Neonatal Hypoglycemia

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Incidence

- 1-5 per 1,000 births
- 8% in LGA
- 15% SGA (IUGR)
- 30% entire population of high risk infants
A. Glucose Homeostasis in Utero

- Energy as glucose, lactate, FFAs, ketones, surplus amino acids
- Facilitated diffusion across the placenta
- Fetal blood glucose concentration approx 70% of maternal value
Glucose Homeostasis in Utero

Insulin appears in the fetal pancreas and plasma at 12 weeks gestation

- permissive in accumulation of hepatic glycogen stores

- high insulin: glucagon
  - increases glycogen synthesis and suppression of glycogenolysis
  - suppresses lipolysis
Glucose Homeostasis in Utero

- Marked increase in glycogen synthesis during early and mid gestation associated increase in circulating concentration of both insulin & cortisol

- Fetal hormonal and metabolic milieu establishes a ready substrate supply that can be used during the metabolic transition from fetus to newborn.
Glucose Homeostasis in Newborn

AT DELIVERY:
- rapid glycogenolysis
- Adaptive response → surge in plasma glucagon & decrease in plasma insulin (high glucagon: insulin) → mobilizes glucose & fatty acids from glycogen & triglyceride depots
- high glucagon: insulin → induces synthesis of enzymes required for gluconeogenesis
- Low blood glucose values are usually NOT related to any significant problem but are 20 to normal process of metabolic adaptation to extrauterine life
To maintain normal levels of hepatic glucose in newborn:

- Adequate stores of glycogen and gluconeogenic precursors (fatty acid, glycerol, amino acids, lactate)
- Appropriate concentration of hepatic enzymes required for glucogenolysis and gluconeogenesis
- Normally functioning endocrine system
Definition of Hypoglycemia?

- Population based statistical values rather than functional values resulting in very low cut off levels of blood glucose.
Four approaches to defining hypoglycemia, all flawed:

1. **Clinical approach**
   - changed level of consciousness, irritability, lethargy, stupor, apnea/cyanotic spells, coma, poor feeding, hypothermia, hypotonia/limpness, tremor, seizures

2. **Epidemiological approach**
   - have been erroneously interpreted & used to define cut off points between normoglycemia & hypoglycemia or hyperglycemia rather than recognizing that hypoglycemia reflects a continuum of biological abnormalities ranging from mild to severe.

3. **Approach based on acute metabolic, endocrine, and neurological function**
   - still inadequate evidence because of few datas in small groups of subjects

4. **Approach based on long-term neurologic outcome**
   - still inadequate evidence
   - data are limited because of lack of suitable non hypoglycemic controls
Definition of neonatal hypoglycemia

• The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.


Definitions of Hypoglycemia

Suggested Treatment Thresholds

- **Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds**
  

- “Blood glucose levels at which clinical interventions should be considered”
Operational Threshold

• Indication for intervention
  - Based on evidence currently available in the literature
    Concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ
  - Provides large margin of safety by designating the lower level of glucose that a neonate can safely tolerate based on physical maturity and influence of pathology
Definition of Hypoglycemia

- Plasma glucose $< 40 \text{ mg/dl}$ in both preterm and term infants
- Serum glucose $< 45 \text{ mg/dl}$ if symptomatic will be treated as hypoglycemia
- Less than $40-50 \text{ mg/dl}$ after 24 hours
Risk Factors for Hypoglycemia

Changes in maternal metabolism:
- Intrapartum administration of glucose
- Drug treatment with terbutaline, ritodrine, propanolol, oral hypoglycemics
- Diabetes in pregnancy

Associated neonatal problems:
- Perinatal hypoxia-ischemia
- Infection
- Hypothermia
- Hyperviscosity
- Erythroblastosis fetalis, hydrops fetalis
- Iatrogenic causes
- Congenital cardiac malformations

Others
- Intrauterine growth restriction
- Hyperinsulinism
- Endocrine disorders
- Inborn errors of metabolism
Who’s at Risk? What could be the cause?

3 basic mechanisms:

• Limited glycogen stores

• Hyperinsulinism

• Diminished glucose production
A. Limited Glycogen store/supply

- Prematurity
- Perinatal stress/distress
- SGA
- Disorders of Glycogen metabolism
  - Glucose 6-phosphatase def
  - Amylo-1,6 glucosidase def
  - Phosphorylase def

  - limit either glycogen metabolism or glucose release resulting in excess glycogen stores, hepatomegaly and hypoglycemia
  - inherited primarily as autosomal recessive
B. Hyperinsulinism

- Infant of Diabetic mother
- Beckwith – Wiedemann Syndrome
- Erythroblastosis fetalis
B. Hyperinsulinism

