Objectives

▪ Discuss the effects of maternal diabetes on the fetus
▪ Identify potential neonatal complications from maternal hyperglycemia
▪ Review morbidities associated with IDM
▪ Describe glucose metabolism in the newborn and current management in the hypoglycemic infant
Definitions

▪ GDM: carbohydrate intolerance of variable severity with onset or first recognition during pregnancy
▪ IDM: Any offspring of a gestational or insulin dependent diabetic woman

Classification of diabetes in pregnancy

Pregestational:
● Type 1 Diabetes Mellitus
● Type 2 Diabetes Mellitus

Gestational:
● GDM A1 – Impaired glucose tolerance: diet controlled
● GDM A2 – medication tx
IDM: The Numbers

- Infants of Diabetic Mothers Are...
  - Twice as likely to suffer serious birth injury
  - 3 times as likely to be born by cesarean section
  - 4 times as likely to be admitted to a neonatal intensive care unit
  - 5 times more likely to be stillborn

GDM Incidence by Race/Ethnicity in CA 2005

- California 5.88 GDM per 100 deliveries
- Asian/Pacific Islander 8.73%
- Hispanic* 8.06%
- White 4.67%
- African American 5.43%

* Hispanic refers to all of Hispanic ethnicity regardless of race
(Bardenheier et al., 2012)
Morbidities in the IDM: A to Z

- Asphyxia
- Birth injury
- Cardiomyopathy
- Caudal regression
- Congenital anomalies
- Double outlet right ventricle
- Heart failure
- Hyperbilirubinemia

Morbidities in the IDM: A to Z

- Hypocalcemia
- Hypoglycemia
- Hypomagnesemia
- Increased blood volume
- Macrosomia
- Neurologic issues
- Organomegaly
- Polycythemia and hyperviscosity
Morbidities in the IDM: A to Z

- Renal vein thrombosis
- Respiratory distress
- RDS
- Septal hypertrophy
- Shoulder dystocia
- Small left colon syndrome
- Transient hematuria
- Truncus arteriosus

Teratogenesis

- Process by which congenital malformations are produced in an embryo or fetus
- Congenital malformations account for approx. 50% of perinatal deaths in IDMs
- Mechanism not well understood
- Abnormal metabolic environment is teratogenic
Teratogenesis

- Hyperglycemic state may damage mitochondria, increase free radicals and oxidative stress in cells
- Regulating genes altered
- Alters cellular mitosis
- Exaggerated apoptosis
- Leads to spontaneous abortions and malformations
Figure this out
Tanya Hatfield, 7/20/2018
Diabetic Embryopathy

- Caused by maternal hyperglycemia in the 1\textsuperscript{st} trimester
- Primarily in pregnancies with pregestational diabetes
- Results in major birth defects and spontaneous abortions
- Risk of major malformations is 5 to 6\%, with a higher prevalence rate of 10 to 12\% when mothers require insulin therapy

Diabetic Fetopathy

- Occurs in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
- Results in fetal hyperglycemia, hyperinsulinemia, and macrosomia
Maternal Hyperglycemia

- Maternal hyperglycemia results in fetal hyperglycemia
  - glucose readily crosses through the placenta
  - Insulin does not
- Before 20 weeks gestation the fetal islet cells are not capable of responsive insulin secretion
- After 20 weeks gestation the fetus has a functioning pancreas and is responsible for its own glucose homeostasis

Fetal Response to Maternal Hyperglycemia

- Fetal hyperglycemia results in fetal hyperinsulinemia
  - fetal hyperinsulinism related to suppressed surfactant production
  - Islet cell hyperplasia
  - Increased growth
  - Excess accumulation of glycogen in liver
  - Inadequate utilization of fatty acids in adipose tissue
2

figure it out

Tanya Hatfield, 6/25/2018
Fetal Response to Maternal Hyperglycemia

- Increases metabolic rate and O2 consumption leading to hypoxemia
  - Fetal hypoxemia contributes to increased mortality, metabolic acidosis, alteration in fetal iron distribution and increased erythropoiesis
- Increased production of erythropoietin
  - leads to polycythemia
  - promotes catecholamine production, which can result in hypertension and cardiac hypertrophy
Effects of Maternal Hyperglycemia on the Fetus

Barnes - Powell, 2007

Fetal Hyperinsulinemic State

Barnes - Powell, 2007
Uncontrolled hyperglycemic mother

Fetal hyperglycemia

Fetal hyperinsulinemia

In first trimester leads to congenital anomalies

Anabolic effect
- glucogenesis
- lipogenesis
- protein synthesis

Neonatal hypoglycemia
- Hypocalcemia
- Hypomagnesemia

Increased metabolic rate
- hypoxemia

Anticortisol effect
- Suppress alveoli Type II

Decrease surfactant synthesis
- Increase risk of RDS

Peripheral hyperinsulinemia
- enlarged viscera
- macrosomia

Obstructed labor and birth trauma

Asymptomatic, jittery, seizures, lethargy, apnea

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Increased metabolic rate
- hypoxemia

Increased erythropoiesis

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Increased metabolic rate
- hypoxemia

Increased erythropoiesis

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Anticortisol effect
- Suppress alveoli Type II

Decrease surfactant synthesis
- Increase risk of RDS

Increased metabolic rate
- hypoxemia

Increased erythropoiesis

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Increased metabolic rate
- hypoxemia

Increased erythropoiesis

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Anticortisol effect
- Suppress alveoli Type II

Decrease surfactant synthesis
- Increase risk of RDS

Increased metabolic rate
- hypoxemia

Increased erythropoiesis

Polycythemia, increased viscosity

Hyperbilirubinemia

Vascular sludging

Stroke, jaundice, PPHN

Anticortisol effect
- Suppress alveoli Type II

Decrease surfactant synthesis
- Increase risk of RDS
Potential neonatal complications

