

# Problems of the Infant of the Diabetic Mother

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**Author Disclosure**  
Dr Ogata has disclosed that he has stock options in Bioniche Pharma, Galway, Ireland. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## Abstract

Great progress has been made in the care of the pregnant woman who has diabetes. Despite this, the risk of the infant of a diabetic mother (IDM) having macrosomia, hypoglycemia, hypocalcemia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, and cardiomyopathy remains. In addition, the IDM has an increased incidence of congenital anomalies, poor neurobehavioral development, and obesity and metabolic abnormalities in later life. Fastidious attention to maternal diabetic control in both the preconceptional and pregnancy periods reduces the risk of these morbidities.

## Objectives After completing this article, readers should be able to:

1. Review common problems experienced by IDMs.
2. Describe some of the mechanisms responsible for such problems.
3. Delineate clinical recommendations for IDMs.

## Introduction

The delineation of the mechanisms and impact of the altered intrauterine environment on the fetus and neonate, as pioneered by Pedersen, Freinkel, and most recently Barker, has improved the outcome of pregnancy for the woman who has pregestational or gestational diabetes. Nonetheless, the neonatal and long-term consequences of maternal diabetes, particularly pregestational disease, on the offspring still exist, despite 80 years of effort. Well-known problems of the IDM who has pregestational diabetes are listed in the Table. At our center, the incidence of some morbidities (hypoglycemia, polycythemia, hyperviscosity, intrauterine growth restriction) has decreased due to improved maternal care. Others, particularly macrosomia with consequent birth trauma and neonatal hypoglycemia, continue to challenge those who work to improve the outcomes of diabetic pregnancies.

Although rigidly controlled trials are lacking, observational reports suggest that tight glycemic control before and during pregnancy can minimize morbidity in infants of women who have pregestational diabetes. Some of these associations require further delineation, such as the association of improved maternal metabolic control with a reduced incidence of neonatal hypocalcemia.

## Macrosomia

Macrosomia, excessive weight for gestational age, is the hallmark of the diabetic pregnancy. Despite advances in normalizing glucose in women who have pregestational and gestational diabetes, fetal overgrowth continues to occur at rates considerably greater than normal in pregnancy. Neonatal macrosomia results from increased adiposity (hyperplasia and hypertrophy) and increased liver and skeletal mass as a result of insulin-stimulated fetal growth (Figure). The acceleration in growth begins about the 25th to 28th week of gestation, which explains why very preterm IDMs do not exhibit macrosomia. Metabolic fuels are available in sufficient amounts to be laid down as energy sources in the late second and early third trimester in both normal and diabetic pregnancies. Up to this point, all substrate available to the fetus is used for growth and development. Because macrosomia is due primarily to insulin stimulation of adipose tissue, brain and head growth are normal,

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### Table. Problems of the Infant of the Diabetic Mother

- Macrosomia
- Hypoglycemia
- Respiratory distress syndrome
- Polycythemia
- Hyperbilirubinemia
- Unexpected fetal death
- Cardiomyopathy
- Congenital anomalies

which results in disproportionality between head and shoulder size, where considerable intrascapular fat develops. Early body composition studies demonstrated as great as 50% more total body fat in macrosomia among IDMs compared with infants of mothers who have normal metabolism. This greatly increases the risk of shoulder dystocia. In addition, IDMs have increased abdominal girth as a consequence of increased subcutaneous and intra-abdominal fat as well as hepatomegaly from insulin-driven glycogen storage.

Although measuring maternal hemoglobin A1C is useful to monitor maternal glucose control during pregnancy, it is not sufficiently sensitive as a measure of glucose and amino acid provision to the fetus. In fact, the numerous and ongoing fluctuations in maternal and, thereby, fetal glucose highlight the challenge of maintaining “tight” metabolic control. Insulin pump therapy has had a limited impact in the pregnant woman.

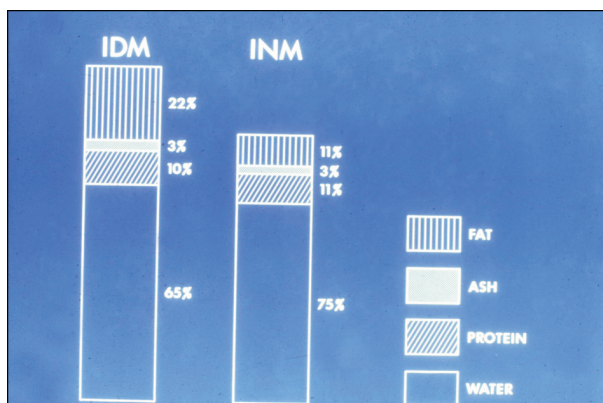


Figure. Body composition of infants of diabetic mothers demonstrating increased body fat, the primary cause of macrosomia. IDM=infant of a diabetic mother, INM=infant of a nondiabetic mother. Reprinted with permission from Fee BA, Weil WB, Jr. Body composition of infants of diabetic mothers by direct analysis. *Ann NY Acad Sci.* 1963;110:869–897.

