● **Original** research

# SHORT- AND LONG-TERM GROWTH AS A FUNCTION OF ABNORMAL DOPPLER FLOW IN GROWTH-RESTRICTED FETUSES

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***Abstract***

*OBJECTIVES: To evaluate short- and long-term growth in fetuses with growth restriction (FGR) and elevated umbilical artery Doppler (UAD) systolic/diastolic (S/D) ratios.*

*METHODS: In this prospective observational study, two UAD waveforms were obtained from each umbilical artery weekly and were classified as normal or abnormal. Fetal growth was assessed every 3 weeks. Short-term growth was calculated from the first visit with elevated ratios until next growth assessment. Results were grouped by number of initial elevated S/D ratios (maximum, 4). Long-term growth was evaluated by change in estimated fetal weight from diagnosis of FGR to birth weight. Fetuses were grouped by average number of elevated S/D ratios and compared to a reference population of growth restricted fetuses with normal testing.*

*RESULTS: Of 241 fetuses evaluated, 105 demonstrated elevated S/D ratios. Short-term growth was impaired when fetuses had elevated S/D ratios. Long-term growth was affected when the average number of elevated S/D ratios was ≥1 per visit. Progressive 3 or 4 growth delay was noted as the average number of abnormal S/D ratios increased.*

*CONCLUSIONS: Short- and long-term fetal growth are affected by elevated UAD S/D ratios. Fetuses with more abnormal values initially and those with a higher average of elevated values over pregnancy demonstrate decreased growth.*

***Key words:*** *fetal growth restriction, umbilical artery systolic/diastolic ratios, estimated fetal weight, long-term growth, short-term growth*

## INTRODUCTION

Umbilical artery Doppler (UAD) is integral to the evaluation and management of the growth-restricted fetus. Abnormal UAD testing is associated with adverse perinatal outcomes,[1-3] and UAD surveillance in pregnancies complicated by fetal growth restriction (FGR) has been shown to decrease perinatal mortality.[4-6]

We observed that the measurement of the umbilical artery systolic/diastolic (S/D) ratio can differ within the same artery and between the two umbilical arteries, yielding both normal and abnormal results. Heterogeneity of values may be seen both within a single visit and between separate visits, leading to ambiguity that complicates the interpretation of results. Discordant results may be indicative of placental insufficiency, or they may represent measurement variation associated with a normal pregnancy course. Additionally, if only one artery is measured, this may result in a false positive or negative test, leading to over- or under-treatment.

Our initial results suggested that much of the Doppler discordance between and within the arteries involves elevated S/D ratios. The 2012 Society for Maternal Fetal Medicine publication on Doppler assessment of the growth-restricted fetus focuses primarily on absence and reversal of flow as an indicator of abnormal placental function.[7] In contrast, the PORTO trial included an elevated UAD pulsatility index, in addition to absence or reversal of flow, in its definition of abnormal Doppler, and this was significantly associated with the composite adverse perinatal outcome.[8] While there is little disagreement that absence or reversal of UAD flow is a poor prognostic sign, it is less clear if elevated S/D ratios, particularly if intermittent or inconsistently expressed, are indicative of significant placental pathology.

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We sought to assess the relative impact of varying degrees of Doppler abnormality, specifically with respect to elevated UAD S/D ratios, on both short-term and long-term fetal growth. We attempted to address this question by analyzing the rate of fetal growth over a period of 3 to 5 weeks after the first episode of elevated S/D ratios. We also examined long-term fetal growth from a perspective of average Doppler abnormality over the period of FGR surveillance.

## MATERIALS AND METHODS

This was an IRB approved prospective observational study of patients seen in the Geisinger Health System between 2012 and 2015. Women with a singleton gestation diagnosed with fetal growth restriction, defined as an estimated fetal weight less than the 10th percentile (Hadlock), were approached for study participation. All the participants signed an informed consent. Exclusion criteria included a single umbilical artery, multiple gestation, age 17 or less, non-English speaking women, women whose fetuses had absent or reduced end-diastolic flow, and those patients in whom follow-up information was missing or insufficient for the analyses. Patients were monitored with weekly UAD waveforms and fetal growth assessments every 3 weeks. Two UAD waveforms were obtained from each umbilical artery in a free loop of umbilical cord. The S/D ratios of all four waveforms were classified separately as normal per gestational age nomograms or abnormal (elevated S/D ratios >95%, absent or reversed end-diastolic flow).[9] Management occurred per department guidelines. Discordance was defined as a discrepancy in normal or abnormal values between each artery (inter-artery variation) rather than differences within the same artery (intra-artery variation).