1. Growth/Metabolic Imprinting
2. Glucose Metabolism/Hypoglycemia
3. Electrolyte imbalances
4. Respiratory Issues
5. Cardiovascular Issues
6. Hematologic Changes
7. Birth Trauma
8. Neurologic Issues
9. GI/GU Issues

1. Growth
   - Poor maternal glycemic control predicts neonatal macrosomia
   - > 95%-tile considered abnormal
   - IDM generally have increased fat mass so will have higher weight than length and head circumference percentiles
Growth-Macrosomia

- Infants with BW ≥4000gms or >90%tile, with excess fat accumulation in abdominal and scapular regions, along with visceromegaly

- Risk increases when:
  - Mean maternal glucose chronically exceeds 130 mg/dL
  - When rises in maternal glucose levels are episodically elevated with surges increasing fetal insulin production

Growth-Macrosomia

- Occurs in >25% of diabetic pregnancies and puts babies at risk for birth injuries
- Disproportionate growth: higher chest-to-head and shoulder-to-head ratios
- More likely to have hyperbilirubinemia, hypoglycemia, acidosis, respiratory distress, shoulder dystocia, brachial plexus injury
Impaired Fetal Growth

- SGA
- BW <10th percentile
- May occur in up to 20% of diabetic pregnancies
- Associated with pregnant mothers with renal, retinal or cardiac diseases
- More likely to deliver SGA, premature, poor fetal outcome, fetal distress, or fetal death

Growth-Metabolic Imprinting

- Macrosomic IDM s have tendency to regain adiposity in late childhood/adolescence
- National Collaborative Perinatal Project (1959-1965) compared GDM to non GDM offspring
  - 61% higher chance of being overweight at age 7 than non GDM
  - Adjusted for maternal BMI, income, race and BW
Growth-Metabolic Imprinting

- Pima Indian Studies
  - Compared siblings exposed to diabetes in utero with those born before mom diagnosed
  - Exposed siblings had higher BMI
  - No difference in BMI after father’s diagnosis of Type 2
  - Data suggests exposure to GDM influences growth and body size independent of genetic predisposition

(Bergeon & Dabelea 2009)

---

Growth-Metabolic Imprinting

- Pima Indian Studies
  - 45% of offspring of mothers with GDM develop Type 2 diabetes between 20 and 24 years of age (1988)
  - In follow-up study more than 2/3 of offspring of mothers with GDM developed Type 2 diabetes by 34 years of age (2000)
  - Thought to stem from exposure to hyperglycemia and increased insulin secretion leading to abnormal glucose uptake and utilization in peripheral tissue, especially muscle
2. Glucose Metabolism

▪ The fetus glucose concentration is proportional to maternal concentrations and measures about 70-80% of maternal levels

▪ Almost all of this comes from facilitated diffusion across the placenta

▪ Glycogen stored in liver, heart, lung and skeletal muscle
  • Glycogen content slowly increases during first two trimesters
  • Majority made and stored in the liver during the third trimester

Glucose Metabolism

▪ IDM infant undergoes sudden interruption of glucose delivery, which when accompanied by high neonatal insulin levels results in neonatal hypoglycemia

▪ Up to 50% of IDMs experience significant hypoglycemia after birth

▪ Nadir in blood glucose usually occurs between 1 and 3 hours of life

▪ Hyperinsulinemia may persists up to 72 hours and may last up to 1 week
Insulin and the Fetus

- Major stimulus for fetal growth
- Present in the fetal pancreas by 8-10 weeks of gestation
- Increased production approaching term
- Insulin inhibits fasting metabolic systems at birth therefore infant can not mobilize glycogen stores

3. Electrolyte Imbalances: Hypocalcemia

- Serum Ca <7 mg/dL or ionized Ca < 1mmol/L
- Occurs in up to 30% of IDM
- Usually occurs in first 24-72 hours of life
- Caused by poor late-trimester transfer of calcium across the placenta, delay in normal postnatal parathyroid hormone elevation, and poor fetal and neonatal bone mineralization (ie, poor calcium stores).
- Not routinely screened unless symptomatic
- S/Sx: asymptomatic and self-resolves or jitteriness, tachypnea, seizures/tetany, lethargy and apnea
Electrolyte Imbalances: Hypomagnesemia

- Serum magnesium <1.5 mg/dl
- Occurs in up to 40% IDMs within first 72h of life
- Most likely due to maternal hypomagnesemia caused by increased urinary losses
- Usually not treated, but may need treatment if infant is hypocalcemic as well
- S/Sx: usually transient and asymptomatic, sweating, tachypnea, irritability, seizures, jitteriness

4. Respiratory Issues: RDS

- Respiratory Distress Syndrome six times more frequent in IDMs until 38 weeks*
- RDS more common for moms with unstable Type I
- Possible causes:
  - premature delivery
  - maternal hyperglycemia delays surfactant synthesis
  - Fetal hyperinsulinemia interferes with the induction of lung maturation by glucocorticoids
Respiratory System: TTN and PPHN

▪ Transient tachypnea of the newborn
  ▪ occurs 2-3x more in IDMs
  ▪ related to reduced fluid clearance in the diabetic lung and cesarean delivery
▪ Persistent pulmonary hypertension of the newborn
  ▪ Possibly related to vascular sludging
  ▪ L/S ratio >3 for IDMs associated with decreased incidence of PPHN

5. Cardiovascular Issues

▪ Hypertrophic cardiomyopathy
  ▪ caused by fat and glycogen deposition into myocardial cells causing thickening of intraventricular septum with reduction in the size of ventricular chambers
  ▪ results in potential obstructed left ventricular outflow
  ▪ infants often asymptomatic but 5-10% have respiratory distress or signs of poor cardiac output
  ▪ usually transient and resolves as plasma insulin levels normalize
  ▪ Symptomatic infants recover after 2-3 weeks of supportive care and ECHO findings resolve within 6 to 12 months
5. Cardiovascular Issues

