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Perinatal outcomes after intrauterine growth restriction & umbilical artery Doppler Pulsatility Index of less than the 5th percentile

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Abstract

Objective: To analyze perinatal morbidity and stillbirth after intrauterine growth restriction (IUGR) with an umbilical artery Doppler Pulsatility Index (UA PI) less than the 5th centile.

Study Design: This retrospective cohort study included non-anomalous singleton, IUGR pregnancies receiving UA PI testing at a tertiary-care prenatal diagnostic center. Women with persistently elevated UA PI, absent or reversed end-diastolic flow on UA PI, or who had only one UA PI result were excluded. Low UA PI was defined as having ≥1 UA PI <5%. Women with low UA PI were matched by gestational age at IUGR diagnosis in a random 1:1 computer-generated algorithm to those with normal UA PI (≤95% and ≥5%). The primary outcome was composite neonatal morbidity and mortality (stillbirth, mechanical ventilation, sepsis, intraventricular hemorrhage, and necrotizing enterocolitis). Secondary outcomes included 5-minute APGAR, umbilical artery pH, delivery type, and interval from IUGR diagnosis to delivery. We compared outcomes after low UA PI to those after normal UA PI with multivariable logistic regression, adjusting for gestational age at delivery, betamethasone use, infant gender, & maternal factors.

Results: Of 1893 IUGR pregnancies, 25 (1.3%) had low UA PI <5% and were randomly matched via computer algorithm to 100 controls. There were no stillbirths in either group; the odds of composite neonatal morbidity was similar among IUGR pregnancies with UA PI <5% versus normal (adjusted Odds Ratio 0.89 (95% Confidence Interval 0.27 – 2.75)). There was no difference in 5-minute APGARs, umbilical artery pH, rate of cesarean delivery for fetal distress, or interval from IUGR diagnosis to delivery between the two groups.

Conclusion: Among IUGR pregnancies, UA PI <5% is uncommon and not associated with improved neonatal outcomes compared to normal UA PI. These findings suggest low UA PI can continue to be managed as normal UA PI.

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Keywords

intrauterine growth restriction; neonatal morbidity; umbilical artery pulsatility index; normal umbilical artery Doppler; stillbirth

Introduction

Intrauterine growth restriction (IUGR) is common and associated with increased risk of stillbirth and perinatal morbidity and mortality.[1,2] Current practice guidelines for both fetal surveillance and optimal delivery timing among pregnancies affected by IUGR center on whether the umbilical artery (UA) Doppler is normal (≤95%), elevated (>95%), or has absent or reversed end-diastolic flow.[2] The two most common Doppler indices used to monitor pregnancies with IUGR are the peak systolic to end-diastolic (S/D) ratio and the pulsatility index (PI), defined as the difference between peak systolic and end-diastolic flow divided by the average frequency shift value of the entire cardiac cycle.[2] One advantage of the UA PI is that when diastolic flow is absent, the S/D ration is incalculable whereas the UA PI can still be used.[2]

The reason that UA Doppler is so importance in surveillance of pregnancies with IUGR is that abnormal UA Doppler has been associated with increased risk of adverse perinatal outcomes compared to those with normal UA PI.[3–6]Conversely, until 39 weeks gestation, the risk of adverse perinatal outcomes among IUGR pregnancies with normal UA PI appears similar to that of normally grown fetuses.[7,8] However, practice guidelines suggest IUGR pregnancies with normal UA Doppler can be delivered either at early-term or at term, depending on the presence of other risk factors for stillbirth or adverse neonatal outcomes.[1,2]

In our tertiary care prenatal diagnostic center, UA PI have been recorded that are less than the 5th centile. No data have been published describing the prevalence or clinical significance of having low UA PI among IUGR pregnancies, and the implications of this ultrasound finding in terms of neonatal morbidity and perinatal outcomes remain unclear. It is possible that having a low UA PI is protective against pediatric morbidity when compared to IUGR pregnancies with normal UA PI. If low UA PI is in fact protective, clinical practice algorithms could be updated such that IUGR pregnancies with low UA PI would be delivered at full term regardless of maternal comorbidities, consequently eliminating the known neonatal risks associated with early-term delivery[9] for these IUGR pregnancies.