Short-term growth as a function of abnormal UAD results was assessed by comparing the change in estimated fetal weight (EFW) in grams (g) from the first visit with elevated S/D flow until the next growth assessment, adjusted for gestational age. If elevated S/D ratios occurred during the interval between growth evaluations, we calculated the difference between the following two EFW assessments (maximum interval of 5 weeks). Results were grouped by the degree of initial UAD abnormality, either 1, 2, 3, or 4 abnormalities out of 4 values. Patients were excluded from this analysis if they delivered prior to attaining the second estimated fetal weight.

Long-term growth was evaluated by assessing the change in fetal weight in grams from the diagnosis of FGR to delivery birth weight, adjusted for gestational age (GA). A composite average of the abnormal UAD S/D values was calculated by adding the number of abnormal values per visit (out of 4) across the surveillance period and dividing by the number of visits. Fetuses were grouped by average value (labeled groups A through E) and compared to the reference population of growth-restricted fetuses with no abnormal Doppler results. Fetuses were excluded from this analysis if the final birthweight was not obtained or if the birthweight was less than the estimated fetal weight.

We also assessed the interval until delivery from the first abnormal Doppler finding (irrespective of subsequent findings) stratified by number of abnormal Doppler findings out of four, i.e., 1/4, 2/4, 3/4, 4/4.

Descriptive statistics including plots for each variable were performed to identify influential points and to assess normality. Means, standard deviations, medians, ranges (maximum and interquartile), frequencies and percentages were calculated as appropriate for all patient characteristic variables in both the normal and abnormal UAD S/D groups. Comparisons between groups were performed using the Wilcoxon rank sum test and Pearson Chi-square for continuous and categorical variables, respectively. Those patient characteristics were included as covariates in the model development period. Individual linear regression models were used to evaluate the association between abnormal UAD Doppler flow measurements and short-term and long-term growth. All models were adjusted for gestational age (GA) since gestational age is known to be highly associated with both short-term and long-term growth. Tests were two-sided with p-values $< 0.05$ considered significant, and the analyses were completed using SAS v9.4 software (SAS Institute Inc., Cary, NC, USA).

| Variables | Normal Doppler N = 131 | Abnormal Doppler N = 110 | P value |
|---|---|---|---|
| **Age, years* mean (SD)** | 27.4 (6.0) | 28.1 (5.8) | 0.33 |
| **Education in years mean (SD)** | 13.2 (2.6) | 12.9 (2.1) | 0.33 |
| **Race, n (%): White** | 117 (90.7) | 104 (95.4) | 0.20 |
| **Marital Status, n (%): Married** | 49 (37.7) | 43 (39.1) | 0.97 |
| **Insurance Public, n (%)** | 70 (54.7) | 60 (54.6) | 0.79 |
| **Pre-pregnancy body mass index,kg/m2, mean (SD)** | 28.7 (8.6) | 27.9 (8.8) | 0.51 |
| **Multiparous, n (%)** | 66 (50.4) | 52 (47.3) | 0.47 |
| **Tobacco use, n (%): Yes** | 48 (36.6) | 46 (41.8) | 0.41 |

*Table 1. Demographics of the study population.*

## RESULTS

We evaluated 241 fetuses, of which 110 demonstrated abnormal values. Five fetuses were excluded from this analysis due to having absent or reversed end-diastolic flow, leaving 105 fetuses who demonstrated elevated S/D flow as their only abnormality. Fourteen fetuses (all with abnormal values) were excluded from the short-term analysis because a second growth assessment was not available for comparison, yielding 91 fetuses eligible for analysis. Twenty-four fetuses (10 with

| Number of abnormal Doppler values out of the 4 values obtained | N | Mean (grams) | Expected change (g) adjusted for GA | P value |
|---|---|---|---|---|
| 1/4 | 33 | 603 | Ref | Ref |
| 2/4 | 41 | 553 | -50 | 0.59 |
| 3/4 & 4/4 | 17 | 274 | -335 | 0.005 |

