The Effects of Maternal Diabetes on the Fetus and Neonate

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The outlook for the fetus and infant of the diabetic mother has changed remarkably over the past 70 years. Following the discovery of insulin in 1922, young diabetic women who were previously practically infertile, were introduced to the option of conceiving and bearing children. Pregnancy-related maternal mortality, which had previously been extremely high in this group of patients, fell dramatically after the advent of exogenous insulin. Nevertheless, perinatal morbidity and mortality remained unacceptably high. Over the past 20 years, there has been growing understanding of the pathophysiology of the diabetic pregnancy, development of specialized health care centers for pregnant diabetic women, and remarkable improvements in neonatal care. All these have conjointly resulted in a markedly improved prognosis for the infant of the diabetic mother. Despite these optimistic undertones, it is prudent to bear in mind that these unborn infants developing in the sweet maternal environment are set out for a bitter struggle against some rather unfavorable odds.

Genetic Considerations

One of the issues which is often concerning to the diabetic patient is the risk of transmitting the disease to the offspring. This will depend on the type of diabetes in question. Type I, insulin-dependent diabetes mellitus (IDDM, juvenile-onset diabetes) is a chronic, autoimmune disease that occurs in genetically susceptible individuals. Although no genetic marker has yet been identified for IDDM, a major component of genetic susceptibility has been identified within the D region of the HLA complex, on the short arm of chromosome 6. It seems that IDDM is a polygenic disorder with variable forms of expression, possibly requiring the interaction of at least five different susceptibility genes and
environmental factors. Interestingly, several investigators have reported a greater risk of IDDM for offspring of diseased fathers (4.1 percent to 6.1 percent) than of mothers (1.3 percent to 1.7 percent).29,157,168 Possible mechanisms to explain these sex differences could be increased fetal wastage of the infant at risk for diabetes born to a diabetic mother, and some form of protection acquired by the fetus exposed to maternal diabetes in utero.166

Type II non-insulin dependent diabetes mellitus (NIDDM, adult-onset) is the most common form of diabetes, and many women with this disorder are in the reproductive age group. There are no proven genetic markers for NIDDM but it clearly has strong heterogenic genetic associations. Thus, it is extremely difficult to counsel the patient on the risk of the offspring eventually developing NIDDM later in life.

Diabetic Embryopathy

The developing embryo of the insulin dependent diabetic (IDD) mother is exposed to an altered milieu which may exert devastating toxic effects, resulting in a spectrum of pathologic consequences. An early insult following fertilization may result in a blighted ovum. Later, such an insult may result in spontaneous abortion or disruption of embryogenesis with the development of major congenital malformations. Later on, insults may result in minor congenital malformations. Besides timing, the intensity of the insult may also be important in determining its consequences. In addition, diabetic embryopathy may be conditioned by the interplay between genetic predisposition and environmental triggers.

The specific toxic mediators and teratogenic mechanisms in diabetes have yet to be determined. Current data suggest that some aspect of glycemic control, or perhaps a related factor such as ketogenesis, is important. Animal studies have ascribed embryopathy to the effects of β-hydroxybutyrate,142 insulin,79 disruption of arachidonic acid52 and glycolytic metabolic pathways,41 decreased fetal zinc uptake, increased fetal manganese uptake,34 somatomedin inhibitors,40,139 hyperosmolarity,19,40 and biophysical modifications via non-enzymatic glycosylations.40 Taken together, these studies indicate that no single parameter of the diabetic state can be viewed in isolation in an attempt to correlate diabetic embryopathy with maternal diabetic control.

Spontaneous Abortion

Whether or not IDDs do indeed have an increased rate of spontaneous abortion (SA) is a matter of controversy. A recent comprehensive review68 of 58 studies spanning 37 years stated an overall rate of 10 percent, probably not different than the rate of SA in the general population (which may also be impossible to ascertain categorically). However, most of these studies suffer from methodological shortcomings that cloud their interpretation. The rate of SA in prospective, well designed studies of IDD pregnancies, has ranged from 15 to 30 percent.96,111,114 Several investigators have reported an association between SA and poor glycemic control in the first trimester, as reflected by higher glycohemoglobin concentrations54,72,96,114,117 (table I). Furthermore, SA were shown to be related to glycemic control in the period close to conception rather than prior to the abortion itself (table II).111 Patients that gain experience in a program specializing in diabetic pregnancies, and patients participating in a preconceptional program have improved glycemic control early in pregnancy and have less SA.31,110,137 The association between SA and poor glycemic control has been demonstrated even in SA occurring after
TABLE I

