

Assessing fetal growth and risks for adverse pregnancy outcomes (APOs) - a literature review

- New methodologies - *assessment of growth velocity*
- Validation of existing Hudson Valley Radiology Associates (HVRA) protocols.

The following article summaries will:

- Highlight the differences between the ACOG and the Society of Maternal Fetal Medicine (SMFM) model and the European Delphi consensus model in the assessment of fetal growth. The Delphi model has been adopted by the International Society of Ultrasound in Obstetrics and Gynecology ISUOG and forms the basis of HVRA's protocols.

*see article by **Powel**.

- Present data supporting *HVRAs new inclusion of decreased growth velocity* and reinforce HVRA's long-standing employment of uterine artery UtA and middle cerebral artery MCA Doppler to distinguish between pathologic small for gestational age SGA at increased risk for APOs (fetal growth restriction FGR) from constitutional SGA not at increased risk.

*see articles by **Powel; Roriguez-Sibaja; Larson**.

- Introduce the concept that AGA fetuses with significant reduction in growth velocity between the second and third trimesters represent a cohort at increased risk for APOs.

*see articles by **Kennedy; Hendrix; and Orzel**

INTRODUCTION

The definition of fetal growth restriction FGR endorsed by ACOG and SMFM is an estimated fetal weight EFW or abdominal circumference AC of <10th centile at all gestational ages - a definition that fails to distinguish those fetuses whose growth has been pathologically restricted (FGR) from constitutionally small healthy fetuses (SGA.)

The Delphi consensus procedure defines FGR at increased risk for APOs by the following criteria:

-EFW <3%tile at any gestational epoch in a euploid non anomalous fetus with or without abnormal Doppler studies.

-EFW and/or AC <10th centile with:

- abnormal Doppler studies: uterine artery (UtA) Doppler PI >95th percentile; umbilical artery (UA) PI >95th centile and/or cerebroplacental CPR ratio (UA / MCA) <5th centile
- and/or a >50% centile drop in EFW and/or AC.

The Delphi consensus procedure recommends at the initial diagnosis of SGA, multi-vessel Doppler studies (UtA, UA, MCA, CPR and ductus venosus) should be performed.

*ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020; 56: 298–312.

*Cruz-Martinez. Clinical utility of third-trimester uterine artery Doppler in the prediction of brain hemodynamic deterioration and adverse perinatal outcome in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2015; 45:273–278.

*McCowan. A pilot randomized controlled trial of two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery doppler velocimetry. Am J Obstet Gynecol 2000; 182: 81–86.

Powel. Risk of adverse perinatal outcomes in pregnancies with “small” fetuses not meeting Delphi consensus criteria for fetal growth restriction. Am J Obstet Gynecol 2023;229:447.e1-13.

Conclusion

This study found ***no evidence that fetuses with EFW and/or AC at the 3rd to 9th percentile that fail to meet the Delphi consensus criteria for FGR - meaning normal Doppler studies and normal growth velocity - are at increased risk of APOs.*** Although the growth of these fetuses should be monitored closely to rule out evolving growth restriction, most cases are healthy constitutionally small fetuses. The management of these fetuses in the same manner as those with suspected pathologic

growth restriction may result in unnecessary antenatal testing and increase the risk of iatrogenic complications resulting from preterm or early term delivery of small fetuses that are at relatively low risk of adverse perinatal outcomes.

Introduction

FGR confers increased risk for perinatal mortality and lifelong morbidity for survivors. Previous research endeavors that sought evidence to inform clinical management to avoid APOs in FGR were limited by a lack of agreement regarding its definition.

The definition of FGR endorsed by the American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) is an EFW or AC of <10th percentile at all gestational ages - *a definition that fails to distinguish those fetuses whose growth has been pathologically restricted from constitutionally small healthy fetuses.*

Failure to establish this distinction may result in unnecessary antenatal testing and increase the risk of iatrogenic complications resulting from preterm or early term delivery of small fetuses that are at relatively low risk of adverse perinatal outcomes.

The ACOG and SMFM consider measurement of the pulsatility index (PI) of both the uterine artery (UtA) and middle cerebral artery (MCA) experimental modalities for the diagnosis and management of FGR.

Why was this study conducted?

We sought to assess the association between APO and differing definitions of FGR as defined by ACOG / SMFM versus the European Delphi consensus model. Our hypothesis was that no independent association exists between an EFW and/or AC of <10th percentile and APO in pregnancies where the Delphi consensus based criteria for FGR are *not* met (no abnormal Doppler findings and no dramatic decrease in growth velocity.)

APO for this study is defined as perinatal demise, 5-minute APGAR score <7 and/or abnormal cord pH.

Key findings

After propensity score matching and adjustment for nulliparity, body mass index of 35, chronic hypertension, hypertensive disorders of pregnancy, and FGR, the odds of APO for small fetuses not meeting Delphi consensus criteria (SGA with no abnormal Doppler findings and no dramatic decrease in growth velocity) was similar to that of an appropriate-for-gestational-age comparator group.

