyxia.

Hypomagnesemia, defined as a serum magnesium concentration of less than 1.5 mg/dL, may complicate hypocalcemia in newborn IDMs and make treatment of hypocalcemia more difficult. The cause of hypomagnesemia is likely related to the same parathyroid issues that underlie hypocalcemia but may be complicated by maternal hypomagnesemia secondary to renal insufficiency in mothers with long-standing diabetes. Excessive maternal urinary magnesium losses may decrease available magnesium for placental transport to the fetus [1].

The signs and symptoms of neonatal hypocalcemia and hypomagnesemia are similar to those of hypoglycemia and include jitteriness, sweating, tachypnea, irritability, and seizures. They present at 24 to 72 hours, somewhat later than hypoglycemic symptoms. Only IDMs with symptomatic hypocalcemia should be treated by administering 10% calcium gluconate slowly and cautiously, preferably through a central venous catheter. Treatment of hypocalcemia is rarely successful unless accompanying hypomagnesemia is also rectified. Symptomatic hypomagnesemia can be corrected by the slow intravenous administration of 0.5 to 2.5 mL/kg of a 5% solution of magnesium sulfate over 1 hour [27]. Continuous echocardiographic monitoring is mandatory during infusion because of the risk of heart block, refractory bradycardia, and hypotension.

**Hematologic status**

Polycythemia, defined as central hemoglobin concentrations more than 20 g/dL and hematocrit levels more than 65%, is present in 20% to 30% of IDMs at birth [5]. When evaluating for polycythemia, reliance on heelstick hematocrit determinations is not appropriate because the hematocrit from such a specimen is frequently erroneously elevated. Symptoms related to polycythemia are manifestations of resulting blood hyperviscosity. Because blood viscosity is not routinely measured, red cell indices are used as markers of hyperviscosity and associated risks. Chronically accelerated erythropoiesis results in polycythemia, which in turn contributes to the increased incidence of stroke, seizures, necrotizing enterocolitis, and renal vein thrombosis seen in the newborn IDM.

The polycythemic IDM is plethoric, sluggish, and lethargic. Sludging of hyperviscous blood in the cerebral microcirculation may be responsible for these symptoms and those of irritability, jitteriness, and high-pitched cry. These infants are at risk for venous sinus thrombosis that can be detected with neuroimaging studies. The absence of this finding in a symptomatic infant does not mean that
sludging has not occurred, however. The lesions may be in the microvasculature and be undetectable on scan. Polycythemic IDMs with neurologic symptoms should be treated with partial exchange transfusion regardless of whether abnormalities are detectable on neuroimaging tests.

Similarly, renal, intestinal, and pulmonary vascular bed sludging may present overtly or remain subtle. Renal vein thrombosis is more common in IDMs and presents with hematuria, flank masses, thrombocytopenia, and hypertension. Intestinal sludging may present with feeding intolerance or full-blown necrotizing enterocolitis. Pulmonary vascular bed sludging may manifest as persistent pulmonary hypertension and can compromise significantly the IDM with RDS.

An initial hematocrit and platelet count should be obtained shortly after birth. The hematocrit should be followed on a daily basis, with an increase being common in the first 3 days of life. This increase is secondary to the free water diuresis and low fluid intake that occurs during the first 3 days in all newborns. Although a severely polycythemic fetus is at risk for intrauterine infarcts, the risk may increase further in the first 3 days of postnatal life because of this phenomenon. A falling platelet count in a polycythemic IDM is an indicator of significant microvascular sludging and thrombosis in any number of vascular beds secondary to polycythemia.

Management of neonatal polycythemia and hyperviscosity should be based on clinical symptoms rather than absolute hematocrit values. Hematocrit and blood viscosity do not necessarily correlate in individual patients. Consequently, infants with a hematocrit of less than 65% may be symptomatic, whereas infants with hematocrits of more than 65% may remain asymptomatic. Asymptomatic infants with hematocrits from 65% to 70% should be hydrated with intravenous fluids at a rate of at least 100 mL/kg/d, and the hematocrit should be measured daily for the first 3 days. A partial volume exchange transfusion should be performed if the infant becomes symptomatic or the hematocrit rises despite therapy. All symptomatic infants, regardless of hematocrit, and all IDMs with a central hematocrit of more than 70% require an immediate partial exchange transfusion to dilute the blood viscosity.

