The Growth Retarded Infant: Initial Diagnostic Workup and Discharge Concerns

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Pertinent history

- 34 4/7 week 715g female born to 34 yo G2P1 mother
- Pregnancy complicated by:
  - maternal chronic hypertension worsened by pregnancy
  - gestational diabetes mellitus (diet controlled)
  - IUGR <6%ile
  - Oligohydramnios with AFI 3.4
- Infant was delivered by c/s for fetal heart rate decelerations after mother admitted for observation of IUGR and oligohydramnios
- Prior to delivery OB reported reverse end-diastolic umbilical artery flow

Delivery

- Uneventful resuscitation
- Symmetric growth restricted parameters all <3%ile; exam c/w IUGR neonate, but otherwise unremarkable

Admission xray/lab evaluation

- Blood type O+; DAT negative
- CBC: WBC 2.9 with 29 polys, 50 lymphs, 24 monos; ANC 840; H/H 15/45; platelets 76K

Hospital Course

- Initial blood sugar instability: required 4 boluses of D10W over 2 days for dex of 26 and 27 despite successive increases in GIR from 4 to 7
- Neutropenia improved but thrombocytopenia persisted with platelet counts consistently <80K
- Blood culture remained negative

Intrauterine Growth Restriction

- Pertinent history
- Delivery
- Admission xray/lab evaluation
- Hospital Course
Objectives

- Describe symmetrical and asymmetrical IUGR and how this distinction relates to timing of the intrauterine insult and ultimate prognosis.
- Etiologies of IUGR.
- Short-term complication of IUGR.
- Possible long-term sequelae of IUGR.

Definition

- Intrauterine growth restriction (IUGR)—a rate of fetal growth that is less than normal for the growth potential of a specific infant. Specifically related to a reduced growth velocity as documented by at least 2 intrauterine growth assessments over time. Indicates the presence of a pathophysiologic process that inhibits fetal growth.

SGA refers to all infants born with a weight for gestational age that fall below the 10th percentile. Includes 10% of normal, healthy population. IUGR—a subgroup of infants in which a pathological process during pregnancy has resulted in fetal growth restriction. May be SGA or AGA; 3-10% pregnancies.

IUGR vs SGA

- Distinction between IUGR and SGA is important. 50-70% of infants born SGA are constitutionally small, with fetal growth appropriate for parental size and ethnicity—usually associated with normal placental function and normal outcome. IUGR infants have marked increased risk of perinatal mortality and morbidity as well as long-term outcome risks.

Normal Fetal Growth

- **Stage 1 (up to 20 weeks)**
  - Rapid mitosis and increased cell number (hyperplasia)
  - Approximately 5g/day
- **Stage 2 (20-28 weeks)**
  - Includes both hyperplasia and hypertrophy
  - Approximately 15-20g/d
- **Stage 3 (28 weeks-term)**
  - Hypertrophy, increased fat, muscle, and connective tissue
  - Approximately 30-35g/d

Etiology

- Intrinsic (fetal) causes:
  - Genetic
    - Chromosomal (7-20%), congenital abnormalities
  - Toxic
    - ETOH, nicotine (3.5X risk), cocaine, hydantoin, coumarin, radiation
  - Infection
    - TORCH, viruses, syphilis, malaria
**Etiology**

- **Extrinsic (maternal/placental) causes:**
  - Maternal age - <16 yr or >35yr
  - Maternal illness - cardiac, anemia, malnutrition
  - Placental dysfunction - htn., infection, vascular disease (one of the main causes)
  - Multiple gestation
  - Demographic - low SES, race
  - Behavioral - stress, teenage pregnancy
  - In-utero constraint - tumor, mass

**Symmetrical IUGR**

- Symmetrical IUGR is related to an insult during early pregnancy when growth is characterized by cellular hyperplasia
  - Examples - Genetic, TORCH, some chromosomal

