DIABETES IN PREGNANCY

- **Background:** Diabetes has long been associated with maternal and perinatal morbidity and mortality. Before the discovery of insulin in 1921, diabetic women rarely reached reproductive age or survived pregnancy. In fact, pregnancy termination was recommended routinely for pregnant diabetic patients because of high mortality rates.
- Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal, fetal, and neonatal care. Since then, infants of diabetic mothers (IDMs) have experienced a nearly 30-fold decrease in morbidity and mortality rates. Today, 3-10% of pregnancies are affected by abnormal glucose regulation and control. Of these, 80% are related to abnormal glucose control of pregnancy or gestational diabetes mellitus.
- Infants born to mothers with glucose intolerance are at an increased risk of morbidity and mortality related to the following:
- Respiratory distress
- Growth abnormalities (large for gestational age [LGA], small for gestational age [SGA])
- Hyperviscosity secondary to polycythemia
- Hypoglycemia
- Congenital malformations
- Hypocalcemia, hypomagnesemia, and iron abnormalities
- These infants are likely to be born by cesarean section for many reasons, among which are such complications as shoulder dystocia with potential brachial plexus injury related to the infant's large size. It is important for these mothers to be monitored closely throughout pregnancy. If optimal care is provided, the perinatal mortality rate, excluding congenital malformations, is nearly equivalent to that observed in normal pregnancies.

- **Pathophysiology:** It is necessary to understand the physiology of fetal glucose control to appreciate the causes of the associated complications. Increased levels of both estrogen and progesterone affect glucose homeostasis as counter-regulatory hormones in the mother early in pregnancy. As a result, beta-cell hyperplasia occurs in the pancreas, stimulating an increased release of insulin.
- Increased insulin levels stimulate glycogen deposition and decrease hepatic glucose production. It is not uncommon to recognize a decreased need for insulin in the diabetic patient in early pregnancy. Furthermore, amino acids decrease and fatty acid triglycerides and ketones both increase with increased fatty acid deposition. As a result, increased protein catabolism and accelerated renal gluconeogenesis occurs.
- As pregnancy progresses, human placental lactogen is released by the syncytiotrophoblast, leading to lipolysis in the mother. The subsequent release of glycerol and fatty acids reduces maternal use of glucose and amino acid, thus preserving these substrates for the fetus.
- The release of increasing amounts of contrainsulin factors as placental growth continues causes up to a 30% increase in maternal insulin needs as pregnancy progresses. Mothers with previous borderline glucose control, obesity, or frank diabetes may require initiation of or increase in their insulin requirements to maintain glucose homeostasis.

- Glucose and amino acids traverse the placental membrane. On the other hand, insulin is unable to cross from maternal to fetal circulations. Using a carrier-mediated facilitated diffusion mechanism, fetal glucose levels are maintained at a level that is 20-30 mg/dL lower than those of the mother.
- The fetus is subjected to high levels of glucose during times of maternal hyperglycemia. Before 20 weeks' gestation, fetal islet cells are incapable of responding, subjecting the fetus to unchecked hyperglycemia and decreased fetal growth. Poor growth is especially noted in mothers with diabetic vascular disease. After 20 weeks' gestation, the fetus responds to hyperglycemia with pancreatic beta-cell hyperplasia and increased insulin levels.
- Proinsulin (insulinlike growth factor-1 [IGF-1], insulinlike growth factor–binding protein-3 [IGFBP-3]) also acts as a growth factor that, in the presence of increased fetal amino acids, results in fetal macrosomia. Fetal growth acceleration can be noted on ultrasound by 24 weeks' gestation, especially with fluctuating maternal glucose levels. The combination of hyperglycemia and insulin increases fat and glycogen stores, resulting in weight increases marked by hepatosplenomegaly and cardiomegaly without an increase in head circumference.
- Chronic fetal hyperglycemia and hyperinsulinemia increase the fetal basal metabolic rate and oxygen consumption, leading to a relative hypoxic state. The fetus responds by increasing oxygen-carrying capacity through increased erythropoieten production, possibly leading to polycythemia. The fetus redistributes iron from developing organs, including the heart and brain, to support this expanded blood mass, leaving these organs iron deficient and with possible long-term functional consequences.
- Prior to birth, elevated insulin levels may inhibit the maturational effect of cortisol on the lung, including the production of surfactant from type 2 pneumocytes. This puts the fetus at risk for developing respiratory distress syndrome after birth