- Hypertrophic cardiomyopathy

Cardiovascular

- Other defects associated with IDM:
  - TGA
  - VSD, ASD
  - Coarctation of the aorta
  - Single ventricle, hypoplastic left ventricle
  - Pulmonic stenosis
  - Pulmonary valve atresia
  - DORV
  - Truncus Arteriosus
  - Tricuspid Atresia
  - PDA
2458 infants of mothers with type 1 diabetes w/glycated haemoglobin measurement +/- 3 months conception
1,159,865 infants of mothers without diabetes
6. Hematologic Changes

- Hyperglycemia decreases fetal oxygen tension
- Chronic fetal hypoxemia stimulates production of erythropoietin
- ↑ RBC production
  - leads to polycythemia
  - hyperbilirubinemia
- Intervention required when central Hct >65 with symptoms or > 70 when asymptomatic

---

Hematologic Changes

- Hyperviscosity
  - ↑ risk of vascular sludging, ischemia, seizures, necrotizing enterocolitis, renal vein thrombosis, infarction of vital organs
  - Pulmonary vascular bed sludging can lead to PPHN
- Low iron stores
7. Birth Trauma

- Shoulder dystocia
  - occurs in 1/3 of IDM that are macrosomic
- Cephalhematoma
- Brachial plexus injury
- Erb’s palsy
- Facial nerve palsy
8. Neurologic Issues

- CNS damage from:
  - Asphyxia
  - Birth trauma
  - Hypoglycemia
  - Hyperviscosity
  - Electrolyte abnormalities
Neurologic Malformations

- CNS malformation incidence in IDMs vs non-IDMs
  - Anencephaly 13x
  - Spina bifida 20x
  - Caudal regression 200x

Caudal Regression Syndrome

- Incomplete development of the lumbar and sacral vertebrae
- Spectrum of structural defects possible
- Associated with neurologic impairment due to involvement of distal spine
Neurodevelopmental outcome

- Outcome of infants of well-controlled diabetic mothers appear similar to that of normal infants
- Poorly controlled may result in developmental abnormalities
  - Head circumference at 3 years of age negative correlated with HbA1c levels during pregnancy
  - Smaller H.C. associated with poorer intellectual performance

9. GI/GU Issues

- GI Anomalies
  - Situs inversus
  - atresias (duodenal, anorectal)
  - small left colon syndrome
  - Imperforate anus
- GU Anomalies:
  - Ureteral duplication
  - Renal agenesis
  - Hydronephrosis
Glucose Homeostasis

- Balance between hepatic glucose output and peripheral glucose utilization
- Peripheral utilization varies with demands on the neonate
  - Hypoxia/Hypoxemia
  - Hyperinsulinemia
  - Cold stress
- Hepatic output depends on glycogenolysis and gluconeogenesis
Glucose Homeostasis

- Glucose concentration at which physiologic disturbances occur differ between infants
  - The healthy breastfed term infant has significant levels of circulating ketone bodies
  - The infant with hyperinsulinemia cannot produce ketones or release stored glycogen from the liver

Glucose Physiology in the Neonate

- Glycogenolysis is the mobilization of glucose from hepatic glycogen during the first 6-12 hours of life for cellular use
  - The hormones epinephrine and glucagon stimulate glycogenolysis
Glucose Physiology in the Neonate

- Lipolysis, fatty acid oxidation and ketogenesis: occurs 12-16 hours into the fasting and spares muscle breakdown

- Making of free fatty acids (a fuel that can be used by the muscles but not the brain) from adipose tissue and fatty acid-derived ketones (fuels that the brain can use) from the liver

Normal Glucose Physiology at Delivery

- Adaptation response
- Increase in plasma glucagon
- Decrease in plasma insulin
- Mobilization of glucose and fatty acids from glycogen and triglyceride deposits
Glucose Physiology after the Delivery

- Maternal supply of glucose is interrupted
- Fetal glycogen storage is temporarily inactivated and blood glucose falls
- Glycogen phosphorylase breaks down hepatic glycogen stores to supply glucose
- Gluconeogenesis increases
- High catecholamine levels stimulate the release of substrates in the form of free fatty acids and free amino acids

What is Hypoglycemia?

- NO UNIVERSAL DEFINITION
- Operational threshold is defined as that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature
  - This threshold is currently believed to be a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL).
Committee on Fetus and Newborn. Postnatal Glucose Homeostasis in Late-Preterm and Term Infants
*Pediatrics* 2011; 127(3); 575-9

- Blood glucose concentrations as low as 30 mg/dL are common in healthy neonates by 1-2 hrs after birth
- Low concentrations are usually transient, asymptomatic and considered to be part of normal adaptation to postnatal life

---

**Clinical Hypoglycemia**

- Newborns < 24 hours of age: blood glucose levels should be consistently > 40mg/dl
- Newborns > 24 hours of age: blood glucose levels should be consistently > 50mg/dl
- Preterm infants should have blood glucose consistently > 50.
Incidence of Hypoglycemia

- 1 – 5 per 1000 births
- 5-15% in healthy infants
- 8% in LGA infants
- 15% in SGA infants
- Up to 40-45% of IDMs (half are asymptomatic)

Etiology of Hypoglycemia

- Decreased hepatic glucose production
- Immature liver
  - Impaired gluconeogenesis
  - Impaired glycogenolysis
- Decrease substrate availability due to oral or parental intake issues
Etiology of Hypoglycemia

- Sustained hypoxic stress
- Anaerobic metabolism
- Increased neurologic needs from a proportionally large brain
  - 13 % of total body mass to 2 % for an adult
  - The increase needs by the brain places increase risks of potential neurologic side effects during hypoglycemia