First Trimester Glycemic Control and Spontaneous Abortions in insulin-dependent Diabetes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Good Control</th>
<th>Poor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al</td>
<td>GH &lt;13%</td>
<td>≥13%</td>
</tr>
<tr>
<td></td>
<td>SAB 21.4%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Miodovnik et al</td>
<td>GH &lt;12%</td>
<td>≥12%</td>
</tr>
<tr>
<td></td>
<td>SAB 16.2%</td>
<td>45.4%</td>
</tr>
<tr>
<td>Key et al</td>
<td>GH &lt;13.4%</td>
<td>≥13.4%</td>
</tr>
<tr>
<td></td>
<td>SAB 16.6%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Mills et al</td>
<td>GH ≤8 SD</td>
<td>&gt;8 SD</td>
</tr>
<tr>
<td></td>
<td>SAB 11.1%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Greene et al</td>
<td>GH ≤9 SD</td>
<td>&gt;9 SD</td>
</tr>
<tr>
<td></td>
<td>SAB 10.5%</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

**GH** = first trimester glycohemoglobin concentration.
**SAB** = spontaneous abortions.
**SD** = standard deviations above mean of non-diabetic population.

Whatever the mechanism, it appears that obtaining good glycemic control prior to conception and throughout the first trimester can reduce the risk of SA in diabetic pregnancies.

**Congenital Malformations**

Congenital malformations (CM) have emerged as the single most important cause of perinatal mortality among infants of diabetic mothers (IDMs), accounting for 50 percent of perinatal deaths, compared to 20 to 30 percent in infants of non-diabetic mothers.69

Women who are insulin-dependent at the time of conception are at high risk for having a malformed fetus, a fact that has been appreciated for decades. Women with gestational diabetes are probably not at increased risk, but it is unclear what the risk for CM is in women who are Type II non-insulin dependent diabetics diagnosed prior to or with the onset of pregnancy. Although there are clear genetic linkages with both Type I and Type II diabetes, this does not seem to bear any relationship to the incidence of CM in diabetic pregnancies, since there is no increased risk for infants of fathers with diabetes.5 Based on data from the World Health Organization, major CM occur in 1.65 percent of the general population.76 The rate of major CM in IDMs is at least three to five times higher than in the non-diabetic population,3,20,44,76,85,132 reported in four to 11 percent of IDD pregnancies. In this sense, diabetes may be considered a teratogen, but it differs from other known teratogens in generally not having a specific phenotypic expression, such as may often be encountered with other teratogenic agents. A whole range of organ systems may be affected in IDD pregnancies, resulting in defects in the cardiac, central nervous, genitourinary and skeletal systems. Many of the defects that are most common in the general population occur at increased rates in IDMs. Certain anomalies, such as sacral dysgenesis, or holoprosencephaly, carry an extremely high risk in IDMs, but their actual incidence is very small as they are extremely rare in the general population. Con-
TABLE II *

Glycemic Control and Spontaneous Abortion in Insulin dependent Diabetic Women

<table>
<thead>
<tr>
<th></th>
<th>Pregnancies of 20 Weeks’ Gestation or More</th>
<th>Spontaneous Abortions</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>60</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>66</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Maternal age (yr)</td>
<td>24.9 ± 0.5</td>
<td>24.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>11.3 ± 0.7</td>
<td>13.6 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Weeks of outcome</td>
<td>36.4 ± 0.3</td>
<td>11.9 ± 0.4</td>
<td>—</td>
</tr>
<tr>
<td>Mean initial maternal glycohemoglobin (%) a</td>
<td>10.7 ± 0.3</td>
<td>12.0 ± 0.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Weeks of gestation at glycohemoglobin sampling</td>
<td>7.4 ± 0.2</td>
<td>7.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean initial glycosylated proteins (%) b</td>
<td>22.2 ± 0.7</td>
<td>22.7 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Mean initial glycosylated albumin (%) c</td>
<td>15.1 ± 0.6</td>
<td>14.2 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Weeks of gestation at glycosylated proteins and albumin sampling</td>
<td>9.0 ± 0.2</td>
<td>8.9 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard error. NS = not significant.

a Normal range: 5.5 – 8.5 percent.
b Normal range: 9.8 – 22.5 percent.
c Normal range: 7.2 – 22.1 percent.

