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Intrauterine Growth Restriction in the Triad: Understanding Outcomes Associated with Differential Management of Severe Early IUGR

Fore M¹,², Barron T¹, Street L¹,³, Nitsche JF¹, Quinn K¹ and Denney JM¹*

¹Wake Forest School of Medicine, Department of Obstetrics and Gynecology, Section on Maternal-Fetal Medicine, Winston-Salem, NC, USA
²Penn State College of Medicine, Department of Obstetrics and Gynecology, Hershey, PA, USA
³Augusta University, Medical College of Georgia, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Winston-Salem, NC, USA

*Correspondence: Denney JM Department of Obstetrics and Gynecology Section for Maternal-Fetal Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, North Carolina, 27157, USA, Phone: 336-618-1560; Fax: 336-716-6937; E-mail: jdenney@wakehealth.edu

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Abstract

Objective: Preterm delivery of growth restricted (IUGR) fetuses prior to 32 wks is rarely indicated, occurring in <1.9% of all pregnancies. We sought to determine if delaying delivery until non-reassuring fetal heart tracing (NRFT) increases adverse outcomes.

Materials and Methods: This is a cohort of pregnant women with IUGR identified prior to 32wks. Serial fetal growth and umbilical artery Doppler (UAD) were assessed. Two groups were compared: those delivered for abnormal UAD studies and those delivered for non-reassuring fetal heart tracing (NRFT). Fetuses with absent (AEDF) or reversed end diastolic flow (REDF) were placed on continuous monitoring until delivery. Maternal comorbidities, delivery indications, and neonatal outcomes were compared between the 2 groups. T-test and Chi-square were performed where appropriate.

Results: 43 singleton gestations with IUGR were identified at <32 weeks gestation from 2012-2015. Pregnancies were excluded for multiple gestation or when delivered for maternal deterioration. Mean GA at diagnosis 24.7 +/-3.1wks (range 18-30.3wks). 30 delivered for abnormal UAD and 13 for NRFT. Pregnancy characteristics were similar between groups. Those women who progressed to urgent delivery due to NRFT were more likely to undergo cesarean (CD) than SVD (p=0.01). 83.9% of both groups were delivered via CD and were significantly smaller compared to those able to be born via SVD (p=0.026). Women with HTN, preeclampsia or GHTN were also more likely to undergo CD than SVD (p=0.04). Expectant management for abnormal UAD did not decrease requirement for CPR at delivery or incidence of IVH, RDS, or death. Although not statistically significant, the length of stay was 50.9 days in those delivered for Doppler while 61.2 days in the group delivered emergently (p=0.23); see Table 1.

Conclusion: Expectant management for fetal growth restriction and waiting to deliver until there was NRFT does not appear to decrease neonatal morbidity/mortality, increases risk for emergency CD, and may increase length of stay in NICU.

Keywords: Early IUGR; Abnormal Doppler; Fetal Growth Restriction; Expectant Management Emergent Delivery;
Introduction

While obstetric literature is littered with myriad of terms and criteria used to clinically categorize the fetus failing to achieve individual growth potential, one widely accepted convention is to classify a fetus with intrauterine growth restriction (IUGR) when composite biometry measured by ultrasound generates an estimated fetal weight (EFW) at less than the 10th percentile for gestational age [1]. However, most fetuses less than the 10th percentile are not truly growth restricted [1, 2]. Given that growth restricted fetuses tend to have restricted fetal-placental blood flow, Doppler measurement of blood flow between fetus and placenta is a reliable modality obstetricians can use to discern which fetuses are most at risk for adverse outcome [3]. Hence, the assessment of the systolic to diastolic velocity in umbilical artery is utilized to correlate the biometric measurements with increased resistance in fetal-placental circulation and in turn determine which fetuses are at highest risk for stillbirth with expectant management [3, 4].

Since diastolic blood flow is the most important part of the cardiac cycle for delivery of oxygen to the fetal organs, elevated S/D ratio two standard deviations above the mean, absent end diastolic flow (AEDF), and reversal in diastolic flow (REDF) have been linked to increasingly higher risk for stillbirth as well as poor neonatal health following delivery. Close monitoring of UAD studies is therefore necessary to time delivery prior to fetal death [5-9].

