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SYSTEMATIC REVIEW

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Midtrimester isolated short femur and perinatal outcomes: A systematic review and meta-analysis

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Abstract

Introduction: Fetal femur length below the expected value has been described as a marker of aneuploidy, skeletal dysplasia, intrauterine growth restriction and small-for-gestational-age neonate. The aim of this systematic review and meta-analysis was to evaluate the strength of association between isolated short femur length and intrauterine growth restriction or small-for-gestational-age, and perinatal adverse outcomes.

Material and methods: PubMed, EMBASE and Medline were searched from the inception of each database to May 2018. Selection criteria included prospective and retrospective cohort studies of singleton pregnancies between 18 and 28 weeks of gestation, with sonographic finding of isolated short femur length, without any structural chromosomal abnormality. The meta-analysis was performed by computing odds ratios using both fixed and random-effects models. Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale.

Results: Six studies including 3078 cases of isolated short femur length (study group) and 222 303 normal femur length (control group) were included. The prevalence of intrauterine growth restriction or small-for-gestational-age in the study group was 14.2%, compared with 5.2% in the control group (odds ratio of 4.04, 95% confidence interval 3.63-4.50). Isolated short femur length was associated with a higher incidence of low birthweight (study group: 22.10% vs control group: 8.57%, odds ratio 3.24, 95% confidence interval 2.34-4.48), Apgar <7 at 5 minutes (study group: 3.98% vs control group: 1.79%, odds ratio 3.56, 95% confidence interval 1.87-6.77), preterm birth (study group: 12.16% vs control group: 8.16%, odds ratio 3.09, 95% confidence interval 1.57-6.08), fetal death (study group: 1.83% vs control group: 0.44%, odds ratio 6.48, 95% confidence interval 3.70-11.35) and neonatal intensive care unit admission (study group: 15.34% vs control group: 14.81%, odds ratio 2.11, 95% confidence interval 0.56-7.93).

Conclusions: There is a significant association between isolated short femur length and intrauterine growth restriction or small-for-gestational-age and poor perinatal outcome.

KEYWORDS

intrauterine growth restriction, obstetric outcomes, perinatal outcomes, short fetal femur length, small-for-gestational-age

Abbreviations: CI, confidence interval; FL, femur length; IUG, Rintrauterine growth restriction; NICU, neonatal intensive care unit; NOS, Newcastle-Ottawa Scale; OR, odds ratio; SD, standard deviation; SG, Asmall-for-gestational-age.

1 | INTRODUCTION

Femur length (FL) is the only long bone measurement required by international guidelines during the routine second trimester scan. Careful sonographic assessment of the only ossified portion of the diaphysis is needed to obtain accurate biometry. A short FL has been defined as the presence of a biometric value of fetal FL below the 5th percentile or −2 standard deviations (SD) for gestational age at ultrasound examination.[1] A short FL was also defined as a biparietal diameter to FL ratio above 1.5 SD for gestational age or as observed to expected FL ratio ≤0.91 for gestational age.[2-4] Variations in FL length are present with respect to maternal race. In particular, fetuses of Asian women have a smaller than expected FL than white women in the second trimester, whereas a greater than expected FL is often found in fetuses of black women.[5,6] Short FL may also be explained by ethnic origin and due to inaccurate dating.[7]

The detection of a fetal FL below the expected value might be a diagnostic challenge for the examiner. It is described as a marker of aneuploidy or skeletal dysplasia but is also associated with other genetic abnormalities.[1] More recent studies have suggested that an isolated short femur in the second trimester of pregnancy could be an early marker of intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) neonate,[8-10] but no meta-analysis about this topic is currently present in the literature.

The primary aim of this systematic review and meta-analysis was to evaluate the strength of association between isolated short FL and IUGR or SGA. The secondary aim was to ascertain the relation between isolated short FL and perinatal adverse outcomes.

Key message

Isolated short femur length is associated with intrauterine growth restriction or small-for-gestational-age and poor perinatal outcome, and its early detection may help prenatal counseling. Obstetricians should use a careful approach to the management of these fetuses monitoring these pregnancies in a tertiary center.

