Neonatal and Long Term Consequences of Fetal Growth Restriction

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Disclosures

- None

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Objectives

1. Understand the pathophysiology of fetal growth restriction.
2. List the common neonatal complications of fetal growth restriction.
3. Understand the long term impacts of fetal growth restriction.

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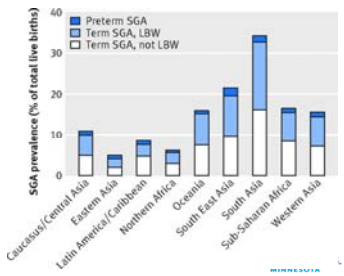
Fetal growth restriction Incidence

- Estimates of 3-9% of pregnancies in the developed world
- 25% of pregnancies in low- middle income countries affected



Fetal Growth Restriction: Definition

- Terminology is inconsistent
- ACOG defines as estimated fetal weight less than 10th percentile
- SGA, used by pediatricians, defined as birth weight less than 10th percentile
- Definition does not take into account individualized growth potential of fetus
- May fail to identify larger fetuses that have not achieved their growth potential and are at risk
- Will misdiagnose fetuses that are constitutionally small
- Formulas have been devised for individualized growth standards however not proven to improve outcomes and not commonly utilized

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Late vs Early Onset

- Early onset FGR
  - <32 weeks gestation
  - More severe phenotype
  - Significant disruption to placental perfusion leading to chronic fetal hypoxia and cardiovascular adaptation
  - Worse neonatal outcomes
- Late onset FGR
  - >32 weeks gestation
  - More common presentation (>80%)
  - More mild placental deficit
  - Less fetal adaptation
  - Elevated risk of stillbirth (high risk of deteriorating rapidly)

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Etiology

- Maternal medical conditions
  - Pre-gestational diabetes; Renal insufficiency; Autoimmune disease; Cyanotic cardiac disease; Hypertensive diseases; Antiphospholipid syndrome
- Substance use and abuse (5%)
  - Smoking associated with 3.5 fold increased risk
- Multiple gestation
- Teratogen exposure
  - Valproic acid; antithrombotic drugs
- Infectious disease (1-10%)
- Genetic/structural disorder in fetus
  - Trisomy 18,13; Congenital heart disease; Gastroschisis
- Placental disorders and umbilical cord abnormalities

Classification

- Based on evaluation and US examination
  - Healthy SCG or constitutionally small
  - True IUGR or pathologically growth restricted
    - Symmetrical IUGR
    - Asymmetrical IUGR
- Pathological process of fetal growth restriction (FGR) associated with:
  - Abnormal placental morphology
  - Abnormal uteroplacental or fetoplacental doppler
- Placenta fails to delivery an adequate supply of oxygen and nutrients to fetus

Importance of diagnosis

- Early identification of infants with FGR who are at risk for neonatal complications
- Identification of infants with FGR who would benefit from interventions to improve outcomes
- Subsequent fetal hemodynamic adaptations in utero lay the foundation for altered organ structure and function in the neonatal period and beyond

Pathophysiology of FGR

- Preferential blood flow redistribution to the vital organs (brain, myocardium, adrenals) while other organs, including GI tract, skin, kidneys, etc. may be deprived of sufficient blood flow
- Adverse impact on fetal organ development and vascular remodeling
  - Ex: Reduced nephron endowment
- Redistribution of blood flow occurs as direct result of hypoxia and can be detected as altered umbilical, uterine and/or MCA Doppler

Fetal growth dependent on Insulin like growth factors

- IGF- I and IGF- II play central roles in normal fetal growth
  - Stimulates fetal cell proliferation and differentiation
  - Protein and glycogen synthesis
  - We know decreased serum IGF- 1 is correlated with reduced fetal growth
  - Pregnancy- associated plasma protein- A (PAPP- A) is secreted by the placental decidua and is a potent inhibitor of IGF bioactivity
    - Low levels of PAPP- A in early pregnancy are linked with increased risk of FGR
  - Recent study investigated whether administration of IGF- 1 into amniotic fluid can improve postnatal growth in a sheep model of FGR and results are promising

Exogenous glucocorticoids

- Preclinical and clinical evidence demonstrates that antenatal steroids may exacerbate FGR (particularly repeat doses)
- FGR fetuses respond differentially to antenatal steroids, likely altered placental response
- Antenatal steroids may not significantly improve neonatal outcomes in FGR preterm infants and may have adverse effects on brain development
  - Further research needed!

