PERINATAL WEBINAR: 
PATHOLOGY OF ABSENT END DIASTOLIC FLOW 
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12:00 Noon 
Perinatal Education Series 2016

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Objectives
- State factors associated with fetal growth restriction
- Verbalize the pathology of absent and reverse end diastolic flow

FETAL GROWTH RESTRICTION

How do we classify fetal growth?
- From ACOG (American College of Obstetrics and Gynecologists)
  - "The terminology for classifying fetuses and newborns who have failed to achieve normal weight is inconsistent."
  - Fetal and newborn weight according to either the absolute weight or the weight percentile for a given gestational age.
  - Fetal growth restriction = used to describe fetuses with an estimated fetal weight that is less than the 10th percentile for gestational age.
  - Small for gestational age (SGA) will be used exclusively to describe newborns whose birth weight is less than the 10th percentile for gestational age.
- Intrauterine growth restriction is the 2nd leading cause of perinatal mortality according to Gabbe, et al in Obstetrics: Normal and Problem Pregnancies.
  - "Compared to appropriately grown counterparts, perinatal mortality rates in growth restricted neonates are 6 to 10 times greater; perinatal mortality rates as high as 300 per 1000 for all cases of IUGR and 80 per 1000 after exclusion of anomalous infants have been reported. As many as 33% of preterm stillbirths and 26% of term stillbirths are growth restricted."

Normal Fetal Growth
- Fetal growth occurs at multiple levels and needs a successful interaction of maternal and fetal components
  - Starting at the anchoring of the trophoblast at the uterine lining to all for development of maternal circulation and intervillous space. This will eventually support placental growth.
    - By term as much as 600 mL/min of maternal cardiac output reaches the placenta, the fetal blood flow volume of 200-300 mL/kg/min throughout gestation.
  - Normal growth involves hyperplasia and hypertrophy on the cellular level.
  - The growth potential of the placenta and the fetus are thought to be predetermined by maternal body mass index and ethnicity.
  - Several possible mechanisms may challenge compensatory capacity of the maternal-placental-fetal unit.

Main goal: autoregulatory mechanisms to enhance perfusion to the vital organs.
Fetal Growth Restriction

- Fetal growth restriction is a syndrome that is marked by failure of the fetus to reach its growth potential with consequences that are related to the underlying disorder as well as the severity of fetal disease.
- Differential diagnoses: maternal disease, placental insufficiency, aneuploidy, nonaneuploid syndromes, viral infection
- Confirm small fetal size, then group for appropriate follow up management:
  - constitutionally small but otherwise normal fetus
  - fetuses with aneuploidy, nonaneuploid syndromes, or viral infection
  - fetuses with placental disease

Growth Restriction and Morbidity/Mortality

- Most common pathology of fetal growth restriction is associated with abnormal placentation that leads to poor placental perfusion.
- Increased risk of Intrauterine demise, neonatal morbidity and neonatal death.
- Studies have also linked growth restricted fetuses with increase risk of developing:
  - Cognitive delay in childhood
  - Type 2 diabetes mellitus
  - Stroke
- Increased risk of stillbirth:
  - Fetal weight less than 10th percentile: risk of fetal death is 1.5%
  - Fetal weight less than 5th percentile: risk of fetal death is 2.5%

Screening for Fetal Growth Restriction

- Who should be screened?
  - All pregnant patients should be screened for risk factors for growth restriction through a review of medical and obstetric history
  - Fundal height measurement at each prenatal visit after 24 weeks GA
- Ultrasound screening in the presence of maternal factors that increase the risk of fetal growth restriction.

Using Ultrasound to Estimate Fetal Weight

- Physical Exam or History
  - Fundal height measurements between 24–38 weeks gestation
  - If mother is obese or uterine leiomyomas limits the accuracy of fundal height, ultrasonography may be a better screening modality.
- Ultrasound Diagnosis and Evaluation
  - Estimated Fetal weight
  - Ultrasound measurements
    - 1) Biparietal Diameter
    - 2) Head circumference
    - 3) Abdominal circumference
    - 4) Femur length
  - Less than 10th percentile for GA, further evaluation needed.
    - Amniotic Fluid Assessment
    - Doppler blood flow studies of the umbilical artery
    - Ultrasound exam of fetal anatomy for structural and genetic abnormalities if not previously done

Now we have a growth restricted fetus – What Now?