Determining when delivery is warranted for inappropriate gestational growth is somewhat nebulous given the wide genetic differences in potential for size. Most fetuses at less than the 10th percentile are actually genetically predisposed to be at less than the 10th percentile. Thus using estimated fetal weight of less than the 10th percentile to define IUGR leads to a significant number of false positives when trying to identify the fetuses at increased risk of adverse outcomes. This can lead to unnecessary preterm deliveries and consequently iatrogenic increase in neonatal complications. However, applying more stringent criteria—two standard deviations below the mean for gestational age—leads to false negative with respective to the at-risk fetus. While this is actually less common, the risk of stillbirth is catastrophic when compared to risks of prematurity, especially later in gestation [10]. In Europe, it is commonplace to perform a customized assessment of fetal growth accounting for maternal height and ethnicity rather than lock-stock and barrel approach of inserting an estimated fetal weight at a given gestational age into population data irrespective of maternal and paternal contribution.

Given such considerations, the American College of Obstetricians and Gynecologists (ACOG) does not recommend intervening by way of delivery solely for abnormal umbilical artery Doppler studies; this is meant to avoid unnecessary preterm deliveries [10]. The gold standard for delivery prior to 32 weeks remains that of nonreassuring fetal testing, namely, the fetal heart tracing [10]. This research seeks to determine what risks the physician and patient take on for the maternal-fetal pair when contracting on a plan for expectant management in the setting of Doppler studies that have deteriorated to the worst endpoint of reversed end diastolic flow with little potential for continued intrauterine growth given the association with poor oxygen delivery in this state. Our group set out to describe the outcomes generated by varied application of the ACOG guidelines in the setting of severe early IUGR.

Materials and Methods

This study involved a retrospective analysis of the charts of forty-seven high-risk women that were patients of the Comprehensive Fetal Care Center in Winston Salem, North Carolina between the years of 2012-2015. Each of these women had been diagnosed by a physician with intrauterine growth restriction prior to 32 weeks gestation. Patients received umbilical artery Doppler studies at least weekly following diagnosis of IUGR. The women were assigned into one of two groups: women that were delivered for abnormal UAD studies and women that were delivered for non-reassuring fetal tracing (NRFHT). Comparisons made between the two groups included mean gestational age at diagnosis, method of delivery, incidence of comorbidities such as preeclampsia or gestational hypertension, length of stay in the neonatal intensive care unit following delivery, use

of CPR, and incidence of intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS) and death.

Collection of data involved retrospectively analyzing patient charts. The notes of physicians and other healthcare providers were reviewed in order to ascertain the necessary data points. Information that was removed from the charts was compiled and kept in a secure Red Cap database. Only singleton pregnancies were included in this study. Statistical analysis was completed using STATA version 7.0 (College Station, TX). Univariate and multivariate analysis were applied where appropriate.

Results and Discussion

Gestational Age at Diagnosis

The mean gestational age (GA) at initial diagnosis of IUGR for all women included in this cohort was 24.7 +/- 3.1 weeks with a range of 18 to 30.3 weeks gestation, making this group representative of a very small subset of the obstetric population as severely early IUGR (<28 weeks) is rare.

Mode of Delivery

83.9% of women in this cohort delivered via cesarean section (CD), while 16.1% had a vaginal delivery (SVD), which indicates that the overwhelming majority of women delivered via cesarean section. Women that were expectantly managed until evidence of NRFHT developed (p=0.01) were more likely to require an emergency CD than the group delivered based on Doppler studies(Figure1). Women with hypertensive disorder of pregnancy (HTN DOP) had a higher incidence (p = 0.04) of CD (Figure 2).

