

INFANTS OF DIABETIC MOTHERS
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Introduction

Hypoglycemia develops in about 25–50% of infants of diabetic mothers and 15–25% of infants of mothers with gestational diabetes. Only a small percentage of these infants however become symptomatic. Unrecognised hypoglycaemia in the newborn can be fatal and is therefore important to suspect in all infants of diabetic mothers.

Pathophysiology

Normal glucose homeostasis

a) Prenatal

Glucose crosses the placenta in an insulin-independent fashion. Hormones which control glucose homeostasis do not cross the placenta. The fetus produces its own glucohomeostatic hormones.

While acute changes in blood sugar do not markedly affect insulin or glucagon secretion in the fetus, long term exposure to hyperglycemia leads to an upregulation in insulin secretion and a downregulation in glucagon secretion in the Islets of Langerhans of the pancreas.

b) Changes at birth

In any infant, independent of its glucose supply prior to birth, cessation of maternal glucose transfer would result in hypoglycemia were it not counterregulated. Hypoglycemia is prevented by activation of the glucohomeostatic system at three different levels:

1. Hormones

Insulin secretion levels off – this removes inhibition of ketogenesis and gluconeogenesis at liver, and decrease uptake of glucose at muscle and fat cells via insulin dependent uptake (GLUT4).

Glucagon increases within minutes after birth. Epinephrine, and Growth hormone levels also rise. These act synergistically to stimulate glycogenolysis and gluconeogenesis in the liver, and activates lipolysis and ketogenesis. These processes supply the glucose to maintain blood glucose levels and sustain tissues dependent on glucose (i.e. brain and anaerobic tissues such as RBC, lens of eye), and produces ketone bodies to sustain tissues with the capability of using ketones as alternate fuel via the Krebs cycle (i.e. muscle, brain).

2. Receptors

Glucagon receptors increase in sensitivity, while insulin receptors decrease in number

3. Enzymes

Enzymes involved in glucose production activate (i.e. Phosphoenol Pyruvate carboxykinase) while the enzymes involved in glycogen production decrease in activity (i.e. glycogen synthase).

2.2 ***Glucose homeostasis in neonates of diabetic mothers***

a) Prenatal

As explained above, long term exposure to unregulated hyperglycemia leads to fetal adaptation. The fetal pancreas compensates for the hyperglycemia by increasing the number of insulin producing beta cells. Insulin acts to decrease blood sugar by stimulating uptake of glucose into fetal myocytes and lipocytes.

Further fetal compensation follows. Extramedullary hematopoiesis and hepatomegaly are consequences of an oxygen deficit explained by the following:

1) Increased Demand

- Insulin stimulates anabolic activity

2) Decreased Supply

- Uteroplacental flow may be compromised due to diabetic cardiovascular disease.
- Glycosylation of the mother's Hemoglobin increases its affinity for O₂, thereby shifting the O₂ dissociation curve to the left and decreasing oxygen transfer to fetal haemoglobin in the placenta.

b) Changes at birth

At birth the constant supply of hyperglycemic blood is removed while the hyperinsulinism remains and hypoglycemia ensues. Glucohomeostatic mechanisms are inadequate to reverse the rapid drop in blood sugar. Compared to normal infants, infants of diabetic mothers respond to glucose or protein by achieving a higher insulin peak more promptly. In contrast, the rise in levels of the counterbalancing hormones, glucagon and epinephrine in response to hypoglycemia is often delayed and diminished due to prematurity of the adrenals and alpha cells of the pancreas.

Clinical Manifestations

Characteristics of Pregnancy

- ❑ Polyhydramnios
- ❑ Preterm labor
- ❑ Restricted growth

- Increased rate of congenital abnormalities (hyperglycemia during first trimester can be teratogenic)
- Increased fetal mortality rate (mainly thought to be due to lactic acidosis)

Physical characteristics

- Birth weight is usually elevated (macrosomia), due to increased anabolism and glucose uptake by fetal cells. It may however also be normal or low if the fetus was subject to severe ischemia, secondary to maternal diabetic vascular disease.
- Enlarged viscera
- Plump plethoric facies (resembles facies from patients treated with corticosteroids)
- Congenital anomalies. Cardiac malformations (ventricular or atrial septal defect, transposition of the great vessels, truncus arteriosus, double-outlet right ventricle, coarctation of the aorta) and lumbosacral agenesis are most common.

