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Isolated Short Femur Length on Second-Trimester Sonography

A Marker for Fetal Growth Restriction and Other Adverse Perinatal Outcomes

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Objectives—To estimate the association between isolated second-trimester short femur length and fetal growth restriction as well as other adverse perinatal outcomes.

Methods—We conducted a retrospective cohort study of patients with singleton gestations presenting for sonography between 16 and 24 weeks' gestation from 1990 to 2009. Cases of aneuploidy, skeletal dysplasia, and major anomalies were excluded. Short femur length was defined as length below the 10th percentile for gestational age and was considered isolated when both the estimated fetal weight and abdominal circumference were above the 10th percentile for gestational age. Isolated short femur length below the 5th percentile was also evaluated. The primary outcome was fetal growth restriction, defined as birth weight below the 10th percentile. Secondary outcomes included preeclampsia and preterm birth before 37 and 34 weeks. Univariable and multivariable logistic regression analyses were used to estimate the risk of these outcomes in fetuses with isolated short femur length.

Results—Of 73,884 patients, 569 (0.8%) had a fetus with a femur length below the 10th percentile, of which 268 (47.1%) were isolated; 210 patients (0.3%) had a fetus with a femur length below the 5th percentile, of which 34 (16.2%) were isolated. Isolated short femur lengths below the 10th and 5th percentiles were associated with an increased risk of fetal growth restriction (<10th: adjusted odds ratio [aOR], 3.4; 95% confidence interval [CI], 2.4–4.6; <5th: aOR, 4.6; 95% CI, 2.0–10.7) and also with an increased risk of preterm birth before 37 and 34 weeks. There was no significant association between isolated short femur length and preeclampsia.

Conclusions—Isolated short femur length on second-trimester sonography is associated with a greater than 3-fold increased risk of fetal growth restriction and an increased risk of preterm birth. Serial growth assessment may be warranted in these cases.

Key Words—fetal growth restriction; preeclampsia; preterm birth; short femur length

Given that fetal biometric measurement is a standard component of the second-trimester anatomic survey, identification of a short femur length on second-trimester sonography is not an atypical finding. Although it could represent a normal variant, a short femur length also may indicate inaccurate pregnancy dating or could be a marker for aneuploidy, congenital malformations, skeletal dysplasia, or early-onset fetal growth restriction.^{1–4} In the absence of these conditions, there are limited data available to guide patient counseling regarding the implication of an isolated short femur length found at the time of the anatomic survey.

It has been suggested that an isolated short femur length 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 In addition, 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 second-trimester short femur length and the subsequent development of fetal growth restriction; however, these studies have been mostly limited to case series and small observational studies.^{5,7-9} Furthermore, most of these studies have not evaluated the association between short femur length and other disorders of placental dysfunction such as preeclampsia and preterm birth. The objective of this study was to estimate the association between isolated short femur length on second-trimester sonography and the subsequent development of fetal growth restriction and other adverse perinatal outcomes using a large sonography and genetics database.

Materials and Methods

We conducted 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, obstetric history, maternal medical comorbidities, sonographic findings, pregnancy complications, and neonatal outcomes were extracted from our sonography and genetics database. This database was created in 1990 and has been maintained by dedicated nurse outcome coordinators. All pregnancy and sonographic data are entered prospectively at the time of the sonographic examination for patients seen at our institution. Neonatal outcome information is obtained through review of electronic medical records, questionnaires, and telephone contact with the patient or referring provider if necessary. All sonographic examinations were performed by registered diagnostic medical sonographers certified in obstetrics, and all examinations were interpreted by maternal-fetal medicine specialists. All pregnancies were dated by the last menstrual period if consistent with a prior first-trimester sonographic examination (± 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 sonographic examination, menstrual dating was used if it was consistent (± 14 days) with second-trimester biometric measurements. Cases of aneuploidy, skeletal dysplasia, and other major congenital malformations, diagnosed either prenatally or postnatally, were excluded.