Fetal congenital malformations are most common when maternal glucose control has been poor during the first trimester of pregnancy. Given that many pregnancies are unplanned, the need for preconceptional glycemic control in diabetic women cannot be overstated.

- Fetal macrosomia
  - Quality of fetal growth is determined by plotting birthweight against gestational age on standard growth curves. Infants whose weight exceeds the 90th percentile for gestational age are classified as large for gestational age. Maternal hyperglycemia during late pregnancy is commonly followed by excessive fetal growth.
  - LGA infants should be routinely screened for potential hypoglycemia. This is particularly important if the mother has received large amounts of glucose-containing fluids during her labor.
  - Fetal macrosomia is observed in 26% of IDMs and in 10% (by definition) of infants of nondiabetic women. While most common as a consequence of maternal hyperglycemia and hyperinsulinemia, fetal macrosomia may occur despite maternal euglycemia.

- Pulmonary disease
  - These infants are at an increased risk of respiratory distress syndrome and may present within the first few hours after birth with tachypnea, nasal or intercostal retractions, and hypoxia. Operative delivery due to macrosomia also increases the risk for transient tachypnea of the newborn, while polycythemia predisposes the infant for persistent pulmonary hypertension of the newborn.
  - Initially, the differential diagnosis might include transient tachypnea of the newborn, respiratory distress syndrome, pneumonia, or persistent pulmonary hypertension.

- Metabolic and electrolyte abnormalities
  - Hypoglycemia may present within the first few hours of life, with such symptoms as jitteriness, irritability, apathy, poor feeding, high pitched or weak cry, hypotonia, or frank seizure activity. This hypoglycemia may persist for as long as one week. More commonly, the neonate is asymptomatic.
  - Hypoglycemia is caused by hyperinsulinemia due to hyperplasia of fetal pancreatic beta cells consequent to maternal-fetal hyperglycemia. Because the continuous supply of glucose is stopped after birth, the neonate develops hypoglycemia because of insufficient substrate. Stimulation of fetal insulin release by maternal hyperglycemia during labor significantly increases the risk of early hypoglycemia in these infants. Perinatal stress may have an additive effect on hypoglycemia due to catecholamine release and glycogen depletion.
  - The overall risk of hypoglycemia is anywhere from 25-40%, with LGA and preterm infants at highest risk.
  - Hypocalcemia or hypomagnesemia also may be apparent in the first few hours after birth; symptoms may include jitteriness or seizure activity. Hypocalcemia (levels <7 mg/dL) is believed to be associated with a delay in parathyroid hormone synthesis after birth.
  - Sixty-five percent of all IDMs demonstrate abnormalities of iron metabolism at birth. Iron deficiency increases an infant's risk for neurodevelopmental abnormalities. Iron is redistributed to the iron-deficient tissues after birth, as the RBC mass is postnatally broken down.

- Cardiovascular anomalies
  - Cardiomyopathy with intraventricular hypertrophy and outflow tract obstruction may occur in as many as 30% of these infants. The cardiomyopathy may be caused by congestive failure with a weakly functioning myocardium or to a hypertrophic myocardium with significant septal hypertrophy and outflow tract obstruction. When cardiomegaly or poor perfusion and hypotension are present, it is important to obtain an echocardiogram to differentiate between these processes.
  - These infants also are at an increased risk of congenital heart defects, including (most commonly) ventricular septal defect (VSD) and transposition of the great arteries (TGA).

