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Short Femur in the Second Trimester Scan Is Related to Maternal Preeclampsia and Small for Gestational Age Newborns

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Keywords
Short femur length · Second trimester scan · Preeclampsia · Small for gestational age

Abstract
Objective: To determine the contribution of short femur diaphysis length (FDL) at 19–22 weeks of gestation in the prediction of adverse pregnancy outcomes. ***Methods:*** The study included singleton pregnant women who underwent a routine anomaly scan at 19–22 weeks of gestation at the Virgen de la Arrixaca University Clinical Hospital (Murcia, Spain) between August 2011 and August 2012. Fetal biometry and Doppler ultrasound of uterine arteries were assessed as part of the anomaly scan, and the mean pulsatility index of both uterine arteries was recorded. Maternal obstetric characteristics, such as ethnicity, age, weight, parity, cigarette smoking, and medical history including hypertension and diabetes mellitus were collected from our database system. ***Results:*** A total of 6,366 women were included in the study after excluding cases with abnormal karyotype, major fetal abnormalities, or termination of pregnancy. There were 88 cases of preeclampsia (PE) (1.4%). Logistic regression was performed including maternal and fetal characteristics. Short FDL at 19–22 weeks was significantly associated with subsequent development of PE (OR = 0.89, 95% CI: 0.80–0.99, $p = 0.025$). The best model to predict PE from our sample included gestational age at scan, parity, maternal weight, chronic hypertension, mean pulsatility index in the uterine arteries, and FDL (AUC = 0.78, 95% CI: 0.71–0.84). Regarding small for gestational age (SGA) neonates, there were also significant differences in FDL and FDL <5th centile between the control group and SGA newborns below the 3rd, 5th, and 10th centile. In the groups of preterm births (delivery before 32, 34, and 37 weeks), there were no differences in FDL compared with the control group (term births). ***Discussion:*** Our results suggest that FDL at 19–22 weeks of gestation is an independent predictor of PE and SGA newborns.

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Introduction

Preeclampsia (PE) and fetal growth restriction constitute two of the major complications during pregnancy, being the main contributors of maternal and fetal morbidity and mortality [1].

Femur length is routinely measured during the second trimester anomaly scan to determine gestational age and the estimated fetal weight in combination with biparietal diameter, abdominal circumference, and head circumference [2]. The detection of a short femur length, particularly below the 5th centile is often a diagnostic dilemma. It might be associated with fetal growth restriction at the time of the ultrasound examination [3, 4] or it could be associated with fetal anomalies such as skeletal dysplasia [5]. Some authors have pointed it out as a marker of chromosomal abnormalities such as trisomy 21 [6–9], trisomy 18 [10], or trisomy 13 [11], and it is also associated with other genetic abnormalities. However, a short femur is likely to be a normal variant in a constitutionally small fetus, especially when it is an isolated finding [12].

Recent studies have reported the association of short femur length in the second trimester and subsequent placental related conditions [13], such as PE, small for gestational age (SGA), low birth weight, and preterm birth [14–21].

Here, we aim to determine the association of an isolated short femur in the second trimester anomaly scan with placenta-related adverse outcomes, such as the subsequent development of PE, SGA, and preterm delivery.

Materials and Methods

Study Population and Clinical Measurements

This was a retrospective study including pregnant women undergoing a routine fetal anatomy scan at 19–22 weeks of gestation at the Virgen de la Arrixaca University Clinical Hospital (Murcia, Spain) between August 2011 and August 2012. Maternal obstetric characteristics, such as ethnicity, age, weight, parity, cigarette smoking, and medical history including chronic hypertension and diabetes mellitus were collected from our database (ViewPoint, Webling, Germany). Gestational age was determined from the measurement of fetal crown–rump length at 11–13 weeks [22]. Outcomes were recorded from labor ward and hospital notes. Exclusion criteria were fetal malformations, aneuploidy, spontaneous fetal loss discovered during the second trimester ultrasound scan, termination of pregnancy, and multiple pregnancy.