- Next Step – Assessment with Doppler Velocimetry
  - Used to determine the volume and rate of blood flow through maternal and fetal vessels
  - Column of red blood cells flowing through the circulation and the reflected sound waves are observed by the ultrasound transducer.
  - "Doppler ultrasound is a noninvasive technique to assess blood flow by characterizing downstream impedance." (Williams Obstetrics, 23rd edition)
  - Three vascular circuits that are used to determine fetal health and help time delivery for growth restricted fetuses:
    1. Umbilical artery
    2. Middle cerebral
    3. Ductus venosus
  - "Normally, the end-diastolic velocity in the umbilical arteries increases with advancing gestation secondary to the decreased resistance in the placenta as more tertiary vessels develop." (Blackburn, s. Maternal, fetal & Neonatal Physiology – A Clinical Perspective)
Why use Doppler flow studies?

- Ultrasound and Doppler flow measurements provide means to visualize the umbilical cord and to evaluate the fetal blood flow.
- To gain an overall measure of fetal health - measuring the amount of forward blood flow through the umbilical artery during both fetal systole and diastole.
- The more forward blood flow from the fetus to the placenta through the umbilical artery, the healthier the fetus.
- Assessment of fetal blood flow through the umbilical cord by ultrasound color Doppler sonography has proven to be a valuable noninvasive procedure for assessing fetal well-being during pregnancy.


Doppler Basics

- The systolic-diastolic ratio (S/D ratio), which collapses showing how much blood flow is flowing in the umbilical artery through Doppler evaluation.
- Arterial Doppler waveforms provide information on downstream vascular resistance, which may be altered due to structural changes in the vasculature or regulatory changes in vascular tone.
- Three indices to analyze arterial blood flow:
  1. Systolic/diastolic ratio
  2. Resistance index
  3. Pulsatility index
- An increase in blood flow resistance manifests itself with a decrease in end-diastolic velocity resulting in an increase in all three Doppler indices.

1. https://criticalcaremcqs.com/2011/01/20/

Doppler Ultrasound in Pregnancy - NORMAL

Normal umbilical artery

- <20 weeks GA: Placental flow is in a high-resistance bed and the value of umbilical artery velocimetry is limited. End-diastolic flow is often absent.
- >20 weeks GA: Progressive increase in diastolic flow velocities resulting in a progressive decrease in measured indices.
- A low resistance pattern with high forward flow velocities in both the systolic and diastolic component of the cardiac cycle.
- The PI, RI, and S/D ratio all decrease with advancing gestation, probably due to a decrease in placental vascular resistance.

http://www.fetalultrasound.com/online/text/3-131.htm

Doppler Velocimetry

- Important to obstetrics, Doppler may be used to determine the volume and rate of blood flow through maternal and fetal vessels. In this situation, the sound source is the ultrasound transducer, the moving target is the column of red blood cells flowing through the circulation, and the reflected sound waves are observed by the ultrasound transducer.

https://criticalcaremcqs.com/2011/01/20/

Typically, flow velocity waveforms obtained by the analysis of Doppler signal derived from pulsating vessels display changes in flow velocity over the cardiac cycle.

Flow velocity waveform characteristics depend on the following variables:
1. Heart rate
2. Distance of the sampling site from the heart
3. Vessel elastic properties
4. Input pressure
5. Downstream impedance to flow that strongly affects diastolic velocity


http://www.birthandbrain.org/velocimetry.html
Assessment of Doppler Velocimetry

- **Umbilical Artery:**
  - The umbilical artery normally has forward flow throughout the cardiac cycle and the amount of flow during diastole increases as gestational age advances.
  - Therefore, the S/D ratio decreases from 4.0 at 20 weeks to 2.0 at term.
  - If the S/D ratio is above the 95th percentile for gestational age, it is considered abnormal.

- **Uterine Artery:**
  - Characterized by high flow velocities similar to those in systole.
  - There is highly turbulent flow.
  - Studies linked increased impedance of uterine artery velocimetry at 16-20 weeks was predictive of Superimposed Preeclampsia.