- Congenital malformations
  - Central nervous malformations are 16 times more likely in these infants. In particular, the risk of anencephaly is 13 times higher, while the risk of spina bifida is 20 times higher. The risk of caudal dysplasia is up to 600 times higher in these infants.
- Renal (eg, hydronephrosis, renal agenesis, ureteral duplication), ear, cardiovascular (eg, single umbilical artery, VSDs, atrial septal defects, TGA, coarctation of the aorta, cardiomegaly), and gastrointestinal (eg, duodenal or anorectal atresia, small left colon syndrome) anomalies are more frequent in these infants

- **Causes:**
- HbA1C levels
  - Complications caused by maternal hyperglycemia during pregnancy are reflected by elevated HbA1C levels, particularly during the first trimester of pregnancy.
  - Because HbA1C is a direct measure of glucose control in the mother, higher levels are predictive of increased risks for congenital complications. Thus, the incidence of complications has been reported as 3.4% with HbA1C levels lower than 8.5% and 22.4% with levels higher than 8.5%.
  - There is speculation that birth defects in IDMs may be related to reduced arachidonic acid and myoinositol levels and elevated sorbitol and trace metal levels in the fetus.
  - Others speculate about the role of excess oxygen radicals and hydroperoxides in the mitochondria of susceptible fetal tissues because these prostacyclin inhibitors may cause disruption in the vascularization of developing tissues.
  - A past history of LGA infants, diabetes, stillbirth, hypertension, gestational diabetes, obesity, or glycosuria, or a current history of excessive weight gain in the present pregnancy or low socioeconomic class place the mother at an increased risk of poor glucose control during pregnancy and increase her risk of delivering an infant with subsequent complications.

- **Lab Studies:**
- Complete blood cell count
  - Polycythemia, commonly defined as a central hematocrit higher than 65% or hemoglobin concentration higher than 20 g/dL, is a potential concern.
  - Maternal-fetal hyperglycemia is a strong stimulus for fetal erythropoietin production and subsequent increase in fetal hemoglobin concentration secondary to chronic in utero hypoxia, which can be associated with the infant of a diabetic mother. Fetal hyperviscosity, intravascular sludging, regional ischemia, and hypoxemia are all potential complications. Thrombocytopenia may occur because of impaired thrombopoiesis due to "crowding-out" of thrombocytes by the excess of erythroid precursors in the bone marrow.

- Glucose concentration (serum or whole-blood)
  - Seizures, coma, and long-term brain damage may occur if neonatal hypoglycemia is unrecognized and untreated.
  - Most centers recognize levels lower than 20-40 mg/dL within the first 24 hours after birth as abnormal, but the precise level remains controversial. A policy to screen IDMs for hypoglycemia should be in place in every hospital. A recent suggestion of operational thresholds was proposed by Cornblath et al. Their suggestion in an infant with compromised metabolic adaptation (ie, IDMs) should include blood glucose measurements (1) as soon as possible after birth, (2) within 2-3 hours after birth and before feeding, and (3) at any time abnormal clinical signs are observed.
- Magnesium concentration (serum)
  - Hypomagnesemia is related to younger maternal age, severity of maternal diabetes, and prematurity. Neonatal magnesium levels are also related to maternal serum magnesium, neonatal calcium and phosphorus levels, and neonatal parathyroid function.
  - The clinical significance of low magnesium levels in these infants remains controversial and uncertain.
- Calcium concentration (serum, ionized or total levels): Low serum calcium levels in IDMs are common. They are speculated to be caused by a functional hypoparathyroidism; however, their clinical relevance remains uncertain and controversial.
- Bilirubin level (serum, total and unconjugated): Hyperbilirubinemia is notably more common than in the general population of neonates. Causative factors include prematurity, hepatic enzyme immaturity, polycythemia with hyperviscosity and "sludging," and reduced red blood cell half-life.
- Arterial blood gas: Assessing oxygenation and ventilation is essential in infants with clinical evidence of respiratory distress. Although noninvasive methods (eg, transcutaneous oxygen and carbon dioxide electrodes, oximeters) have gained wide acceptance at many centers, comparison of results with those from arterial blood is intermittently required