This study aimed to first determine the prevalence of low UA PI and then estimate the risk of neonatal morbidity and adverse perinatal outcomes among IUGR pregnancies with low UA PI compared to that of IUGR pregnancies with normal UA PI, which we defined for this study as UA PI ≤95% and ≥5%. We hypothesized that low UA PI was uncommon and, when present, was associated with decreased odds of neonatal morbidity and cesarean delivery for fetal distress compared to those with normal UA PI.

Methods

We conducted a retrospective cohort study of patients with IUGR that received UA PI testing and delivered at our tertiary-care university hospital from January, 2010 until September, 2016. This study was approved by the Washington University School of Medicine Human Research Protection Office.

All patients examined in our prenatal diagnostic center are prospectively entered into a database by trained perinatal research nurses, who then extract sociodemographic, obstetric, and perinatal data from each patient's medical record after delivery. For this analysis, we included all non-anomalous, singleton pregnancies with IUGR diagnosed at or after 24 weeks gestation. We excluded patients with multiple gestations, fetal anomalies, persistently elevated UA PI, absent or reversed end-diastolic flow in the UA PI, or who had only one UA PI result. For this project, trained research staff conducted additional chart review to collect information on betamethasone administration and maternal medical co-morbidities like tobacco use, hypertensive disorders, or diabetes.

IUGR was defined as a sonographically obtained estimated fetal weight of less than 10th percentile for that gestational age, as per the Hadlock fetal growth curve.[10] IUGR pregnancies were ascertained via routine growth ultrasounds for maternal conditions like chronic hypertension or diabetes or for clinical concern the fetus was small for gestational age. We do not perform routine third-trimester ultrasound to assess fetal growth. Our institutional protocol for IUGR surveillance manages pregnancies with normal or elevated UA PI similarly via weekly UA PI testing and twice weekly antenatal testing in the outpatient setting. This surveillance is escalated to twice weekly UA PI testing and twice daily antenatal testing as an inpatient in the setting of absent or reversed end-diastolic flow, which occurs from diagnosis until delivery.[2] All ultrasounds were performed by sonographers who are Registry for Diagnostic Medical Sonography (RDMS) certified in Obstetrics & Gynecology. Sonographers used transabdominal ultrasound with color flow to conduct UA PI testing; UA waveforms were obtained from at least three distinct areas of the umbilical cord and recorded as an average pulsatility index. The reference chart used for the UA PI threshold throughout the study period was derived from a well-validated cross-sectional cohort of more than 1500 uncomplicated pregnancies.[11] In the absence of other indications for delivery, patients with IUGR <10% with normal UA PI were delivered at 39 weeks, IUGR <5% or IUGR <10% with oligohydramnios, maternal comorbidities, or elevated UA PI were delivered at 37 weeks, IUGR <10% with absent end-diastolic flow at 34 weeks, and IUGR <10% with reversed end-diastolic flow at 32 weeks. During the study period, all women with low UA PI (<5%) were managed as having normal UA PI (≥5% and ≤95%) and were delivered at 39 weeks or at gestational age of diagnosis if beyond 39 weeks. Administration of betamethasone to IUGR pregnancies with normal UA PI was not standard practice during the study period.

The *primary outcome* was a composite of neonatal morbidity and mortality, defined by the occurrence of one or more of the following neonatal morbidities: stillbirth, mechanical ventilation, sepsis, necrotizing enterocolitis, or intraventricular hemorrhage. As described previously,[12] the attending neonatologist confirmed all neonatal diagnoses. Mechanical

ventilation occurred after intubation was deemed necessary to adequately oxygenate the neonate; transient oxygen administration or nasal continuous positive airway pressure administration were not included. Sepsis was diagnosed via positive blood cultures and/or abnormal complete blood cell counts 6–12 hours after birth (leukopenia or leukocytosis with left shift) in the setting of respiratory distress, temperature instability, apnea, or lethargy. The diagnoses of necrotizing enterocolitis and intraventricular hemorrhage were obtained via clinical examination and confirmed with imaging findings. *Secondary outcomes* included individual measures of the morbidity and stillbirth composite as well as 5-minute APGAR score, umbilical cord artery pH, overall rate of cesarean delivery (CD), rate of CD for fetal distress, and interval from diagnosis of IUGR until delivery.