Iron deficiency

Studies have shown that 65% of all IDMs and up to 95% of large-for-dates IDMs demonstrate abnormalities of iron metabolism at birth [20,28]. Most of these infants have low ferritin concentrations, but more severely affected infants have increased total iron binding capacity concentrations, decreased transferrin saturation, and increased free-erythrocyte protoporphyrin concentration, which indicate accelerated erythropoiesis. The degree of iron abnormalities is a function of fetal hyperglycemia and maternal glycemic control [20]. The functional consequences of neonatal iron abnormalities are under investigation. In theory, compromised non-heme tissue iron status (eg, heart and brain) [19] results in similar myopathy and abnormal neurologic functioning that is seen in infants with postnatal iron deficiency. If this is the case, tissue iron deficiency may provide
a partial explanation for the fragility of these infants in the newborn intensive care unit.

Iron-deficient infants are at increased risk for neurodevelopmental and neuro-behavioral abnormalities [29]. Animal models demonstrate that gestational and early postnatal iron deficiency affects myelination [30], brain energy metabolism [31], and brain monoamine neurotransmitter metabolism [32]. Perinatal iron deficiency seems to increase the vulnerability of the neonatal brain, particularly the hippocampus, to hypoxic-ischemic insult [33]. Perinatal iron deficiency may place IDMs, who have an increased risk of acute and chronic hypoxemia, at even greater risk of perinatal brain injury. A recent study provided evidence that IDMs demonstrate abnormal cognitive processing in the newborn period [34] and that this effect may be related partly to iron status.

Treatment with iron in the newborn period is not likely to be acutely productive because infants are not anemic and repletion of tissue iron is a slow process. A natural redistribution of iron occurs as the newborn IDM breaks down the excess fetal red cells [15] postnatally and iron becomes available to iron-deficient tissues. Spontaneous partial recovery of iron status in these infants has been documented (see later discussion) [35].

Cardiorespiratory function

IDMs are more likely to have respiratory symptoms in the newborn period from either RDS (surfactant deficiency) or retained fetal lung fluid (transient tachypnea of the newborn) after operative delivery. They are more prone to developing RDS than age-matched controls born to mothers without diabetes [4]. This increased risk persists until approximately 38 weeks’ gestation. RDS occurs more frequently in IDMs because of later onset of maturity of the type II alveolar cells [21]. Insulin is believed to antagonize the maturing effect of cortisol, which results in blunted production of dipalmityl lecithin [21]. RDS is secondary to pulmonary surfactant deficiency and is characterized by a loss of lung volume with accompanying microatelectasis.

Ideally, RDS is prevented by excellent maternal glycemic control during pregnancy. Realistically, RDS is best prevented in the IDM by avoiding delivery while the lungs are immature. Because of a known delay in pulmonary maturation in infants born to mothers who are White class A-D, IDMs should be delivered when the lecithin/sphingomyelin (L/S) ratio exceeds 2:1 and phosphatidylglycerol is more than 3% in amniotic fluid samples [22]. Persistent pulmonary hypertension complicates the course of RDS in the IDM, usually in the setting of polycythemia. Polycythemia and RDS are comorbid in IDMs because they both stem from the effects of fetal hyperinsulinemia.

Cardiac functional abnormalities are present in up to 30% of IDMs and include intraventricular septal hypertrophy and cardiomyopathy; 10% may have frank heart failure [1,5]. The intraventricular septal pathology is related directly to the degree of maternal—and thus fetal—hyperglycemia and concomitant fetal hyperinsulinemia, and it is caused by glycogen loading of the septum. It is fre-
quentely seen in association with cardiomyopathy, because septal hypertrophy can result in hypertrophic subaortic stenosis physiology and can compromise cardiac contractility. Although intraventricular hypertrophy and cardiomyopathy are frequently seen together, they are not always comorbid, which suggests that there may be other causes (eg, iron deficiency) for the cardiomyopathy.

During the newborn period, the IDM with septal hypertrophy presents with symptoms of left ventricular outflow obstruction. Dehydration and hyperviscosity caused by polycythemia exacerbate the symptoms. Because the degree of impairment varies considerably, treatment needs vary from close monitoring to full cardiovascular and ventilatory support for congestive heart failure. Inotropes and hypovolemia exacerbate the condition, whereas beta-blockers relieve the outflow obstruction. Ultimately, the lesion is transient and resolves over a period of weeks to months.