Initial glycohemoglobin (reflecting glycemic control during the previous four to eight weeks) is significantly higher in pregnancies that resulted in spontaneous abortions. Glycosylated proteins and glycosylated albumin (reflecting recent glycemic control during the previous two to four weeks) are not different between groups.


versely, although the relative risk for cardiac anomalies is only approximately three to four times higher,76,115 these malformations constitute the greatest problem in IDMs because of their high frequency in the general population.

Given the known organogenetic sequences in the embryo, the most common anomalies in IDMs cannot occur later than three to six weeks after conception.94 For example, the central nervous system is formed by four weeks, the urinary system by five weeks, and the cardiac structures by six weeks after conception. Thus, the critical period for CM is usually over by the time pregnancy becomes clinically apparent and the mother seeks prenatal care.

Several studies have established the relationship between CM and poor glycemic control during the first trimester in IDDs.43,54,72,86,91,109,178 These observations support the aforementioned contention that the timing of uncontrolled diabetes is a major determinant of the embryopathic manifestations.105 An increased risk of CM has also been associated with the presence of vasculopathy in the diabetic mother.91,109 A recent prospective and controlled nationwide collaborative study failed to demonstrate the expected relation of increased malformation rates to glycemic control. Given the theory of fuel-mediated teratogenesis,40 this finding is somewhat surprising, particularly as the very same study did find a relationship between spontaneous abortion and glycemic control in IDDs.96 However, patients in this study were all recruited either precon-
ceptionally or within three weeks of conception, and it may well be that most did not have uncontrolled diabetes during the critical period of organogenesis, beyond the theoretical threshold for an observed increase in the rate of CM. Furthermore, major malformations were defined in this study as those causing death or a serious handicap requiring medical therapy or surgical correction (and not necessarily major surgery), and lesions such as paraurethral cyst, strawberry hemangioma and labial fusion were included in this category. There is no uniform agreement that these lesions would be considered major malformations. In addition, glycohemoglobin concentrations were determined using a thiobarbituric acid method which may be affected by storage. The authors themselves were careful in emphasizing that there is ample evidence to justify the recommendations to attain stable, good diabetic control in the periconceptional period and throughout pregnancy.

In a recent study from our group, minor CM were found in 19 percent of IDDs, associated with poor glycemic control late in the first trimester and early in the second, suggesting that these malformations are related to glycemic control in the late embryonic and early fetal development period (table III). Studies relating congenital malformations to glycemic control early in pregnancy are summarized in table IV.

Prevention of CM in IDMs focuses on preconceptional and early postconceptional control of IDDs, and early detection of CM in utero. Clearly, the patient with abnormally high glycohemoglobin levels (for which there is currently no standard definition), is at increased risk for an infant with CM. Early and thorough sonographic examinations and fetal echocardiography will identify many of the anomalies in these pregnancies. Screening patients for alpha-fetoprotein levels in the serum is performed routinely in all pregnant women for early detection of neural tube defects. However, it should be noted that these levels may be consistently lower in poorly controlled diabetic women compared to non-diabetic women, and results must be interpreted accordingly.

<table>
<thead>
<tr>
<th>TABEL III *</th>
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<tbody>
<tr>
<td>Minor Malformations in Infants of Insulin-dependent Diabetic Mothers</td>
</tr>
<tr>
<td>Association with Glycemic Control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks Gestation</th>
<th>Malformation (n = 32)</th>
<th>No Malformation (n = 139)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycohemoglobin (%)</td>
<td>8</td>
<td>10.6 ± 1.7</td>
<td>9.8 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10.0 ± 1.6</td>
<td>9.0 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>9.1 ± 1.5</td>
<td>8.3 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8.9 ± 1.3</td>
<td>7.9 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>8.1 ± 0.9</td>
<td>7.8 ± 1.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Glycohemoglobin at 12, 16, and 20 weeks' gestation is significantly higher in the group whose infants were born with minor congenital anomalies, reflecting poor glycemic control during late embryonic and early fetal development.