Glycogenolysis and Gluconeogenesis

- Glycogenolysis
  - Maintains plasma glucose through breakdown of hepatic glycogen
- Gluconeogenesis
  - Plasma glucose maintained through synthesis of glucose from lactate, glycerol and amino acids
- Lipolysis
  - Breakdown of fat
  - What happens if first feed is delayed?
Delayed first feeding

- However, if the first feeding is delayed for three to six hours after birth, approximately 10 percent of normal term newborns cannot maintain a plasma glucose concentration above 30 mg/dL (1.7 mmol/L)

Normal low neonatal blood glucose levels

- Normal levels in utero about 70% of mothers blood glucose
- Loss of transplacental glucose supply
- Nadir around 2 hours (<40 mg/dl)
- Stabilize by 4-6 hours of age to late gestation fetal glucose levels (40-80 mg/dl)
- Consistent with adult levels by 3-4 days of life
**Suckling Ketogenesis**

- Ketones are an alternative fuel for the brain during a fast or periods of hypoglycemia
- Produced from breakdown of fatty acids in the colostrum (high fat content), peaks on 3rd day
- Response is blunted with formula
- May protect newborn brain for injurious affects of hypoglycemia

(Hawdon, Ward Platt, & Aysnley-Green, 1992)

---

**Inadequate/diminished glucose supply**

- **Inadequate glycogen stores**
  - Prematurity
  - Fetal growth restriction (FGR/IUGR)

- **Impaired glucose production**
  - Glycogenolysis
  - Gluconeogenesis
  - Inborn errors of metabolism
  - Endocrine disorders
  - Other causes (maternal causes, hypothermic infants, hepatic dysfunction)
Increased Glucose Utilization

- **With Hyperinsulinism**
  - Infants of diabetic mothers
  - Fetal growth restricted (FGR) infants
  - Beckwith-Wiedemann syndrome (BWS)
  - Perinatal asphyxia or stress

---

Increased Glucose Utilization

- **Without** hyperinsulinism
  - Asymmetric FGR
  - Anaerobic glycolysis
    - Decreased tissue perfusion, poor oxygenation, interference with aerobic glucose metabolism
  - Polycythemia
  - Heart failure
  - Perinatal asphyxia
  - Sepsis
  - Drug withdrawal
  - Cold stress
Anaerobic glycolysis

Etiology of Hypoglycemia Cold Stress...
Perinatal Asphyxia…

- What group of babies are at higher risk of perinatal asphyxia? Shoulder dystocia?

**IDM babies!!**

- IDM infant prone to hypoglycemia… and now, to make matters more complicated…

---

**Original Articles**

Hypoglycemia is Associated with Increased Risk for Brain Injury and Adverse Neurodevelopmental Outcome in Neonates at Risk for Encephalopathy

Emily W. Y. Tam, MDCM, MAS, FRCPC1,2,3, Laurel A. Hauesslein, BA1, Sonia L. Bonifacio, MD1, Hannah C. Glass, MDCM, MAS1,2, Elizabeth E. Rogers, MD1, Rita J. Jeremy, PhD1, A. James Barkovich, MD1,3,4, and Donna M. Ferrier, MD, MS5

---

A  

B
Hypoglycemia is Associated with Increased Risk for Brain Injury and Adverse Neurodevelopmental Outcome in Neonates at Risk for Encephalopathy

- Hypoglycemia (glucose <46) seen in the first 24 hours after birth in 16% of the cohort.
- After adjusting for potential confounders of early perinatal distress and need for resuscitation
- Neonatal hypoglycemia was associated with:
  - 3.72-fold increased odds of corticospinal tract injury ($P = .047$)
  - 4.82-fold increased odds of worsened neuromotor score ($P = .038$)
  - Lower cognitive and language score on the Bayley Scales of Infant Development ($P = .015$).

**Neonatal hypoglycemia is associated with additional risks in the setting of neonatal encephalopathy with increased corticospinal tract injury and adverse motor and cognitive outcomes.**

Nursing Care of the IDM

Comprehensive physical assessment

- Macrosomic?
- IUGR?
- Increased or decreased subcutaneous tissue?
- Plethoric?
- Jaundiced?
- Resp distress?
Neonatal Management

▪ Prior to delivery:
  • Assess need for neonatal resuscitation based on GA, anticipated BW, presence of a congenital anomaly or labor complications/mode of delivery

▪ After delivery:
  • Routine care:
    – warm/dry/stim, clearing airway, rapid assessment and examination to identify congenital anomalies
    – Glucose monitoring per unit policy
    – Routine newborn care

Neonatal Management

- Further evaluation:
  – Cyanosis/resp distress: assess for cardiac and respiratory disease
    ▪ CXR
    ▪ Pre/post ductal oxygen saturations
    ▪ 4 limb BP
    ▪ EKG
    ▪ ECHO
  – Bilirubin, hematocrit checks
  – Electrolytes in symptomatic infants
Physical Assessment
The Macrosomic Infant

FEED ME!!

I'm Hungry TOO!!

Erb’s Palsy
Facial nerve palsy

Plethoric Baby
“This Baby is Jittery…”

▪ What is the history?
▪ When is the onset?
▪ Hypoglycemia?
▪ Hypomagnesemia?
▪ Hypocalcemia?
▪ Hyperviscosity?

Neurogenic (autonomic) symptoms

▪ Jitteriness/tremors
▪ Sweating
▪ Irritability
▪ Tachypnea
▪ Pallor
Neuroglycopenic symptoms

- Poor suck or poor feeding
- Weak or high-pitched cry
- Change in level of consciousness
- Seizures
- Hypotonia

Additional hypoglycemia symptoms

- Apnea
- Bradycardia
- Cyanosis
- Hypothermia
- NO SYMPTOMS AT ALL
Jittery Infant

- http://med.stanford.edu/newborns/professional-education/photo-gallery/neo-reflexes.html#jittery_movements

Seizing Infant

- http://med.stanford.edu/newborns/professional-education/photo-gallery/neo-reflexes.html#seizure_activity
Who should be evaluated?