**Bilirubin metabolism**

IDMs are at increased risk for hyperbilirubinemia because of an expanded red cell mass, ineffective erythropoiesis, and relative immaturity of hepatic bilirubin conjugation and excretion. The larger red cell mass commonly seen in IDMs provides a 30% larger source of bilirubin that must be conjugated and excreted by the liver. Inefficient conjugation by the relatively immature glucuronosyltransferase enzyme system results in increased serum unconjugated bilirubin concentrations. IDMs have an additional source of bilirubin because of inefficient erythropoiesis. Red cell precursors are circulated but are trapped in the spleen and removed. The breakdown of these red cells contributes an additional bilirubin load to the liver. The inefficient bilirubin processing system in the newborn IDM results in a more rapid rate of rise accompanied by a later peak in the serum bilirubin concentration. Because the neonatal hemoglobin is a function of the lack of maternal glycemic control [16], one can expect that macrosomic IDMs will have the most abnormal bilirubin metabolism. Serum bilirubin concentrations should be monitored starting in the first 24 hours and may need to be followed for up to 5 days, potentially requiring outpatient assessment.

**Neurologic function**

IDMs can present with acute neurologic abnormalities secondary to central nervous system dysfunction. Central nervous system changes occur as a result of perinatal asphyxia, glucose and electrolyte abnormalities, polycythemic vascular sludging, and birth trauma [1,4,12,16]. The timing of the neurologic symptoms may provide clues as to cause. Symptoms from perinatal depression or hypoglycemia typically have their onset in the first 24 hours postpartum, whereas symptoms from hypocalcemia or hypomagnesemia present between 24 and 72 hours of life. Cerebral symptoms may include seizures, jitteriness, lethargy, changes in tone, and movement disorders. The spinal cord is also vulnerable to birth trauma with symptoms related to palsies of the brachial plexus.
The macrosomic IDM is particularly vulnerable to birth asphyxia as a consequence of fetal macrosomia, which increases the risk of shoulder dystocia during delivery, and a compromised prenatal milieu characterized by fetal hypoxia, cardiomyopathy, and tissue iron deficiency. The latter three factors may decrease the IDM’s tolerance to the stress of delivery and may limit the response of the infant to respond optimally to resuscitation. Signs and symptoms of perinatal asphyxia include initial hypotonia or flaccidity followed by increasing tone, jitteriness, and seizure risk. The risk of seizures from birth asphyxia typically peaks at 24 hours of age [36]. Initial treatment consists of correcting any underlying metabolic or hematologic abnormality before the initiation of anticonvulsant agents. Treatment of the underlying disorder frequently aborts the seizures without recurrence.

Neurologic state changes are common in compromised IDMs. More commonly, symptoms include lethargy and hypotonia, but jitteriness and hypertonicity can occur. Potential factors that contribute to the classic picture of the plethoric, sluggish IDM are perinatal depression, glucose and electrolyte abnormalities, polycythemia, cardiomyopathy, and tissue (eg, brain) iron deficiency. These symptoms may persist for up to a week. The lethargic IDM tends to be a poor feeder.

Jitteriness is defined as extreme irritability or hypertonicity with tremulousness that ceases with physical restraint. It can be distinguished from seizure activity, which is not extinguished with restraint. The cause of jitteriness is likely multifactorial and typically relates either to glucose or electrolyte abnormalities, which make the brain more irritable (ie, hypoglycemia, hypocalcemia, hypomagnesemia), or to hypoxic events at delivery.

Brachial plexus injuries, including Erb’s palsy (roots C5-7), Klumpke’s paralysis (roots C7-8), diaphragmatic nerve paralysis (roots C3-5), and recurrent laryngeal nerve damage (roots T1-2), are more common in the macrosomic IDM and are related to the stretching of the neck during delivery [5].

**Long-term sequelae in offspring of mothers with diabetes**

The long-term health of IDMs can be affected by the periconceptional, fetal, and neonatal pathologies discussed previously. The major issues revolve around long-term risks of obesity and diabetes, neurologic outcome, and iron status. There is no strong evidence that large-for-date newborn infants grow up to be fat children and adults. Most seem to return to a genetically programmed growth curve well within the population standards. Diabetes mellitus clearly has a genetic component; thus, it is not surprising that some IDMs will be more likely to develop diabetes later in their lives.

IDMs are at increased risk for delayed motor and cognitive development that may manifest later in life [37]. The long-term delays can be a function of acute perinatal events (eg, birth asphyxia) or may be related to alterations in brain development from the adverse intrauterine environment characterized by hypoxemia, hypo- or hyperglycemia, acidosis, and iron deficiency. The risk of adverse
neurologic outcome is a function of abnormal neonatal glucose, calcium and magnesium metabolisms, degree of fetal hypoxia, polycythemia, and iron deficiency, and the presence of birth trauma and asphyxia.