Patients who were expectantly managed until NRFHT were more likely to undergo emergency
CD than SVD (10 of 25 CD vs. 1 of 8 SVD in context of NRFHT; p=0.01

Patients with HTN, preeclampsia, or GHTN were more likely to undergo CD vs. SVD (HTN d/o pregnancy [HTNDOP] 24/26 vs. no HTN 12/17; p=0.04)

Comorbidities in Women

The mean maternal age was 27.5 years in the group delivered for abnormal UAD studies and 30.6 in the group delivered for NRFHT was 30.6 (p = 0.15). Average gravidity in the group delivered for abnormal UAD studies group was 2.7 and 3.2 in the group delivered for NRFHT (p = 0.45). There was a 10% prevalence of diabetes mellitus in women delivered for UAD studies compared to 15% in women delivered for NRFT (p = 0.61). 27% of women that delivered for UAD studies had preeclampsia, while 15% of women delivering for NRFT had preeclampsia (p = 0.56). Chronic hypertension was evident in 33% of women delivering for UAD studies and 15% of women delivering for NRFT (p = 0.23). Smoking was recorded in 30% of UAD study deliveries and 31% of NRFT deliveries (p = 0.58). Substance abuse was reported in 13% of women delivering for UAD studies and 23% of NRFT deliveries (p = 0.63).

Fetal Outcomes Post Delivery

The mean gestational age for babies delivered due to abnormal UAD studies was 28.17 weeks (p = 0.44) and 27.44 weeks for babies delivered due to NRFHT (Table 1).

The mean birthweight was 844.3 grams in deliveries based on UAD studies and 712.5 grams for NRFT deliveries (p = 0.32). CPR was performed at delivery in 10% of cases where delivery occurred due to abnormal UAD studies, and it was performed in 8% of cases where delivery occurred due to NRFT (p = 0.65). IVH occurred in 20% of neonates delivered for abnormal UAD studies and 23% of neonates delivered for NRFHT deliveries (p = 0.82). RDS was present in 83% of infants delivered for abnormal UAD studies and 77% of infants delivered for NRFT (p = 0.62). 73% of infants delivered for abnormal UAD studies survived, while 77% of infants delivered for NRFT survived (p = 0.50). Infants delivered via cesarean section had a lower birthweight (p < 0.03) than delivered vaginally (Figure 3).

Neonates requiring delivery by cesarean (for a reason other than malpresentation) were smaller in size by mean birthweight (675 gm CD vs. 795 gm SVD; p<0.03)

Conclusion

This study demonstrated that birthweight does have a significant relationship with the method of delivery. Neonates delivered via CD were on average 675 grams, while those delivered via SVD averaged 795 grams (p < 0.03). It is unclear from this study whether low birth weight is secondary to other complications in utero at an earlier gestational age, thus resulting in a need for CD rather than SVD. Further studies are needed to understand whether CD is specifically necessary due to low fetal weight or whether low birth weight is as a result of other complications that necessitate CD. Current literature suggests that there is no statistically significant
Patients who were expectantly managed until NRFHT were more likely to undergo emergency CD than SVD (10 of 25 CD vs. 1 of 8 SVD in context of NRFHT; p=0.01).

Patients with HTN, preeclampsia, or GHTN were more likely to undergo CD vs. SVD (HTN d/o pregnancy [HTNDOP] 24/26 vs. no HTN 12/17; p=0.04) difference in mortality and morbidity in low birthweight infants delivered via CD compared to SVD [11]. CD is rationalized for use in the instance of low birth weight to avoid further fetal stress that could be experienced during a SVD [12]. It is unclear whether physicians in these cases operated under the premise that CD is better indicated for fetuses of low birthweight, thus resulting in a lower average birth weight in CD compared to SVD.

Results from this study also indicated that women that were managed and delivered only upon incidence of NRFHT were more likely to undergo emergency CD.

Delaying delivery until NRFHT did not result in a significant difference in survival rates of infants, necessity for CPR at delivery, IVH, or RDS. Allowing the fetus to continue developing in utero until the presence of NRFHT therefore may not decrease morbidity compared to fetuses delivered due to abnormal UAD studies. Similarly, birthweight was not significantly different between women that were delivered due to abnormal UAD studies compared to NRFHT. Delaying delivery for NRFHT therefore may not significantly impact birthweight.

A number of maternal demographics were not significantly impacted by indication for delivery. Maternal age, gravidity, presence of diabetes mellitus, preeclampsia, chronic hypertension, smoking, and substance abuse did not have a significant relationship with delivery for abnormal UAD studies compared to NRFHT. Women...
with conditions such as DM, preeclampsia, a history of smoking, and substance abuse therefore did not significantly correlate with delivery indication in this study.