TABLE IV
First Trimester Glycemlc Control and Congenital Malformations In Infants of Diabetic Mothers

<table>
<thead>
<tr>
<th>Reference</th>
<th>Good Control</th>
<th>Poor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al \textsuperscript{91}</td>
<td>GH &lt; 10 %</td>
<td>≥ 10 %</td>
</tr>
<tr>
<td>Yllnen et al \textsuperscript{179}</td>
<td>GH &lt; 10 %</td>
<td>≥ 10 %</td>
</tr>
<tr>
<td>Fuhrman et al \textsuperscript{43}</td>
<td>GH &lt; 10 %</td>
<td>≥ 10 %</td>
</tr>
<tr>
<td>Key et al \textsuperscript{72}</td>
<td>GH &lt; 9.5 %</td>
<td>≥ 9.5 %</td>
</tr>
<tr>
<td>Mlodovnik et al \textsuperscript{109}</td>
<td>GH ≤ 4 SD</td>
<td>&gt; 4 SD</td>
</tr>
<tr>
<td>Mills et al \textsuperscript{95}</td>
<td>GH ≤ 4 SD</td>
<td>&gt; 4 SD</td>
</tr>
<tr>
<td>Greene et al \textsuperscript{54}</td>
<td>GH &lt; 9.4 %</td>
<td>≥ 9.4 %</td>
</tr>
<tr>
<td>Lucas et al \textsuperscript{86}</td>
<td>GH &lt; 8 %</td>
<td>≥ 8 %</td>
</tr>
<tr>
<td>Rosenn et al \textsuperscript{136}</td>
<td>GH\textsubscript{20} &lt; 2 SD</td>
<td>≥ 2 SD</td>
</tr>
</tbody>
</table>

GH = first trimester glycohemoglobin concentration.

GH\textsubscript{20} = glycohemoglobin concentration at 20 weeks' gestation.

SD = standard deviations above mean of non-diabetic population.

CM = major congenital malformations.

MnCM = minor congenital malformations.

Abnormal Fetal Growth

MACROSOMIA

Macrosomia has long been recognized as one of the hallmarks of diabetic fetopathy, found in 15 to 40 percent of diabetic pregnancies.\textsuperscript{6,22,59,62,81} Macrosomia is most commonly defined as birth weight that exceeds the 90th percentile of a reference population, by gestational age, or birth weight greater than 4000 grams. Normal infants who are constitutionally large will obviously, also be labeled macrosomic, but the macrosomia characteristic of the diabetic pregnancy is associated with altered body composition with increased body fat and may, therefore, be considered abnormal. Excessive fetal size is the principal factor contributing to the increased risk of birth trauma in IDM s, with such mishaps as shoulder dystocia, asphyxia, brachial plexus injuries, and facial nerve palsies.\textsuperscript{81,160} Macrosomia is also a major factor in the increased rate of cesarean delivery among diabetic women.\textsuperscript{81} Despite the prevailing trend in maintaining fairly strict glycemic control throughout pregnancy, it seems that the frequency of macrosomia has not decreased over the past decade.\textsuperscript{126,141}

A biphasic intrauterine growth pattern has been observed in IDM s.\textsuperscript{143} An initial phase of early fetal growth delay in the first half of pregnancy,\textsuperscript{35,124} affecting both head and abdominal growth, is followed by the typical accelerated abnormal fetal growth in the third trimester, with abnormal adipose deposition and distribution, visceral organ hypertrophy and hyperplasia, and acceleration of skeletal growth.\textsuperscript{119}