Our primary exposures included isolated short femur length below the 10th and 5th percentiles for gestational age at the time of the anatomic survey. Femur length was measured according to standards from the "AIUM Practice Guideline for the Performance of Obstetric Ultrasound Examinations."¹⁰ 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 above the 10th percentile for gestational age. All gestational age-specific biometric values were determined by standards derived by Hadlock et al.¹¹ Management of the isolated short femur length was left to the discretion of the patient's provider.

Our primary outcome of interest was fetal growth restriction, defined as birth weight below the 10th percentile for gestational age. Secondary outcomes included preeclampsia, intrauterine fetal death, and preterm birth before 37 and 34 weeks' gestation. Preeclampsia was defined as blood pressure of 140 mm Hg or higher (systolic), 90 mm Hg or higher (diastolic), or both on 2 or more occasions with proteinuria of 300 mg or greater 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 a urine dipstick.¹² Intrauterine fetal death was defined as fetal death at or after 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 femur length below the 10th or 5th percentile and patients with a normal femur length. Student *t* tests were used to compare continuous variables, and χ^2 and Fisher exact tests were used to compare categorical variables, as appropriate. Univariable analysis was then used to estimate the relative risk of the primary and secondary outcomes. Multivariable logistic regression analysis was used to obtain adjusted odds ratios and their 95% confidence intervals, 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 fetal growth restriction were then performed to further refine risk estimates for our secondary outcomes. $P < .05$ was considered statistically significant. All statistical analyses were performed using STATA 10 Special Edition software (StataCorp, College Station, TX).

Results

Our study cohort consisted of 76,453 patients. After patients with aneuploidy, skeletal dysplasia, major congenital anomalies, and incomplete pregnancy outcome data were excluded, 73,884 patients remained for analysis. A total of 569 patients (0.8%) had a short femur length measuring below the 10th percentile, of which 268 (47.1%) were isolated; 210 patients (0.3%) had a short femur length measuring below the 5th percentile, of which 34 (16.2%) were isolated. There were 5259 cases of fetal growth restriction in the study cohort, for an overall incidence of 7.1%. The most common indication for sonography was a routine anatomic survey (48.3%), followed by advanced maternal age (21.5%), abnormal serum screen results (8.8%), history of a child with a congenital anomaly (2.9%), suspected fetal anomalies (2.6%), and history of teratogen exposure (1.4%). The remaining 14.5% of sonographic examinations were performed for a variety of other less common indications.

On average, patients with a normal femur length at or above 10th percentile were similar to patients with an isolated short femur length below the 10th percentile with regard to maternal age, gravidity, parity, and baseline incidence of chronic hypertension and pregestational diabetes. However, patients with an isolated short femur length below the 10th percentile were more likely to be white and were more likely to report a history of tobacco use. Patients with an isolated short femur length below the 10th percentile were also more likely to have a diagnosis of this finding at an earlier gestational age and more likely to be delivered at an

earlier gestational age (Table 1). The incidence rates of isolated short femur length below the 10th percentile were 0.43% from 1990 to 1999 and 0.31% from 2000 to 2009. The incidence rates of isolated short femur length below the 5th percentile were 0.05% from 1990 to 1999 and 0.04% from 2000 to 2009.

Patients with an isolated short femur length below the 10th percentile were at least 3 times more likely to have fetal growth restriction later in pregnancy compared to patients with a normal femur length after controlling for chronic hypertension, African American race, pregestational diabetes, and tobacco use (Table 2). Patients with an isolated short femur length below the 10th percentile were also more likely to have preterm delivery before 37 and 34 weeks (Table 2) after controlling for chronic hypertension, African American race, and pregestational diabetes. There was no statistically significant increased risk of preeclampsia in patients with an isolated short femur length below the 10th percentile compared to patients with a normal femur length (Table 2).