*Table 2. Short-term growth as a function of abnormal Doppler flow in growth restricted fetuses*

abnormal values, 14 with all normal values) were excluded from the long-term analysis due to missing birthweight or a birthweight less than the estimated fetal weight, resulting in 95 fetuses in the analysis group for long-term growth. The population of women with normal and abnormal Doppler flow was similar (Table 1).

Fetuses with one or two elevated UAD S/D ratios at their first visit had approximately 600 grams of interval growth. In contrast, fetuses with three or four elevated values grew only 274 grams by the next growth assessment. After adjusting for gestational age, the interval growth in fetuses with 3 or 4 abnormal values was 335 grams less than in fetuses with only 1 abnormal value (Table 2) ($p = 0.005$).

*Table 3. Days between GA at diagnosis of abnormal flow and delivery**

| Doppler Values | Mean | Median (IQR) |
|---|---|---|
| 1/4 abnormal | 50.7 | 43.5 (29, 76) |
| 2/4 | 49.5 | 49.5 (26.5, 73.5) |
| 3/4 & 4/4 | 41.3 | 41 (27, 62) |

** Data expressed as mean and median (interquartile range).*

Table 3 depicts the mean days to delivery stratified by the initial UAD S/D ratio abnormality. The mean time to delivery showed a decreasing trend with advancing degree of initial Doppler abnormality, but did not reach significance.

Fetuses with elevated S/D ratios were stratified by degree of average abnormality over the course of the pregnancy and the effect of elevated S/D ratios on long-term growth was evaluated. Group A fetuses had no abnormal Doppler values over the course of the pregnancy, and these growth restricted fetuses were used as the reference population. Fetuses in Group B demonstrated similar growth to the fetuses in Group A. However, fetuses in Groups C, D and E had progressively less growth as compared to Group A. After adjusting for gestational age, the significant decrease in fetal growth in these groups persisted (Table 4).

## DISCUSSION

In FGR fetuses presenting with their first episode of elevated UAD S/D ratios, short-term interval growth was similar if only 1 or 2 of the 4 assessed Doppler values were elevated. However, short-term interval growth was significantly impaired when fetuses had 3 or 4 out of 4 elevated UAD S/D values at their first visit in which abnormal elevated Doppler flow was noted ($p=0.005$).

When evaluating fetal growth over the entire period of antenatal Doppler surveillance, fetuses with no abnormalities and those with an average of less than 1 of 4 elevated Doppler S/D ratios demonstrated similar growth. This is an expected finding, as an average of less than 1 of 4 abnormal values indicates that at most visits the fetus had few, if any, abnormal Doppler values. Those fetuses with an average of at least 1 out of 4 abnormal Doppler values grew significantly less than those with < 1 out of 4 abnormal values, and this difference was progressive with respect to the degree of average Doppler abnormality ($p<0.01$). In the most severe cases, this approached an expected growth lag of nearly two pounds.

These results imply that elevated UAD S/D ratios reflect placental changes that impact fetal growth, and that the consistency and frequency of abnormal results when evaluating both arteries has significance with respect to the fetal growth over the subsequent weeks. Interestingly, despite the effect on fetal growth, the degree of initial Doppler abnormality did not appear to affect timing of delivery.

We are unaware of other papers evaluating the impact of elevated UAD S/D ratios on fetal growth. A recent review of a retrospective cohort of fetuses with elevated S/D ratios examined fetuses with a very similar protocol of weekly UAD assessments, although they measured only 3 values and did not specify from one or both arteries. They noted that 29% of fetuses had only a single elevated S/D ratio, and 40% had over half of the S/D ratios elevated.[10] We noted similar variation in S/D ratio values in our study, suggesting that variation of UAD values within and between arteries, as well as among measurement periods separated by time, represents a valid observation of fetal blood flow patterns in the umbilical arteries.