The prognosis of IDMs with neonatal seizures varies depending on the cause of the seizures [36]. Infants who experience seizures secondary to metabolic derangement (eg, hypoglycemia, hypocalcemia) carry a 10% to 50% risk of subsequent neurodevelopmental abnormality; 80% of infants who suffer seizures from hypoxic-ischemic encephalopathy exhibit developmental delays [36].

Several recent studies have centered on the long-term neurodevelopmental outcome of IDMs [34,37,38]. Evidence points toward an increased risk of developmental abnormalities secondary to metabolic derangements. Rizzo et al [37] studied the effect of abnormal antepartum maternal glucose and lipid metabolism on the long-range neurobehavioral development of children. Despite vigilant antepartum and obstetric management of maternal diabetes, they found numerous significant correlations between indices of maternal second- and third-trimester lipid and glucose regulation and child intellectual performance up to age 11 years. All such correlations suggested that poorer maternal metabolic regulation correlated with poorer child performance on standard measures of neuropsychological functioning.

One of the confounding variables encountered in interpreting the effects of fetal or neonatal events on neurodevelopment is the fact that the subjects are tested long after the insult has occurred. Abnormalities in a population detected at school age may reflect the effects of an adverse intrauterine environment or, alternatively, may be a function of the postnatal environment between birth and testing. Recently, great strides have been made in tools that assess brain structure and function of newborn infants, which allow a more definitive association with fetal and neonatal events.

To this end, we have used event-related potentials to assess recognition memory processing in newborn IDMs [34]. Event-related potentials are epochs in the electroencephalographic record obtained from a standard newborn montage that are time-locked to the performance of a memory task. In the case of newborns, the ability to discriminate a familiar sound stimulus (eg, mother’s voice) from a new stimulus (eg, a stranger’s voice) can be discriminated by different patterns of electroencephalographic activity 800 to 2000 msec after stimulus onset [34]. Whereas control infants born to mothers without diabetes mellitus show significant differences in event-related potentials waveform to mother-versus-stranger stimuli, IDMs do not [34]. The structures underlying recognition memory include the hippocampus [39], a brain area that in animal models is vulnerable to hypoxia-ischemia [40], hypoglycemia, and iron deficiency [31]. Follow-up event-related potentials testing at 6 and 8 months using visual recognition memory and cross-modal learning demonstrates continued impairment of these hippocampally based cognitive functions [38,41]. Structural damage to the developing hippocampus during fetal life may be responsible for these persistent findings.

Follow-up studies of iron nutrition in a small number of IDMs suggest that they are truly iron deficient and do not simply exhibit a redistribution of fetal
iron. They demonstrate significantly lower 9-month ferritin concentrations, which potentially confer a greater risk of late-onset iron deficiency during the second postnatal year [35]. There have been no controlled trials of iron supplementation in newborn IDMs. In a small cohort followed prospectively without iron supplementation beyond the milk source, no infant with low iron stores at birth had iron deficiency or iron-deficiency anemia at follow-up [35]. The mean ferritin concentration in the group with low birth iron was significantly lower than the control group with normal birth iron. Infants who are not breastfed should receive a formula that contains at least 4.5 mg of iron per liter during the first year because of the risk of iron deficiency and its attendant developmental sequelae [42]. We recommend that all large- and small-for-date IDMs have serum ferritin and hemoglobin concentrations measured in the newborn period. Infants with abnormally low ferritin concentrations should have follow-up values determined at 6 to 9 months of age. If the values are persistently low, iron supplementation, using the same supplementation regimen as for other iron-deficient children, should be considered.

**Prenatal diagnosis and management of diabetes during gestation**

Strict maternal glycemic control during a pregnancy complicated by diabetes mellitus reduces neonatal morbidity and mortality. Periconceptional glucose control seems to reduce the incidence of congenital anomalies. Fetal hyperinsulinemia and its associated metabolic abnormalities can be reduced by maintaining tight glycemic control after 28 weeks’ gestation [5]. Similarly, fetal macrosomia can be prevented by appropriate glycemic control from 32 weeks’ gestation until term.

Controversy has existed regarding appropriate diagnosis and management of gestational diabetes. Unfortunately, well-designed studies are lacking in regard to these issues. The American College of Gynecologists has issued a practice bulletin based on available clinical research and expert opinion, however [43]. A 1-hour oral glucose challenge of 50 g should be performed at 24 to 28 weeks’ gestation. A serum glucose level of less than 130 to 140 g/dL 1 hour after ingestion is considered normal. Women who fail the 1-hour screening should proceed to a 3-hour glucose tolerance test.