Given the association between fetal growth restriction and indicated preterm birth, a stratified analysis based on the presence or absence of fetal growth restriction was performed to further refine the observed association between isolated short femur length and preterm birth. In patients with fetal growth restriction, there remained a statistically significant association between isolated short femur length below the 10th percentile and both preterm birth before 37 and 34 weeks. In patients without fetal growth restriction, there still remained a significant association between isolated short femur length below the 10th percentile and

Table 1. Maternal Demographics and Pregnancy Characteristics Comparing Patients With an Isolated Short Femur Length Below the 10th Percentile to Those With a Femur Length at or Above the 10th Percentile

Characteristic	Isolated FL <10th (n = 268)	FL ≥10th (n = 73,345)	P
Maternal age, y	30.5 ± 6.2	29.8 ± 6.4	.07
Gestational age at sonography, wk	18.5 ± 1.6	19.2 ± 1.7	<.001
Gravidity	2.6 ± 1.6	2.7 ± 1.6	.54
Parity	1.0 ± 1.3	1.0 ± 1.2	.96
Maternal race, %			
White	75.3	59.2	<.001
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	<.001
History of chronic hypertension, %	2.2	2.5	.81
History of pregestational diabetes, %	3.4	1.8	.06
Gestational age at delivery, wk	36.6 ± 6.7	38.5 ± 3.7	<.001

Values are mean ± SD where applicable. FL indicates femur length.

preterm birth before 34 weeks; however, there was no longer an association observed between isolated short femur length below the 10th percentile and preterm birth before 37 weeks (Table 3). In the absence of fetal growth restriction, it is still possible that patients with preterm birth before 34 weeks represent a more severe end of the spectrum of placental dysfunction compared to patients with preterm birth before 37 weeks and therefore manifest signs of early placental dysfunction such as isolated short femur length. The findings from this stratified analysis suggest that the association between isolated short femur length below the 10th percentile and preterm birth before 34 weeks is independent of fetal growth restriction.

Similar findings were observed for isolated short femur length below the 5th percentile, which was associated with a significantly increased risk of fetal growth restriction and preterm delivery before 37 and 34 weeks. For fetal growth restriction, the magnitude of risk was overall similar for isolated short femur length below the 10th and

5th percentiles; however, for preterm birth, the magnitude of risk was significantly higher in the setting of isolated short femur length below the 5th percentile compared to isolated short femur length below the 10th percentile. Again, there was no significant association observed between isolated short femur length below the 5th percentile and preeclampsia (Table 4). Given the relatively small number of patients with an isolated short femur length below the 5th percentile, a stratified analysis based on fetal growth restriction could not reliably be performed.

There was a higher incidence of intrauterine death in fetuses with an isolated short femur length below the 10th percentile (3.36% versus 0.64%; $P < .001$) and an isolated short femur length below the 5th percentile (8.82% versus 0.69%) compared to fetuses with a normal femur length. Of these intrauterine fetal death cases, 5 of 9 with an isolated short femur length below the 10th percentile and 2 of 3 with an isolated short femur length below the 5th percentile were also growth restricted.

Table 2. Unadjusted and Adjusted Risk Estimates for Adverse Outcomes in Fetuses With an Isolated Short Femur Length Below the 10th Percentile for Gestational Age

Outcome	Isolated FL <10th (n = 268)	FL ≥10th (n = 73,345)	Unadjusted RR (95% CI)	aOR (95% CI)	P
FGR, % (n = 5,259)	21.5	8.3	2.6 (2.0–3.3)	3.4 ^a (2.4–4.6)	<.001
Preeclampsia, % (n = 5,166)	8.4	8.0	1.0 (0.7–1.6)	ND	.85
PTB <37 wk, % (n = 7,421)	17.7	11.4	1.5 (1.2–2.0)	1.8 ^b (1.3–2.5)	.001
PTB <34 wk, % (n = 1,948)	10.3	2.9	3.5 (2.4–5.2)	4.6 ^b (3.0–7.0)	<.001

aOR indicates adjusted odds ratio; CI, confidence interval; FGR, fetal growth restriction; FL, femur length; ND, not determined; PTB, preterm birth; and RR, relative risk.