- **Maternal Drug Effects on neonatal glucose metabolism**
  - Chlorpromazine & benzothiazides
  - Propanolol
  - Beta symphatomimetic (Terbutaline)
  - Inappropriate intrapartum maternal glucose administration

- **Islet cell adenoma or Nesidioblastosis**
  - Primary abn of pancreatic beta cell development resulting in sustained or persistent neonatal hyperinsulinism and hypoglycemia.
C. Diminished Glucose Production

• SGA
  ➢ Decreased glycogen stores and impaired gluconeogenesis due to:
    - elevated levels of gluconeogenic precursors (particularly alanine) in their blood
    - defects in phosphoenol pyruvate carboxylase activity (rate limiting enzyme for gluconeogenesis)

• Inborn error of metabolism
  > Aminoacidopathies (amino acids involved in gluconeogenesis)
D. Others

- **Hypothermia, Sepsis, increased work of breathing, perinatal asphyxia**
  - Normal glycogen stores but inadequate to meet increase energy demand
  - Increase glucose utilization
- **Cortisol and Growth hormone deficiencies**
  - Secondary to effects on hepatic glycogenolysis and gluconeogenesis
- **Polycythemia**
  - Direct result of increased glucose consumption by the red cell mass as well as secondary to effects on the intestinal absorption of substrates.
Clinical Presentation

- No pathognomonic signs or symptoms
- Lethargy
- Apathy
- Irritability
- Tachypnea
- Jitteriness
- Seizure
- Apnea
- Bradycardia
- Cyanosis
- Coma
- Asymptomatic high risk infant
Determining Etiology

- Presence of risk factor
- Plot growth parameters (SGA, AGA, LGA)
- Consider sepsis for patient without risk factor
- If more than one week, consider hyperinsulinemia, endocrine disorder or error of metabolism
When do you screen these “at risk” babies?

FIRST OF ALL in ANY BABY:
If symptomatic: SCREEN IMMEDIATELY

If asymptomatic but AT HIGH RISK including infant of diabetic mom, septic, premature (<32 wks), <1500g: Screen at 30-60 min of life
Practical Points for Blood Glucose Estimation

False positive:
- hematocrit <35%,
- contamination with isopropylalcohol.

False negative:
- hematocrit >55%.
- delay in lab analysis, --
- glucose values > 200 mg/dl

• False results if done < 18 degree C or > 35 degree C.
So………
you’ve got a low glucose,
Now WHAT DO YOU DO???
Management

Goal:

- To normalize blood glucose concentrations as quickly as possible to avoid further episodes of hypoglycemia by providing adequate substrate until normal glucose homeostasis can be established.
Management

• **Enteral feeding**: term, asymptomatic, mild hypoglycemia

• **Standard infant formula** provide carbohydrate in the form of lactose plus protein and fats which are metabolized slowly

• Blood glucose increase by 1.67 mmol/L (30 mg/dl) within the first hour after a feeding of 30-60 ml of formula
Management

• Infants whose blood glucose normalize following an enteral feeding should continue to have glucose monitoring before each feeding for 12 to 24 hrs.

When is enteral feeding considered a failure?
• If value before the next feeding is again in the hypoglycemic range, candidate for IV therapy
• Prompt IV therapy avoid repeated episode of hypoglycemia
Management

• IV therapy

  Indications:
  - symptomatic infants
  - unable to tolerate feedings
  - those in whom disturbance in glucose homeostasis is severe or is expected to last more than a few hours.
Management

• IV therapy
  • initial bolus 200 mg/kg of 10% DW (2ml/k D10W) followed by continuous infusion of 5-8 mg/k/min
  • Blood glucose checked after 30 mins then every 1-2 hrs
  • If subsequent value falls, bolus should be repeated and infusion rate increased by 10% to 15% (12-15 mg/k/min). Umbilical venous catheter or PICC line is needed
Management

IV therapy

- permitted to continue feedings especially carbohydrate

When can an infant be weaned from IV therapy?

- Decrease infusion rate by 10-20% each time blood glucose is > 50-60 mg/dl
- Failure to tolerate IV glucose indicates further evaluation
Additional Management

- Reduce energy needs
  > Correct acidosis, avoid cold stress
- Monitor treatment at least every 30 mins until the infant’s condition is stable
- Consider sepsis for patients with no risk factor
Management

• Avoid iatrogenic hyperinsulinism from umbilical arterial glucose infusion into pancreatic artery and rebound hypoglycemia following rapid IV bolus of hypertonic glucose

• Frequent boluses of D10W will induce a INSULIN SURGE and REBOUNDED HYPOGLYCEMIA → Try to use a max of 2 boluses of D10W
What if hypoglycemia occurs prolonged, recurrent or persistent?