The challenge of normalizing fetal growth has been compounded further by the recognition that substances other than glucose and insulin drive fetal growth. Such substances include insulin-like growth factor-1 and insulin-like growth factor binding protein-3. Leptin, adiponectin, cortisol, and other factors have been measured in newborn IDMs, but a clear role for them in modulating fetal growth or causing other morbidities has not been determined. Similarly, the mechanisms by which diabetic pregnancies sometimes can result in intrauterine growth restriction (IUGR) are not clearly understood. Although IUGR has been attributed to vascular insufficiency in the woman who has severe pregestational diabetes, which limits gaseous exchange and metabolic fuel provision to the fetus, the actual mechanisms for fetal growth restriction are not known.

### Hypoglycemia

The carryover of the fetal hyperinsulinemic state into the immediate neonatal period places the IDM at risk of developing hypoglycemia. Hypoglycemia occurs shortly after delivery because the abrupt cessation of maternally derived glucose with cord clamping does not immediately result in a decrease of insulin secretion in the neonate. Counterregulatory hormones, glucagon and catecholamines, may not increase sufficiently to stimulate glycogen mobilization and gluconeogenesis. The strategy for treatment is to administer glucose in sufficient quantities to attain normoglycemia while avoiding glucose stimulation of the hypertrophied neonatal pancreas to secrete more insulin. The hyperinsulinemic state is self-limited, and our observations suggest that the better managed the pregnancy, the less likely and severe neonatal hypoglycemia will be.

### Hypocalcemia

IDMs who have hypocalcemia may be asymptomatic, jittery, or rarely develop seizures. Although a delay in the surge of normally expected parathyroid hormone possibly after birth is believed to be the cause of hypocalcemia, this hypothesis has yet to be confirmed. Limited data suggest that maternal diabetes causes increased urinary loss of magnesium, which blunts parathyroid hormone secretion, causing neonatal hypocalcemia.

### Respiratory Distress Syndrome (RDS)

In the past, IDMs were at a four- to sixfold greater risk for RDS than infants of nondiabetic mothers. The fetal hyperinsulinemic state restricts substrate availability for surfactant biosynthesis and impedes fibroblast-pneumocyte factor, which stimulates type II alveolar cells to produce

surfactant. Also, previously inaccurate assessment of gestational age because of fetal macrosomia caused inadvertent preterm delivery with associated RDS. Tight maternal metabolic control and modern obstetric management have greatly reduced the risk of RDS.

### Polycythemia

IDMs are at risk of polycythemia and possibly hyperviscosity syndrome in the neonatal period. The mechanisms responsible for increased fetal erythropoiesis are not clear, but erythropoietin does not appear to be responsible for polycythemia in IDMs. Animal studies suggest that fetal hyperinsulinemia and fluctuation in fetal glucose concentrations may affect fetal oxygen availability, thereby possibly increasing erythropoiesis. In vitro studies of late erythroid progenitor colonies from IDMs indicate that they are particularly sensitive to insulin, suggesting that the fetal hyperinsulinemic state may increase the risk of polycythemia. This state also may account for the finding of increased nucleated red blood cells in IDMs. Hyperviscosity resulting from polycythemia may cause renal vein thrombosis, stroke, and other organ damage.

### Hyperbilirubinemia

Hyperbilirubinemia is extremely common in IDMs, in part because of their tendency to have high red cell mass. Those who have macrosomia tend to be bruised at birth, and resorption of subcutaneous blood can contribute to hyperbilirubinemia. Such infants have significantly increased bilirubin concentrations compared with IDMs who do not have macrosomia. In addition, plasma carboxyhemoglobin concentration, an indicator of red cell hemolysis, is significantly increased in the IDM who has macrosomia and hyperbilirubinemia, substantiating the likelihood that bruising is the cause of hyperbilirubinemia.

### Unexpected Fetal Death

In the past, the risk for unexpected fetal death in late gestation was substantial. Improved maternal metabolic control and frequent assessment of fetal status has greatly reduced the risk of this complication. The causes of unexpected fetal death are not completely understood.

### Cardiomyopathy

IDMs are at increased risk for various cardiomyopathies, including thickening of the interventricular septum and left or right ventricular wall. Fortunately, most are asymptomatic, although aortic outflow obstruction may be sufficiently severe to cause left ventricular failure in a

small fraction of IDMs. Such abnormalities generally regress during the first postnatal year. The hypertrophy is a result of fetal insulin secretion stimulating cardiac muscle growth; septal hypertrophy occurs not only in IDMs but in newborns who have nesidioblastosis.