Pedersen's original hypothesis\textsuperscript{123} suggested that macrosomia in IDM s is related to fetal pancreatic \( \beta \) cell hypertrophy and hyperinsulinism, secondary to maternal hyperglycemia. There is, indeed, evidence that \( \beta \) cells in these infants undergo hypertrophy and hyperplasia, and also demonstrate increased insulin content.\textsuperscript{16} Insulin is a major anabolic growth hormone of the fetus\textsuperscript{80} that increases cell size by stimulating protein synthesis\textsuperscript{18} and increases glucose uptake and glycogenesis in peripheral tissues.\textsuperscript{9} This intrauterine hyperinsulinemic state results in increased tissue fat, liver glycogen content, and total body size.\textsuperscript{39}
It is possible that fetal hyperglycemia, secondary to maternal hyperglycemia, is not the sole etiologic stimulus for endogenous fetal hyperinsulinemia. The roles of insulinogenic amino acids and of insulin-like growth factors in this context have not been established. Furthermore, although it is generally believed that maternal insulin binds to placental receptors, but does not cross the placenta, antibody-bound maternal insulin may be found in the fetal circulation and may, in theory, exert anabolic effects. A recently published study demonstrated the transfer of considerable amounts of antibody-bound insulin from mother to fetus in some IDDs treated with animal insulin. Cord serum concentrations of animal insulin and anti-insulin antibodies correlated with the maternal concentrations of anti-insulin antibody. Concentrations of animal insulin in cord serum also correlated with fetal macrosomia leading to the authors' conclusion that antibody-bound animal insulin transferred to the fetus has an etiologic role in fetal macrosomia. However, this conclusion does not seem to be supported by the authors' data: the infants with macrosomia also had significantly higher cord serum concentrations of human (presumably of fetal origin) and total insulin than the infants without macrosomia. The incidence of macrosomia has recently been studied by us in 209 IDDs, 170 of whom were treated with animal insulin and 39 with human insulin. There were no differences between groups in infants' birth weights, ponderal indices or rate of macrosomia. Whether or not strict glycemic control of the pregnant IDD can prevent macrosomia is a controversial issue. Although some investigators have found an association between glucose control and macrosomia with no excessive birth trauma in infants of well-controlled diabetics, many others have failed to demonstrate such a relationship.

Thus, it appears that unless excellent glycemic control is maintained throughout pregnancy (and possibly even so), approximately 20 to 30 percent of IDMs will be born with excessive weight and size. Ultrasound is routinely used for identifying the macrosomic infant before delivery so that steps may be taken to avoid birth trauma. Nevertheless, most widely used formulae for calculation of fetal weight using ultrasound measurements underestimate actual weight by 300 to 1000 grams, a fact that should be considered in regard to obstetric management in these patients.

**Hypertrophic Cardiomyopathy**

Infants of diabetic mothers are at known risk for developing a hypertrophic type of cardiomyopathy with a thickened interventricular septum and thickened ventricular walls. Myocardial changes include hypertrophy and hyperplasia of the myofibrils and a peculiar disruption of the normal myofibrillar pattern. The hypertrophic muscle restricts filling and obstructs outflow, thus decreasing stroke volume and cardiac output. The severity of IDM cardiomyopathy can vary from incidental echocardiographic findings to severe heart failure. Several studies have noted that the risk of cardiomyopathy is associated with poor maternal glycemic control. As noted previously, maternal hyperglycemia is associated with fetal hyperinsulinemia, macrosomia, and visceromegaly of the liver, heart and placenta. Cardiac hypertrophy was also found in fetal Rhesus monkeys who were rendered hyperinsulinemic.

The spectrum of cardiorespiratory symptoms in the newborn with cardiomyopathy includes cyanosis, tachypnea, tachycardia, and features of congestive heart failure. The majority of these infants need only supportive care, since the cardiorespiratory symptoms usually
resolve within the first weeks of life, although the septal and wall hypertrophy may take many months to resolve.

Metabolic Aberrations

**HYPOCALCEMIA AND HYPOMAGNESEMIA**

The most significant clinical problem of calcium metabolism in the diabetic pregnancy is neonatal hypocalcemia, which may occur in 50 percent of IDMs during the first three days of life. Furthermore, the rate and severity of hypocalcemia are directly related to the severity of maternal diabetes. Hypomagnesemia also occurs frequently in IDMs, reported in up to 38 percent of newborns and associated with the severity of maternal diabetes and with prematurity. Amniotic fluid concentrations of magnesium are decreased in diabetic pregnancies. The cause of hypomagnesemia and hypocalcemia in IDMs is not fully understood. It has been suggested that the hypomagnesemia in IDMs may develop owing to maternal magnesium losses related to diabetes during pregnancy which result in reduced maternal and secondarily reduced fetal serum magnesium concentrations, which causes decreased fetal urinary excretion of magnesium and decreased amniotic fluid magnesium concentrations. Magnesium deficiency in the infant may cause a functional hypoparathyroidism that could result in neonatal hypocalcemia when the newborn is no longer provided with calcium of maternal origin through the placenta.