All patients who met inclusion criteria were included; no a priori sample size estimation was calculated. Women with low UA PI (<5%) were then randomly matched via computer algorithm by gestational age at IUGR diagnosis to those with normal UA PI (≥5% and ≤95%). Baseline characteristics and outcomes were compared between patients with IUGR who had low UA PI and those with IUGR who had normal UA PI. Categorical variables were compared with the chi-square or Fisher exact test, as appropriate. Continuous variables were assessed for normality with the Kolmogorov-Smirnov test, and compared using the Student *t*-test or Mann-Whitney *U* test as appropriate. Odds ratios were calculated for primary and secondary outcomes, and multivariable logistic regression adjusted for gestational age at delivery, betamethasone use, hypertensive disorders, diabetes, infant gender, and maternal tobacco use and ethnicity, with backwards elimination utilized to decrease the number of variables in each model. All tests were two-tailed with $p<0.05$ considered significant. Analyses were performed using Stata statistical software (Special Edition 12.1; StataCorp LP; College Station, TX).

Results

1893 women were included; of these, 25 (1.3%) had low UA PI and were matched 1:1 via random-computer generated algorithm to 100 controls of women diagnosed with IUGR pregnancies with normal UA PI via gestational age at IUGR diagnosis. Sociodemographic and obstetric characteristics between women with IUGR who had low UA PI compared to normal UA PI are shown in Table 1. Women with IUGR pregnancies with low UA PI were more likely to be nulliparous compared to those with normal UA PI (13 (52.0%) versus 42 (42.0%), $p=0.04$). However, they were equally likely to have pregestational or gestational diabetes (4 (16.0%) versus 17 (17.0%), $p=0.6$) or a hypertensive disorders including gestational hypertension, preeclampsia, or chronic hypertension (6 (24.0%) versus 12 (12.0%); $p= 0.13$). The infants born to women with IUGR pregnancies with low UA PI were less likely to be male versus those with normal UA PI (6 (24.0%) versus 50 (50.0%); p: 0.02). Maternal age, race/ethnicity, prepregnancy body mass index, rates of tobacco use in pregnancy, betamethasone administration prior to 34 weeks gestation were similar in the two groups. Of note, the gestational age at IUGR diagnosis and at delivery were also similar in the two groups.

The risk of the neonatal morbidity and stillbirth composite and individual components of the neonatal morbidity composite in low versus normal UA PI are shown in Table 2. Overall,

there were no cases of stillbirth in either group, and rates of neonatal morbidity were relatively common, occurring in 12.0% of those with low UA PI and 14.0% of those with normal UA PI. However, the odds of having composite neonatal morbidity was not significantly different in IUGR pregnancies with low versus normal UA PI (adjusted Odds Ratio (aOR) 0.89, 95% Confidence Interval (CI) 0.27, 2.75)). Similarly, the odds of being diagnosed with one of the individual components of the neonatal morbidity composite were similar in both groups. No infants with low UA PI were diagnosed with neonatal sepsis, necrotizing enterocolitis, or intraventricular hemorrhage.

Perinatal and obstetric outcomes are also shown in Table 2. The 5-minute AGPAR score and umbilical cord artery pH were similar in both groups. The overall rate of CD—including planned repeat CD—and rate of CD for fetal distress were both similar among women with low UA PI and normal UA PI (10 (40.0%) versus 33 (33.0%), aOR 0.94 (95% CI 0.33, 2.65); 4 (16%) versus 5 (5.0%%), aOR 2.48 (95% CI 0.51, 12.10); respectively). The interval from IUGR diagnosis and delivery was similar in both groups (8.0 weeks (interquartile range (IQR) 6.7, 11.7) versus 8.0 weeks (IQR 5.8, 12.8); p=0.71).

Discussion

In this cohort of non-anomalous singleton pregnancies with IUGR, we provide the first insight into the prevalence and clinical significance of low UA PI. Among IUGR pregnancies, low UA PI is relatively uncommon—with a prevalence of 1.3%—and appears to be neither protective against nor associated with increased risk of neonatal morbidity, umbilical cord artery pH abnormalities, or CD for fetal distress. These data suggest that normal UA PI should continue to be defined as UA PI ≤ 95$^{\%}$, without delineating <5% as a separate subgroup of IUGR. Thus, our findings support the ongoing management of pregnancies with IUGR and low UA PI in similar fashion as pregnancies with IUGR and normal UA PI in terms of delivering timing.

