Etiology and Management of Fetal Growth Restriction

Juan M. Gonzalez Velez, MD, PhD
Associate Professor
Maternal-Fetal Medicine
Department of Ob/Gyn & RS
University of California, San Francisco

No Disclosures

Diagnosis

• Fetal Growth Restriction (FGR) OR Intrauterine Growth Restriction (IUGR)

• Small for gestational age (SGA) - newborns whose birth weight is less than the 10th percentile for gestational age.

• Screening for risk factors - performing serial measurements of fundal height
  – 24 – 38 weeks of gestation
  – A discrepancy gestational age and fundal height measurement of greater than 3

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Diagnosis

• Fundal height measurement at 32–34 weeks of gestation has been reported to be approximately 65–85% sensitive and 96% specific for detecting the FGR

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Diagnosis

• Limitation of assessing fundal height: maternal obesity, multiple pregnancy, or a history of leiomyomas

• Ultrasound examination is preferred as a screening tool.

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**Diagnosis – Risk Factors**

- Follow-up Third trimester Ultrasound
  - Fetal Diagnosis
  - Placental Diagnosis
  - Obstetrical history of FGR/SGA
  - Maternal medical conditions

**Diagnosis**

- Fetal AC is the most sensitive single measurement
- **Sonographic EFW is the best method for identifying fetuses whose birth weight is likely to be below the 10th percentile for gestational age.**
- EFW <3rd to 5th percentile is consistently associated with adverse outcome.

**Research**

- 2 % of fetuses at the 3rd to 10th percentile adverse perinatal outcome (APO)
- 6.2 % <3rd percentile APO / 8 mortalities in this group.
- EFW <3rd percentile and abnormal UA Doppler was a strong and consistent predictor APO
• Composite fetal morbidity <5th percentile vs 5th to 10th percentile was 39 and 13 percent, respectively (odds ratio 2.41, 95% CI 1.5-3.8)

Diagnosis

• Customized growth curves remain controversial – evidence of benefit has not been demonstrated
Etiology

- History and physical examination identify **maternal disorders** that have been associated with FGR.

- Obstetrical imaging / laboratory evaluations to look for **fetal and placental etiologies**.

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Etiology – Fetal

- 20 - 60% infants with congenital malformations are SGA
  - Omphalocele
  - Diaphragmatic hernia
  - Skeletal dysplasia
  - Congenital heart defects
  - Gastroschisis

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Etiology – Fetal

- Cell free DNA / Fetal karyotype / microarray needs to be considered in the following settings:
  - Early (<24 weeks)
  - Severe (<5th percentile)
  - Symmetrical FGR
  - Major fetal structural abnormalities

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Etiology – Maternal/Fetal

- Infection suspected maternal history or physical examination or fetal ultrasound findings
- Maternal serum should be examined for seroconversion
- Cytomegalovirus, toxoplasmosis, rubella, varicella, syphilis
- Amniotic fluid DNA testing can also be performed for specific infections
- Malaria in pregnancy can also cause FGR
**Etiology – Maternal**

- Obstetrical history of FGR/SGA
- Maternal medical conditions:
  - Pregestational diabetes mellitus
  - Renal insufficiency
  - Autoimmune disease (e.g., systemic lupus erythematosus)
  - Cyanotic cardiac disease
  - Pregnancy-related hypertensive diseases of pregnancy (e.g., chronic hypertension, gestational hypertension, or preeclampsia)
  - Antiphospholipid antibody syndrome

- Teratogen
  - Antineoplastic medications (e.g., cyclophosphamide), antiepileptic drugs (e.g., valproic acid), antithrombotic drugs (e.g., warfarin)

- Substance Abuse
  - Tobacco associated with 3.5-fold increased risk SGA

- Nutrition
  - Extremely poor protein intake < 26 weeks
  - Severe caloric restriction (intake of 600–900 kcal daily)

**Etiology – Placental**

- Confined placental mosaicism 10 percent of placentas associated with otherwise “idiopathic FGR”
- Abruption, circumvallate shape, hemangioma, and chorioangioma
- Umbilical cord abnormalities (e.g., velamentous)
- Single umbilical artery
- Placenta accreta/placenta previa, in studies not consistently associated with fetal growth restriction
Management

• Serial sonograms two- to four-week intervals to ascertain the growth velocity

• Antenatal surveillance with umbilical artery Doppler velocimetry and antepartum testing should not begin before a gest. age when delivery would be considered for perinatal benefit