Bone mineral content is also decreased in IDMs, in direct association with maternal bone mineral content at delivery and poor glycemic control. One speculation that could explain this observation is that increased serum 1,25-(OH)₂D concentrations in these infants have a potent effect on bone resorption and might be detrimental to bone mineralization. Decreased bone mineral content has not been correlated with neonatal hypocalcemia, possibly owing to the large bone reservoir of calcium relative to blood.

**NEONATAL HYPOGLYCEMIA**

Neonatal hypoglycemia is a frequent complication in IDMs. The reported incidence of hypoglycemia, occurring in the first four hours of life in these infants ranges from 10 to 50 percent with little change in this frequency observed over the last 20 years. The mechanism responsible for the occurrence of hypoglycemia has not been clearly established. However, several hypotheses have been proposed. Pedersen's classic model states that maternal hyperglycemia causes fetal hyperglycemia and islet cell stimulation leading to fetal hyperinsulinemia. At birth, interruption of the maternal glucose supply to the hyperinsulinemic neonate results in hypoglycemia. Several authors have suggested alternatively that acute hyperglycemia in the diabetic mother at the time of delivery may be the major etiologic determinant in the occurrence of neonatal hypoglycemia. At birth, peripartum hyperglycemia results in an acute release of insulin by the fetal pancreas and, following the abrupt termination of transplacental glucose supply, hypoglycemia occurs. Another plausible possibility relates to the fact that maternal insulin bound to IgG antibodies freely crosses the placenta and circulates in the fetal blood at levels very similar to those of the mother. Withdrawal of maternal glucose at birth may then result in neonatal hypoglycemia. Whatever the cause, neonatal hypoglycemia tends to be much milder in the infant whose mother is well controlled.
throughout pregnancy, and maintained euglycemic throughout labor and delivery.\textsuperscript{62} Close monitoring of the infant’s blood glucose concentration, and intravenous supplementation when necessary combined with early feeding within the first hours of life, further decrease the incidence of severe neonatal hypoglycemia.

The long-term prognosis of neonatal hypoglycemia is unknown. Low blood glucose values should be recognized and treated promptly, because prolonged hypoglycemia is clearly associated with central nervous system abnormalities in children and adults.\textsuperscript{62}

**Polycythemia**

Neonatal polycythemia, defined as a venous hematocrit of 65 percent or more, occurs in three to five percent of all newborns,\textsuperscript{147,176} but it has been observed in up to 29 percent of IDMs.\textsuperscript{99,106} Neonatal polycythemia and its related increased viscosity may be associated with a spectrum of clinical sequelae, including cardiopulmonary failure, decreased renal function, renal vein thrombosis, necrotizing enterocolitis, and central nervous system damage.\textsuperscript{8}

In the pregnant IDD, fetal hyperglycemia and hyperinsulinemia lead to reduced fetal arterial oxygen content.\textsuperscript{127,151} Hyperketonemia in maternal and fetal sheep have the same effect.\textsuperscript{24,139} Fetal hypoxemia may stimulate erythropoiesis, and elevated concentrations of erythropoietin have, indeed, been demonstrated in cord blood of IDMs\textsuperscript{71} and in hyperglycemic fetal lambs.\textsuperscript{129} Furthermore, acute maternal hypoxia in non-diabetic pregnancies results in acute fetal hypoxia and a significant shift of placental blood volume into the fetal compartment.\textsuperscript{120} A similar pathophysiologic placental “transfusion” may occur under hyperglycemic and hypoxic conditions in the diabetic pregnancy. Although chronic hypoxia and placental trans­fusion may explain the increased incidence of polycythemia in infants of IDMs, it is quite possible that this phenomenon is related to additional factors such as decreased prostacyclin production which may be associated with changes in fetal or placental vasculature,\textsuperscript{152} and body fluid volume shifts, such as transudation of fluid into the extravascular space following delivery.\textsuperscript{55,176}

**Hyperbilirubinemia**

The risk of hyperbilirubinemia in IDMs is higher than in normal infants\textsuperscript{125,156} and has been associated with maternal glycemic control.\textsuperscript{65,179} It is tempting to assume that hyperbilirubinemia is related to the increased incidence of polycythemia in these infants; however, this is not necessarily the case. In infants of non-diabetic mothers, the incidence of hyperbilirubinemia is comparable in polycythemic and control groups.\textsuperscript{7,50,131} Furthermore, partial exchange transfusion for the treatment of polycythemia in newborns of diabetic mothers, does not prevent hyperbilirubinemia in these infants.\textsuperscript{47}