- **Procedures:**
- Nasal or endotracheal continuous positive airway pressure, endotracheal intubation, and mechanical ventilation
  - Nasal continuous positive airway pressure (NCPAP) or endotracheal intubation with CPAP and/or intermittent mandatory or synchronized positive pressure ventilation (IMV, SIMV) may be employed for management of severe respiratory distress.
  - Common criteria for such interventions include inspired oxygen requirements (FiO2) of 60-100% to maintain arterial PO2 of 50-80 mm Hg, arterial PCO2 levels higher than 60-80 mm Hg or rising 10 or more mm Hg/h, and apnea. The specific criteria for using these modes of assisted ventilation may vary considerably among neonatologists or across institutions.
- Indwelling vascular lines (peripheral, umbilical, or central)
  - Noninvasive blood gas monitoring using transcutaneous electrodes (PaO2 and PaCO2) and oximeters (O2% saturation) has greatly reduced the need for invasive indwelling catheters. However, indwelling lines often are needed early in the course of cardiorespiratory disease. In some instances, the need for continuous arterial blood pressure monitoring may warrant placement of a peripheral or umbilical arterial line. Once again, use of these invasive methods varies.
  - Placement of an umbilical venous or a central venous catheter often is employed when the infant requires hyperosmolar intravenous fluids or when peripheral access is limited or exhausted.

- **Medical Care:**
- Communication between members of the perinatal team is of crucial importance to identify infants who are at highest risk of complications from maternal diabetes. A cost-effective screening policy for hypoglycemia during the hours after birth is necessary to detect hypoglycemia.
- Hypoglycemic management
  - It is generally agreed that serum or whole blood glucose levels less than 20-40 mg/dL within the first 24 hours after birth are significantly low. Cornblath et al's recent suggestions for approach at treatment suggest that measurement of the blood glucose level should be determined, as follows:
    - As soon as possible after birth
    - Within 2-3 hours after birth and before feeding
- At any time abnormal clinical signs are observed

- Guidelines based on glucose level
  - Level less than 36 mg/dL (2 mmol/L): Close surveillance of glucose levels with intervention is needed if plasma glucose remains below this level, if it does not increase after a feeding, or if the infant develops symptoms of hypoglycemia.
  - Level less than 20-25 mg/dL (1.1-1.4 mmol/L): Intravenous glucose should be administered, with the target glucose level of more than 45 mg/dL (2.5 mmol/L). This goal of 45 mg/dL is accentuated as a margin of safety. Should the infant be significantly symptomatic with profound, recurrent, or persistent hyperinsulinemic hypoglycemia, then a goal of more than 60 mg/dL (3.3 mmol/L) may be more appropriate.
- It is difficult to determine which infants require the highest dextrose administration to maintain euglycemia. The following suggestions represent a guideline for glucose administration to a hypoglycemic, clinically symptomatic, infant.