- Blood glucose concentrations **should not** be measured in *healthy asymptomatic term* infants born after an uncomplicated pregnancy and delivery.

- Blood glucose concentration should be measured in infants **at risk** for hypoglycemia and in infants who **exhibit signs or symptoms** consistent with hypoglycemia.

---

What babies are at risk?

- Preterm infants including late preterm infants
- Large or small for gestational age infants
- Infants with fetal growth restriction (FGR)
- Infants of diabetic mothers
- Infants who have experienced perinatal stress:  
  - Birth asphyxia/ischemia, Maternal preeclampsia/eclampsia, Meconium aspiration syndrome, Hydrops, Polycythemia
- Postmature infants
- Infants requiring intensive care
Timing and frequency of glucose screening

- Schedule for glucose screening is dependent on the clinical setting:
  - Whenever infant is symptomatic
  - At risk infants
    - One hour after birth
    - Before feeds q3-6 hours for the first 24-48 hours of life
  - Neonates with identified low blood glucose
    - Continue monitoring until concentrations in a normal range

Glucose testing

- Point of care testing
- iStat
- Plasma glucose concentration

Treatment should be started immediately after the blood sample is obtained and before confirmatory results are available
Diagnosis

What makes diagnosing hypoglycemia difficult?

Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants

David H. Adamkin, MD and COMMITTEE ON FETUS AND NEWBORN

KEY WORDS
newborn, glucose, neonatal hypoglycemia, late-preterm infant

ABBREVIATIONS
N—I neonatal hypoglycemia

abstract
This report provides a practical guide and algorithm for the screening and subsequent management of neonatal hypoglycemia. Current evidence does not support a specific concentration of glucose that can discriminate normal from abnormal or can potentially result in acute or chronic irreversible neurologic damage. Early identification of the at-risk infant and institution of prophylactic measures to prevent neonatal hypoglycemia is essential to avoid long-term sequelae associated with this condition.

“...this report does not identify any specific value or range of plasma glucose concentrations that potentially could result in brain injury. Instead, it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed.”
Management of Hypoglycemia

- **Important to have unit policy and procedure**

- **Enteral**
  - breastfeeding
  - donor breast milk
  - dextrose water
  - formula
  - dextrose gel

- **Parenteral**
  - D10W bolus 2ml/kg
  - Start D10W at 80ml/kg/day

---

Management of Hypoglycemia

- Recheck glucose within 30 minutes after intervention
- If glucose does not improve, may need to bolus again and increase IV rate and/or dextrose concentration
- May need to consider central access if requires concentration exceeds D12.5W
- Do not use D25W, D50W or large volume boluses as this creates rebound hypoglycemia
Management of Hypoglycemia

- Weaning IV infusions: when BG levels have been stable for 12-24 hours, Begin decreasing IV infusion by 1-2 ml/hr q 3-4 hours if BG > 50-60mg/dL.
- Further testing should be done in infants who continue to require glucose infusions at rates exceeding 8-10mg/kg/min to maintain normal glucose levels beyond 1st week of life.

Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

(LPT) Infants 34 - 36th weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)

**Symptomatic and <40 mg/dL → IV glucose**

**ASYMPTOMATIC**

<table>
<thead>
<tr>
<th>Birth to 4 hours of age</th>
<th>4 to 24 hours of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL FEED WITHIN 1 hour</td>
<td>Continue feeds q 2-3 hours</td>
</tr>
<tr>
<td>Screen glucose 30 minutes after 1st feed</td>
<td>Screen glucose prior to each feed</td>
</tr>
<tr>
<td>Initial screen &lt;25 mg/dL</td>
<td>Screen &lt;35 mg/dL</td>
</tr>
<tr>
<td>Feed and check in 1 hour</td>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;25 mg/dL</td>
<td>&lt;35 mg/dL</td>
</tr>
<tr>
<td>IV glucose*</td>
<td>IV glucose*</td>
</tr>
<tr>
<td>25-40 mg/dL</td>
<td>35-45 mg/dL</td>
</tr>
<tr>
<td>Refeed/IV glucose* as needed</td>
<td>Refeed/IV glucose* as needed</td>
</tr>
</tbody>
</table>

Target glucose screen ≥45 mg/dL prior to routine feeds

* Glucose dose = 200 mg/kg (Dextrose 10% at 2 mL/kg) and/or IV infusion at 5-8 mg/kg per min (80-100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding. Adamkin and Committee on Fetus and Newborn, 2011
AAP clinical report- when to treat

Symptomatic patients requiring treatment

- Jitteriness/tremors, hypotonia, changes in LOC, apnea/bradycardia, cyanosis, tachypnea, poor suck/feeding, hypothermia, seizures
  - Less than 48 hours of life with plasma glucose levels <50 mg/dL (2.8 mmol/L)
  - Greater than 48 hours of life with plasma glucose levels <60 mg/dL (3.3 mmol/L)

Asymptomatic patients at risk for hypoglycemia, or patients in whom low glucose was identified as an incidental laboratory finding

- Less than 4 hours of life with plasma glucose levels <25 mg/dL (1.4 mmol/L)
- Between 4 and 24 hours of life with plasma glucose <35 mg/dL (1.9 mmol/L)
- Between 24 and 48 hours of life with plasma glucose levels <50 mg/dL (2.8 mmol/L)
- Greater than 48 hours of life with plasma glucose levels <60 mg/dL (3.3 mmol/L)
UCSF NC²
(Northern CA Neonatology Consortium)
- Representatives from multiple northern California hospitals
- Meet quarterly to recommend consensus statements on neonatal conditions
- Consensus statements available on UCSF website
- Statements include:
  - Hypoglycemia
  - Hyperbilirubinemia
  - Early onset sepsis
  - Soon… Apnea of prematurity