^aAdjusted for chronic hypertension, African American race, diabetes, and tobacco use.

^bAdjusted for chronic hypertension, African American race, and diabetes

Table 3. Unadjusted and Adjusted Risk Estimates for Preterm Birth Stratified by Fetal Growth Restriction

Outcome	Isolated FL <10th (n = 268)	FL ≥10th (n = 73,345)	Unadjusted RR (95% CI)	aOR (95% CI)	P
FGR (n = 5,259)					
PTB <37 wk, % (n = 1,166)	40.8	21.8	1.9 (1.3–2.6)	2.9 ^a (1.6–5.2)	.001
PTB <34 wk, % (n = 530)	28.6	9.5	3.0 (1.9–4.7)	4.7 ^a (2.5–8.8)	<.001
No FGR (n = 68,354)					
PTB <37 wk, % (n = 6,255)	11.2	10.5	1.1 (0.7–1.6)	ND	.750
PTB <34 wk, % (n = 1,948)	5.6	2.4	2.4 (1.3–4.3)	2.8 ^a (1.4–5.3)	.004

Abbreviations are as in Table 2.

^aAdjusted for chronic hypertension, African American race, and diabetes.

Discussion

Findings from our large cohort confirm the association between isolated short femur length on second-trimester sonography and fetal growth restriction and also suggest a novel association between isolated short femur length and preterm birth. This association with early preterm birth before 34 weeks appears to be independent of fetal growth restriction and also increases in magnitude as the short femur length measurement decreases. Our study also showed a higher incidence of intrauterine fetal death in patients with an isolated short femur length; however, given the absolute small number of cases, we were unable to determine whether this finding was independent of fetal growth restriction. In 2004, Todros et al⁷ followed 86 pregnancies with a short femur length below the 10th percentile diagnosed at the time of the anatomic survey and noted that 21% of these patients subsequently had fetal growth restriction. On average, fetal growth restriction was diagnosed approximately 9 weeks after the initial finding of a short femur length.⁷ In 2008, Weisz et al⁵ used a stricter definition of isolated short femur length below the 5th percentile and similarly showed an increased risk of fetal growth restriction (odds ratio, 3.0; 95% confidence interval, 1.5–5.9); however, no difference in the incidence of preterm birth was observed in that study when comparing fetuses with an isolated short femur length to those with a normal femur length. Prior studies evaluating the association between isolated short femur length and preeclampsia have been conflicting. In a small retrospective observational study, Zalel et al⁶ observed that 7 of 9 patients with an isolated short femur length had pregnancy-induced hypertension. Todros et al⁷ observed a 19% incidence of preeclampsia in 46 structurally normal fetuses with an isolated short femur length; however, all of those patients also

had a diagnosis of fetal growth restriction. Consistent with our findings, more recent larger observational cohort studies have shown no statistically significant increased risk of hypertensive complications of pregnancy in patients with an isolated short femur length.^{5,9}

One potential mechanism for our findings is that abnormal placentation leads to altered secretion of fibroblast growth factor 2, which 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.^{6,13} 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. Short femur length may represent the earliest sign of this adaptive response observed in cases of placental insufficiency.⁵ Although preeclampsia is a recognized syndrome of placental dysfunction, it is possible that preeclampsia results in altered secretion of a distinctive profile of placental factors that do not include fibroblast growth factor 2, which could explain the lack of association found between isolated short femur length and preeclampsia in our study. The biological mechanism underlying the association between short femur length and preterm birth is less clear; however, abnormal placentation has more recently been shown to play a role in the pathogenesis of preterm birth as well. As in the case of fetal growth restriction, short femur length may be an early sign of abnormal placentation and placental insufficiency, thereby providing biological plausibility to the association observed between short femur length and early preterm birth.^{14,15}

Findings from this study certainly have potential clinical implications for the management of these pregnancies. Given the association between isolated short femur

Table 4. Unadjusted and Adjusted Risk Estimates for Adverse Outcomes in Fetuses With an Isolated Short Femur Length Below the 5th Percentile for Gestational Age

