Detection of small for gestational age in preterm prelabor rupture of membranes by Hadlock versus the Fetal Medicine Foundation growth charts: a prospective cohort study

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Abstract

Objectives: Small for gestational age (SGA) neonates are at increased risk for adverse outcomes, which is also common in pregnancies with preterm prelabor rupture of membranes (PPROM). The primary outcome was to compare the diagnostic accuracy for neonatal SGA by the Hadlock and the FMF charts in our cohort, followed by the ability to predict composite severe neonatal outcomes. Methods: This study was a secondary analysis of a prospective cohort of pregnancies with PPROM from 2015 to 2018, from 23 to 36 completed weeks of gestation. Sensitivity, specificity, and positive and negative predictive values were compared as well as receiver operating curves (AUC). Results: Of the 106 women who met inclusion criteria, 48 (45%) screened positive with the FMF fetal growth chart and 22 (21%) screened positive with the Hadlock chart. SGA was diagnosed in 12 infants (11%). Both fetal growth charts had a comparable diagnostic accuracy and were statistically significant predictors of SGA, Hadlock: AUC: 0.76, RR 7.6 95% CI (2.5- 23), FMF: AUC: 0.76 RR 1.8-13.3 95% CI (1.8 – 99.3). Both growth standards were poor predictors of severe neonatal outcomes. Conclusion: The Hadlock and the FMF fetal growth charts are accurate predictors of SGA in pregnancies complicated by PPROM. The FMF fetal growth chart may result in a two-fold increase of positive screens, potentially increasing fetal surveillance. We acknowledge the need for more diverse studies to corroborate our results and identify the optimal fetal growth standard to detect SGA and severe neonatal outcomes in pregnancies with PPROM.

Introduction

Small for gestational age (SGA) neonates refers to those with a birthweight $< 10^{\text{th}}$ percentile for gestational age.(1) These infants are at increased risk for adverse outcomes(2, 3) and this condition appears to complicate pregnancies with preterm labor and preterm prelabor rupture of membranes more often than uncomplicated pregnancies.(4, 5) Therefore, the accurate prediction of SGA will assist in creating surveillance protocols to reduce such adverse outcomes.(6)

The prevalence of fetal growth restriction (FGR) varies according to the definition used. In the United States the most commonly used definition is an estimated fetal weight $< 10^{\text{th}}$percentile for gestational age, however this definition will most likely include those that are constitutional small.(7) Therefore, a new definition of FGR based on the Delphi criteria has been proposed by a group of international experts,(8) But a recent study found that the implementation of this definition was not associated with adverse outcomes when compared to the definition endorse by ACOG.(9)

The ability to detect SGA by the EFW, varies according the formula used to calculate the EFW and the fetal growth chart utilized to assign the EFW percentile according gestational age. (10-12)

The Hadlock et al(13) formula is the most commonly used method to calculate the EFW, as it appears to be an accurate predictor of the birtweight.(10)

Multiple studies have attempted to identify the most accurate fetal growth chart, and most of their results suggest that none of the recently developed charts appears to be superior to the Hadlock et al(14) growth chart in predicting SGA.(11, 15-17)

Despite the accuracy of the EFW to predict the birthweight, there is a discrepancy between fetal growth charts and neonatal growth charts, specially, in the preterm period.(18, 19) This lack of correlation is most likely due to the inclusion of multiple risk factors that are associated with both FGR and prematurity.(20) To solve this matter, the Fetal Medicine Foundation (FMF) developed a unified fetal and neonatal growth chart.(21) However, this chart has not been validated in specific obstetrical populations, such as PPROM.Thus, our aim was to compare the detection accuracy for SGA by the Hadlock fetal weight chart versus the Fetal Medicine Foundation (FMF) fetal and neonatal weight chart in pregnancies complicated by PPROM.

Methods

This study was a secondary analysis of a prospective cohort of pregnancies complicated by PPROM managed in our institution from October 2015 to June 2018.

The University of Tennessee Health Science Center Institutional Review Board approved our study protocol (XP15-04083).

Inclusion criteria included singleton pregnancies of mothers from 13-46 years of age, from 23-36+6 weeks of gestation, with an EFW within two weeks prior to delivery. We excluded pregnancies with complex fetal anomalies and those with fetal demise. PPROM was diagnosed by a combination of history, physical examination, biochemical, microscopic, and ultrasonographic findings. All included participants signed informed consent. Demographic and clinical characteristics including maternal age, parity, self-reported race, body mass index (BMI) at presentation, gestational age at PPROM, presence of hypertension, diabetes, chorioamnionitis, latency, gestational age at delivery, birthweight (BW) were extracted from maternal medical records. Neonatal outcomes such as the presence of respiratory distress (RDS), grade III- IV intraventricular hemorrhage (IVH), neonatal sepsis, necrotizing enterocolitis stage 2 and 3 (NEC), and neonatal death, were obtained from the infant electronic medical records.