There has been some discussion regarding limiting universal screening, which essentially eliminates the screening of low-risk women who are less likely to benefit from testing [43]. This group of women would have all of the following characteristics: younger than 25 years of age, not a member of a racial or ethnic group with high prevalence of diabetes, body mass index of 25 or less, no history of abnormal glucose tolerance, no previous history of adverse pregnancy outcomes usually associated with gestational diabetes mellitus, and no known diabetes in a first-degree relative. On the other hand, more aggressive testing in high-risk populations seems prudent. This screening would target populations of women from groups with a high prevalence of diabetes (Hispanic, African, Native American, South or East Asian, or Pacific Islands ancestry) [43], women with a
history of abnormal glucose tolerance or a history of adverse pregnancy outcomes usually associated with gestational diabetes mellitus, and obese women. It is possible that preconceptional testing of hemoglobin A1c concentrations in these high-risk populations might identify women at risk for abnormal glucose homeostasis. Such patients could be counseled and followed in the periconceptional period, with a goal of normal glucose homeostasis before pregnancy. The goal of early identification and intervention would be to reduce the incidence of abnormal organogenesis because this fetopathy frequently occurs before a woman knows she is pregnant.

The health care provider who cares for the IDM postnatally should be conversant with the common maternal and fetal surveillance testing procedures during pregnancies complicated by diabetes. Specific knowledge regarding the pregnancy course (including aspects of maternal glycemic control), the plans for timing of the delivery, and the expected neonatal complications should be obtained before the delivery of the infant. A review of antepartum hemoglobin A1c levels before delivery may provide some insight into the potential for neonatal complications in the IDM. The incidence of complications has been reported as 3.4% and 22.4% with HbA1c levels lower than 8.5% and higher than 8.5%, respectively [1]. Specific attention should be paid to values documented after 32 weeks’ gestation, because these values have been correlated with neonatal macrosomia, polycythemia, and hypoglycemia [1]. Infants born to mothers with an HbA1c level more than 10% in late pregnancy should be expected to present with neonatal complications.

The goal of fetal surveillance differs with gestational age. The first trimester goal is to verify viability, whereas structural integrity is validated during the second trimester. The goal during the third trimester is to monitor fetal growth and ensure fetal well-being. A detailed scheme for fetal surveillance throughout pregnancy is outlined by Moore [22]. Maternal serum alpha-fetoprotein levels measured at 16 to 18 weeks’ gestation and fetal ultrasound studies should be reviewed to evaluate for possible congenital anomalies [22]. Non-stress tests are recommended twice weekly starting at 32 weeks’ gestation [22], with a contraction stress test if the non-stress tests are non-reassuring. Results of these tests, maternal history of fetal movement, and quantitative biophysical profile provide information regarding fetal well-being and potential for perinatal asphyxia.

Assessment of fetal lung maturity, particularly in persons with insulin-dependent diabetes with borderline mature pregnancies (eg, 35–37 weeks’ gestation), is important. The managing practitioner should make an attempt to confirm fetal maturity before induction of labor or planned cesarean section. Criteria for confirmation include normal last menstrual period, pelvic examination before 12 weeks’ gestation and sonogram before 24 weeks’ gestation to confirm dates, completion of 38.5 weeks’ gestation, and phosphatidylglycerol more than 3% in amniotic fluid [22].

Preparation for delivery of an IDM who exhibits fetal distress—or any such infant—including preparing for resuscitation of a depressed infant. Because of an increased risk of pulmonary hypertension, supplemental oxygen should be used...
to maintain oxygen saturations more than 95%, which allows for a smooth transition from fetal to neonatal circulation.

Summary

Advances in the management of mothers with diabetes have reduced the rate of morbidity and mortality for their infants. Aggressive control of maternal glycemic status is warranted because most morbidities are epidemiologically and pathophysiologically closely linked to fetal hyperglycemia and hyperinsulinemia. Although rates of complications are lower than in previous eras, there may be a resurgence of IDMs within the next 10 years. The burgeoning public health problem of overweight and obesity in children likely will result in an increased incidence of metabolic syndrome X, characterized by insulin resistance and type II diabetes in adulthood. An early manifestation of this may be glucose intolerance during pregnancy in overweight women without diabetes. Clinicians must continue to have a high degree of suspicion for the diagnosis of diabetes during gestation and for screening the offspring of women with gestational diabetes for neonatal sequelae.

References