Factors independently associated with an increased incidence of APOs included chronic hypertension, hypertensive disorders of pregnancy and early onset FGR (elevated uterine artery Doppler.)

What does this add to what is known?

Our findings provide new evidence from a large US cohort that supports the use of the Delphi consensus criteria to identify SGA fetuses that have no increased risk of APO, calling into question clinical management paradigms that subject all small fetuses to rigorous antenatal testing and potentially iatrogenic early delivery.

Rodriguez-Sibaja. Abdominal circumference growth velocity as a predictor of adverse perinatal outcomes in small-for-gestational-age fetuses. The Journal of Maternal-Fetal & Neonatal Medicine Volume 36, 2023 - Issue 2

Conclusion

The results of the present study show that despite being a population in which very low morbidity would be expected, ***SGA fetuses demonstrating a significant diminution of abdominal circumference growth velocity but no Doppler evidence of placental insufficiency (i.e. those considered constitutionally small) present a high risk of APOs.*** Almost one-third of our cohort (29.2%) had at least one APO. This finding highlights the importance of identifying those fetuses at risk of APO within the population of constitutionally small fetuses.

Introduction

Abdominal circumference growth velocity (ACGV), a proxy of longitudinal fetal growth, has been studied as a predictor of APO in different populations.

*Grantz. Am J Obstet Gynecol. 2018;219(3):285.e1–285.e36.

*Mondry. Ultrasound Obstet Gynecol. 2005;26(6):634–638.

*Caradeux. Ultrasound Obstet Gynecol. 2018; 51(2):219–224.

Methods

Women with a singleton pregnancy and a diagnosis of SGA fetus - EFW between the 3–10th centile for gestational age and normal multivessel Doppler evaluation.

The primary outcome was a composite APO, defined as the presence of one or more of the following - pH <7.1, Apgar at 5 min <7, neonatal intensive care unit admission in the first 48 h of life, hypoglycemia in the first 24 h of life, intrapartum fetal distress requiring expedited delivery, and perinatal death.

Results

A decreased ACGV Z score of <10% (n 78) in comparison to a ACGV Z score >10% (n 76) was associated with:

- incidence of C section for fetal distress 16.7% vs 5.2%
 - composite APO 41% vs 17%.
 - increased risk for APO by an odds ratio of 4.30
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Larsen. Assessment of fetal growth trajectory identifies infants at high risk of perinatal mortality. Ultrasound Obstet Gynecol 2024; 63: 764–771

Conclusion

Within a SGA cohort, a $\geq 50\%$ centile decline in fetal growth trajectory identifies infants at increased risk of perinatal mortality and BW <3rd centile. Findings suggest that it is important to consider not only fetal size prior to delivery, but also individual fetal growth trajectory to optimize risk assessment.

Introduction

Perinatal mortality is defined as a composite of stillbirth and neonatal death within 28 days of delivery. 3 cohorts studied:

Group 1 - SGA fetus throughout pregnancy with appropriate growth trajectory. n = 165

Group 2 - non SGA fetuses with decreased EFW or AC growth trajectory

≥ 50 centiles and but EFW or AC remaining ≥ 10 th centile at their final ultrasound scan. n = 570

Group 3 - SGA fetuses with decreased growth trajectory and EFW or AC <10th centile at their final scan. N =254.

Reference group n = 433

Results

In comparison to reference group:

- group 2 and 3 had increased risk for perinatal mortality with odds ratios of 4.00 and 7.71.
- group 3 had increased risk for birth weight <3% and increased risk for emergency C section for fetal distress with odds ratios of 40.6 and 2.83.

Orzel. Review article. Fetal growth velocity - a breakthrough in intrauterine growth assessment? J. Clin. Med. 2024, 13, 3842.

Undiagnosed growth pathologies among appropriate-for-gestational age AGA fetuses

Applying the 10th centile as an arbitrary threshold in defining SGA neglects the acknowledgment of AGA fetuses and neonates who experience APOs and clinically exhibit the characteristics of fetal growth restriction. 70% of term stillbirths occur in fetuses categorized as AGA. These cases involved fetuses whose weight exceeded the 10th centile, but their growth potential was not met due to placental insufficiency. These infants may constitute an unrecognized group at risk not only for the prenatal, intrapartum and neonatal consequences of fetal growth restriction FGR but also for health issues in infancy and adulthood associated with FGR

Integrating fetal growth velocity assessment into perinatal care protocols holds promise in enhancing diagnostic precision. Growth velocity, involving changes in fetal size over a given period, offers insights into distinguishing between constitutional and pathological growth abnormalities.

Pathologically small fetuses - FGR - are at increased risk for stillbirth, preterm birth and neonatal brain injury and long-term neurodevelopmental disabilities. Pathologic FGR is an acute global problem with long-lasting parental, family psychological trauma and a significant economic burden on society.