Ultrasound Examination

Routine anomaly and Doppler ultrasound examinations were performed by obstetricians with more than 5 years of experience and certified by the Fetal Medicine Foundation of London (www.fetalmedicine.com) using ultrasound equipment (Voluson 730 Expert; GE Medical Systems, Austria). Fetal biometry was recorded including measurements of fetal head circumference, abdominal circumference, and femur diaphysis length (FDL). Fetal weight was estimated from these measurements using the Hadlock formulae [23]. FDL and abdominal circumference centiles were calculated as described by Snijders and Nicolaides [24]. To adjust FDL by gestational age at the time of the scan, z-score values were calculated using the reference tables of the Institute of Child Health of London according to Chitty et al. [25]. Uterine artery pulsatility index (UtA-PI) was measured by transabdominal ultrasound as previously described by Albaiges et al. [26] and the mean of the two values was recorded. Isolated short femur was defined as femur length below the 5th centile for gestational age in a fetus with more than the 10th centile at the time of the ultrasound examination.

Outcomes

The primary outcome was PE. PE was defined as de novo hypertension arising after 20 weeks of gestation, returning to normal

Table 1. Comparison of the PE group and control group (non-PE)

Variables	PE		*p* value
	no (n = 6,278)	yes (n = 88)	
Age, years	30.8±5.5	31.8±6.6	**0.1823**
Ethnicity			
Caucasian	6,188 (98.6)	88 (100)	
Other	90 (1.43)	0	0.258
Conception			
Spontaneous	6,050 (96.4)	83 (94.3)	
In vitro fertilization	228 (3.6)	5 (5.7)	0.309
Previous hypertension	24 (0.4)	6 (6.8)	**<0.001**
Smoking	934 (14.9)	6 (6.8)	**0.034**
Parity			
Nulliparous	3,104 (49.4)	56 (63.6)	
Para 1	2,275 (36.2)	23 (26.1)	
Para ≥2	899 (14.3)	9 (10.2)	**0.030**
FL, mm	34.1±2.6	33.2±2.6	**0.001**
FL z-score	0.45±0.98	0.15±1.12	**0.008**
UtA-PI	1.01±0.3	1.30±0.5	**<0.001**
FL <5th centile	165 (2.6)	8 (9.1)	**<0.001**
AC <5th centile	119 (1.9)	1 (1.1)	0 .600
GA at delivery, weeks	39.4±1.8	36.5±4.0	**<0.001**
Birth weight, g	3,311±521	2,591±970	**<0.001**
SGA			
<10th centile	690 (11.0)	26 (29.6)	**<0.001**
<5th centile	368 (5.9)	20 (22.7)	**<0.001**
<3rd centile	230 (3.7)	20 (22.7)	**<0.001**
Delivery			
Vaginal	5,077 (80.9)	27 (31.0)	
Elective cesarean section	520 (8.3)	14 (16.1)	
Urgent cesarean section	677 (10.8)	46 (52.9)	**<0.001**
Intrauterine death	51 (0.8)	4 (4.6)	**<0.001**

Data are expressed as mean ± SD or n (%) as appropriate. PE, preeclampsia; FL, femur length; UtA-PI, uterine artery pulsatility index; AC, abdominal circumference; GA, gestational age; SGA, small for gestational age. $p < 0.05$ by t test or χ^2 tests.

