Metabolic Problems of SGA and LGA Infants: Now and Later

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Session Summary

The pathophysiology and management of metabolic problems common in the neonatal period for infants born SGA or LGA will be reviewed. We will further explore the growth/nutrition related problems these infants are at risk for later in life.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- discuss the hormonal/metabolic changes that place the SGA and LGA infant at risk of hypoglycemia in the early neonatal period;
- explain the mechanism by which IUGR/SGA infants can present with abnormalities seen in refeeding syndrome;
- list one feeding difficulty associated with SGA and LGA infants in the neonatal period;
- name three metabolic abnormalities seen in SGA/LGA in adolescence and adulthood.

References


Session Outline

See presentation handout on the following pages.
OBJECTIVES:

- Discuss the hormonal/metabolic changes that place the SGA and LGA infant at risk of hypoglycemia in the early neonatal period.
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- Name 3 metabolic abnormalities seen in SGA/LGA in adolescence and adulthood.

Appropriate for Gestational Age (AGA)

- 10-90th %ile

Small for Gestational Age (SGA)

- < 10th %ile

Large for Gestational Age (LGA)

- > 90th %ile

IUGR VERSUS SGA

- Intrauterine growth restriction (IUGR)
  A fetus whose estimated fetal weight is < 10th percentile for gestation age.
  - Symmetric IUGR
    Occurs < 32 weeks; wt/length/HC all < 10%; normal Ponderal Index; think about infections, chromosomal or congenital anomalies.
  - Asymmetric IUGR
    Occurs > 32 weeks; normal length and HC but wt < 10th %; low Ponderal Index; think uteroplacental insufficiency.
- Small for gestational age (SGA)
  An infant born with a birth weight at the lower end of the normal weight distribution.
FENTON GROWTH CURVES

- The 2003 Fenton Preterm Growth Chart is recently revised
- Aims of Study:
  - align the preterm growth chart with the new World Health Organization (WHO) Growth Standard
  - smooth the data between the preterm and WHO estimates, informed by the Preterm Multicentre Growth (PreM Growth) study while maintaining data integrity from 22 to 36 and at 50 weeks
  - re-scale the chart x-axis to actual age (rather than completed weeks) to support growth monitoring.


LGA/IDM INFANTS-MACROSOMIA

- Macrosomia results from fetal hyperglycemia, increased fetal insulin secretion, increased fat production from glucose, glycerol, fatty acids and triglycerides.
- Risk for macrosomia increases with maternal glucose > 130 mg/dL but is worse with postprandial hyperglycemia.
- Increase glycogen content of organs cause organomegaly.

SGA/IUGR-UNDERNUTRITION

- Growth of brain, adrenal gland and heart spared
- Blood flow to muscle, gut and liver is decreased
- Decreased fat mass
- Decreased glycogen stores
- Decreased skeletal muscle however increased insulin receptors present but inactive signaling molecules

HYPOGLYCEMIA
HYPOGLYCEMIA IN LGA/IDM INFANTS
- Maternal supply of glucose is cut off
- Normal neonates mobilize glycogen from the liver to maintain blood glucose levels
- IDM infants have high insulin levels that prevent glycogenolysis and gluconeogenesis
  - Insulin blocks glycogen phosphorylase activity
  - Insulin inhibits PEPCK needed for gluconeogenesis
- Hyperinsulinism also prevents fatty acid release from adipose tissue, therefore fat is not available as alternative energy substrate.

HYPOGLYCEMIA IN SGA/IUGR
- Increased risk for in the first days of life
- Due to decreased glycogen stores (the predominant source of glucose in the first hours after birth)
- Also possible due to decreased glucose production in the liver from alanine and lactate via gluconeogenesis
- IUGR infants also have limited fat stores and may not oxidize free fatty acids and triglycerides
- Hyperinsulinism or excessive sensitivity to insulin can worsen hypoglycemia

HYPOCALCEMIA
- At risk of early neonatal hypocalcemia (occurs in the first 2-3 days of life)
- SGA/IUGR infants occurs due to decreased transfer of calcium across the placenta
- LGA/IDM infants have hypocalcemia due to suppressed PTH levels
- Serum calcium is not a good marker for hypocalcemia
- Ionized calcium is a better indicator but is influenced by acid base balance (decreased with alkalosis and increased with acidosis)

REFEEDING SYNDROME IN VLBW/IUGR INFANTS
- IUGR infants suffer from fetal malnutrition
- Aggressive parenteral nutrition can lead to overfeeding
- This can lead to excess usage and intake of phosphorus at the cellular level, and result in hypophosphatemia
- Severe hypophosphatemia can also prevent adenosine 5’-triphosphate (ATP) synthesis, and could be a life-threatening condition
- This affect respiratory status as ATP needed for diaphragm contractibility
- Definitions:
  - hypophosphatemia (phosphorus <4 mg/dL)
  - severe hypophosphatemia (phosphorus <2.5 mg/dL)
  - hypokalemia (potassium <3.0 mg/dL)
  - hypomagnesemia (magnesium <1.5 mg/dL)
  - Hyperglycemia (glucose>180 mg/dL)

REFEEDING SYNDROME IN VLBW/IUGR INFANTS
- Retrospective chart review of 2253 VLBW infants, IUGR was associated with hypophosphatemia, hypokalemia, hyperglycemia and hypomagnesemia, all laboratory markers of refeeding syndrome.
- Definitions:
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COMPLICATIONS OF SGA/IUGR AFTER THE NEONATAL PERIOD

- Neurodevelopmental disorders
- Short stature
- Metabolic Syndrome later in life
  - Also known as insulin resistance syndrome, a cluster of metabolic abnormalities characterized by insulin resistance/hyperinsulinemia, abnormalities in glucose metabolism, dyslipidemia, hypertension, and obesity
- Important to balance growth to promote optimal neurodevelopmental outcomes while preventing increased metabolic risk
- These infants have decreased lean body mass and increased adiposity.