### Congenital Anomalies

The IDM is at two to four times greater risk of having a congenital malformation than unaffected infants. Cardiac anomalies, spinal agenesis-caudal regression syndrome, neural tube defects, and gastrointestinal and urinary tract anomalies are among the many malformations that can occur.

Strategies to reduce the risk of congenital anomalies have focused on normalizing the intrauterine metabolic environment before conception because a number of clinical studies demonstrate an association between poor maternal metabolic control during early gestation and an increased incidence of congenital abnormalities in the offspring. Laboratory studies also support this concept. These observations have driven the importance of optimizing metabolic control before conception in women who have diabetes.

Neonatal small left colon syndrome is a transient anomaly unique to IDMs. It is also known as neonatal small left colon, microcolon, or lazy colon syndrome. The condition presents as intestinal obstruction, and imaging studies demonstrate a Hirschsprung-like image, although unlike neonates who have Hirschsprung disease, these infants have normal bowel innervation. Ultimately, affected infants develop normal function. Reports suggest that as many as 5% of IDMs may have this transient disorder.

The cause of neonatal small left colon is unknown, although hormone imbalance affecting the autonomic nervous system has been proposed as a mechanism. In this regard, some IDMs have been reported to have increased concentrations of amylin peptide, an inhibitor of gastric motility that is cosecreted with insulin. This might also explain the poor feeding that many IDMs demonstrate during the immediate neonatal period.

### Long-term Development

#### Neurocognitive

Achieving optimal metabolic control during pregnancy reduces but may not absolutely prevent the risk of poor neurodevelopment outcome in the offspring. In the past, when less-than-adequate maternal control was the norm, IDMs in later life were found to have low intelligence scores and neurodevelopment abnormalities. Even with improved maternal care, higher maternal fasting beta-

hydroxybutyrate concentrations in the second and third trimesters are associated with some limitations in intelligence and psychomotor development independent of perinatal complications in offspring. Maternal hypoglycemic events were not related to poor infant outcome. Increased maternal glucose values during gestation are associated with smaller brain size and delayed brain maturation in infancy. The implications of these associations are not clear, although it is recognized that ketones can impair fetal brain development.

### Metabolism

The altered maternal metabolism also has a long-term impact on the future health of the offspring. The risks of obesity, impaired glucose tolerance, blunted insulin secretion, and hypertension developing during late childhood or adolescence and persisting into adult life are increased in offspring of diabetic mothers. These complications substantiate the concept of the permanent impact of an altered intrauterine environment on long-term development of the offspring and emphasize the need for optimal metabolic control and care of the diabetic mother. They also suggest that optimal maternal metabolic regulation may contribute to the improved health of subsequent generations and in a far greater factor than the “genetic” inheritance of type 1 diabetes mellitus. The 20-year cumulative risk of type 1 diabetes mellitus in offspring of women who have type 1 diabetes mellitus is only  $2.1 \pm 0.5\%$ .

### Clinical Recommendations

Optimal obstetric management and communication between obstetrics and neonatology are critical to plan for possible neonatal resuscitation, assessment, and care of the IDM. Evaluating the infant for hypoglycemia, polycythemia, hyperbilirubinemia, and hypocalcemia is important. Long-term follow-up, with particular attention to neurodevelopment and nutrition to lessen the risk of late metabolic problems, is also important.

#### American Board of Pediatrics Neonatal-Perinatal Medicine Content Specification

- Know the effects on the fetus and/or newborn infant of maternal diabetes mellitus (including gestational diabetes) and their management.



**EDITOR'S NOTE.** See also the Perinatal Profile on Jim Farquhar and infants of diabetic mothers. *NeoReviews*. 2009;10:e217–e221.

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## NeoReviews Quiz

4. Macrosomia, excessive body weight for gestational age, is the hallmark of the pregnancy complicated by maternal diabetes mellitus. Of the following, the compound *most* critical for the development of macrosomia in an infant of a diabetic mother is:
  - A. Adiponectin.
  - B. Cortisol.
  - C. Glucagon.
  - D. Insulin-like growth factor.
  - E. Leptin.
  
5. In a woman affected by diabetes mellitus, tight glycemic control before and during pregnancy can reduce the morbidities associated with diabetes in the offspring. Of the following, the morbidity in an infant of a diabetic mother *most* resistant to change, despite improved maternal glycemic control is:
  - A. Intrauterine growth restriction.
  - B. Macrosomia-related birth trauma.
  - C. Polycythemia/hyperviscosity.
  - D. Respiratory distress syndrome.
  - E. Unexpected fetal death.

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