In utero Risk

- Fetal demise in utero and Stillbirth
- Up to 50% of infants who are stillborn were small for gestational age/growth restricted

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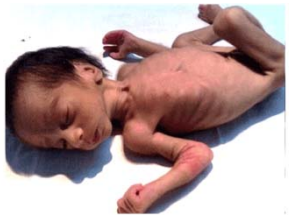
Growth restricted Neonates



- Will spend significantly longer time in NICU compared to normally grown matched counterparts
- Financial costs higher
- Increased risk for several neonatal complications

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Cardiovascular Morbidity

- In early onset FGR, severe placental insufficiency characterized by high vascular resistance within placental vascular beds
  - absent or reverse diastolic umbilical artery flow
  - High pulsatility index in the ductus venosus
  - Increased dilation of cerebral vessels
- Fetal heart contracts against increased afterload, resulting in increased heart wall stress and hypertrophy
  - If sustained -> altered ventricular compliance
  - Presence of increased serum B- natriuretic peptide in FGR infants
- Directly coupled with changes in peripheral vasculature
  - Sustained vasoconstriction and peripheral vascular resistance induces arterial stiffness and elevated central pulse pressure
  - Altered vascular tone in fetal life sets up programming for future hypertension

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Neonatal cardiovascular morbidity

- Early hypotension
- PPHN
- Structural heart changes
- Vessel wall rigidity
- Cardiac function issues
- Late neonatal systemic hypertension
- Secondary pulmonary hypertension

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Long term Cardiovascular Impact

- Hypertension
- Ischemic heart disease
- Stoke
- Atherosclerosis

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Respiratory Morbidity

- Timing and duration of placental insufficiency is a critical determinant of lung dysfunction
- Severity of fetal hypoxia has an inverse relationship with surfactant production
- Hypoxia shown to disrupt alveolarization
- In FGR sheep, fetal breathing movements are significantly reduced
  - ?Reduce metabolic rate and conserve oxygen
  - Disrupted alveolarization
- Sheep model also demonstrates diminished pulmonary vascular function and density

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Neonatal Respiratory Morbidity

- Increased need for respiratory support and ventilator
- Meconium aspiration syndrome
- Pulmonary hemorrhage
- Bronchopulmonary dysplasia (45% more likely)
- Death from respiratory complications

Long term Respiratory Impact

- Chronic respiratory insufficiency
- Reactive airway disease
- Worsened spirometry testing at school age

Neurological morbidity

- "Brain sparing" does not mean normal cerebral development in utero
- Fetuses with the most severe brain sparing are at highest risk of adverse neurodevelopment in childhood
- White and Gray matter changes with both early and late onset FGR
- Cerebral blood flow frequently abnormal for the first few days after birth
  - Potentiates hyperoxia and oxidative stress
  - Risk for IVH

Neonatal neurological morbidity

- Perinatal asphyxia
- Microcephaly
- Cranial US abnormalities (IVH, PVL)
- White and gray matter changes on MRI
- Functional MRI changes
- General movement assessment abnormalities
- EEG abnormalities

Long term neurological impact

- Neurodevelopmental issues
- ADHD
- Behavioral disorders
- Learning difficulties (significant reduction in IQ has been reported)
- Cerebral palsy (30 fold greater)
- Dementia
- Mental health and emotional disorders
- * Preterm and FGR are at highest risk*

Other neonatal morbidities

- Poor transition
- Hypoglycemia
- Hypocalcemia
- Hypothermia
- Sepsis
- Jaundice
- Polycythemia
- Feeding intolerance
- Necrotizing enterocolitis
- Renal tubular injury
- Retinopathy of prematurity

Feeding intolerance or NEC

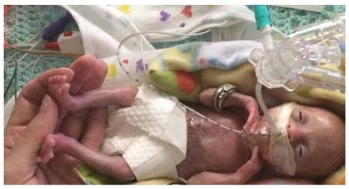
- NEC most common in growth restricted, premature infants
- Chronic fetal hypoxia and shunting of blood flow from GI tract contributes to immature gut development
- Fetuses with abnormal flow in umbilical artery are at highest risk of feeding intolerance
- Near infa- red spectroscopy (NIRS) can detect changes in splanchnic oxygen delivery, which is reduced in growth restricted infants and can predict NEC and feeding intolerance

Other long term impacts

- Failure to thrive
- Obesity
- Immune dysfunction
- Osteoporosis
- Metabolic syndrome
- Renal impairment
- Cancer
- Shortened life span

WHAT DO WE DO?

- Currently no specific treatment available or FGR
- Weighing balance between antenatal compromise and the risks associated with preterm delivery



Interventions for Improved Outcomes

- Improved Placental Function
  - Phosphodiesterase- 5 inhibitors (Sildenfil, Tadalafil)
  - Vascular Endothelial Growth Factor
  - Insulin- like Growth Factor - 1
- Antioxidant and Anti- Inflammatory Function
  - Vitamin C
  - Melatonin
  - Allopurinol
  - Lactoferrin

Thank you!

References

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