There is an increased production rate of bilirubin in IDMs compared to normal controls (up to 30 percent higher), which is unrelated to the hemoglobin concentration\textsuperscript{125,149} and may be an important contributing factor to the propensity for severe hyperbilirubinemia. Infants of diabetic mothers may also be subject to impairment of hepatocyte function, namely uptake of bilirubin, conjugation or excretion, resulting in delayed clearance of bilirubin.\textsuperscript{150}

Chronically induced hyperinsulinemia in fetal Rhesus monkeys results in increased concentrations of erythropoietin and increased erythropoiesis and reticulocytosis, without polycythemia.\textsuperscript{148} These findings are suggestive of ineffective erythropoiesis or mild compensated
hemolysis. As blood erythropoietin concentrations are elevated in as many as a third of IDM's and an association between blood erythropoietin concentrations and bilirubin production has been observed in these infants, ineffective erythropoiesis is a plausible explanation for the observed hyperbilirubinemia. Thus, it appears that there may be multiple causes of hyperbilirubinemia in IDMs, and since IDMs are often born prematurely, this is often a contributing factor. Treatment for prevention of kernicterus is usually by phototherapy, but “exchange” blood transfusions may be necessary if bilirubin concentrations are exceedingly high.

**Respiratory Decompensation**

**ASPHYXIA**

Perinatal mortality in diabetic pregnancies has decreased dramatically over the past 60 years. Even in the 1950's, the perinatal mortality rate was extremely high, reaching 20 percent, with half of the deaths occurring antenatally and the other half during the early neonatal period. Currently, reported perinatal mortality rates of IDMs are approximately twice those observed in the general obstetric population. In tertiary centers with special programs for diabetic pregnancies, the rates are comparable to those of non-diabetic mothers. The reduced risk of intrauterine fetal death in IDMs has been associated with improvement in glycemic control during pregnancy, development of methods for fetal surveillance, and advances in neonatology. However, even recent studies have shown that 25 to 28 percent of IDMs may have evidence of intrapartum asphyxia.

Considerable experimental data have linked derangements in maternal and fetal carbohydrate metabolism with fetal asphyxia. Studies in fetal sheep have demonstrated that maternal hyperketonemia may lead to a significant reduction in fetal oxygenation. Fetal hyperinsulinemia and hyperglycemia have been associated with decreased fetal oxygenation in sheep. These studies show that hyperketonemia may lead to fetal hypoxemia within hours, whereas hyperglycemia causes a slow and progressive fall in fetal oxygenation over the course of more than a week. It has been suggested that increased concentrations of glycohemoglobin in diabetic women results in increased oxygen affinity to hemoglobin, leading to decreased availability of oxygen to the fetus. Another possibility is that diabetes associated vasculopathy also affects placental vessels and their oxygen diffusion capacity. Electron microscopy has revealed that the thickness of the basement membrane between the maternal and fetal circulations is increased in pregnancies complicated by diabetes. Additional pathophysiologic factors may be the increased proliferation of cytotrophoblastic cells and the enlargement of endothelial cells in villous capillaries. Experimental evidence that oxygen delivery to the fetus is related to maternal glucose control has also been obtained in human pregnancies. Fetal activity decreases during maternal hyperglycemia and fetal acidemia and fetal heart rate variability is reduced during periods of maternal hyperglycemia.

Various techniques of antenatal surveillance have been used and studied over the past 15 years to provide a rational basis for the management of diabetic pregnancies during the final six weeks of gestation, the period of greatest risk for fetal asphyxia and intrauterine demise. As a rule, these techniques have few false-negative results and, therefore, permit safe prolongation of pregnancy and allow the fetus to benefit from further maturation in utero. The non-stress test (NST), that evaluates basal fetal heart
rate and the presence of accelerations, is a simple, noninvasive test, that has become the preferred test for antenatal screening of fetal condition in pregnancies complicated by diabetes. This test appears abnormal in 10 percent of cases, has a false negative rate of less than one percent, but a rather high rate of 75 to 90 percent false-positive results. When the NST is abnormal, further evaluation of fetal status may be obtained by performing a contraction stress test, which involves evaluation of the fetal heart rate while provoking uterine contractions (10 percent abnormal tests, 50 percent false-positive results), or by obtaining a biophysical profile which involves a combination of a non-stress test with four parameters assessed by real-time ultrasoundography (two percent abnormal tests, 20 percent false-positive results).45