2 | MATERIAL AND METHODS

2.1 | Protocol, eligibility criteria, information sources and search strategy

This review was performed according to an a priori designed protocol recommended for systematic review and meta-analyses.[11-13] We extracted relevant citations from PubMed, EMBASE and Medline from the inception of each database to May 2018, to identify English language published articles that described the correlation between short fetal femur and IUGR/SGA. Preliminary keywords and MeSh terms were combined to generate lists of studies: "isolated short fetal femur and IUGR or SGA." No restriction about the date of publication was imposed on our research.

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to perform search strategy and selection processes.[14] Before data extraction, the review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42018089342).

2.2 | Study selection and data extraction

Inclusion criteria for study selection were: singleton pregnancy, minimum and maximum gestational age at examination between 18 and 28 weeks, without any structural chromosomal abnormality. Studies were eligible if they included and described an association between isolated short FL and IUGR or SGA. Short FL was defined as an isolated, sonographic finding of FL below the 5th percentile for gestational age. Studies reporting pregnancy and perinatal outcomes in terms of hypertensive disorders, intrauterine death, preterm birth, Apgar score <7 at 5 minutes, low birthweight, and neonatal intensive care unit (NICU) admission were also included. Prospective and retrospective cohort studies were considered eligible for inclusion if the above criteria were met. Only full-text articles were considered eligible for inclusion; personal communications, case reports, conference abstracts and case series with <3 cases of short FL, irrespective of whether the anomalies were isolated or not, were also excluded to avoid publication bias. Exclusion criteria were: omitting at least one inclusion criterion and data reported in graph or percentage form rather than proportional rates. Two authors (V.D.A. and F.V.) independently reviewed articles and abstracted data. Discordance was resolved with discussion with a third reviewer (A.G.).

2.3 | Assessment of risk of bias

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies (Table 1). According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[15]

2.4 | Data synthesis and outcomes

The primary aim of this systematic review and meta-analysis was to evaluate the strength of association between isolated short FL

TABLE 1 Quality assessment of the included studies, according to Newcastle-Ottawa Scale (NOS). A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability

Study	Year	Selection	Comparability	Outcome
Aviram et al[19]	2015	**	*	**
Goetzinger et al[20]	2012	**	*	**
Mathiesen et al[22]	2013	**	*	**
Mailath-Pokorny et al[9]	2015	***	*	**
Ventura et al[21]	2012	***	*	**
Weisz et al[8]	2008	***	*	**

and IUGR or SGA. The secondary aim was to ascertain the relation between isolated short FL and perinatal adverse outcomes. Statistical analysis was performed using REVIEW MANAGER 5.0 (http://www.cochrane.org).

Extracted results were pooled in a meta-analysis. The meta-analysis was performed by computing odds ratios (ORs) using random-effects model (weighting by inverse of variance). Between-study heterogeneity was assessed using tau^2, χ^2 (Cochrane Q) and I^2 statistics.

Forest plots were used for graphic representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CIs) for each study are displayed as a horizontal line through the box. The pooled OR is symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95% CI of the OR. A significant two-way *P*-value for comparison was defined as $P < 0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $P < 0.1$) and the I^2 value. A value of 0% indicates no observed heterogeneity, whereas I^2 values ≥50% indicate a substantial level of heterogeneity. Given the inherent heterogeneity (different designs and definitions), a random-effect model was used, regardless of the I^2 value.[16] Publication bias was examined using analyses described by Egger et al.[17,18]

3 | RESULTS

3.1 | General characteristics

Our preliminary literature search identified 7278 publications, of which 7265 studies were excluded based on title or abstract. We selected 13 potentially eligible studies. Seven studies were excluded after a careful qualitative analysis; the list of excluded studies and reason for exclusion are available in Supporting Information Table S1. In total, we included six qualifying studies in our analysis (Figure 1).[8,9,19-22] The results of the quality assessment of the included studies using NOS are presented in Table 1. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups and for ascertainment of the outcome of interest.[15] Table 2 shows the characteristics of the six included studies. In four studies, SGA was defined as birthweight below the 10th percentile,[8,9,19,21] in one study SGA was defined as birthweight below −2 SD or less of the expected gestational age.[22] IUGR was considered birthweight below the 10th percentile for gestational age[20] estimated fetal weight or abdominal circumference below the 5th percentile at the midtrimester anomaly scan[8] or abdominal circumference below the 10th percentile.[19]