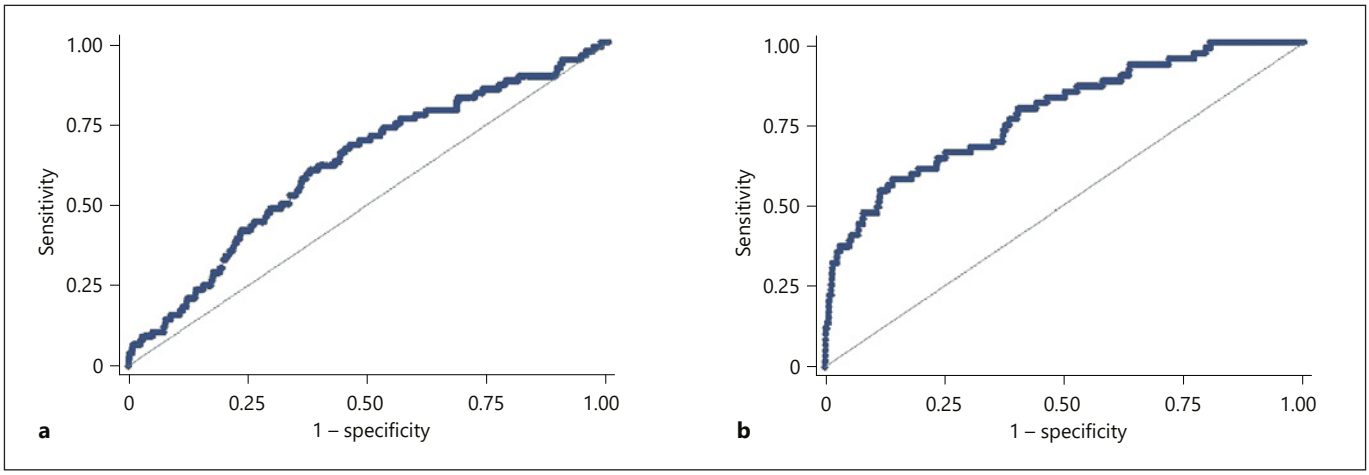

Fig. 1. ROC curves for femur diaphysis length (mm) in the second trimester scan and presence of PE. **a** Logistic regression model based on FDL and gestational age at scan. **b** Logistic regression model based on the combination of FDL, gestational age at scan, parity, chronic hypertension, mean UtA-PI, maternal weight, and cigarette smoking.

in the postpartum, with proteinuria according to the criteria of the International Society for the Study of Hypertension in Pregnancy [27]. The secondary outcomes were: (1) SGA neonates, classified according to birth weight below the 3rd, 5th, and 10th centile at any gestational age [28], and (2) preterm birth (delivery before 37 weeks of gestation).

Statistical Analysis

Descriptive statistics are shown using raw data. Continuous variables are summarized by arithmetic mean and standard deviation, and categorical variables are shown as number and percentage. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Parametric and nonparametric data were compared using the unpaired Student *t* test and Mann-Whitney U test, respectively. The χ^2 test was used for categorical variables. Univariate logistic regression analysis was used to determine the unadjusted odds ratios (ORs) of FDL (mm) for PE and SGA. Multiple logistic regression analysis was performed for variables with statistically significant ORs in the univariate analysis to calculate the adjusted ORs and determine the independent effect of FDL on PE and SGA, incorporating maternal covariates including gestational age at scan, age, ethnicity, conception, parity, previous hypertension, and cigarette smoking, and mean UtA-PI was measured by transabdominal Doppler ultrasound.

Additionally, receiver operating characteristic (ROC) analyses were undertaken to evaluate the predictive accuracy of the adjusted models. Analyses were performed with the statistical software STATA 13.1 version (StataCorp LP, College Station, TX, USA). All tests were two-tailed at 0.05 significance level.

Results

A total of 6,366 women between 19 and 22 weeks of gestation were included in the study after excluding cases with abnormal karyotype, mayor fetal abnormalities, or termination of pregnancy. Eighty-eight patients developed PE (1.4%). There were 690 women who delivered SGA neonates below the 10th centile (11.2%), 368 below the 5th centile (5.8%), and 230 (3.7%) below the 3rd centile, not associated with PE. Demographic details and obstetric characteristics of patients with PE compared to non-PE women are shown in Table 1. There were no differences in maternal age, conception, or ethnicity between the PE group and the control group (non-PE). Women who developed PE had more frequently previous hypertension ($p < 0.001$), smoking status ($p = 0.03$), and low parity ($p = 0.03$) than those who did not. Patients with PE presented significantly higher UtA-PI ($p < 0.001$) than the control group. Additionally, gestational age and birth weight at delivery were significantly lower in women with PE than in the control group. The rate of urgent cesarean section, intrauterine death, and SGA (below 10th, 5th, and 3rd centile) were significantly higher in the PE group. Furthermore, patients with PE presented significantly shorter FDL (mm) and z-score FDL than women without PE ($p < 0.001$ and $p = 0.008$, respectively). FDL (mm), assessed as a quantitative variable, was an independent predictor of PE in the univariate (OR = 0.87, 95% CI: 0.80–0.94, $p = 0.001$) and multivariate analysis (OR = 0.87, 95% CI: 0.77–0.99, $p = 0.025$). After multivariate analysis, the best model to predict PE in our population included gestational age at scan, parity (primiparous women), previous hypertension, mean UtA-PI, maternal weight, cigarette smoking, and FDL at the routine scan at 19–22 weeks. ROC analysis shows good predictive capacity for the model including all the covariates (AUC = 0.78, 95%