The primary outcome of this study was to calculate and compared the diagnostic accuracy for neonatal SGA by the Hadlock and the FMF charts in our cohort.

SGA was suspected when the estimated fetal weight (EFW) was $<10^{\text{th}}$ percentile by the Hadlock and FMF charts (FGR). Neonatal SGA was diagnosed with a birthweight $<10^{\text{th}}$ percentile based on the Alexander et al(22) BW chart.

The secondary outcome was to compare the ability of FGR by both growth charts to predict a composite of severe neonatal outcomes (SNO) when at least one of the following were diagnosed: RDS, IVH, NEC, neonatal sepsis, and perinatal death.

We also calculated the rate accuracy of the FMF fetal growth chart to diagnosed SGA utilizing the proposed FMF neonatal birthweight chart. (23) The rate of SGA utilizing this approach was also obtained. In this study RDS was defined as having clinical and radiologic evidence of surfactant deficiency,(24) grade III and IV IVH was defined according to the Papille et al(25) classification, necrotizing enterocolitis stage 2 and 3 was defined according to Bell's staging,(26) neonatal sepsis was confirmed with positive blood cultures, and perinatal death was comprised of deaths occurring from 20 weeks of gestation to the first year of life.

Ultrasound assessments were performed using a GE Voluson E8 by a maternal-fetal medicine fellow or an obstetrics and gynecology resident. The EFW was calculated every 2 weeks utilizing the Hadlock et al formula.(13)

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Statistical analysis

Statistical analysis was performed using STATA 15 (StataCorp., College Station, TX, USA). Categorical data were compared usingX^2 test or Fischer exact as appropriate and was presented as number (%). For continuous variables distribution of the data was judged by the Skewness and Kurtosis test. Wilcoxon rank sum test was used for statistical analysis when the data was not normally distributed; the continuous variables are presented as median and interquartile ranges.

The risk ratios (RR) and 95% CI were estimated using the non SGA group as the reference group. Sensitivity, specificity, and positive and negative predictive values for the primary and secondary outcomes using these fetal weight standards were calculated. The discriminatory ability of each fetal growth chart was compared using area under receiver operating characteristic curves (AUC). A p value $< .05$ was consider significant.

Results

A total of 127 women were treated for PPROM in our institution during the study time period. Of these, 106 women met inclusion criteria and were included in analysis (Table 1). All of our patients completed at least one course of betamethasone prior to delivery. Among these, 48 (45%) screened positive with the FMF fetal growth chart and 22 (21%) screened positive for SGA by the Hadlock method (RR 7.6 95%CI: 2.4 -24.3; $p < .001$). SGA was diagnosed in 12 infants (11%). Both fetal growth charts were statistically significant predictors of SGA, Hadlock: AUC = .76, RR 7.6 95%CI: 2.5- 23; $p < .001$, FMF: AUC: .76 RR 1.8-13.3 95% CI: 1.8 – 99.3; $p = < .001$. The diagnostic accuracy for SGA of the Hadlock fetal growth chart was similar to the FMF fetal growth chart (Figure 3). The sensitivity, specificity, positive and negative predictive values are presented in Table 2. Four SGA neonates were missed with the Hadlock fetal growth chart, and only one SGA was missed with the FMF fetal growth chart.

For our secondary outcomes, FGR by the Hadlock and FMF fetal growth chart had similar poor prediction ability for the composite of severe neonatal outcomes (Hadlock: AUC: .51, RR: .84 95%CI: .5-1.6 vs. FMF: ROC: .56 RR: 1.6 95%CI: .7-3.5; p = .23) (Figure 3). SNO complicated only two of the 12 SGA infants (17%) vs. 40 (42%) of the infants with appropriate weight for gestational age (AGA); RR .4 95% CI: .1-1.4; p = .012. Both of the SGA infants with SNO had RDS and one was also diagnosed with NEC.

SGA would have been diagnosed in 39% of our participant when both the fetal and neonatal FMF growth charts vs. 11% utilizing the Alexander birthweight growth chart (RR= 3.3 95% CI: 2.3-4: $p = < .001$). The FMF fetal chart was a statistically significant predictor of SGA defined by the FMF neonatal standard (AUC: .74, RR: 3.5 95% CI: 2- 6.2; $p = < .001$), but the FMF neonatal standard was not accurate predictor for the composite of neonatal outcomes (AUC: .56 RR:1.3 95%CI: .8-2.1; p = .23). The sensitivity, specificity, positive, and negative predictive value accuracy of the FMF standards are presented in Table 2.