Outcome	Isolated FL <5th (n = 34)	FL ≥5th (n = 73,674)	Unadjusted RR (95% CI)	aOR (95% CI)	P
FGR, % (n = 5,207)	29.6	8.4	3.5 (2.0–6.3)	4.6 ^a (2.0–10.7)	<.001
Preeclampsia, % (n = 5,155)	15.1	8.1	1.9 (0.8–4.2)	ND	.18
PTB <37 wk, % (n = 7,391)	34.6	11.4	3.0 (1.8–5.1)	4.3 ^b (1.9–9.8)	.002
PTB <34 wk, % (n = 1,924)	30.8	3.0	10.4 (5.8–18.5)	17.8 ^b (7.7–41.6)	<.001

Abbreviations are as in Table 2.

^aAdjusted for chronic hypertension, African American race, diabetes, and tobacco use.

^bAdjusted for chronic hypertension, African American race, and diabetes.

length and fetal growth restriction, repeated sonography for fetal growth during the third trimester may be warranted. Because our study was not designed to evaluate the timing of fetal growth restriction development in these fetuses, it is not possible to draw a conclusion regarding the ideal gestational age at which to perform a single repeated growth assessment or whether serial sonographic evaluations throughout the third trimester are necessary. For the association observed between isolated short femur length and preterm birth, heightened clinical awareness of signs and symptoms of preterm labor certainly is warranted. Future studies regarding the performance of other preterm birth screening and prevention strategies in this particular group of patients may provide more information on the appropriate clinical management.

To our knowledge, this is the largest study to date evaluating the association between isolated short femur length and adverse perinatal outcomes. Given the large sample size derived from our robust sonography and genetics database, we were able to evaluate the definitions of both short femur length below the 10th percentile and short femur length below the 5th percentile as well as provide quantitative estimates of risk, adjusting for potential confounding factors. In addition, we were able to reliably evaluate only cases of isolated short femur length by excluding all patients with aneuploidy, congenital anomalies, skeletal dysplasias, and early-onset fetal growth restriction.

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.^{16,17} This study took place over a 19-year period, and sonographic examinations were performed by multiple sonographers using a variety of different ultrasound machines. Although this factor could be viewed as a limitation, we believe it also contributes to the generalizability of our findings. When dividing our cohort in half, we observed a comparable number of cases of isolated short femur length diagnosed in both study periods, indicating that this diagnosis has remained stable over time despite advances in sonography practice and technology. Despite our large cohort, the finding of an isolated short femur length was still relatively rare, thereby limiting some aspects of our analysis. The small number of cases of isolated short femur length below the 5th percentile precluded stratified analyses and also resulted in risk estimates with wide confidence intervals. In addition, we were unable to completely separate spontaneous and indicated preterm birth using our

perinatal database; however, we were able to stratify on the basis of fetal growth restriction, a common indication for preterm delivery. The combination of spontaneous and indicated preterm birth into a single category certainly creates a potentially heterogeneous outcome with contributions from both known and unknown confounders; however, more recent data suggest that spontaneous and indicated preterm birth may have similar underlying pathophysiologic characteristics, therefore making this distinction less essential.¹⁸ Finally, although our population did include multiple ethnic groups, our study cohort was still primarily composed of white patients. It has been suggested that race-specific definitions of short femur length may improve its discriminatory value in the setting of Down syndrome screening; however, that association has not been shown in our patient population.¹⁹

In conclusion, the finding of isolated short femur length below the 10th or 5th percentile at the time of second-trimester sonography is associated with a greater than 3-fold increased risk of the subsequent development of fetal growth restriction as well as an increased risk of preterm birth before 34 and 37 weeks. Isolated short femur length may be the first identifiable biometric marker for placental insufficiency. Repeated sonography for fetal growth as well as heightened awareness of signs and symptoms of preterm labor should be considered in cases of isolated short femur length identified at the time of the anatomic survey.

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