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Isolated Short Femur Length on Mid-Trimester Ultrasound: A Marker for Fetal Growth Restriction and Other Adverse Perinatal Outcomes

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Abstract

Objective—To estimate the association between isolated mid-trimester short femur length (FL) and fetal growth restriction (FGR) as well as other adverse perinatal outcomes.

Methods—A retrospective cohort study of patients with singleton gestations presenting for ultrasound between 16-24 weeks' gestation from 1990-2009. Cases of aneuploidy, skeletal dysplasia and major anomalies were excluded. Short FL was defined as FL<10th percentile for gestational age (GA). Short FL was considered isolated when both the estimated fetal weight and abdominal circumference were >10th percentile for GA. Isolated short FL<5th percentile was also evaluated. The primary outcome was FGR defined as birth weight <10th percentile. Secondary outcomes included pre-eclampsia and preterm birth (PTB) <37 weeks and <34 weeks. Univariable and multivariable logistic regression analyses were used to estimate the risk of these outcomes in fetuses with isolated short FL.

Results—Of 73,884 patients, 569 (0.8%) had a fetus with a FL<10th percentile. Of these, 268 (47.1%) were isolated. 210 patients (0.3%) had a fetus with a FL<5th percentile, of which 34 (16.2%) were isolated. Both isolated short FL<10th percentile and <5th percentile were associated with an increased risk for FGR. (<10th percentile: aOR 3.4, 95% CI 2.4-4.6; <5th percentile: aOR 4.6, 95% CI 2.0-10.7). Isolated short FL<10th percentile and <5th percentile were also associated with an increased risk for PTB <37 weeks and <34 weeks. There was no significant association between isolated short FL and pre-eclampsia.

Conclusions—Isolated short FL on second-trimester ultrasound is associated with a greater than 3-fold increased risk for FGR as well as an increased risk for PTB. Serial growth assessment may be warranted in these cases.

Keywords

short femur length; fetal growth restriction; pre-eclampsia; preterm birth

Introduction

Given that measurement of fetal biometry is a standard component of the second-trimester anatomic survey, identification of a short femur length (FL) on mid-trimester ultrasound is not an atypical finding. While this could represent a normal variant, a short FL also may indicate inaccurate pregnancy dating or could be a marker for aneuploidy, congenital

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malformations, skeletal dysplasia, or early-onset fetal growth restriction (FGR).[1-4] In the absence of these conditions, there is limited data available to guide patient counseling regarding the implication of isolated short FL found at the time of anatomic survey.

It has been suggested that an isolated short FL may be an early marker of placental dysfunction as highly oxygenated fetal blood is preferentially shunted toward vital organs such as the heart and lungs at the expense of the extremities.[5] Additionally, the abnormal placenta may secrete altered levels of growth factors which are involved in normal fetal skeletal development.[6] Prior studies have suggested an association between mid-trimester short FL and the subsequent development of FGR; however, these studies have been mostly limited to case series and small observational studies.[5,7-9] Furthermore, the majority of these studies have not evaluated the association between short FL and other disorders of placental dysfunction such as pre-eclampsia and preterm birth (PTB). The objective of this study was to estimate the association between isolated short FL on mid-trimester ultrasound and the subsequent development of FGR and other adverse perinatal outcomes using a large ultrasound and genetics database.

Materials and Methods

This was a retrospective cohort study of all consecutive, singleton gestations between 16 and 24 weeks presenting to Washington University Medical Center between 1990 and 2009. Approval from the institutional review board was obtained. Maternal demographic information, obstetrical history, maternal medical co-morbidities, ultrasound findings, pregnancy complications, and neonatal outcomes were extracted from our ultrasound and genetics database. This database was created in 1990 and has been maintained by dedicated nurse outcome coordinators. All pregnancy and ultrasound data is entered prospectively at the time of ultrasound exam for patients seen at our institution. Neonatal outcome information is obtained through review of electronic medical records, questionnaire, and telephone contact with the patient or referring provider if necessary. All ultrasound exams were performed by registered diagnostic medical sonographers certified in obstetrics, and all exams were interpreted by maternal-fetal medicine specialists. All pregnancies were dated by last menstrual period (LMP) if consistent with a prior first-trimester ultrasound (± 7 days) or by crown-rump length measurement if it was not consistent with menstrual dating. For patients who did not have a first-trimester ultrasound performed, menstrual dating was used if it was consistent (± 14 days) with second-trimester biometry. Cases of aneuploidy, skeletal dysplasia, and other major congenital malformations, diagnosed either prenatally or postnatally, were excluded.