Recurrent of Persistent Hypoglycemia:

1) Require infusions of large amounts of glucose (>12→16 mg/kg/min) to maintain normoglycemia
What if hypoglycemia occurs prolonged, recurrent or persistent?

1) Persisting or recurring beyond the first 7-14 days of life

**Prompt recognition is essential!!

These conditions are associated with severe disease at substantial risk of developing severe mental retardation and epilepsy.

These include many conditions stated previously including: Hormone deficiencies, Hyperinsulinism syndromes, Defects in carbohydrate, amino acid, fatty acid metabolism
What tests should you do? What is your management?

- Assay for insulin, C-peptide, cortisol, growth hormone, B-hydroxybutyrate, lactate, free fatty acids, T4, TSH
- Urine for reducing substances, ketones, organic acids
## Adjunct therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>Decrease peripheral glucose utilization</td>
<td>Hydrocortisone 5-15 mg/k/d or prednisone 2mg/kg</td>
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<tr>
<td>Glucagon</td>
<td>Stimulates glycogenolysis</td>
<td>30mcg/k if normal insulin 300mcg if increased insulin</td>
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<td>Diazoxide</td>
<td>Inhibit insulin secretion</td>
<td>15mg/kg/day</td>
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<tr>
<td>Somastostatins (long acting octreotide)</td>
<td>Inhibit insulin and growth hormone release</td>
<td>5-10mcg/k every 6-8 hours</td>
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Consequences of Hypoglycemia

• Selective neuronal necrosis in multiple brain regions including the superficial cortex, dentate gyrus, hippocampus and caudate putamen

• In PT, predispose to intraventricular hemorrhage

• Impairement in the cognitive and motor function
Neuropathology in hypoglycemia

**Acute changes:**
Pathological studies of severely hypoglycemic neonatal brains showed:
- neuronal injury in cerebral cortex, hippocampus, basal ganglia, thalamus, brainstem, and spinal cord.
- neuronal necrosis occurred more than ischemic injury
- widespread glial cell degeneration
- periventricular leukomalacia in a few cases

**Chronic changes:**
Pathological studies long after the neonatal period showed:
- significant microcephaly
- diffuse loss of neurons in cortex
- increase in astrocytes and microglia
- calcifications in the necrotic zones
- sparing of the cerebellum


Neuroimaging in hypoglycemia (cont’d)

Symptomatic hypoglycemia is associated with parieto-occipital white matter abnormalities, as well as abnormal signals in the deep grey matter structures of the thalamus and basal ganglia.

Neuroimaging in hypoglycemia

Spar et al. (1994) were the first to describe neuroimaging changes in neonatal hypoglycemia.

Case report of one infant with **symptomatic hypoglycemia** at 58 hours of age, with hypoglycemia well-documented at over 15 hours.

MRI at DOL#19 showed:
- bilateral occipital lobe parenchymal tissue loss
- near complete absence of cerebral cortex in posterior parietal and occipital areas
- generalized thinning of the cerebral cortex

No other factors were found to explain this brain damage, and thus was attributed to the hypoglycemic insult.

Neuroimaging in hypoglycemia (cont’d)


In a study of 18 term infants with symptomatic hypoglycemia:

• 39% showed MRI or ultrasound abnormalities

• 4 showed patchy hyperintense lesions on MRI in occipital periventricular white matter or thalamus

• 3 of 4 did not show these lesions on follow-up MRI

Multi-center study of 661 preterm infants weighing < 1850 g, with outcomes determined at 18 months of age.

Reduced mental and motor developmental scores were found to be related to increasing number of days with glucose levels < 2.6 mmol/L (<47 mg/dl).

Relative risk for neurodevelopmental impairment was 3.5x greater in infants with blood glucose < 2.6 mmol/L (<47mg/dl) for > 5 days.

Long-term study of 13 children with neonatal hypoglycemia of < 1.5 mmol/L (<27mg/dl), compared to 15 children without neonatal hypoglycemia.

Assessments done at an average of 7.75 years of age showed:

- significantly more difficulties in a screening test for minimal brain dysfunction
- more hyperactivity, impulsivity, and inattentiveness
- lower developmental scores

Compared to controls.
Conclusions

• Disturbance of glucose homeostasis that result in hypoglycemia are common among newborns

• Hypoglycemia is a common disorder in neonates, however no clear definition for the condition exists.

• The level of blood glucose that warrants treatment depends much on other factors including gestational age, concomitant risk factors, and condition of the patient.
Conclusions

- Awareness of risk factors allows for screening of those at risk so that clinically undetectable hypoglycemia can be treated promptly.
- Significant neurodevelopmental deficits can occur in neonates who experience numerous days of hypoglycemia.
- Much work still needs to be done to clarify all of these areas, including the definition, thresholds to treatment, utility for neuroimaging, and prognostication of neonatal hypoglycemia.
References


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References