The lack of association between low UA PI and adverse perinatal outcomes is biologically plausible. First, the etiologies of IUGR are complex and include pathologic and physiologic factors. For example, decreased placental function is the most common pathology associated with IUGR and is usually associated with increased umbilical artery impedance, but constitutional IUGR—a fetus achieving optimal growth potential but categorized as IUGR due to an estimated fetal weight than the 10th centile—is thought to be the most common etiology of IUGR and is associated with normal UA PI.[1,2] IUGR pregnancies with consistently normal UA PI have been shown to have similar rates of neonatal morbidity as normally grown fetuses,[7,8] and our data suggest that low UA PI does not confer additional protection compared to normal UA PI among IUGR pregnancies. Thus, the small subset of IUGR pregnancies with low UA PI likely represents fetuses who have physiologic IUGR and have achieved their optimal growth potential. Second, UA PI measurements are known to have variable reproducibility, even with optimally obtained.[1,2] Thus, low UA PI may simply represent variations of normal UA PI testing, particularly since the practice at our institution is to interrogate the umbilical artery in a free loop of umbilical cord and not at the abdominal insertion site.[2] However, the location of UA PI sampling at our institution remained consistent during the study period, and the majority of IUGR pregnancies in our

study population retained consistently normal UA PI, suggesting that low UA PI reflected actual clinical difference. In addition, the risk of false UA PI testing was likely reduced because all UA PI measurements were obtained by experienced RDMS-certified Obstetric sonographers.

Our study offers several strengths. First, using prospectively collected data as part of an institutional database including maternal and infant outcomes for all pregnancies receiving ultrasounds at our institution minimizes the potential for bias innate within retrospective data collection. Second, though we included surrogate markers for neonatal well-being like 5-minute APGARs and umbilical cord blood pH as secondary outcomes, our primary outcome was a composite of objective diagnosed neonatal morbidity, which strengthens our conclusion that low UA PI is not associated with increased (or decreased) odds of neonatal morbidity. Third, our cohort of non-anomalous infants from an academic tertiary care center is likely similar to that of other tertiary care centers in the United States, which increases the generalizability of our findings. Lastly, our results are derived from a large study population in which neonatal outcomes were directly abstracted from the neonatal medical record by a trained study nurse instead of from merging an obstetric database into a separate neonatal database. The homogeneity of our database strengthens our conclusions.

Some limitations of our study should be considered. First, though the overall rate of neonatal morbidity was relatively common, our primary outcome was a composite of stillbirth and neonatal morbidity, which could potentially limit the ability either to determine whether a single outcome within the composite drives the results or to detect the impact of low UA PI on specific neonatal morbidities. However, we included all individual morbidities within the composite as secondary outcomes and found no difference between low UA PI and normal PI for each individual morbidities. Second, there were no stillbirths identified in our study population of IUGR pregnancies. The lack of stillbirth in our cohort could be attributed to patient adherence to a rigorous outpatient surveillance regimen or to our study's exclusion criteria (IUGR pregnancies with absent or reversed diastolic flow were not included). Regardless of the etiology, the lack of stillbirth renders us unable to comment on the association between low versus normal UA PI and stillbirth, though this association is unlikely given we did not find an increase in neonatal morbidity with low UA PI. Finally, though we used appropriate statistical methods and adjusted in our multivariable modeling for all statistically significant demographic factors as well as those which approached significance, the possibility of residual confounding by unmeasured factors like indications for urgent delivery may still remain.

In conclusion, we found that low UA PI is relatively uncommon and is not protective against adverse neonatal morbidity or perinatal outcomes compared to normal UA PI. These findings suggest that low UA PI is clinically insignificant and that clinical management of IUGR pregnancies with these Doppler findings should remain similar to that of IUGR pregnancies with normal UA PI in terms of delivery timing.