- Immediate intravenous therapy with 2-mL/kg infusion of dextrose 10% (D10 provides 100 mg/mL of dextrose, starting dose is 200 mg/kg of dextrose) is required in any symptomatic hypoglycemic infant. Administration over 5-10 minutes usually is recommended because of the high osmolarity. This is especially true for immature infants younger than 32 weeks' gestational age who are at some risk for intracranial hemorrhage. This procedure originally was described as a 2-minute infusion, and it accomplishes a filling of the glucose space analogous to the volume of distribution of glucose.
- Maintenance of a continuous infusion of dextrose at an infusion rate of 6-8 mg/kg/min of dextrose is necessary once bolus therapy is complete. Failure to do so may result in rebound hypoglycemia as a result of heightened pancreatic insulin release triggered by the glucose infusion.
- Frequent serum or whole blood glucose analyses are important to properly titrate the dextrose infusion. Should follow-up glucose levels remain less than 40 mg/dL, the dextrose infusion may be increased by 2 mg/kg/min until euglycemia is achieved.
- If the infant requires a dextrose concentration more than D12.5 through a peripheral vein at 80-100 mL/kg/d, placement of a central venous catheter may be considered to avoid venous sclerosis. Continued enteral feedings hasten improvement in glucose control because of the presence of protein and fat in the formula.
- Once the infant's glucose levels have been stable for 12 hours, intravenous glucose may be tapered by 1-2 mg/kg/min, depending on maintenance of preprandial glucose levels higher than 40 mg/dL.

- Electrolyte management
  - Hypocalcemia and hypomagnesemia may complicate the clinical course.
  - Because low serum calcium levels cannot be corrected in the presence of hypomagnesemia, correction of low magnesium levels is an initial step in the treatment of hypocalcemia.
  - In IDMs, calcium and magnesium levels are commonly measured within the first hours after birth. Ideally, ionized levels of these electrolytes should be obtained and employed to properly manage these electrolyte disturbances.
  - True symptomatic hypocalcemia is extremely rare in these infants. In most cases, symptoms interpreted to be caused by low calcium or magnesium levels are due to low glucose levels associated with perinatal asphyxia or associated with a variety of central nervous system problems.
  - When these low levels are treated, an infusion of 10% calcium gluconate at 2 mL/kg often is administered over 5 minutes (18 mg/kg of elemental calcium). This treatment has particular hazards because the hyperosmolal mixture may cause serious tissue necrosis and sclerosis; also, serious cardiac arrhythmias may occur during the infusion. It is routine in many centers to monitor the infant's ECG during infusion.

- Respiratory management
  - Pulmonary management is tailored to the individual infant's signs and symptoms.
  - Increased ambient oxygen concentrations may be required to maintain oxygen saturations higher than 90%, transcutaneous oxygen tensions at 40-70 mm Hg, or arterial oxygen tensions at 50-90 mm Hg.
  - When an inspired oxygen concentration (FiO2) higher than 40% is required, the most important task is to determine a precise diagnosis of the cause for the hypoxemia. Principals of management, which are generally agreed on, are based on monitoring of blood levels of oxygen and carbon dioxide, as well as their maintenance within physiologic ranges using the least invasive techniques that are successful.

- **Complications:**
- All risks are directly proportional to the degree of maternal hyperglycemia in utero.
- Thompson and associates found that tight control of euglycemia in the patient with gestational diabetes led to normal perinatal outcomes. When comparing good glucose control (mean plasma glucose level <120 mg/dL) with poor glucose control (mean plasma glucose level >140 mg/dL), the hyperglycemic group was found to have more preeclampsia, maternal urinary tract infections, premature deliveries, cesarean deliveries, macrosomia, respiratory distress, neonatal hypoglycemia, congenital malformations, and perinatal mortality.
- Congenital anomalies: The overall risk is 8-15%, with 30-50% of perinatal fatalities related to major congenital malformations. Poor glycemic control early in pregnancy directly correlates with a higher incidence of congenital malformations.
- Perinatal mortality
  - In the past, 10-30% of pregnancies terminated with sudden and unexplained stillbirth. This is believed to have been secondary to chronic fetal hypoxia with subsequent polycythemia and vascular sludging. A higher incidence was noted in pregnancies further complicated by maternal vascular disease.
  - A considerable proportion of perinatal problems are a consequence of fetal macrosomia. Macrosomia is associated with protracted labor, perinatal asphyxia, shoulder dystocia and brachial plexus injury, other skeletal and nerve injuries, and an elevated rate of operative deliveries.

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- **THE END!!**