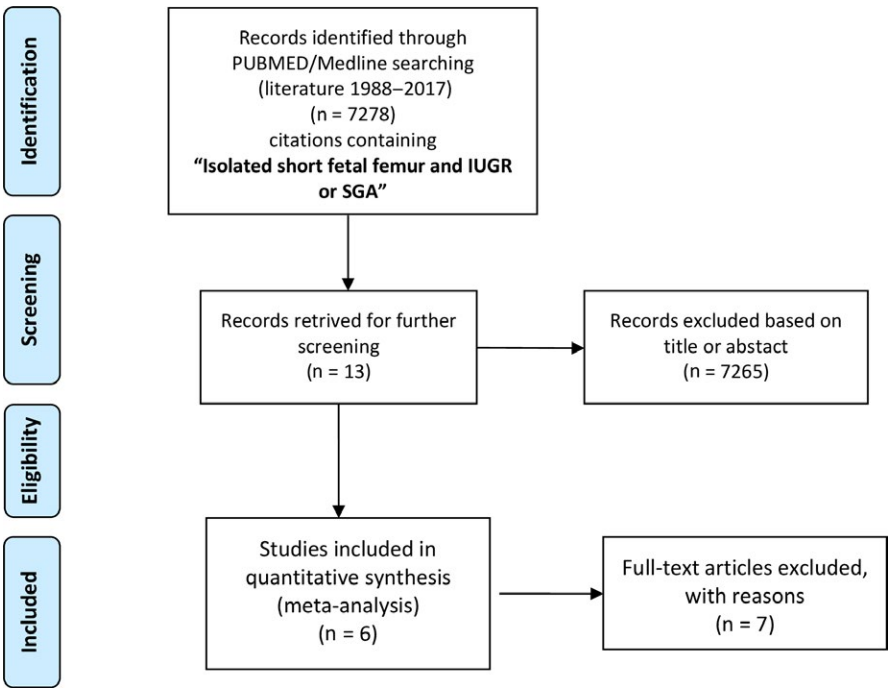

FIGURE 1 Flow chart for study selection. IUGR, intrauterine growth restriction; SGA, small-for-gestational-age [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Characteristics of the included studies

	Aviram et al[19]	Goetzinger et al[20]	Mathiesen et al[22]	Mailath-Pokorny et al[9]	Ventura et al[21]	Weisz et al[8]
Population	Singleton pregnancies between 14 and 28 wk of gestation with FL <5th percentile for gestational age	Singleton pregnancies between 16 and 24 wk of gestation with FL <5th percentile for gestational age	Singleton pregnancies between 17 and 22 wk of gestation with FL <5th percentile for gestational age	Singleton pregnancies between 16 and 24 wk of gestation with FL <5th percentile for gestational age	Singleton pregnancies between 18 and 24 wk of gestation with FL <5th percentile for gestational age	Singleton pregnancies between 18 and 22 wk of gestation with FL <5th percentile for gestational age
Measurement	Midtrimester sonographic measurement of FL	Sonographic measurement of FL	Sonographic measurement of FL	Sonographic measurement of FL	Sonographic measurement of FL	Sonographic measurement of FL
Comparison	FL ≥ 5th percentile for gestational age	FL ≥ 5th percentile for gestational age	FL ≥ 5th percentile for gestational age	FL ≥ 5th percentile for gestational age	FL ≥ 5th percentile for gestational age	FL ≥ 5th percentile for gestational age
Outcomes	Placenta-related complications, including hypertensive disorders, SGA and oligohydramnios; preterm delivery, neonatal outcomes	Fetal growth restriction, preeclampsia, intrauterine fetal death, preterm birth	Miscarriage, stillbirth, preterm birth, SGA	SGA, low birthweight, preterm birth, intrauterine fetal death, low Apgar score at 5 minutes, admission to NICU	SGA, low birthweight, preeclampsia, gestational hypertension, low Apgar score at 5 minutes	SGA, low birthweight, preterm birth, gestational hypertension, low Apgar score at 5 minutes
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective

FL, femur length; NICU, neonatal intensive care unit; SGA, small-for-gestational-age.