**Asymmetrical IUGR**

- Asymmetrical IUGR is related to under nutrition or hypoxia in late pregnancy results in an infant where the head circumference is preserved
  - Result of physiological adaptation (brain-sparing) in which blood flow to the brain, heart and adrenals is redistributed at the expense of the intestines, kidneys, skin, and lungs
  - Fat deposition and cellular hypertrophy phase of growth
  - Examples: placental dysfunction, maternal malnutrition, IDM classes D-F, aneuploidy

**Diagnosis**

- Begins with accurate pregnancy dating
  - CRL (ULS before 13 weeks), LMP
- Fundal height, serial exams (insensitive measure)
- ULS biometry:
  - BP diameter, HC, AC, FL (can be highly variable)
- Shepard and Hadlock formulae to give EFW
- Doppler flow studies
- More than 50% of IUGR infants are not identified before birth
**Doppler Studies**

- **Maternal uterine arteries:**
  - Increased vascular resistance may be an early indicator of pregnancies at risk for IUGR

- **Umbilical artery:**
  - Decreased, absent or reversed diastolic waveform reflects increased placental resistance (placental insufficiency)
  - Multiple studies confirming utility of UA doppler in reducing perinatal death and avoiding unnecessary inductions and c-sections
  - Significant morbidity is rarely present in fetuses with EFW < 10% with normal doppler studies and normal amniotic fluid volume
  - Reversed or absent diastolic waveforms in the umbilical arteries represent severe fetal hypoxia and are associated with worse perinatal outcome and high perinatal mortality (depending on gestational age)³

**Doppler Studies**

- Decreased UA flow leads to placental respiratory failure and fetal hypoxemia
- Compensatory changes in fetus include redistribution of blood flow towards brain, heart and adrenals at the expense of other organs
- May result in decreased pulsatility index in MCA, decreased amniotic fluid volume, and bowel echogenicity

**Pathophysiology**

- Pathophysiological processes that occur at the cellular and molecular level are still largely unknown

  **Simply put:**
  - Reduction in the supply of substrates that are necessary for normal cellular function
  - Alteration in mediator molecules that regulate cellular growth and differentiation

**Management**

- **Delivery Room:**
  - Routine resuscitation with careful avoidance of hypothermia, increased vigilance for signs of respiratory distress or perinatal asphyxia
  - Cord blood for lactate and pH
  - Inspection of placenta

- **The fetus adapts to poor nutrition either from hypoxia or placental insufficiency by:**
  - Changing metabolism
  - Altering production of hormones and tissue sensitivity to hormones
  - Redistributing blood flow
  - Slowing growth rate²

- Generally accepted that IUGR often associated with decreased uteroplacental blood flow, and subsequent reduction in oxygen and nutrient supply across the placenta (even in fetal etiologies—often associated with abnormal vascularization)²
Management

- Exam:
  - Dysmorphic features
  - Soft tissue wasting, redundant skin
  - Dry, peeling skin, advanced sole creases, long fingers
  - Plethoric
  - Relatively large head, large fontanelles
  - Thin umbilical cord
  - Neuro- hyper-alert or jittery, exaggerated moro. If severe, may be depressed
  - Stigmata of infection- rash, organomegaly, cataracts

Management

- Need for further evaluation guided by history and exam
- Consider CBC, serum glucose, serum calcium, CMV and toxo titers, karyotype

Consequences...

- Associated with preterm birth
  - The processes causing severe IUGR can lead to preterm labor and preterm delivery, and there are a number of maternal conditions that are associated with both
  - Frequency of IUGR is inversely proportional to GA, and more than 50% of infants born at fewer than 26 weeks demonstrate significant growth restriction
  - Fetal hypoglycemia, hypoxemia and acidosis lead to increased production of prostaglandins and the activation of labor-promoting cytokines
  - Uteroplacental insufficiency is associated with an increased risk of fetal demise as gestation increases, especially between 31 and 33 weeks