Specific systems most often affected

a) Central Nervous system

The infants tend to have an increased startle reflex and are tremulous during the 1st 3 days of life, although hypotonia, lethargy, and poor sucking may also occur. Seizures, if they occur are due to hypoglycemia or hypocalcemia. Mechanism for low calcium is as follows: The mother with Type 2 Diabetes is likely to have decreased blood Mg levels (due to (1) excretion in kidney and (2) increased insulin-mediated uptake into cells). Low Mg levels in the infant inhibit the parathyroid gland to respond to hypocalcemia through the release of PTH.

b) Pulmonary system

Tachypnea develops in many infants of diabetic mothers during the 1st 2 days of life and may be a manifestation of delayed lung maturity, hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. Infants of diabetic mothers have a higher incidence of respiratory distress syndrome than do infants of nondiabetic mothers born at comparable gestational age; the greater incidence is possibly related to an antagonistic effect of insulin on stimulation of surfactant synthesis by cortisol.

c) Cardiovascular system

Cardiomegaly is common (30%), and heart failure occurs in 5–10% of infants of diabetic mothers. Asymmetric septal hypertrophy may occur and become manifested similar to idiopathic hypertrophic subaortic stenosis.

d) Hematologic system

Polycythemia

Renal vein thrombosis may occur and should be suspected in infants with a flank mass, hematuria, and thrombocytopenia.

e) Gastrointestinal system

Small left colon syndrome and decreased intestinal motility may be present. Look for signs of intestinal obstruction, including feeding intolerance, vomiting, and abdominal distention.

Laboratory investigations

- ❑ Blood glucose - The lowest point in an infant's blood glucose concentration is usually reached between 1 and 3hr. Screen all infants of diabetic mothers with a blood glucose around 2 hours of age.
- ❑ Iron studies, including ferritin, total iron binding capacity – erythropoiesis deplete iron stores
- ❑ Electrolytes – insulin alter concentrations of many such potassium, calcium, phosphate and magnesium
- ❑ Bilirubin – Screen for hyperbilirubinemia, which may result due to 1) polycythemia and 2) blunted cortisol surge inhibits bilirubin metabolism
- ❑ CBC – Screen for polycythemia in the plethoric infant

Treatment

Prenatal

Treatment of infants of diabetic mothers should be initiated before birth by frequent prenatal evaluation of all pregnant women with overt or gestational diabetes, by evaluation of fetal maturity, by biophysical profile, by Doppler velocimetry, and by planning the delivery of these infants in

hospitals where expert obstetric and pediatric care is continuously available. Periconception glucose control reduces the risk of anomalies. Mothers with Hemoglobin A1c 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%. Similarly, glucose control during labour reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy deliver infants with birthweights and anthropomorphic features that are similar to those of infants of nondiabetic mothers. Women with gestational diabetes may be treated successfully with glyburide, which may not cross the placenta. In these mothers, the incidence of macrosomia and neonatal hypoglycemia was similar to that in mothers with insulin-treated gestational diabetes.

5.2 At Birth

Macrosomia places the infant of a diabetic mother at greater risk for birth trauma because of cephalopelvic disproportion. Not surprisingly, cesarean delivery rates remain higher in infants of diabetic mothers with increased birth weight as estimated from ultrasound. In light of the many complications to be anticipated with the delivery of a child of a diabetic mother, the presence of an obstetric team is highly warranted.

Regardless of size, all infants of diabetic mothers should initially receive intensive observation and care. Asymptomatic infants should have a blood glucose determination between 1 and 2 hrs of birth and then every hour for the next 6–8hr; if clinically well and normoglycemic, oral or gavage feeding with breast milk or formula should be started as soon as possible and continued at 3hr intervals. If any question arises about an infant's ability to tolerate oral feeding, the feeding should be discontinued and glucose given by peripheral intravenous infusion at a rate of 4–8mg/kg/min or via nasogastric lavage feeds. Hypoglycemia should be treated, even in asymptomatic infants, by frequent feeding and/or intravenous infusion of glucose. Bolus injections of hypertonic glucose should be avoided in the asymptomatic infant because they may cause further hyperinsulinemia and potentially rebound hypoglycemia.

Furthermore a complete physical exam is essential to look for congenital anomalies. Although clinical suspicion for anomalies must be high, screening of all infants of diabetic mothers for congenital anomalies via imaging modalities are not currently standard practise.

See the CPS statement on screening and management strategies for newborns at risk with hypoglycaemia for further details, beyond the scope of this review.

<http://www.cps.ca/english/statements/FN/fn04-01.htm>

Prognosis

Physical development is normal, but oversized infants may be predisposed to childhood obesity that may extend into adult life. Disagreement persists about whether these infants have a slightly increased risk of impaired intellectual development unrelated to hypoglycemia; symptomatic hypoglycemia increases the risk, as does maternal ketonuria. The incidence of diabetes mellitus in infants of diabetic mothers is increased in comparison to that of the general population.

References

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