GROWTH IN SGA/IUGR INFANTS

- Accelerated linear growth during the first 12 months of life
- Most of the catch-up growth occurs during the first year and is near completion by 2 yr of age
- Prematurely and more severe degrees of growth retardation (especially reduced birth length) are less likely to reach a stature within the normal range. It may take until age 4 to demonstrate catch up growth
- Those with taller parents are more likely to reach a normal adult height
- Those born SGA should have measurements of length, weight, and head circumference every 3 months for the first year of life and every 6 months thereafter.
- Lack of catch-up growth in the first 6 months of life or those who remain short by 2 yr of age may need further work up

INFLUENCE OF CATCH UP AND CATCH DOWN GROWTH ON EARLY CHILDHOOD BMI

- Catch-up growth in children with a small and appropriate weight for gestational age and lack of catch-down growth in children born with a large weight for gestational age were associated with higher body mass index in preschool children.
- 3,841 Dutch children (191 SGA and 199 LGA) for birth weight, growth of the head circumference, length and weight during the preschool period.
- Generation R Study, a population-based prospective cohort study from fetal life until young adulthood in Rotterdam

DOES INFANT FEEDING INFLUENCE RISK OF LATER LIFE OBESITY?

- Two different study groups (Study 1: n = 153 and Study 2: 90) randomly assigned at birth to receive either a control formula or a nutrient-enriched formula (≥37 weeks, SGA infants)
- At 5-8 y of age, researchers looked at fat mass using bioelectric impedance analysis in study 1 and deuterium dilution in study 2.
- Fat mass was lower in children assigned to receive the control formula than in children assigned to receive the nutrient-enriched formula in both trials
“THRIFTY PHENOTYPE”
- IUGR fetus develops in a hypoglycemic, hypoinsulinemic environment
- Within 48 hours after birth they have increased insulin sensitivity and accelerated growth
- They are born with decreased fat mass which increases greatly between 2-12 months of age leading to increased BMI and truncal fat distribution later in life
- Hypothesis that “thrifty genes” develop during periods of starvation that lead to accelerated ability to store fat during periods of normal feeding
- This leads to insulin resistance

DUTCH FAMINE
- During WWII-Rations for the general adult population was 1800 cal in December 1943, then decreased to 1400 calories in October 1944.
- 1000 calories in late November 1944.
- From December 1944 to April 1945, the daily rations varied between 400 and 800 calories.
- Pregnant and lactating women were entitled to an extra amount of food but did not always get it.
- After the liberation of the Netherlands in early May 1945, the food situation improved swiftly. In June 1945, the rations had risen to more than 2000 calories

ORAL FEEDING DIFFICULTIES IN LGA/IDM INFANTS
- Neurologic immaturity leads to poor suck
- 47 IDM infants (16 mothers treated with insulin and 31 treated with diet alone) vs 55 healthy controls (37-41 weeks EGA)
- On DOL 3, feeding patterns assessed using Kron’s Feeding Apparatus
- Newborns of the insulin-treated mothers averaged 5.2 fewer bursts and 42 fewer sucks (P = .013 and P = .04, respectively). There were no differences in sucking patterns between newborns of diet-managed mothers and control newborns.
**LGA/IDM INFANTS - METABOLIC RISK**

- IDM is associated with increased childhood obesity
- The infants have increased risk of insulin resistance
- Environmental programming in the context of fetal hyperglycemia, hyperinsulinemia and hyperlipidemia results in likelihood to develop metabolic syndrome later in life.

**IDM AND INTRAHEPATIC FAT**

- 25 neonates born to normal weight mothers (n = 13) and to obese mothers with GDM (n = 12) underwent MRI for the measurement of subcutaneous and intra-abdominal fat and MRS for the measurement of intrahepatocellular lipid (IHCL) fat at 1-3 weeks of age.
- Infants born to obese/GDM mothers had a mean 68% increase in IHCL compared with infants born to normal-weight mothers. For all infants, IHCL correlated with maternal prepregnancy body mass index.
- May explain early origins of NAFLD

**IUGR AND MACROSOMIA - RISKS LATER IN LIFE**

- Both are associated with increased risk of metabolic syndrome (hypertension, cardiovascular complications and type 2 diabetes)
- Exact causes unknown but likely due to insulin resistance, fetal hyperleptinemia, hypothalamic changes and most probably epigenetic changes
- These infants likely need diet restriction and increased physical activity early in life to prevent later complications

**FUTURE QUESTIONS**

- What is the optimal growth rate for infants born LGA and SGA infants in infancy and throughout childhood?
- What is best to feed these infants to minimize the risk for metabolic complications?
- Can the risk of metabolic complications be reduced or does our focus need to be in the perinatal period?
- How should we monitor these infants throughout childhood?
- Does our care in the NICU increase metabolic risk?