3.2 | Synthesis of the results

In these studies, 3078 cases of isolated short fetal femur (study group) and 222 302 cases of normal length fetal femur (control group) were described. The detection rate and the false-positive rate for the ability of short FL to detect cases of IUGR or SGA, were reported for each study.

The overall prevalence of IUGR or SGA in the study group was 14.2% (438/3078), compared with 5.2% in control group (11 634/222 302). Meta-analysis showed a higher incidence of IUGR or SGA in the study group than in the control group with an OR of 4.04 (95% CI 3.63-4.50). The results showed low heterogeneity (0%)[8,9,19-22] (Figure 2). In addition, a higher incidence of perinatal complication was found in fetuses with isolated short femur length: Low birthweight (study group: 22.10% [72/326] vs control group: 8.57% [307/3580])[8,9,19,21] with an OR of 3.24 (95% CI 2.34-4.48) (Figure 3); Apgar <7 at 5 minutes (study group: 3.98% [13/326] vs control group: 1.79% [64/3580]) with an OR of 3.56 (95% CI 1.87-6.77)[8,9,19,21] (Figure 4); preterm birth (study group: 12.16% [367/3017] vs control group: 8.16% [18 140/222 119]) with an OR of 3.09 (95% CI 1.57-6.08)[8,9,19,20,22] (Figure 5); fetal demise (study group: 1.83% [52/2837] vs control group: 0.44% [962/220 742]) with an OR of 6.48 (95% CI 3.70-11.35)[19,20,22] (Figure 6); NICU admission (study group: 15.34% [31/202] vs control group: 14.81%)329/2220]) with an OR of 2.11 (95% CI 0.56-7.93)[9,19] (Figure 7); neonatal death (study group: 0.68% [1/148], vs control group: 0% [0/3197]) with an OR of 56.52 (95% CI 2.28-1401.5)[8,19] (Figure 8); hypertensive disorder (study group: 13.2% [32/243] vs control group: 8% [6066/75 254]) with an OR of 1.88 (95% CI 1.22-2.88)[8,19-21] (Figure 9). For most of the analyzed variables, results showed low heterogeneity.

4 | DISCUSSION

The detection of a fetal FL below the expected value (<5th percentile) is a diagnostic challenge for clinicians, with difficult counseling due to different possible diagnoses, since it may be a marker of aneuploidy or be associated with other genetic abnormalities, such as skeletal dysplasia.[1,23] Recent literature highlighted an increased risk of IUGR or SGA in the case of isolated short femur diagnosis during the second trimester ultrasound scan (40% in Papageorghiou, 39% in Todros, 43% in Vermeer).[1,24,25]

The present meta-analysis shows that an isolated short femur increases IUGR or SGA risk fourfold in contrast with fetuses with a normal femur biometry.[8,9,19-22] In particular, we found an overall prevalence of IUGR or SGA of 14.2% in the short femur group, compared with 5.2% in the general population with an OR of 4.04 (95% CI 3.63-4.50). These data support the hypothesis that an isolated short FL might be considered an early marker for placental dysfunction.[26] Accordingly, it has been proposed that a short FL could be a sign of an adaptive response to chronic hypoxia[20] or a consequence of an alteration in secretion of growth factors. Fetal adaptive response to chronic hypoxia consists in a redistribution of blood flow to vital fetal organs (brain, myocardium and adrenal glands) at the expense of the extremities. Furthermore, IUGR and