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Table 1:

Sociodemographic and obstetric characteristics, stratified by umbilical artery pulsatility index lower than 5th centile or persistently normal

	Umbilical Artery Pulsatility Index (UA PI) <5% (N=25)	UA PI ≥5% and ≤95% (N=100)	P value
Maternal age			
<18 years	0 (0.0%)	4 (4.0%)	0.6
18–34 years	22 (88.0%)	85 (85.0%)	
≥ 35 years	3 (12.0%)	11 (11.0%)	
Maternal race/ethnicity			
Asian	1 (4.0%)	9 (9.0%)	0.3
Black	11 (44.0%)	57 (57.0%)	
Latina	1 (4.0%)	2 (2.0%)	
White	10 (40.0%)	30 (30.0%)	
Multiracial	2 (8.0%)	2 (2.0%)	
Maternal pregestational Body Mass Index (kg/m^2)			
<18.5	2 (8.0%)	7 (7.0%)	1.0
18.5 – 24.9	13 (52.0%)	50 (50.0%)	
25.0 – 29.9	4 (16.0%)	18 (18.0%)	
30.0 – 34.9	3 (12.0%)	12 (12.0%)	
35.0 – 35.9	1 (4.0%)	5 (5.0%)	
40.0 +	2 (8.0%)	8 (8.0%)	
Parity			
1st birth	13 (52.0%)	42 (42.0%)	0.04
2nd to 4th birth	8 (32.0%)	52 (52.0%)	
5th or more birth	4 (16.0%)	6 (6%)	
Tobacco use in pregnancy	3 (12.0%)		
Hypertensive disorders[1]	6 (24.0%)	12 (12.0%)	0.13
Diabetes Mellitus, gestational or pregestational	4 (16.0%)	17 (17.0%)	0.6
Infant sex			
Male	6 (24.0%)	50 (50.0%)	0.02
Betamethasone administration prior to 34 weeks gestation	1 (4.0%)	2 (2.0%)	0.6
Gestational age in weeks at IUGR diagnosis (median (interquartile range (IQR)))	29 (25, 32)	29 (26, 32)	0.9
Gestational age in weeks at delivery (median (IQR))	37 (37, 39)	37 (37, 39)	1.0

Data presented as n (%) unless otherwise stated

[1] Includes chronic hypertension, gestational hypertension with or without severe features, and preeclampsia with or without severe features

Table 2:

Risk of neonatal morbidity and perinatal and obstetric outcomes among intrauterine-growth-restricted infants with umbilical artery pulsatility indices (UA PI) lower than 5th percentile or persistently normal

	UA PI <5% (N=25)	UA PI ≥5% and ≤95% (N=100)	Unadjusted Relative Risks (95% Confidence Interval, CI)	Adjusted Odds Ratio (95% CI)*	p
Composite neonatal morbidity	3 (12.0%)	14 (14.0%)	0.84 (0.22–3.17)	0.89 (0.27, 2.75)	-
Stillbirth	0 (0.0%)	0 (0.0%)	--	--	--
Ventilation	3 (12.0%)	13 (13.0%)	0.91 (0.24, 3.49)	0.93(0.25, 4.11)	-
Neonatal Sepsis	0 (0.0%)	2 (2.0%)	-	-	0.48
Necrotizing enterocolitis	0 (0.0%)	0 (0.0%)	--	--	--
Intraventricular hemorrhage	0 (0.0%)	0 (0.0%)	-	-	-
Secondary Aims					
5-minute APGAR (median (Interquartile range (IQR))	9 (9, 9)	9 (9, 9)	-	-	0.44
Umbilical artery pH (mean ± Standard deviation)	7.24 ± 0.08	7.28 ± 0.06	-	-	0.10
Cesarean delivery	10 (40.0%)	33 (33.0%)	1.35 (0.53, 3.33)	0.94 (0.33, 2.65)	-
Cesarean for fetal distress	4 (16.0%)	5 (5.0%)	3.62 (0.89, 14.63)	2.48 (0.51, 12.10)	-
Interval from diagnosis of IUGR and delivery (median weeks (IQR))	8.0 (6.7, 11.7)	8.0 (5.8, 12.8)	-	-	0.62

Data presented as n (%)

*Adjusted for gestational age at delivery, Betamethasone use, hypertensive disorders, diabetes, infant gender, and maternal tobacco use and race/ethnicity