Discussion

Main Findings

In this cohort study of pregnancies with PPROM, SGA was diagnosed in 11% of the infants and we found that both the Hadlock and the FMF fetal growth charts are accurate predictors of SGA. However, the rate of FGR with the FMF was 45% versus 21% with the Hadlock chart. Both fetal growth standards were not statistically significant predictors of severe neonatal outcomes, but only 2 of the 12 SGA neonates were complicated by severe neonatal outcomes.

We have previously reported the rate of FGR (21%) in this cohort of pregnancies with PPROM.(27) The rate of FGR and SGA in PPROM depends on the definition, population, gestational age, and weight chart utilized. In a large multicenter randomized trial that included more than 1800 pregnancies with PPROM from 34-36 weeks of gestation randomized to immediate delivery versus expectant management, an SGA rate of 3.6% was reported. (28) Another large multi-center observational study from France that included 702 gestations, evaluating the effect of the duration of latency in pregnancies with PPROM from 24-32 weeks, only reported on those with birthweight $< 3^{rd}$percentile (7.5% of their cohort).(29) Neither of these studies

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described which weight charts were used. A small cohort from Italy of 69 pregnancies with PPROM form 24-31 weeks reported rates of FGR of 39% and SGA rates of 26%.(30) and they utilized an Italian neonatal birthweight chart.(31)

Interpretation

On the question of what chart to use to predict SGA, this still remains unclear. In theory, the optimal fetal growth chart will not only accurately detect SGA but will also identify those with adverse outcomes among those to screen positive. A retrospective cohort from New Mexico that included over 1500 women concluded that the Hadlock fetal growth chart was superior to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) race/ethnicity-specific standard for the prediction of both neonatal morbidity and small for gestational age.(15) While another single center retrospective study from Detroit that included 3437 African American mothers, reported that the NICHD race specific weight standard was superior to the Hadlock and other weight charts for the prediction of adverse outcomes in SGA infants.(11) Another study from two institutions compared the Hadlock fetal chart with the NTERGROWTH-21st Century growth and they concluded that although the Hadlock may chart may have a superior ability to predict SGA, none of these charts were accurate predictors of adverse neonatal outcomes.(16)

Strengths and limitations

In our study, the Hadlock and the FMF growth charts were not accurate predictors of severe neonatal outcomes. However, we recognize the lack of power to detect such difference.

Other limitations of our study include that we only assessed the ability of two of the many fetal growth standards described in the literature,(32-34) nevertheless, we included the Hadlock chart, as is the one utilized in our institution and similar studies have also compared two standards.

We also acknowledge that our study participant number is inferior to other studies(11, 15, 16)and it was carry out in a single institution. Therefore, our results may not generalizable to other populations. However, we evaluated the accuracy of these growth charts only in pregnancies complicated by PPROM that only complicates 2-3% of the obstetrical population.(35)

Our strengths include that for our first outcome we included the detection SGA in a population where this diagnosis has been associated with an increased risk for infant morbidity and mortality.(36, 37) In addition, the evaluated adverse neonatal outcomes in our secondary outcomes have been previously validated and known to cause severe morbidity and mortality in premature infants.(36, 38). In our cohort we did not appreciate an association with SGA and SNO.

Conclusion

In conclusion, it appears that both the Hadlock and the FMF fetal growth charts are accurate predictors of SGA in pregnancies complicated by PPROM, but the use of the FMF fetal growth chart may result in a two-fold increase of positive screens, potentially increasing fetal surveillance in these patients. We acknowledge the need for more diverse studies to corroborate our results and identify the optimal fetal growth standard to detect SGA and severe adverse neonatal outcomes in pregnancies with PPROM.

Disclosure of Interests

The authors have no conflict of interest to report.

Contribution to Authorship

JD, first author and corresponding author was participated on enrollment, performed the ultrasounds, designed the study, and drafted parts of the manuscript. KL Drafted the manuscript and tables and GV performed the statistical analysis and review of the manuscript.

Detail on ethics approval

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The University of Tennessee Health Science Center Institutional Review Board approved our study protocol (XP15-04083) on October, 2015.

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Figure legends:

Fig 1. Table 1: Demographic and obstetric characteristics

Fig 2. Table 2: Small for gestational age (SGA) and severe neonatal outcomes (SNO)

Fig 3. Graph: Area under the receiver-operating-characteristics curves (AUC) for the prediction small for gestational age (SGA) and severe neonatal outcomes (SNO) by Fetal Medicine Foundation (FGR FMF) and the Hadlock fetal growth chart (FGR Hadlock)

Fig 4. Study population flowchart

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`Table 1. OB characteristcs SGA PPROM.docx` available at https://authorea.com/users/317883/articles/447952-detection-of-small-for-gestational-age-in-preterm-prelabor-rupture-of-membranes-by-hadlock-versus-the-fetal-medicine-foundation-growth-charts-a-prospective-cohort-study

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