Hypoglycemia

- Higher risk:
  - Reduced glycogen stores—less accretion but also more depletion due to release of catecholamines in response to hypoxia
  - Hyperinsulinemia—plasma insulin concentrations in relation to glucose concentrations are greater; can persist for months
  - Reduced fat stores
  - Increased brain/body mass ratio (increased consumption of glucose)
  - Immaturity of hepatic enzymes
  - Reduced expression of glucose 6 phosphatase; can persist
  - Reduced ketogenesis
  - Failure of counterregulation

Polycythemia

- Results from chronic hypoxia, increased EPO levels and increased red cell mass
- Associated with hypoglycemia, thrombosis, poor feeding, NEC
- Debated, but most agree that partial exchange transfusion is indicated in symptomatic infants with HCT >65% or >70% in asymptomatic infants
- Other hematologic abnormalities: lower levels of platelets, coagulation factors V and VII and neutrophils
- Neutropenia and thrombocytopenia due to increased production of red cells (body puts more effort into RBCs)

Hypothermia

- Prematurity
- Increased surface area/body mass ratio
- Diminished glucose supply
- Diminished fat for insulation and energy
- Impaired lipid metabolism
Necrotizing Enterocolitis

- Increased incidence in IUGR, especially with absent or reversed end-diastolic flow
- Chronic hypoxia leads to dysmaturity as well as increased risk of mucosal injury from ischemia
- Ischemia and underperfusion of the intestines may alter motility and release of vasoactive substances with feeding
- Oligohydramnios and reduced ingestion of amniotic fluid has currently incompletely identified consequences in gut maturation and hormonal regulation

Infection

- Rates of blood culture + sepsis and neonatal death are significantly increased in infants at or <3rd %ile
- Neutropenia often occurs in preterm IUGR infants
- Altered immunity:
  - Reduced IgG levels
  - Decreased thymic weight
  - Decreased T-cell numbers and function

Neurological Complications

- Perinatal asphyxia:
  - Hypoxia during labor with compromised placental flow
  - Increased risk of in-utero passage of meconium
- Brain injury: increased incidence of IVH on preterm infants with IUGR. No studies indicating increased risk for PVL

Prognosis- Early

Perinatal mortality rates for infants who have IUGR are 8-10X greater than infants who are AGA

Long-term sequelae

- Neurocognitive outcome:
  - CP (especially infants born at 33-37 wks)
  - Lower IQ, higher rates of school failure
  - Increased inattentiveness, other behavioral problems
  - Retardation of head growth before 26 weeks associated with deficits in perceptual performance, motor ability, general cognitive index, general developmental delay and poorer school achievement
  - When compared to controls matched for prematurity, familial and socioeconomic factors IUGR infants had deficits in short-term memory but preservation of recognition and learning memory thought to represent executive-attention deficit rather than hippocampal injury

Growth

- 15-20% of IUGR infants will have short stature by age 4 and 7.9% at 18 years of age
- In most children catch-up growth is complete by 2-3 years of age
- If catch up growth has not been achieved by 3 years of age endocrine evaluation is warranted
Metabolic Adaptation

- Higher risk for type 3 diabetes mellitus, dyslipidemia, cardiovascular disease, and hypertension
- Significant differences were found between preterm IUGR and preterm controls; higher mean values of systolic and diastolic blood pressures as well as mean arterial pressures at 4-6 years of age
- Impaired insulin sensitivity reported in prepubertal children born IUGR
- Survival of the undernourished fetus requires metabolic adaptations; redistribution of blood flow occurs at the expense of tissues such as muscle and pancreas and may result in insulin resistance and possibly insufficiency²

Hypertension/Diabetes

- More likely as a result of alteration in renal and blood vessel development
- IUGR correlates with decreased nephron numbers, which are associated with elevations in arterial blood pressure and changes in postnatal renal function
- IUGR is associated with both anatomic changes in the pancreatic islets and with changes in intracellular insulin signaling pathways
- IUGR infants may have reduced ability to secrete insulin due to reduced numbers of pancreatic islets
- May also have impaired insulin responses to glucose

References