- **Middle Cerebral Artery**
  - Anatomically, the path of the artery allows for scan with ultrasound through the fontanel to make assessment easy.
  - 2 uses:
    - Fetal Anemia: Peak systolic velocity is increased with increased cardiac output and decreased blood viscosity.
    - Growth restriction: Progression of Doppler findings show increased impedance of flow detected in the umbilical artery first, followed by redistribution of blood flow to the brain with decreasing resistance (brain sparing), then noted abnormalities in flow.

What is different in Growth Restricted Fetuses?

- In placenta-based IUGR, the resistance does not fall, and may increase progressively.
- May lead to reduction of end-diastolic blood flow, which in severely affected fetuses may decline until there is absent end-diastolic velocity or even reversed end-diastolic velocity.
  - For reversed end-diastolic velocity, elastic recoil in placental and cord vessels is so high that after the pulse wave passes, retrograde blood flow occurs.
  - Whom placental resistance reaches this point, ineffective placental circulation and hypoxic stillbirth may ensue.


Growth Restriction & Doppler Studies

- The utility of Doppler velocimetry evaluation, especially of the umbilical artery, has been studied and reviewed extensively in cases of fetal growth restriction.
- Absent or reversed end-diastolic flow in the umbilical artery is associated with an increased risk of perinatal mortality.
  - The rate of perinatal death is reduced by as much as 29% when umbilical artery Doppler velocimetry is added to standard antepartum testing in the setting of fetal growth restriction.
- Flow in the ductus venosus also has been measured in an attempt to assess fetal status, but its use has not been shown to improve outcomes.
Doppler Ultrasound Measurements

- Creasy and Resnik state that Gray-scale ultrasound is one of the most important tools in current obstetrics.
- But, it is limited due to the decreased ability to see hemodynamics.
- By using doppler ultrasound (with color added), blood flow can be seen through each vessel’s unique blood flow velocity waveform.
- Common ratios are:
  - Systolic to diastolic blood flow velocity (S/D)
  - Pulsatile index (PI)
  - Resistance index (RI)

Doppler Velocimetry

- allows assessment of placental status
- helps to place other testing results in context as well as helping to determine the relative risk of sudden fetal deterioration
- categories of risk can help to determine the frequency of BPP testing
- Extreme Doppler abnormalities may indicate intervention
- Umbilical artery Doppler - reflects placental vascular resistance.
  - strongly correlates with fetal growth restriction and multiple critical fetal and neonatal outcome characteristics, progressively worsening as reduction, loss, and reversal of diastolic flow in a deteriorating sequence.

Absence End Diastolic Flow

- Abnormal wave forms correlate with hypovascularity of the umbilical placental villous structure.
- 60-70% of the small placental arterial channels need to be lost before Doppler waveform becomes abnormal.
- As placental resistance increases, the flow of blood through the major vessels like the umbilical artery and middle cerebral artery will have a loss of forward flow.
- When the resistance in the placenta increases further, absent diastolic flow becomes reverse diastolic flow in which the Doppler waveform is observed to be below the baseline.
- When the fetus develops this type of abnormality, intense surveillance is required if the fetus is less than 32 to 34 weeks and delivery if it is greater than 32 to 34 weeks.
- Currently recommendation is evaluation of the ductus venosus and/or inferior vena cava, and antepartum testing.

Reverse End Diastolic Flow

- When the placenta increases further, absent diastolic flow becomes reverse diastolic flow in which the Doppler waveform is observed to be below the baseline.
- When the fetus develops this type of abnormality, intense surveillance is required if the fetus is less than 32 to 34 weeks and delivery if it is greater than 32 to 34 weeks.
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Umbilical Artery

- Arises from the common iliac arteries and represent the dominant outflow of the distal aortic circulation
- Mirrors the downstream resistance of the placental circulation
- Normal umbilical artery - resistance falls progressively through pregnancy, reflecting the increased numbers of tertiary stem villous vessels
- In pathologic conditions increased resistance in the umbilical arteries represents pruning of the placental arterial tree
  - As umbilical artery resistance increases, diastolic velocity falls and ultimately becomes absent
  - As resistance rises even further, an elastic component is added, which induces reversed end-diastolic velocity as the insufficient, rigid placental circulation recoils after being distended by pulse pressure.
Understanding Diastolic Flow

- Umbilical Artery
  - Normally has forward flow throughout the cardiac cycle
  - Amount of flow during diastole increases as gestation advances
  - S/D ratio is generally less than 0.5 in the 3rd trimester
  - Umbilical artery Doppler may be a useful adjunct in the management of pregnancies complicated by fetal growth restriction
  - Umbilical artery Doppler is considered abnormal if the S/D ratio is above the 95th percentile for gestational age

Middle Cerebral Artery

- The MCA is short, straight, and uniformly positioned relative to the fetal skull and other intracranial landmarks. Doppler measurements taken from this vessel are more reproducible than those taken from other vascular beds and have few collateral circulatory influences while representing a critical component of the fetal circulation.