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Table 2. Characteristics and outcomes of the SGA fetuses

Variables	SGA								
	<3th centile			<5th centile			<10th centile		
	no (n = 6,041)	yes (n = 230)	p	no (n = 5,903)	yes (n = 368)	p	no (n = 5,581)	yes (n = 690)	p
Age, years	30.87±5.53	30.11±5.67	**0.042**	30.84±5.53	30.69±5.69	0.590	30.87±5.51	30.51±5.74	0.1064
Ethnicity									
Caucasian	5,954 (98.56)	227 (98.7)		5,817 (98.54)	364 (98.91)		5,497 (98.49)	684 (99.13)	
Other	87 (1.44)	3 (1.30)	0.865	86 (1.46)	4 (1.09)	0.563	84 (1.51)	6 (0.87)	0.185
Conception									
Spontaneous	5,821 (96.36)	222 (96.52)		5,690 (96.39)	353 (95.92)		5,381 (96.42)	662 (95.94)	
In vitro fertilization	220 (3.64)	8 (3.48)	0.897	213 (3.61)	15 (4.08)	0.642	200 (3.58)	28 (4.06)	0.530
Previous hypertension	22 (0.36)	2 (0.87)	0.223	20 (0.34)	4 (1.09)	**0.024**	17 (0.3)	7 (1.01)	**0.004**
Smoking	852 (14.1)	81 (35.22)	**<0.001**	819 (13.87)	114 (30.98)	**<0.001**	745 (13.35)	188 (27.25)	**<0.001**
Parity									
Nulliparous	2,960 (49)	139 (60.43)		2,880 (48.79)	219 (59.51)		2,696 (48.31)	403 (58.41)	
Para 1	2,203 (36.47)	70 (30.43)		2,159 (36.57)	114 (30.98)		2,058 (36.88)	215 (31.16)	
Para ≥2	878 (14.53)	21 (9.13)	**0.002**	864 (14.64)	35 (9.51)	**<0.001**	827 (14.82)	72 (10.43)	**<0.001**
FL, mm	34.2±2.6	33.1±2.5	**<0.001**	34.2±2.6	33.1±2.6	**<0.001**	34.2±2.6	33.3±2.5	**<0.001**
FL z-score	0.46±0.97	−0.071±0.94	**<0.001**	0.48±0.97	−0.03±0.99	**<0.001**	0.50±0.97	0.02±0.95	**<0.001**
UtA-PI	1.01±0.28	1.18±0.39	**<0.001**	1.00±0.27	1.16±0.37	**<0.001**	1.00±0.27	1.13±0.36	**<0.001**
FL <5th centile	149 (2.48)	16 (7.02)	**<0.001**	139 (2.37)	26 (7.12)	**<0.001**	126 (2.27)	39 (5.69)	**<0.001**
AC <5th centile	109 (1.81)	10 (4.37)		101 (1.72)	18 (4.90)	**<0.001**	85 (1.53)	34 (4.93)	**<0.001**
Delivery									
Vaginal	4,901 (81.2)	171 (74.4)		4,794 (81.3)	278 (75.5)		4,525 (81.14)	547 (79.3)	
Elective cesarean section	496 (8.22)	24 (10.4)		484 (8.2)	36 (9.8)		467 (8.37)	53 (7.7)	
Urgent cesarean section	640 (10.6)	35 (15.2)	**0.031**	621 (10.5)	54 (14.7)	**0.019**	585 (10.5)	90 (13)	0.114
Intrauterine death	44 (0.73)	6 (2.61)	**0.002**	43 (0.73)	7 (1.9)	**0.014**	40 (0.72)	10 (1.45)	**0.041**

Data are expressed as mean ± SD or n (%) as appropriate. SGA, small for gestational age; FL, femur length; UtA-PI, uterine artery pulsatility index; AC, abdominal circumference. $p < 0.05$ by t test or χ^2 tests.