Several investigators have reported that stricter glycemic control is associated with a decreased incidence of antepartum and intrapartum interventions prompted by suspected fetal jeopardy.46,67,73,83 Such data support the contention that maintaining maternal normoglycemia reduces the risk of fetal hyperglycemia and hyperinsulinemia and consequently reduces the risk of fetal hypoxemia and the need for elective intervention. Given the current standards of management and the availability of specialized programs for diabetic pregnancies, the overall rate of intervention for abnormal fetal testing in these pregnancies is now less than five percent.30,32,41,78,89 Non-stress testing in diabetic pregnancies is routinely performed twice weekly from the 34th week of gestation, and the frequency of intrauterine fetal demise with such protocols is in the range of five per 1000 pregnancies (excluding congenital anomalies).

Respiratory Distress Syndrome

Maternal diabetes has been traditionally considered a predisposing factor for respiratory distress syndrome in neonates.48,63,103,135,165,169 The high incidence of respiratory distress syndrome (RDS) in IDMs may be due to a direct effect of maternal diabetes on fetal lung development, but the precise mechanism involved in delayed lung maturation remains to be elucidated. Animal studies addressing this issue have been conducted in sheep, rats, rabbits and monkeys,134,144,153,167 and all have virtually confirmed that fetal lung maturation is delayed in maternal diabetes. Characteristic findings in these studies were decreased deflation stability, reduced incorporation of precursors into phosphatidyl choline and phosphatidyl glycerol, immature cellular ultrastructural aspects of lung parenchyma, delayed glycogenolysis, and decreased disaturated lecithin and/or phosphatidyl glycerol content of lung tissue or lung fluid.10

Measurement of the lecithin/sphingomyelin (L/S) ratio in amniotic fluid has been used for many years to predict fetal lung maturity.49 A value greater than 2.0 is highly predictive of fetal lung maturity in normal pregnancies. However, there is evidence that this test is less useful in diabetic pregnancies, following observations that IDMs have been born with RDS despite “mature” L/S ratios in amniotic fluid.25 In these pregnancies, prediction of fetal lung maturity can be enhanced by documenting the presence of phosphatidyl glycerol in amniotic fluid,61,77,159 and a combination of both these methods may be used to obtain accurate prediction of RDS, transient tachypnea, symptomatic pneumothorax, and persistent fetal circulation.61

More recent studies have shown a decline in the incidence of RDS in IDMs,38,103 an observation that may reflect the notable improvements in current management of diabetic pregnancies (table V). Indeed, some investigators have shown that the risk of RDS decreases with improved glycemic con-
Respiratory Distress Syndrome in Infants of Insulin-dependent Diabetic Mothers

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Diabetic Group (RDS / No RDS)</th>
<th>Control Group (RDS / No RDS)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 36 (N = 21 in each group)</td>
<td>8 / 13</td>
<td>5 / 16</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 36 (N = 106 in each group)</td>
<td>9 / 97</td>
<td>14 / 92</td>
<td>NS</td>
</tr>
<tr>
<td>Total, N = 127 in each group</td>
<td>17 / 110</td>
<td>19 / 108</td>
<td>NS</td>
</tr>
</tbody>
</table>

Rate (%) 13.4 15.0

NS = not significant.

trol of the diabetic mother.26,71 Given the current practice of delivering diabetic patients at term and the availability of specialized prenatal care for these patients, the incidence of RDS in their infants may be expected to be comparable with that of the general population.

Summary

Even though perinatal mortality of IDMs has decreased remarkably in recent years and now approaches that of the general population, these infants still face a multitude of potential complications and the propensity for increased morbidity, both in utero and postnatally. Many of these complications are clearly related to the metabolic status of the diabetic mother. Hopefully, increasing awareness among IDD patients and health providers of the need for glycemic control, and the ever growing understanding of the peculiarities of diabetic pregnancies, will eventually combine to provide the best possible outcome for these infants.

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