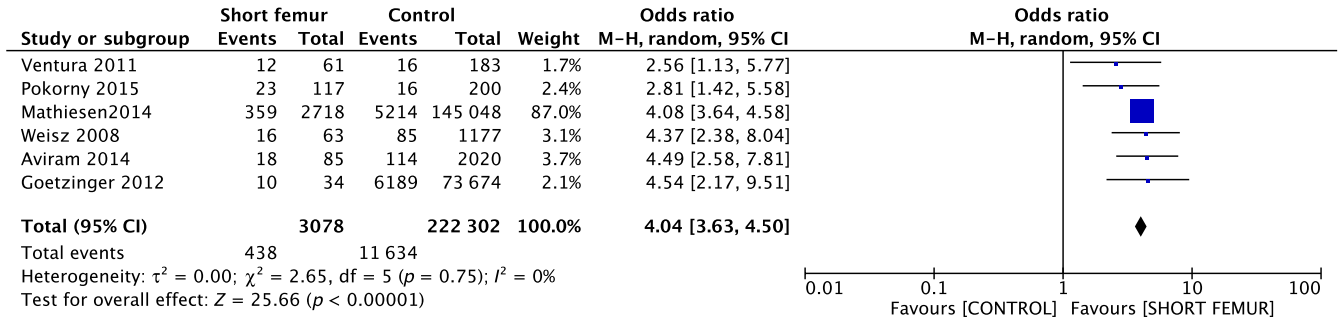

FIGURE 2 Meta-analyses for intrauterine-growth restriction or small-for-gestational-age [Color figure can be viewed at wileyonlinelibrary.com]

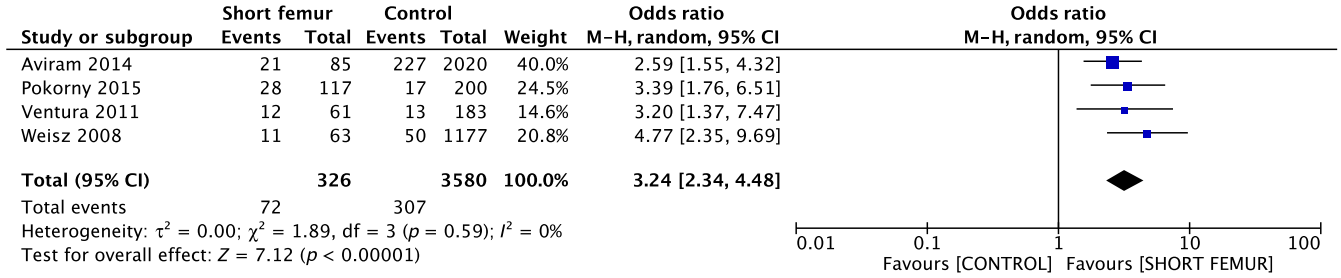

FIGURE 3 Meta-analysis for low birthweight [Color figure can be viewed at wileyonlinelibrary.com]

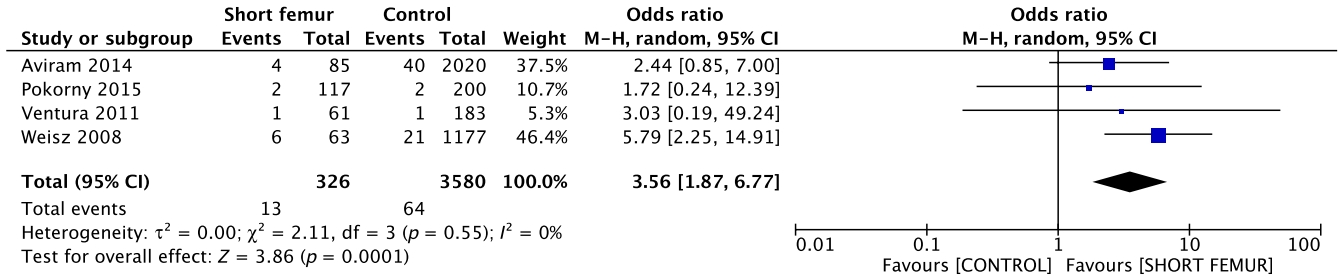

FIGURE 4 Meta-analyses for Apgar <7 at 5 min [Color figure can be viewed at wileyonlinelibrary.com]