CD was found to be a more likely form of delivery compared to SVD in patients with HTN, preeclampsia, or GHTN. Hypertensive disorders therefore may factor into whether delivery via CD or SVD is more likely to be indicated for a patient.

There are limitations to the data collected in this study. It is difficult to account for the rationale used to deliver fetuses for abnormal UAD studies compared to waiting for the emergence of NRFHT. The criteria used to determine the need for CD compared to SVD in cases of NRFHT was not recorded for each patient and therefore was excluded from this analysis. Understanding the state of the neonate at the time of delivery for reasons of NRFHT is also paramount to determining whether CD is exclusively indicated or whether SVD may have also been indicated. Further data is needed on the state of the mother and neonate just prior to delivery that would provide a more conclusive picture of what specific factors contributed to the decision to deliver via CD for NRFHT. Further studies should also assess the correlation between neonatal outcomes such as CPR after delivery, IVH, RDS, or demise and maternal demographics such as preeclampsia, DM, CHTN, smoking, and substance abuse in patients that delivered for abnormal UAD studies compared to NRFHT. Additionally, because this study was a retrospective analysis of charts, data points were not collected in a standardized way from patients and are subject to errors when being recorded into patient medical records.

This research sought to provide data on a number of outcomes that may be influenced by the timing of delivery in growth restricted fetuses. While recommendations currently exist on how to approach growth restricted fetuses, more research is needed to inform physicians of the potential issues that can arise when growth-restricted infants are managed until the point of NRFHT. Despite allowing the fetus continue growing beyond initial IUGR diagnosis, there were not significant differences in birthweight, survival, or fetal outcomes such as CPR at delivery, IVH, or RDS. This information provides a more holistic understanding of how the status of the fetus will be affected depending on time of delivery and may assist in deciding how best to approach cases of IUGR. Foundational research such as this is paramount moving forward in order to better understand the benefits and drawbacks of managing fetuses beyond the advent of abnormal Doppler studies.

References
**Table 1:** Comparison Of Delivery For Abnormal Uad Vs. Nrfht

<table>
<thead>
<tr>
<th>Maternal Demographics/Neonatal Characteristics</th>
<th>Scheduled Delivery for AEDF/REDF</th>
<th>Delivery for Non-reassuring Fetal Status</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (mean yrs)</td>
<td>27.5</td>
<td>30.6</td>
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<tr>
<td>Gravidity (mean)</td>
<td>2.7</td>
<td>3.2</td>
<td>0.45</td>
</tr>
<tr>
<td>DM</td>
<td>3/30 (10%)</td>
<td>2/13 (15%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>8/30 (27%)</td>
<td>2/13 (15%)</td>
<td>0.56</td>
</tr>
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<td>CHTN</td>
<td>10/30 (33%)</td>
<td>2/13 (15%)</td>
<td>0.23</td>
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<td>Smoking</td>
<td>9/30 (30%)</td>
<td>4/13 (31%)</td>
<td>0.58</td>
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<tr>
<td>Substance Abuse</td>
<td>4/30 (13%)</td>
<td>3/13 (23%)</td>
<td>0.63</td>
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<tr>
<td>Gestational Age at delivery</td>
<td>28.17</td>
<td>27.44</td>
<td>0.44</td>
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<tr>
<td>(mean weeks)</td>
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<tr>
<td>Birthweight</td>
<td>844.3</td>
<td>712.5</td>
<td>0.32</td>
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<tr>
<td>(mean gm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR at delivery</td>
<td>3/30 (10%)</td>
<td>1/13 (8%)</td>
<td>0.65</td>
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<td>IVH</td>
<td>6/30 (20%)</td>
<td>3/13 (23%)</td>
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<td>RDS</td>
<td>25/30 (83%)</td>
<td>10/13 (77%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Survival</td>
<td>22/30 (73%)</td>
<td>10/13 (77%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

the preterm infant. Am J Obstet Gynecol. 158: 1382-1390

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