UCSF NC² Asymptomatic Infants/at-risk

APPENDIX 2: Screening & Management of Neonatal Hypoglycemia in ASYMPTOMATIC infants ≥ 34wks GA

- CRITERIA:
  - IDM (DM1 or 2, GDMA1 or A2)
  - Late preterm (34-37wks) or Post-term (≥42wks)
  - SGA or LGA (see table)

<table>
<thead>
<tr>
<th></th>
<th>37 wks</th>
<th>38 wks</th>
<th>39 wks</th>
<th>40 wks</th>
<th>41 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA (&lt;5th%)</td>
<td>2100 gm</td>
<td>2400 gm</td>
<td>2600 gm</td>
<td>2700 gm</td>
<td>2800 gm</td>
</tr>
<tr>
<td>LGA (&gt;97.5th%)</td>
<td>4100 gm</td>
<td>4300 gm</td>
<td>4400 gm</td>
<td>4500 gm</td>
<td>4600 gm</td>
</tr>
</tbody>
</table>

- TIMING:
  - Screen after initial feeding @ 1 hr, then @ 2, 4, 6, 9, 12 hrs (prior to feedings)
  - Screen SGA & late preterm infants @ 24 hrs (prior to feedings)
  - If glucose ≥45 x 3 → stop screening + re-check @ 24 hrs if SGA or late preterm
**UCSF NC² Asymptomatic Infants - at risk**

**Target glucose = 45 prior to routine feeds**

**Birth - 4 Hours**
- Initial feed within 1 hour
- Screen glucose 30 minutes after 1st feed

- < 25
  - Feed & re-check in 1 hour
- ≥ 25
  - Routine care

- Continue glucose screening @ 2, 4 hours (before feeds)
- < 25
  - IV treatment
- 25 - 40
  - Oral treatment (IV treatment PRN)

**4 - 24 Hours**
- Screen @ 6, 9, 12 hours
  + Screen @ 24 hours if SGA / Preterm (before feeds)

- < 35
  - Feed & re-check in 1 hour
- ≥ 35
  - Routine care

- Continue glucose screening (before feeds)
- < 35
  - IV treatment
- 35 - 45
  - Oral treatment (IV treatment PRN)

If persistent glucose < 45, Consider evaluation for underlying etiology

---

**UCSF NC² Symptomatic Infants**

**APPENDIX 3: Screening & Management of Neonatal Hypoglycemia in SYMPTOMATIC infants ≥ 34wks GA**

**“CONCERNING” symptoms**
- Seizure
- Lethargy
- Hypotonia
- Apnea
- Cyanosis

**“POSSIBLE” symptoms**
- Jitteriness / tremors
- Irritability
- Exaggerated Moro reflex
- High-pitched cry
- Poor feeding

**Target glucose ≥ 45 prior to routine feeds**

**“Concerning” Symptoms**
- Check glucose
  - < 45
    - IV treatment
  - ≥ 45
    - Evaluate for other cause of symptoms

**“Possible” Symptoms**
- Check glucose
  - < 45
    - Feed & re-check in 1 hour
  - ≥ 45
    - Evaluate for other cause of symptoms

If persistent glucose < 45, Consider evaluation for underlying etiology
**UCSF Newborn Nursery Policy**

- Glucose testing done at 1, 3, 6, 9, 12 hours of life
  - All blood sugars except 1 hour to be done prior to feeds (AC)
- LGA, IDM, asymptomatic stable infants can d/c testing after 3 consecutive BS >45
- SGA or LPI also need BS at 18, 24 and 36 hours of life (also completed AC)

---

**UCSF Newborn Nursery Policy**

- If glucose >45 and infant asymptomatic, test at next specified time
- If glucose <45 repeat with different strip and/or meter if possible
  - If test strip is 30-45, place infant skin-to-skin, allow breastfeeding, recheck 1 hour from initiation of feed
  - If the infant is not interested in breastfeeding or mother is not available
    - Oral feed infant D5W or formula at 7 ml/kg and recheck blood sugar 1 hour after initiation of feeding
UCSF Newborn Nursery Policy

- If recheck glucose is > 45 mg/dL, continue with glucose check at next specified time per protocol
- If recheck, glucose is still 30-45 mg/dL, and baby is asymptomatic follow procedural steps above
  - If upon recheck glucose is still 30-45 mg/dL and baby is symptomatic:
    - Notify nursery provider.
    - Oral feed infant D5W or formula at 7mL/kg.
    - If baby has 3 values 30-45 notify provider

UCSF Newborn Nursery Policy

- If the glucose test is 20-30 mg/dL repeat the glucose test with a different strip and/or meter if possible
  - Notify provider STAT
  - Oral feed infant D5W or formula at 7mL/kg and recheck on hour from initiation of feeding
    - If recheck glucose test strip is still 20-30 mg/dL: Draw serum glucose STAT and send to lab.
    - Notify provider STAT.
    - Oral feed infant D5W or formula at 7 mL/kg.
    - Further instructions per provider. Provider may consider IV glucose infusion.
UCSF Newborn Nursery Policy

- If glucose test is < 20mg/dL repeat the glucose test with a different test strip and/or meter if possible.
  - Draw serum glucose STAT and send to lab.
  - Notify provider STAT
  - Oral feed infant D5W or formula at 7 mg/kg if baby willing
  - Further instructions per provider. Provider may consider IV glucose infusion.

NICU and Special Care / Transitional Care Nursery

- Treatment thresholds and treatment methods are different for infants in these higher level of care settings; consult neonatology for recommendations.