Decreased growth velocity in SGA fetuses (EFW <10% centile) and in newborns with EFW between 10 and 80 centiles

* Hugh. Fetal weight projection model to define growth velocity and validation against pregnancy outcome in a cohort of serially scanned pregnancies. *Ultrasound Obstet. Gynecol.* 2022, 60, 86–95.

The study demonstrated significant associations between growth velocity and adverse pregnancy outcomes APOs including stillbirth, neonatal death, SGA, LGA at birth, 5-min Apgar score <7 and neonatal intensive care unit admission. Slow growth between the last two scans, in both SGA and non-SGA at the last scan, was identified as a predictor of stillbirth.

Decreased EFW growth velocity in combination with EFW and middle cerebral artery / umbilical artery Doppler cerebro-placental ratio (CPR) <5th centile predicted APOs.

Decreased EFW growth velocity among AGA fetuses exhibited a relationship with nonreassuring fetal heart rate (NRFHR) at birth and an increased rate of unplanned Cesarean sections

Abnormal AC growth velocity (ACGV) was a parameter correlated with APOs. This relationship was also observed in a group of newborns with EFW in between 10 and 80 centiles, underlying the accuracy of the growth velocity rather than singular US measurements.

***Kennedy. Reduced growth velocity from the mid-trimester is associated with placental insufficiency in fetuses born at a normal birth weight.**

BMC Medicine 2020. 18:395

Conclusions

Reduced growth velocity between 20 and 36 weeks among AGA fetuses is associated with antenatal, intrapartum and postnatal indicators of placental insufficiency. These fetuses potentially represent an important, under-recognized cohort at increased risk of stillbirth.

These findings suggest that a fall of 30 or more EFW or AC centiles between the 20- and 36-week scans could be used as a pragmatic clinical cut-off to define low fetal growth velocity, given the consistent associations with markers of placental insufficiency.

Future research will involve testing this threshold in a larger prospective study to more comprehensively determine its diagnostic performance for adverse perinatal outcomes. If confirmed, AGA fetuses with reduced growth velocity may be candidates for increased surveillance and timely delivery to reduce stillbirth risk.

Introduction

Small-for-gestational-age (SGA), defined as ultrasound estimated fetal weight (EFW), abdominal circumference (AC) or infant birth weight below the 10th centile, is the most commonly used proxy for FGR. Its use as a surrogate for FGR has limitations, as SGA captures a heterogeneous population of both constitutionally (small but healthy) and pathologically, small fetuses. Further, the use of the 10th centile as an arbitrary cut-off fails to recognise those appropriate-for-gestational-age (AGA) fetuses and neonates who have also experienced placental insufficiency. Such infants may have failed to achieve their growth potential, despite having a birth-weight above the 10th centile for their gestational age.

Significantly, 70% of stillbirths occurring at term occur in fetuses classified as AGA. These AGA infants are likely to have experienced late-onset FGR. The size of the fetus is affected to a lesser extent than in early onset FGR, as fetal nutritional demands plateau while oxygen demands increase. If identified, timely delivery could prevent stillbirth in these cases. However, late-onset FGR is more difficult to detect antenatally, requiring a comprehensive approach that may incorporate assessment of both fetal size and growth.

Methods

EFW and AC growth velocities between 20–36 weeks, were examined as predictors of four clinical indicators of placental insufficiency: (i) low 36-week MCA/US Doppler cerebro placental ratio CPR (CPR < 5th centile reflects cerebral redistribution—a fetal adaptation to hypoxia), (ii) neonatal acidosis (umbilical artery pH < 7.15) after the hypoxic challenge of labour, (iii) low neonatal body fat percentage (BF%) reflecting reduced nutritional reserve and (iv) placental weight < 10th centile.

Results

In comparing two cohort's of low growth velocity (>30 centile change) versus growth velocity not low (<30 centile change):

*CPR <5th centile conferred a relative risk RR of 2.23 in predicting a drop-off in growth of EFW and/or AC of >30 centiles between 20-36 weeks (17% in comparison to 7.6%).
p 0.03

* EFW low growth velocity cohort in comparison to EFW not low growth velocity cohort predicted placental weight <10th centile with a RR of 2.66. (44% in comparison to 16.7%.) p <0.0001.

* AC low growth velocity cohort in comparison to not EFW low growth velocity cohort predicted placental weight <10th centile with a RR of 2.19. (45.5% in comparison to 20.8%.) p 0.01.

***Hendrix. Postnatal growth during the first five years of life in SGA and AGA neonates with reduced fetal growth.** Early Hum Dev. 2020 Dec;151:105199.

Postnatal catch-up growth can be a sign that a fetus may have experienced intrauterine growth restriction (IUGR) which could - amongst other factors - be linked to placental insufficiency.

Postnatal catch-up growth may also occur in AGA neonates with birth weights >10% centile indicating a compensatory mechanism for undiagnosed intrauterine placental insufficiency, including AGA fetuses with reduced fetal growth velocity.

Potential concerns with catch-up growth:

Increased risk of metabolic issues - neonates and infants who rapidly catch up growth may have a higher risk of developing metabolic problems like obesity and insulin resistance later in life.