Table 3. Characteristics and outcomes of the preterm fetuses

Variables	Preterm birth								
	<32 weeks			<34 weeks			<37 weeks		
	no (n = 6,232)	yes (n = 46)	p	no (n = 6,169)	yes (n = 82)	p	no (n = 5,888)	yes (n = 390)	p
Age, years	30.82±5.5	32.39±6.0	0.0568	30.83±5.53	31.72±6.2	0.1484	30.80±5.52	31.34±5.92	0.0643
Ethnicity									
Caucasian	6,143 (98.57)	45 (97.83)		6,107 (98.56)	81 (98.78)		5,806 (98.61)	382 (97.95)	
Other	89 (1.43)	1 (2.17)	0.672	89 (1.44)	1 (1.22)	0.870	82 (1.39)	8 (2.05)	0.289
Conception									
Spontaneous	6,008 (96.41)	42 (91.3)		5,975 (96.43)	75 (91.46)		5,687 (96.59)	363 (93.08)	
In vitro fertilization	224 (3.59)	4 (8.7)	0.065	221 (3.57)	7 (8.54)	**0.017**	201 (3.41)	27 (6.92)	**<0.001**
Previous hypertension	24 (0.39)	0 (0)	0.673	23 (0.37)	1 (1.22)	0.216	19 (0.32)	5 (1.28)	**0.003**
Smoking	925 (14.24)	9 (19.57)	0.370	919 (14.83)	15 (18.29)	0.382	858 (14.57)	76 (19.49)	**0.008**
Parity									
Nulliparous	3,078 (49.39)	26 (59.52)		3,059 (49.37)	45 (54.88)		2,912 (49.46)	192 (49.23)	
Para 1	2,265 (36.34)	10 (21.74)		2,253 (36.36)	22 (26.83)		2,146 (36.45)	129 (33.08)	
Para ≥2	889 (14.27)	10 (21.74)	0.085	884 (14.27)	15 (18.29)	0.179	830 (14.10)	69 (17.69)	0.108
FL, mm	34.1±2.6	33.8±3.2	0.416	34.1±2.6	33.8±3.0	0.3028	34.1±2.6	34.2±2.7	0.6460
FL z-score	0.45±0.98	0.24±1.17	0.1322	0.45±0.98	0.26±1.16	0.0632	0.45±0.97	0.49±1.13	0.4043
UtA-PI	1.01±0.28	1.16±0.37	**0.0178**	1.01±0.28	1.18±0.41	**0.0017**	1.01±0.26	1.09±0.36	**0.0002**
FL <5th centile	162 (2.61)	3 (6.52)	0.099	161 (2.61)	4 (4.94)	0.194	149 (2.54)	16 (4.12)	0.060
AC <5th centile	119 (1.92)	0 (0)	0.314	119 (1.93)	0 (0)	0.207	113 (1.93)	6 (1.55)	0.599
Birth weight, g	3,327±487.4	1,161.2±491.4	**<0.001**	3,335±476.2	1,507.1±596.5	**<0.001**	3,368±453.8	2,455.3±688.8	**<0.001**
SGA									
<10th centile	680 (10.92)	10 (22.2)	**0.016**	672 (10.9)	18 (22.2)	**0.001**	639 (10.86)	51 (13.11)	0.170
<5th centile	360 (5.78)	8 (17.78)	**0.001**	353 (5.7)	15 (18.5)	**<0.001**	336 (5.71)	32 (8.23)	**0.041**
<3rd centile	223 (3.58)	7 (15.56)	**<0.001**	216 (3.5)	14 (17.3)	**<0.001**	206 (3.5)	24 (6.17)	**0.007**
Delivery									
Vaginal	5,054 (81.15)	23 (50)		5,038 (81.4)	39 (47.6)		4,819 (81.9)	258 (66.15)	
Elective cesarean section	513 (8.24)	7 (15.2)		507 (8.2)	13 (15.85)		464 (7.89)	56 (14.36)	
Urgent cesarean section	661 (10.61)	16 (34.78)	**<0.001**	647 (10.45)	30 (36.59)	**<0.001**	601 (10.21)	76 (19.5)	**<0.001**
Intrauterine death	40 (0.64)	11 (23.91)	**<0.001**	35 (0.56)	16 (19.5)	**<0.001**	30 (0.51)	21 (5.38)	**<0.001**

Data are expressed as mean ± SD or n (%) as appropriate. FL, femur length; UtA-PI, uterine artery pulsatility index; AC, abdominal circumference; SGA, small for gestational age. $p < 0.05$ by t test or χ^2 tests.