Ductus Venosus

- The ductus venosus is a sharply tapered conduit that shunts blood from the proximal umbilical vein directly into the inferior vena cava as its connection to the right atrium.
  - Hourglass shape regulates inflow to the central circulation through a narrow aperture that is constricted in the healthy near-term fetus, allowing only 20% of umbilical venous return into the right atrium.
  - This narrow jet delivers highly oxygenated blood at high velocity directly to the foramen ovale, keeping it open and promoting right-to-left shunting of nutrient-rich stream.
  - In healthy fetuses, the ductus venosus regulates the distribution of oxygen and placental nutrients by restricting centralization of flow.
  - The reflected wave seen in the ductus venosus waveform represents the impact of cardiac actions.

Doppler Velocimetry of the Middle Cerebral Artery

Doppler Velocimetry of the Uterine Artery

Doppler Velocimetry of the Ductus Venosus

Doppler Velocimetry of the Umbilical Artery

Images from:
Uterine Artery

- Uterine blood flow increases from 50 mL/min early in gestation to 500 to 750 mL/min by term.
- The uterine artery Doppler waveform is unique and characterized by high diastolic flow velocities similar to those in systole, and by highly turbulent flow, which displays a spectrum of many different velocities.
- Increased resistance to flow and development of a diastolic notch have been associated with pregnancy-induced hypertension.

Abnormal uterine artery flow velocimetry waveforms are a manifestation of delayed trophoblast invasion.

Changes in the uterine artery flow patterns precede those observed in the umbilical artery and precede fetal growth restriction.

Uterine artery Doppler is better at predicting severe rather than mild disease.

SIGNIFICANCE OF RESULTS / BENEFITS OF TESTING / OUTCOMES

Umbilical Artery Doppler waveforms

- Normal diastolic flow.
- Absence of end-diastolic flow.
- Reversed end-diastolic flow.

Patterns of Deterioration

- Placental abnormalities may persist for months before other Doppler parameters deteriorate.
- As placental resistance increases, the cerebroplacental ratio eventually shifts, reflecting a change in balance between placental and systemic perfusion and resulting in cerebral redistribution.
  - Brain sparing is seen as progressive abnormalization of umbilical artery circulation, which are associated with increasingly higher diastolic velocities in the MCA.
  - By this time, subjective elements of behavior, such as increasing intervals of quiet sleep, decreased velocity of fetal movements, and elements of subjectively decreased amniotic fluid may begin to appear.
- With onset of AEDV:
  - progressive redistribution yields overt centralization,
  - oligohydramnios becomes more common.
  - The NST parameters often become flatter,
  - reversal of end-diastolic velocities in the umbilical artery may occur, along with progressive loss of fetal breathing movements, loss of fetal tone, and abolition of all movements as the BPP becomes overtly abnormal.
Clinical Significance

- Absent flow and reversed flow represent progressively ominous findings necessitating close monitoring or consideration of delivery based on the gestational age.
- AEDV may exist in equilibrium over a long period, particularly in the very preterm fetus, but in many fetuses, AEDV is not stable and will progress to REDV over time.
- REDV is frequently an unstable clinical state that may precede fetal death by only hours to days.
- REDV is often associated with very significant abnormalities of cerebral and venous circulations.

Issue then becomes when to optimize delivery timing in the very preterm fetus, before significant complications in the neonatal period related to the etiology of IUGR.

Neonatal asphyxia

- It is readily apparent that abnormal venous Doppler waveforms in the preterm IUGR fetus are indicative of poor acid-base status and outcome.