Our primary exposures included isolated short FL <10^{th} percentile and <5^{th} percentile for gestational age at the time of anatomic survey. Femur length was measured according to standards from the American Institute of Ultrasound in Medicine Practice Guidelines for the Performance of Obstetrical Ultrasound Examinations. Only the femoral diaphysis length was included in the measurement with the beam of insonation perpendicular to the femoral shaft. This measurement technique remained consistent throughout the study period. A short femur was considered isolated when both the abdominal circumference and estimated fetal weight measured greater than the 10^{th} percentile for gestational age. All gestational age-specific biometry values were determined by standards derived by Hadlock.[10] Management of isolated short femur length was left to the discretion of the patient's provider.

Our primary outcome of interest was FGR, defined as infant birth weight <10^{th} percentile for gestational age. Secondary outcomes included pre-eclampsia, intrauterine fetal demise (IUFD), PTB <37 weeks' gestation, and PTB <34 weeks' gestation. Pre-eclampsia was defined as blood pressure of ≥140 mm Hg systolic and/or 90 mm Hg diastolic on two or

more occasions with proteinuria of 300 mg or more in a 24 hour urine specimen occurring after 20 weeks' gestation in a woman with previously normal blood pressure. If a 24-hour urine sample was not available, proteinuria was diagnosed as 1+ or greater on urine dipstick.[11] IUFD was defined as fetal death ≥20 weeks' gestation.

Baseline maternal characteristics as well as the incidence of the primary and secondary outcomes were compared between patients with an isolated short FL <10th or <5th percentile and patients with a normal FL. Student's t-tests were used to compare continuous variables, and chi-squared and Fisher's exact tests were used to compare categorical variables, as appropriate. Univariable analysis was then used to estimate the relative risk (RR) of the primary and secondary outcomes. Multivariable logistic regression analysis was used to obtain adjusted odds ratios (aOR) and their 95% confidence intervals (CI), accounting for potential confounders identified both historically and as significant in the univariable analysis. Logistic regression models were produced using a backward, stepwise elimination method. Analyses stratified by the presence and absence of FGR were then performed to further refine risk estimates for our secondary outcomes. P-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA 10, Special Edition (College Station, TX).

Results

Our study cohort consisted of 76,453 patients. After excluding patients with aneuploidy, skeletal dysplasia, major congenital anomalies, and incomplete pregnancy outcome data, 73,884 patients remained for analysis. 569 (0.8%) patients had a short FL measuring <10th percentile, of which 268 (47.1%) were isolated. 210 (0.3%) patients had a short FL measuring <5th percentile, of which 34 (16.2%) were isolated. There were 5,259 cases of FGR in the study cohort, for an overall incidence of 7.1%. The most common indication for ultrasound was routine anatomic survey (48.3%) followed by advanced maternal age (21.5%), abnormal serum screen (8.8%), history of prior child with a congenital anomaly (2.9%), suspected fetal anomaly (2.6%), and history of teratogen exposure (1.4%). The remaining 14.5% of ultrasound exams were performed for a variety of other less common indications.

On average, patients with a normal FL measuring ≥10th percentile were similar to patients with an isolated short FL <10th percentile with regard to maternal age, gravidity, parity, and baseline incidence of chronic hypertension and pre-gestational diabetes. However, patients with an isolated short FL <10th percentile were more likely to be Caucasian and were more likely to report a history of tobacco use. Patients with an isolated short FL <10th percentile were also more likely to be diagnosed with this finding at an earlier gestational age and more likely to be delivered at an earlier gestational age. (Table 1) The incidence of isolated short FL <10th percentile was 0.43% from 1990-1999 and 0.31% from 2000-2009. The incidence of isolated short FL <5th percentile was 0.05% from 1990-1999 and 0.04% from 2000-2009.