---

UCSF Neonatal Hypoglycemia in the Critical and Transitional Care Setting

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Blood Glucose mg/dL</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (Including NICN)</td>
<td>&lt;25 mg/dL</td>
<td>✔️</td>
<td>✔️</td>
<td>Notify MD/NNP Place IV Obtain order for: D5W bolus – 2 mL/kg D5W @ 80 mL/kg/day</td>
</tr>
<tr>
<td>NICN Patients with: Encephalopathy - HIE • Perinatal stroke • Seizures</td>
<td>&lt;60 mg/dL</td>
<td>✔️</td>
<td>✔️</td>
<td>Notify MD/NNP Place IV Obtain order for: D5W bolus – 2 mL/kg D5W @ 80 mL/kg/day</td>
</tr>
<tr>
<td>All Infants Identified as “at Risk” (Except NICN)</td>
<td>&lt;50 mg/dL</td>
<td>✔️</td>
<td></td>
<td>Notify MD/NNP IV Dextrose per order AND/OR Feeding per order</td>
</tr>
<tr>
<td>All Infants Identified as “at Risk” (Except NICN)</td>
<td>&lt;50 mg/dL</td>
<td>✔️</td>
<td></td>
<td>Notify MD/NNP Feeding per order AND/OR IV Dextrose per order</td>
</tr>
</tbody>
</table>
What if the blood sugar is still low??

Treatment for Refractory Hypoglycemia

▪ Hydrocortisone if GIR >12-15 mg/kg/min
  ▪ If GIR >15, consider Endocrine consult
▪ Glucagon (wont work if neonate has decreased stores)
▪ Diazoxide
▪ Octreotide
▪ Calcium channel blockers
▪ Surgery

IV Therapy for Hypoglycemia

▪ D10W 2 ml/kg IV bolus, followed by:
▪ D10W @ 80 ml/kg/day (3.5 ml/kg/hr)
  ▪ Glucose infusion rate (GIR) 5.5 mg/kg/min
  ▪ Increase D10W in increments of 20 ml/kg/day (0.8 ml/kg/hr) if needed for persistent hypoglycemia
  ▪ If fluid administration exceeds 150 ml/kg/day consider increasing Dextrose concentration to avoid fluid overload
▪ Continue therapy until glucose levels are stable >50, then gradually wean IV fluids
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years

- Neonatal hypoglycemia was not associated with adverse neurologic outcomes when infants were treated with the aim of maintaining a blood glucose concentration of at least 47 mg per deciliter.

- The possibility that blood glucose concentrations at the high end of the normal range or unstable blood glucose concentrations and rapid correction of hypoglycemia may be harmful requires further investigation.

Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years

New evidence showing an association of neurodevelopmental impairment with rapid correction of hypoglycemia has led to a suggested approach of bypassing the 2 ml/kg bolus of glucose in favor of simply starting a continuous glucose infusion of 4 to 6mg/kg/min in asymptomatic patients with a gestational age ≥35 weeks, and at risk for hypoglycemia.
Results of Interstitial Glucose Monitoring in Children with and Those without Neurosensory Disability at 2 Years.

So, You Want Some Sugar??

- The *Sugar Babies Study* designed to test efficacy of dextrose gel for treatment of hypoglycemia
- 514 infants identified as at risk for hypoglycemia (SGA, LGA, IDM, LPI)
- Screened BG @ 1 hr then ac q 4 x 24 hrs then q 8 x 24 hrs
- Measured incidence of blood glucose (BG) ≤ 47 mg/dL and ≤ 36 mg/dL

The Sugar Babies Study

- 51% of all pts had BG ≤ 47 mg/dL
- 19% had BG ≤ 36 mg/dL
- 19% had more than one episode
- Most babies (79%) who became hypoglycemic showed *no clinical signs*
- Supports AAP recommendations for screening these groups
Management of Study Participants

- Skin to skin contact and early feeding encouraged for all patients in study
- Infants fed on demand but no more than 3 hrs between feeds
- Hypoglycemic infants received glucose gel or placebo and encouraged to feed (or were cup or tube fed if unable to suck)
- If after 30 mins, if the baby was still hypoglycemic, the same process was repeated

The Sugar Babies Study - Measured outcomes

- Primary outcome
  - Treatment failure: (BG < 47) after 2 treatment attempts
- Secondary Outcomes
  - Admission to the NICU
  - Feeding frequency
  - Volume of expressed breast milk
  - Need for further dextrose (IV or oral)
  - Rebound hypoglycemia
  - Duration of hypoglycemia (up to 48hrs after birth)
The Sugar Babies Study - Results

▪ Primary outcome data showed fewer babies in the dextrose gel group (14%) failed treatment compared to the placebo group (24%) p value 0.04

▪ Babies in the dextrose gel group were less likely to need extra doses of dextrose
  • However those who did receive IV dextrose had similar amounts

▪ Admission rates to the NICU were similar, but the dextrose gel group was less likely to be admitted for hypoglycemia

The Sugar Babies Study - Results

▪ Giving dextrose gel had no adverse effects on breastfeeding

▪ Babies in the dextrose gel group:
  • Breastfed more frequently
  • Received less expressed breastmilk
  • At 2 weeks of age, fewer babies were formula feeding
  • Fewer episodes of recurrent hypoglycemia
The Sugar Babies Study - Results

▪ No adverse effects noted from the dextrose gel

▪ Treatment with 40% dextrose gel is more effective than feeding alone for reversal of neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth

The Sugar Babies Study - Impact on Practice

▪ Dextrose gel provides a viable first-line/intermediate treatment for neonatal hypoglycemia
▪ Easy to administer
▪ Keeps mother and baby together
▪ Extremely inexpensive
▪ Less invasive
▪ High availability
Implementing a Protocol Using Glucose Gel to Treat Neonatal Hypoglycemia

- Neonates are placed skin to skin and breastfed for the first hour of life
- A BG level is obtained 30 minutes after this feed is completed
- If the BG level is <35, the nurse administers a weight based dose of 40% glucose gel by syringe to the neonate’s buccal cavity and then places with the mother to feed
- A BG level is repeated 1 hour after gel administration

- If this BG level is >35 mg/dl, the neonate’s BG levels are assessed before feedings until two consecutive readings are >45 mg/dl.
- If the neonate’s BG level is <35, a second dose of gel is given, and again placed with mother to feed
- In the event that a second dose is needed, a BG level is obtained 1 hour after gel administration.
- If hypoglycemia is not reversed after the second dose of 40% glucose, the physician is contacted for further orders.