Management

Doppler Ultrasound for Fetal Surveillance

- REDV at any gestational age beyond 28 weeks should prompt immediate delivery.
- Some experts would consider continuously monitoring these fetuses and giving a course of betamethasone prior to delivery, and continuing expectant management until 32 weeks as long as fetal surveillance remains reassuring.
- Use of venous Doppler appears to improve the prediction of stillbirth and acidemia when arterial Doppler has identified a fetus at risk. This is the next step in the evaluation of these fetuses and may help to identify fetuses who require immediate delivery versus those in whom delivery can be delayed.
- In general, cesarean delivery is a reasonable choice in most cases of AEDV, as fetal tolerance to labor is poor in this situation. Cesarean delivery is clearly indicated in the presence of REDV or ominous fetal monitoring findings.

Is There Benefit to Using Doppler Ultrasound?

- A recent opinion paper from the Society for Maternal-Fetal Medicine addressed the issue of the utility of Doppler ultrasound for the assessment of the fetus with IUGR.
  - It summarized all published studies with the highest level of evidence and concluded that umbilical artery Doppler studies significantly decreased the likelihood of perinatal death, cesarean delivery, and labor induction.
  - The opinion further stated that, because of the lack of randomized trials to prove benefit, the use of middle cerebral artery and ductus venosus Doppler studies should be considered experimental.
  - The temporal sequence of Doppler-measured flow abnormalities in the arterial and venous circulations of the IUGR fetus has been delineated.
  - It is readily apparent that abnormal venous Doppler waveforms in the preterm IUGR fetus are indicative of poor acid-base status and outcome.

Impacts of Monitoring on Perinatal Mortality and Long-Term Outcomes

- Use of the BPP and Doppler velocimetry for fetal assessment has been implemented in clinical practice, but it remains difficult to obtain robust data on the impact of this testing in a variety of populations.
- Lower BPP scores have been associated with higher perinatal mortality rates, and early studies comparing the perinatal mortality rate for an untested population to that for a tested, high risk population demonstrated a lower rate of perinatal mortality in the tested population.
- Although the strength of this evidence is not ideal, it does suggest that monitoring can identify fetuses at risk and allow for timely delivery to reduce the risk of perinatal mortality.

Neonatal Impact of Growth Restriction

- Complications in the neonatal period related to the etiology of the growth insult as well as antepartum and intrapartum factors:
  - Neurodevelopmental
  - Mesenchymal anomalies
  - Hypoglycemia
  - Metabolic abnormalities
  - Polyhydramnios
  - Beyond the neonatal period
  - Negative effects on cognitive function in term and near-term infants born after 32 weeks' gestation.
  - Maternal and fetal malnutrition seem to have both short- and long-term effects:
    - Growth restriction
      - Includes growth of both mother and fetus, maternal size and obstetric history, perinatal and obstetric factors.

Long Term Outcomes

- Growth potential for growth-restricted infants:
  - The degree of catch-up growth observed in several longitudinal studies suggests that these infants can be expected to have normal growth curves and a normal, albeit slightly reduced size as adults.
  - In general, those infants who suffered growth restriction near the time of delivery do tend to catch up. However, those neonates with earlier onset and more longstanding growth restriction in utero continue to lag behind.

- Long term neurologic sequelae – still not fully understood:
  - Multiple studies with varying outcomes.
  - One thought is that the studies while all have varied outcomes, it is thought that the neurologic outcome depends on the degree of growth restriction, especially the impact on head growth, its time of onset, the gestational age of the infant at birth, and the postnatal environment.

- GRIT study:
  - The Growth Restriction Intervention Trial (GRIT) compared two management strategies: immediate versus delayed delivery in high-risk pregnancies when clinical uncertainty prevailed.
  - The results demonstrated that differences in perinatal morbidity and mortality, neurological outcome 2 years after birth, and long-term outcome were not statistically significant between the two groups.
  - Antenatal testing via BPP and Doppler (with the exception of the umbilical artery) were not used for fetal surveillance in all cases.
  - Gestational programming of growth-restricted fetuses has received considerable attention over the past 10 to 15 years.
  - Infants born growth restricted have an increased risk of metabolic syndrome, obesity, hypertension, diabetes, and stroke from coronary artery disease.

- Fetal Programming – Epigenetic effects that could be multi-generational are a concern.

References:

Questions?

- Post your questions in the box...
- Lines now open
- Please make sure your phones is not muted so we can hear your questions!

Thank you!

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- Return the evaluation to the Perinatal Systems office and you will receive your Nursing CE electronically via email. Please be sure to include your email address on the evaluation form.
- Any further questions, please contact our Michelle at the following:
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