Patients with an isolated short FL <10th percentile were at least three times more likely to develop FGR later in pregnancy compared to patients with a normal FL after controlling for chronic hypertension, African American race, pre-gestational diabetes and tobacco use. (21.5% vs. 8.3%; aOR 3.4, 95% CI 2.4-4.6) Patients with an isolated short FL <10th percentile were also more likely to experience preterm delivery at <37 weeks (17.7% vs. 11.4%; aOR 1.8, 95% CI 1.3-2.5) and preterm delivery at <34 weeks (10.3% vs. 2.9%; aOR 4.6, 95% CI 3.0-7.0) after controlling for chronic hypertension, African American race, and pre-gestational diabetes. There was no statistically significant increased risk for pre-

eclampsia in patients with an isolated short FL <10th percentile compared to patients with a normal FL. (Table 2)

Given the association between FGR and indicated PTB, a stratified analysis based on the presence or absence of FGR was performed to further refine the observed association between isolated short FL and PTB. In patients with FGR, there remained a statistically significant association between isolated short FL<10th percentile and both PTB <37 weeks and <34 weeks. In patients without FGR, there still remained a significant association between isolated short FL <10th percentile and PTB <34 weeks; however, there was no longer an association observed between isolated short FL <10th percentile and PTB <37 weeks. (Table 3) In the absence of FGR, it is still possible that patients with PTB <34 weeks represent a more severe end of the spectrum of placental dysfunction compared to patients with PTB <37 weeks and, therefore, manifest signs of early placental dysfunction such as isolated short FL. The findings from this stratified analysis suggest that the association between isolated short FL<10th percentile and PTB <34 weeks is independent of FGR.

Similar findings were observed for isolated short FL <5th percentile. Isolated short FL <5th percentile was associated with a significantly increased risk for FGR and preterm delivery <37 weeks and <34 weeks. For FGR, the magnitude of risk was overall similar for isolated short FL <10th percentile and <5th percentile; however, for PTB, the magnitude of risk was significantly higher in the setting of an isolated short FL <5th percentile compared to an isolated short FL <10th%ile. Again, there was no significant association observed between isolated short FL <5th percentile and pre-eclampsia. (Table 4) Given the relatively small number of patients with isolated short FL <5th percentile, a stratified analysis based on FGR could not reliably be performed.

There was a higher incidence of IUFD in fetuses with isolated short FL <10th percentile (3.36% v. 0.64%, p<0.001) and isolated short FL <5th percentile (8.82% v. 0.69%) compared to fetuses with normal femur length. Of these IUFD cases, 5 of 9 with isolated short FL <10th percentile and 2 of 3 with isolated short FL <5th percentile were also growth-restricted.

Discussion

Findings from our large cohort confirm the association between isolated short FL on mid-trimester ultrasound and FGR and also suggest a novel association between isolated short FL and PTB. This association with early PTB <34 weeks appears to be independent of FGR and also increases in magnitude as the measurement of short FL decreases. Our study also demonstrated a higher incidence of IUFD in patients with isolated short FL; however, given the absolute small number of cases, we were unable to determine if this finding is independent of FGR. In 2004, Todras *et al.* followed 86 pregnancies with a short FL <10th percentile diagnosed at the time of anatomic survey and noted that 21% of these patients subsequently developed FGR. On average, FGR was diagnosed approximately 9 weeks after the initial finding of a short FL.[7] In 2008, Weisz *et al.* used a stricter definition of isolated short FL <5th percentile and similarly demonstrated an increased risk for FGR (OR 3.0, 95% CI 1.5-5.9); however, no difference in the incidence of PTB was observed in that study when comparing fetuses with isolated short FL to those with normal FL.[5] Prior studies evaluating the association between isolated short FL and pre-eclampsia have been conflicting. In a small retrospective observational study, Zalel *et al.* observed that seven of nine patients with an isolated short FL developed pregnancy-induced hypertension.[6] Todras *et al.* observed a 19% incidence of pre-eclampsia in 46 structurally normal fetuses with an isolated short FL; however, all of those patients also were diagnosed with FGR.[7] Consistent with our findings, more recent, larger observational cohort studies have demonstrated no

statistically significant increased risk hypertensive complications of pregnancy in patients with an isolated short FL.[5,9]