An interesting parallel can be drawn when comparing the findings in this study compared to the effects of tobacco use, which is a well-known inhibitor of fetal growth. In a study evaluating the effect of tobacco use on fetal growth, Wen et al. demonstrated an approximate 130 g to 300 g overall decrease in fetal weight.[11] Another study evaluating the effect of gene polymorphisms on tobacco-induced growth reduction indicated a 377 g decrease in birth weight in women who smoke in pregnancy.[12] This is similar to the magnitude of effect seen in short-term growth when 3 or 4 out of 4 Doppler values are elevated, and 200 g to 500 g less that the decrease noted in long-term growth in our study when there was an average of 1 of 4 abnormal values or more.

| Average UAD grouping | N | Mean (g) | Expected change (g)adjusted for GA | P value |
|---|---|---|---|---|
| A: 0/4 | 117 | 1398 | Ref | Ref |
| B: <1/4 | 68 | 1543 | -3 | 0.97 |
| C: 1/4 ➡ <2/4 | 16 | 1018 | -498 | < 0.01 |
| D: 2/4 ➡ < 3/4 | 7 | 1004 | -626 | < 0.01 |
| E: 3/4 ➡ 4/4 | 4 | 276 | -836 | < 0.01 |

*Table 4. Change in weight from first abnormal visit to birthweight*

Key strengths of this study include the prospective study design, large sample size and uniform treatment approach (a single practice with all providers managing per department guidelines). Additionally, the group of sonographers obtaining the measurements was consistent throughout the study period, enhancing the reliability of the results.

Twelve patients were lost to follow-up due to deliveries outside the system. Half of these patients had only normal values and half had abnormal values, so this is unlikely to skew the results. Additionally, the low rate of adverse outcomes resulted in the inability to adequately assess for differences in the study populations with respect to abnormal Apgar scores, cord gases, NICU admissions, and stillbirth.

Umbilical arteries with different diameters and discordant UAD flow have been described in the literature.[13-15] It is unclear whether discordant umbilical artery size represents an associated placental or umbilical cord abnormality. Upon pathologic examination of 14 cases of discordant umbilical arteries (1.4%), 8 of the patients had an identifiable abnormality in the placenta or umbilical cord placental insertion site.[14] Raio et al. concluded that placental abnormalities are common when discordant umbilical arteries are seen; they cautioned that the discrepancy between small and large arteries may represent a benign process associated with normal neonatal outcomes.[14] Predanic evaluated the S/D ratios of parallel umbilical arteries in a cohort of uncomplicated singleton pregnancies and noted a difference of 20% or more between the individual umbilical artery S/D ratios in over 25% of the evaluated patients. As the pregnancy progressed, the difference decreased so that only 8.6% of term pregnancies were significantly different.[16] Further research into the development of the umbilical arteries, including the location of the placental cord insertion, volume of distribution of the individual arteries, and the presence of vascular anastomoses between the vessels may provide a physiologic mechanism to explain the variability in Doppler testing noted in our study. Additionally, future studies evaluating a large population and incorporating Doppler analysis, pathologic assessment, and neonatal outcomes would allow for in-depth correlation of Doppler and pathology findings, as well as the impact on the fetus.

In conclusion, both short-term and long-term fetal growth are affected by the presence of elevated UAD S/D ratios. Fetuses with more abnormal values on the initial assessment, as well as those with increasing consistency and frequency of abnormal results over the pregnancy duration demonstrated decreased growth over the measurement period. Therefore, it is reasonable to consider modifying the diagnostic and treatment approach to account for variation in the individual arteries.

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***Division of work:***

*John Ross and Dhanya Mackeen have contributed equally to design of the study, acquisition and analysis of data, and drafting and revision of manuscript.*

*Alexandria Betz contributed to acquisition and analysis of data.*

*Michael Paglia made substantial contributions to design of the study, interpretation of data, and revising for intellectual content of manuscript.*

*Wen Feng contributed to statistical design, data analysis and interpretation, and writing statistical methods for the manuscript.*

*A. George Neubert made substantial contributions to design of the study, and revising for intellectual content of manuscript.*

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