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Table 4. Logistic multivariate regression analysis for femur length and PE

	Unadjusted		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Femur diaphysis length	0.87 (0.80–0.94)	0.001	0.87 (0.77–0.99)	0.039
Gestational age at scan	0.58 (0.35–0.97)	0.037	0.80 (0.41–1.55)	0.514
Maternal weight	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	<0.001
Previous hypertension	19.07 (7.59–47.88)	<0.001	11.02 (3.03–40.1)	<0.001
Primiparous	1.79 (1.16–2.77)	0.009	2.27 (1.28–4.01)	0.005
Mean UtA-PI	9.38 (5.36–16.41)	<0.001	9.35 (5.04–17.4)	<0.001
Smoking	0.42 (0.18–0.96)	0.04	0.43 (0.16–1.22)	0.116

PE, preeclampsia; UtA-PI, uterine artery pulsatility index.

Table 5. Logistic univariate and multivariate regression analysis for SGA below the 3rd centile not related with PE

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Femur diaphysis length	0.84 (0.80–0.89)	<0.001	0.79 (0.73–0.86)	<0.001
Gestational age at scan	1.14 (0.87–1.51)	0.337	1.88 (1.31–2.70)	0.001
Primiparous	1.56 (1.21–2.08)	0.001	1.65 (1.19–2.28)	0.003
Mean UtA-PI	5.21 (3.47–7.80)	<0.001	5.02 (3.18–7.93)	<0.001
Smoking	3.31 (2.50–4.38)	<0.001	3.65 (2.41–4.55)	<0.001
Maternal weight	0.98 (0.97–0.99)	<0.001	0.98 (0.96–0.99)	0.007

SGA, small for gestational age; PE, preeclampsia; UtA-PI, uterine artery pulsatility index.

CI: 0.71–0.84; sensitivity = 0.58 and specificity = 0.86) (Fig. 1b). The Hosmer-Lemeshow test confirmed the goodness-of-fit of the model ($p = 0.909$). Figure 1a represents the model which includes only isolated FDL and gestational age at the time of the scan (AUC = 0.62, 95% CI: 0.56–0.68; sensitivity = 0.61 and specificity = 0.62). From the 88 patients who developed PE, 19 cases (21.6%) were early-onset PE (PE requiring delivery before 34 + 0 weeks of gestation). In these patients, FDL and FDL z-score were significantly lower than in the control group (FDL: early-onset PE: 32.7 ± 2.4 mm vs. non-PE: 34.1 ± 2.6 mm, $p = 0.02$; FDL z-scores: early-onset PE: 0.00076 ± 1.08 vs. non-PE: 0.45 ± 0.98, $p = 0.05$). However, after multivariate analysis including potential covariates, this difference did not achieve statistical significance to predict PE before 34 weeks, probably due to the small number of cases.

Regarding to SGA neonates, there were significant differences in parity, mean UtA-PI, FDL (mm), FDL z-score, and FDL <5th centile between the control group and all SGA groups (below the 3rd, 5th, and 10th centile) as shown in Table 2.

In the preterm birth group (Table 3), there were no differences in FDL (mm) and FDL z-scores or in FDL <5th centile compared with the control group. Significant differences were found in mean UtA-PI between the control group and all preterm birth groups (delivery before 32, 34, and 37 weeks).

Univariate analysis revealed that the presence of isolated short femur was associated with a significantly increased risk for SGA below the 10th, 5th and 3rd centiles but not for preterm birth. The presence of an isolated short femur continued to be a risk factor for these conditions in the multiple logistic analysis (Table 4). Adjusted ORs for SGA below the 10th, 5th, and 3rd centile of FDL in the multivariate analysis were 0.88, 0.85, and 0.85, respectively ($p < 0.0001$) (results for the 3rd centile are shown in Table 5).