One potential mechanism for our findings is that abnormal placentation leads to altered secretion of fibroblast growth factor 2 (FGF-2). FGF-2 is normally secreted by the human placenta and plays a role in skeletal development. Altered secretion of this growth factor could result in inhibition of long bone growth in the fetus.[6,12] Another potential mechanism involves the fetal adaptive response to chronic hypoxia in which highly oxygenated blood is shunted toward vital fetal organs such as the brain and heart at the expense of the extremities. A short FL may represent the earliest sign of this adaptive response observed in cases of placental insufficiency.[5] Although pre-eclampsia is a recognized syndrome of placental dysfunction, it is possible that pre-eclampsia results in altered secretion of a distinctive profile of placental factors which does not include FGF-2. This could explain the lack of association found between isolated short FL and pre-eclampsia in our study. The biologic mechanism underlying the association between short FL and PTB is less clear; however, abnormal placentation has more recently been shown to play a role in the pathogenesis of PTB as well. As in the case of FGR, short FL may be an early sign of abnormal placentation and placental insufficiency, thereby providing biologic plausibility to the association observed between short FL and early PTB.[13,14]

Findings from this study certainly have potential clinical implications for the management of these pregnancies. Given the association between isolated short FL and FGR, repeat ultrasound for fetal growth during the third trimester may be warranted. As our study was not designed to evaluate the timing of FGR development in these fetuses, it is not possible to draw a conclusion regarding the ideal gestational age at which to perform a single repeat growth assessment or if serial ultrasound evaluations throughout the third trimester are necessary. For the association observed between isolated short FL and PTB, heightened clinical awareness for signs and symptoms of preterm labor certainly are warranted. Future studies regarding the performance of other PTB screening and prevention strategies in this particular group of patients may provide more information on the appropriate clinical management of these patients.

To date, this is the largest study evaluating the association between isolated short FL and adverse perinatal outcomes. Given the large sample size derived from our robust ultrasound and genetics database, we were able to evaluate the definitions of both short FL $<10^{th}$ percentile and $<5^{th}$ percentile as well as provide quantitative estimates of risk, adjusting for potential confounding factors. Additionally, we were able to reliably evaluate only cases of *isolated* short FL by excluding all patients with aneuploidy, congenital anomalies, skeletal dysplasias, and early-onset FGR.

Limitations of our study include its retrospective design and its inherent potential for misclassification bias; however, our perinatal database is maintained by dedicated nurse outcome coordinators and the follow-up system in our center has been well-validated in previous studies, making the possibility for misclassification minimal.[15,16] This study took place over a 19 year period, and ultrasound exams were performed by multiple sonographers using a variety of different ultrasound machines. While this could be viewed as a limitation, we believe this also contributes to the generalizability of our findings. When dividing our cohort in half, we observed a comparable number of cases of isolated short FL diagnosed in both study periods, indicating that this diagnosis has remained stable over time despite advances in ultrasound practice and technology. Despite our large cohort, the finding of an isolated short FL was still relatively rare, thereby limiting some aspects of our analysis. The small number of cases of isolated short FL $<5^{th}$ percentile precluded stratified analyses and also resulted in risk estimates with wide confidence intervals. Additionally, we were unable

to completely separate spontaneous and indicated PTB using our perinatal database; however, we were able to stratify based on FGR, a common indication for preterm delivery. The combination of spontaneous and indicated PTB into a single category certainly creates a potentially heterogeneous outcome with contributions from both known and unknown confounders; however, more recent data suggests that spontaneous and indicated PTB may have a similar underlying pathophysiology, therefore making this distinction less essential.[17] Finally, while our population did include multiple ethnic groups, our study cohort was still primarily comprised of Caucasians. It has been suggested that race-specific definitions of short FL may improve the discriminatory value in setting of Down syndrome screening; however, this has not been demonstrated in our patient population.[18]

In conclusion, the finding of an isolated short FL <10^{th} or <5^{th} percentile at the time of mid-trimester ultrasound is associated with a greater than 3-fold increased risk for the subsequent development of FGR as well as an increased risk for PTB <34 and <37 weeks. An isolated short FL may be the first identifiable biometric marker for placental insufficiency. Repeat ultrasound for fetal growth as well as heightened awareness of signs and symptoms of preterm labor should be considered in cases of isolated short FL identified at the time of anatomic survey.