Management

• Modified BPP (Nonstress tests/Amniotic fluid) or BPPs recommended once to twice weekly

• RCT monitoring UA Doppler can significantly:
  – reduce perinatal death
  – unnecessary delivery preterm

2013 systematic review 18 trials comparing the use of Doppler with no Doppler in high-risk pregnancies:
  – 29 % reduction in perinatal deaths (odds ratio 0.71, 95% CI 0.52-0.98)
  – significantly fewer labor inductions / cesarean deliveries
Umbilical Artery Doppler (UA)

- Weekly Doppler velocimetry of the UA upon diagnosis of FGR

- 30% of the villous vasculature ceases to function
  - Increase in UA resistance leading to reduced end diastolic flow

- 60 to 70% of the villous vasculature is obliterated
  - UA diastolic flow is absent or reversed and fetal prognosis is poor

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Creasy & Resnik’s Maternal Fetal Medicine 7th Edition


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Increased S/D ratio
Absent end diastolic blood flow

Reverse end diastolic blood flow

Ductus Venosus (DV)

- Changes venous circulation: FGR absent or reversed flow in the DV (absent or reversed a wave) or pulsatile umbilical venous flow, are late findings.

- Usually occur 2 weeks after changes are observed in the arterial circulation
  - Increasing umbilical arterial resistance →
  - Fetal cardiac performance can become impaired →
  - Central venous pressure increases, resulting in reduced diastolic flow in the DV →
  - Vasodilatation of the DV further diverts nutrient and oxygen rich blood to the heart → increases retrograde transmission of atrial pressure.
Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses

A. A. BASCHAT*, U. GEMBRUCH, C. P. WEINER* and C. R. HARMAN*  

Conclusion Prediction of critical perinatal outcomes is improved when venous and umbilical artery qualitative waveform analysis is combined. The incorporation of venous Doppler into fetal surveillance is therefore strongly suggested for all preterm IUGR fetuses. Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.

- DV ultimately with loss of the a wave.

Absent or reversed ductus venous a-wave indicates CV instability and of impending acidemia and death.
Middle Cerebral Artery (MCA)

- MCA examined at origin
- Angle between the US beam + direction of blood flow 0 degrees
- Increases placental blood flow impedance $\rightarrow$ decreases in cerebral blood flow impedance lead to **brain sparing**

MCA Brain Sparing

- Increase in MCA diastolic flow velocities
- Lead to a decrease in the Doppler cerebro-placental ratio
  [defined as cerebral resistance index divided by umbilical artery resistance index]
Temporal Changes in Fetal Doppler

- Doppler changes precede changes in the
- UA and DV Doppler changes approximately 4 days before BPP
- 2 to 3 days before delivery, fetal breathing movement begins to diminish
- 24 hours, amniotic fluid volume begins to decrease
- Composite BPP score decreases abruptly on the day of delivery (loss of fetal movement and tone)

Temporal Changes in Fetal Doppler

- Usually fetuses - FGR with normal modified or BPP and Doppler velocimetry ---- outpatients
- Absent or reverse end-diastolic blood flow is noted in the UA
  - Admit for closer monitoring or delivery depending on GA
  - Delivery not solely based on Doppler abnormalities except absent or reverse a-wave in the DV

Management- Growth Restriction Intervention Trial (GRIT)

- Multinational prospective randomized study, GRIT
  - Immediate versus deferred delivery of fetuses with FGR was compared at ages 2 years and 9 years.
  - FGR between 24 and 36 completed gestational weeks
  - UA Doppler waveform
  - Clinician uncertain whether to deliver the immediately were randomly allocated to either deliver now or defer delivery until decision could not be delayed.
  - GRIT investigators minimal difference in overall mortality or 2-year outcomes.
  - 9 years, there was still no difference between groups regarding numbers of deaths, rate of severe disability or in the mean cognition scores motor scores, and parent-assessed behavior scores.

Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT)

- N= 650 over 36.0 weeks with suspected FGR to IOL or expectant monitoring.
- Primary outcome composite measure adverse neonatal outcome (death, 5-min. Apgar score <7, UA pH <7.05, or admission NICU).
- IOL group delivered 10 days earlier and weighed 130 g less than the expectantly managed group.
- Statistically similar adverse outcome (6.1 versus 5.3 percent with expectant management) and cesarean delivery rates (about 14%).
- Developmental / behavioral outcomes at 2 years of age were similar.
- Both approaches are reasonable, and the choice should depend on patient preference.
Decision-analysis showed compared no-testing strategy:
- BPP–only scheme was associated with a 60% reduction in fetal death, a 59% reduction in neonatal death, 92% reduction in neonatal disability.

UA Doppler US associated reduction:
- perinatal deaths (risk ratio 0.71; 95% CI 0.52–0.98)
- inductions of labor (average risk ratio 0.89; 95% CI 0.80–0.99)
- cesarean deliveries (risk ratio 0.90, 95% CI 0.84–0.97)

Initial Diagnosis

- Establish gestational age as reliably as possible.
- Dx of FGR requires EFW less than the 10th percentile, abdominal circumference less than the 5th percentile, or both.
- Obtain detailed maternal history.
- Review prenatal records.
- Reassess fetal anatomy.
- Reassess fetus for signs of congenital infections.

Maternal Interventions

- No convincing evidence that any intervention in improves the growth of a FGR
- Research is undergoing using phosphodiesterase-5 enzyme inhibitor or a statin
- Antihypertensive therapy does not improve fetal growth
- Intensive smoking cessation program may be of value

Prenatal Monitoring

- Antenatal testing FGR
  - twice-weekly nonstress tests with amniotic fluid assessment (amniotic fluid index or maximum vertical pocket) modified BPP or
  - BPP
- Once per week Doppler ultrasonography of the UA.
  - Consider MCA and DV Doppler assessments if increased systolic-to-diastolic velocity ratio or absent or reverse end-diastolic flow in umbilical artery is noted.
- Admit for close monitoring if absent or reverse end-diastolic velocities are present in the UA.
- Follow-up fetal growth with ultrasonography every 2 weeks.

Inpatient Management

- Consider admission if absent or reverse end-diastolic velocities are present in the UA and if the fetus is viable.
- Administer corticosteroids for fetal lung maturity if admission occurs before 34 weeks of gestation.
- Perform fetal monitoring (nonstress tests) every 8 hours or more frequently as indicated and perform BPP daily or more often as indicated.
- Delivery for decline in BPP score less than six out of eight, nonreassuring fetal heart rate tracing, or inadequate interval growth over the course of 14 days, or a combination of these.

Term (37 0/7 weeks of gestation or more)

- Deliver if EFW is less than the 5th percentile, or oligohydramnios with EFW less than the 10th percentile, or worsening antenatal testing results.
- Otherwise, delay delivery as long as antenatal testing is reassuring.
- Plan elective delivery after 39 weeks of gestation.
- Induction of labor can be attempted depending on the indication for delivery.
- Reserve cesarean delivery for obstetric indications.
Preterm (before 37 weeks of gestation)

- Monitor fetal growth every 2 weeks.
- Consider delivery if no growth occurs over the course of 14 days.
- Delivery should be considered for worsening antenatal testing (BPP score less than six out of eight or nonreassuring fetal heart rate tracing).
- Preterm delivery before 32 weeks of gestation is imminent, consider intravenous magnesium sulfate administration for fetal neuroprotection.
- Delivery for FGR is anticipated before 34 weeks of gestation, the delivery should be planned at a center with a NICU.

History of SGA

- Risk of recurrence of an SGA birth is approximately 20%
- Modifiable risk factors
- Serial ultrasonography for growth assessment
  - optimal surveillance regimen has not been determined

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Summary of Recommendations and Conclusions

• Doppler of any vessel is not recommended as a screening tool for identifying pregnancies that will subsequently be complicated by FGR.

• Antepartum surveillance of a viable fetus with suspected FGR should include Doppler of the UA (associated with a significant decrease in perinatal mortality).

• Once FGR is suspected, UA Doppler studies should be performed usually every 1-2 weeks to assess for deterioration.

• Antenatal corticosteroids should be administered if absent or reversed end-diastolic flow is noted < 34 weeks in a pregnancy with suspected FGR.

• As long as fetal surveillance remains reassuring, women with suspected FGR and absent UA end-diastolic flow may be managed expectantly until delivery at 34 weeks.

• As long as fetal surveillance remains reassuring, women with suspected FGR and reversed UA end-diastolic flow may be managed expectantly until delivery at 32 weeks.