Discussion

This study was carried out in an unselected population of pregnant women undergoing a routine anomaly scan in the second trimester of pregnancy. Herein, we report that an isolated short femur is associated with a subsequent increased risk of PE and SGA in pregnancy. However, no association with preterm birth was found.

Over the last 10 years, some other authors have reported an association between a short femur and many adverse perinatal outcomes. For instance, Weisz et al. [17] reported an OR of 3.0 (95% CI: 1.5–5.9) for fetal growth restriction and femur below the 5th centile. However, their data were obtained from a high-risk population including fetuses with abnormalities. Similarly, Vermeer and Bekker [14] reported that 43% of their population developed SGA, but the patients were all referred for the finding of a short femur. Here, we add evidence that the risk of developing SGA when a short femur is found is still persistent in a nonselected population. These results are also in agreement with those of a similar cohort in a tertiary referral center [21] and with a recent meta-analysis that confirmed a significant association between isolated short femur length and intrauterine growth restriction or SGA and poor perinatal outcome [29].

Regarding preterm birth, we did not find an association between short femur and preterm birth as previously described by some authors [16, 17]. However, Gaillard et al. [30] have reported in a large cohort study that fetal growth characteristics (including femur length) during the three trimesters of pregnancy (especially the third) were associated with the risk of preterm birth. Other authors have also reported a slow growth velocity of fetal femur and an increased risk of spontaneous preterm birth [31]. These discrepancies could be due to the different mechanisms that determine preterm birth and placental insufficiency. More studies are needed in this area to determine an actual association between preterm birth and fetal growth and the potential mechanisms involved therein.

Regarding PE, not many authors have evaluated the association between FDL and PE. Papageorghiou et al. [15] and Todros et al. [32] observed a mild association between a short femur and PE. However, both studies included a small sample of patients. Aviram et al. [20], in a retrospective study, reported a significant association of short femur with severe PE but not mild PE. Other authors have failed in reporting an association with PE [16, 18]. In our nonselected population, we found after multivariate analysis that the shorter the femur, the higher the risk for developing PE (OR = 0.87, 95% CI: 0.77–0.99).

The mechanism involved in shortening of the femur might be related to the altered placentation and a subsequent abnormal secretion of placental fetal growth factor FGF-2, which is known as a main regulator of the longitudinal growth of bones [33]. Similarly, pregnancy-associated plasma protein-A (PAPP-A) has a role in the regulation of osteoblast proliferation and bone metabolism, by enhancing insulin growth factor bioavailability, and interestingly is found to be decreased in a fetus with short femur [34, 35]. Another mechanism involves intrauterine chronic hypoxia and a subsequent brain-sparing effect with decreased blood flow to the lower body [13]. Therefore, it is possible that short femur is linked to PE by these common mechanisms.

It should be noted that the femur length can be very variable according to the ethnic group. As reported previously, fetuses of Asian women can have shorter femur length than those of non-Asian woman. Similarly, black women can have fetuses with a longer femur compared to white women [36]. However, these ethnic differences were not confirmed by other studies [12]. In this study, the majority of women were Caucasian, and therefore we were unable to examine these potential confounding variables. In addition, maternal and paternal height could play a role in fetal size and femur length [37].

The main strength of our study is the screening population from which adverse pregnancy outcomes were examined. We acknowledge some limitations of our study, such as the retrospective design and failure to distinguish between mild and severe PE. In addition, it should be taken into account that the absolute shift in femur length found here is relatively small and could potentially be compromised by an error in measurement.

In summary, an isolated short FDL is associated with placental-related complications including SGA and PE. Moreover, short FDL may be an early first sign of placental dysfunction and warrants increased antenatal surveillance of fetal growth with closer sonographic follow-up and frequent blood pressure measurements. Further studies are needed to develop accurate counseling and management of these patients.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Virgen de la Arrixaca University Clinical Hospital (Murcia, Spain).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.V: protocol/project development and manuscript writing. M.T.P-S: data collection or management, data analysis, and manuscript writing. J.L.D: data analysis and manuscript editing. M.P, A.L, and RC: data collection or management and manuscript editing. CDPM: protocol/project development and manuscript writing.

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