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Table 1

Maternal demographics and pregnancy characteristics comparing patients with isolated short femur <10th%ile to those with a femur length ≥10th%ile

	Isolated Femur Length <10th%ile (n=268)	Femur Length ≥10^{tho}%ile (n=73,345)	p-value
Maternal Age (years)	30.5 ± 6.2	29.8 ± 6.4	0.07
Gestational Age at Ultrasound (weeks)	18.5 ± 1.6	19.2 ± 1.7	<0.001
Gravidity	2.6 ± 1.6	2.7 ± 1.6	0.54
Parity	1.0 ± 1.3	1.0 ± 1.2	0.96
Maternal Race			<0.001
Caucasian	75.3%	59.2%	
African American	9.1%	25.5%	
Hispanic	1.1%	1.1%	
Asian	1.1%	0.9%	
Other	13.4%	13.3%	
Tobacco Use	19.4%	11.7%	<0.001
History of Chronic Hypertension	2.2%	2.5%	0.81
History of Pre-Gestational Diabetes	3.4%	1.8%	0.06
Gestational Age at Delivery (weeks)	36.6 ± 6.7	38.5 ± 3.7	<0.001

Table 2

Unadjusted and Adjusted Risk Estimates for Adverse Outcomes in Fetuses With an Isolated Short Femur Length <10th percentile for Gestational Age

Outcome	Isolated FL <10th%ile (n=268)	FL ≥10th%ile (n=73,345)	Unadjusted RR (95% CI)	aOR (95% CI)	p-value
FGR (n=5,259)	21.5%	8.3%	2.6 (2.0-3.3)	3.4* (2.4-4.6)	<0.001
Pre-Eclampsia (n=5,166)	8.4%	8.0%	1.0 (0.7-1.6)	----	0.85
PTB <37 Weeks (n=7,421)	17.7%	11.4%	1.5 (1.2-2.0)	1.8¶ (1.3-2.5)	0.001
PTB <34 Weeks (n=1,948)	10.3%	2.9%	3.5 (2.4-5.2)	4.6¶ (3.0-7.0)	<0.001

FL=femur length; FGR=fetal growth restriction; PTB=preterm birth; RR=relative risk; CI=confidence interval; aOR=adjusted odds ratio

*Adjusted for chronic hypertension, black race, diabetes, tobacco use

¶Adjusted for chronic hypertension, black race, diabetes

Table 3

Unadjusted and Adjusted Risk Estimates for Preterm Delivery Stratified by FGR

Outcome	Isolated FL <10th%ile (n=268)	FL ≥10th%ile (n=73,345)	Unadjusted RR (95% CI)	aOR (95% CI)	p-value
FGR Present (n=5,259)					
PTB <37 weeks (n=1,166)	40.8%	21.8%	1.9 (1.3-2.6)	2.9 * (1.6-5.2)	0.001
PTB <34 weeks (n=530)	28.6%	9.5%	3.0 (1.9-4.7)	4.7 * (2.5-8.8)	<0.001
No FGR (n=68,354)					
PTB <37 weeks (n=6,255)	11.2%	10.5%	1.1 (0.7-1.6)	---	0.750
PTB <34 weeks (n=1,418)	5.6%	2.4%	2.4 (1.3-4.3)	2.8 * (1.4-5.3)	0.004

FL=femur length; PTB=preterm birth; FGR=fetal growth restriction; RR=relative risk; CI=confidence interval; aOR=adjusted odds ratio

*Adjusted for chronic hypertension, black race, and diabetes

Table 4

Unadjusted and Adjusted Risk Estimates for Adverse Outcomes in Fetuses With an Isolated Short Femur Length <5th Percentile for Gestational Age

Outcome	Isolated FL <5th%ile (n=34)	FL ≥5th%ile (n=73,674)	Unadjusted RR (95% CI)	aOR (95% CI)	p-value
FGR (n=5,207)	29.6%	8.4%	3.5 (2.0-6.3)	4.6* (2.0-10.7)	<0.001
Pre-Eclampsia (n=5,155)	15.1%	8.1%	1.9 (0.8-4.2)	---	0.18
PTB <37 Weeks (n=7,391)	34.6%	11.4%	3.0 (1.8-5.1)	4.3¶ (1.9-9.8)	0.002
PTB <34 Weeks (n=1,924)	30.8%	3.0%	10.4 (5.8-18.5)	17.8¶ (7.7-41.6)	<0.001

FL=femur length; FGR=fetal growth restriction; PTB=preterm birth; RR=relative risk; CI=confidence interval; aOR=adjusted odds ratio

*Adjusted for chronic hypertension, black race, diabetes, tobacco use

¶Adjusted for chronic hypertension, black race, diabetes