FIGURE 1
Percentage of Infants Admitted to NICU for Neonatal Hypoglycemia

FIGURE 3
Glucose Levels One Hour After Administration of Dextrose Gel (n = 278)
Glucose Infusion Rates

- Glucose production rate in healthy fasting term newborns 4-6mg/kg/minute
- D10W at 80ml/kg/day = 5.5mg/kg/min
- Advance GIR to maintain euglycemia
- Further testing should be done in infants who continue to require glucose infusions at rates exceeding 8-10mg/kg/min to maintain normal glucose levels beyond 1st week of life
Oral Sucrose

- Is not treatment for hypoglycemia, and its usage is independent of needed therapy

Legal Implications

- In one review of neonatal litigation cases from 2 years, 37% of the cases dealt with neonatal hypoglycemia

- Lack of screening of high risk neonates, failure to confirm a low glucose concentration and poor documentation of prompt intervention with resolution of clinical symptoms led to litigation
Long Term Sequelae

- Motor cognitive delay
- Impaired glucose tolerance
- Metabolic syndrome in adulthood
- 50% of macrosomic IDMs weigh more than the heaviest nondiabetic children at 5-8 years of age (Touger et al., 2005)
Long term sequelae

- Adolescent offspring of mothers with GDM had a higher median BMI, greater risk of being overweight, larger median waist circumference and higher fasting insulin levels (2009)

- Adolescent offspring of mothers with pregestational Type 1 or Type 2 diabetes had a greater BMI compared to control adolescents born to nondiabetic mothers (2010)
  - Macrosomia often present at birth, resolved by 1 year of age but obesity recurrent in childhood
  - Impaired glucose tolerance occurred in 36%

- Infants of diabetic mothers are at increased risk for future insulin resistance.

- May lead to a significant rise in GDM, throwing future generations to a cycle of obesity, insulin resistance, diabetes and various metabolic complications
Neonatal Hypoglycemia: Answers but More Questions
(Rozance & Hay 2012)

▪ What are the advantages of lower neonatal glucose concentrations for first 3-4 days of life?
▪ Stimulation of glucose production in neonate?
▪ Stimulation of appetite?
▪ Adaptation of fast/feed cycles?
▪ What do our interventions do to interrupt “nature?”

Case Study I

▪ 37 6/7 week female infant born to a G 2, P1-2 mother with poorly controlled GDM.
▪ Maternal history significant for BMI 38; GBS+; GDM 2001 no interval follow up; hemoglobin A1c 10.6 at first prenatal visit
▪ Subsequent Hgb A1C’s 10.4, 10.6 (just prior to delivery)
▪ IOL delayed for immature lungs
Case study

- C/S for intolerance of labor:
  - Birthweight 4065 gm
  - Infant profoundly cyanotic after birth.
  - Echocardiogram reveals transposition of the great arteries (TGA).

- Questions to ask:
  - Why was she induced?
  - How significant is A1C in 3rd trimester?
  - Why were the lungs immature?
  - What caused the TGA?

---

Case Study II
Case Study

▪ Male 5kg infant born to a 27 year old G3P1 woman with GDM
▪ Pushed x 1 hr when OB attempted vacuum x2 but could tell baby would not come down so moved to C/S under general
▪ Thick mec and nuchal cord
▪ PPV and chest compressions initially
▪ Apgars 1, 6, 8

Case Study

▪ CUA: 6.92/82/-18.5
▪ Initial BG 92 HR 160 RR 66
▪ HS blood gases attempted but clotted
▪ 7.05/40/-19 via HS @ 3 HOL
▪ BG 38 @ 3 HOL
▪ 2 ml/kg D10W bolus followed by infusion of D10W @ 80 ml/kg/d
Case Study

- Initially in oxygen via NC at 40% to keep sats 95%
- Developed increased WOB and chest xray revealed patchy infiltrates consistent with meconium aspiration
- Also developed upper extremity jerking and eye deviation
- Transport call placed at 8 hours of life

Case Study

- Review with UCSF neonatologist revealed significant metabolic acidosis at birth and findings consistent with hypoxic ischemic encephalopathy
- Passive cooling initiated
- Transport arrived at 9 hours of life, core temperature 36.5 degrees (97.7 F)
- Target temperature of 33.5 degrees achieved at 10 hours of life (92.3 F)
Brain Care

- What issues could have predisposed this baby to have brain injury?
- What is the criteria for passive cooling?
- What concerning signs were present that might have indicated this baby was at risk for brain injury?

Legal Implications

“Unfortunately, untoward long-term outcomes in infants with one or two low blood glucose levels have become the grounds for litigation and for alleged malpractice, even though the causative relationship between the two is tenuous at best… The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.”

Cornblath et al., 2000
Legal Implications

- In one review of neonatal litigation cases from 2 years, 37% of the cases dealt with neonatal hypoglycemia.

- Lack of screening of high risk neonates, failure to confirm a low glucose concentration and poor documentation of prompt intervention with resolution of clinical symptoms led to litigation.

In summary...

- Neonatal hypoglycemia remains a controversial topic, as no literature defines what blood glucose is too low, for how long, and at what level or time does irreversible neurodevelopmental injury occur.

- Clinical consensus and guidelines recommend levels that symptomatic and at-risk infants should be treated.

- Dextrose/glucose gels are potentially providing a new management approach for hypoglycemia, while promoting exclusive breastfeeding.
References


References


▪ Riskin, A. Infant of a diabetic mother, Post, TW (Ed), UpToDate, Waltham, MA, 2014.


Questions?

Thank you!!

Tanya.Hatfield@ucsf.edu