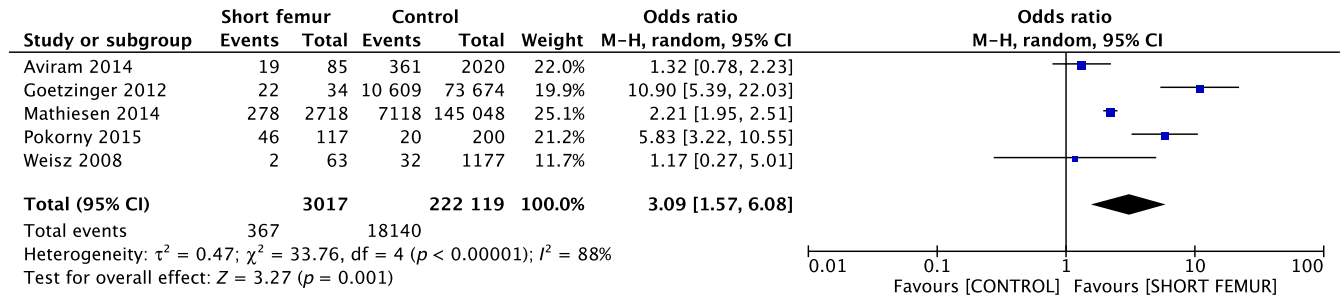

FIGURE 5 Meta-analyses for preterm birth [Color figure can be viewed at wileyonlinelibrary.com]

short FL might be linked to abnormal uterine and umbilical Doppler findings indicating a vascular origin of the growth disorder and pregnancy-induced hypertension such as preeclampsia.[24,26] The abnormal placenta may secrete altered levels of growth factors 2, such as fibroblast growth factor receptor, which are involved in normal fetal skeletal development.[27]

Our findings are concordant with current literature, as the presence of an isolated short FL has been associated with an increased risk of other adverse perinatal outcomes in the second trimester, such as SGA, low birthweight, preterm birth and preeclampsia.[1,8,9,19-21] In this regard, in our study we found an increased risk for preterm birth, fetal demise, low birthweight, Apgar <7 at

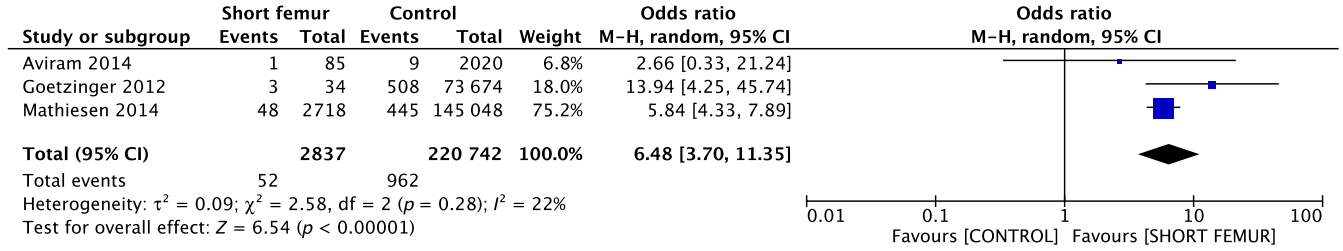

FIGURE 6 Meta-analyses for fetal demise [Color figure can be viewed at wileyonlinelibrary.com]

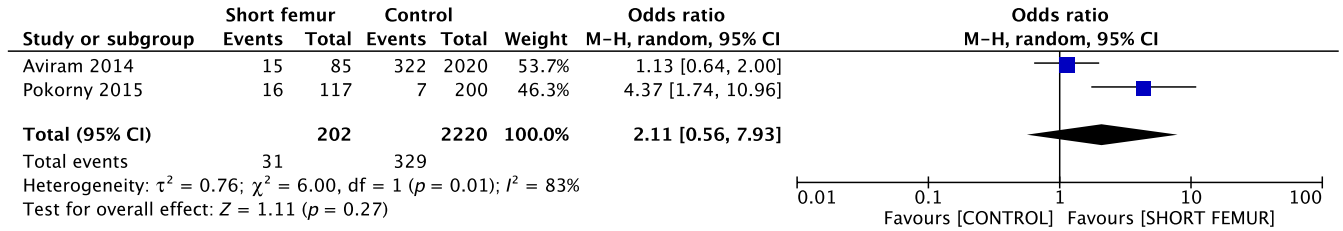

FIGURE 7 Meta-analyses for NICU admission [Color figure can be viewed at wileyonlinelibrary.com]

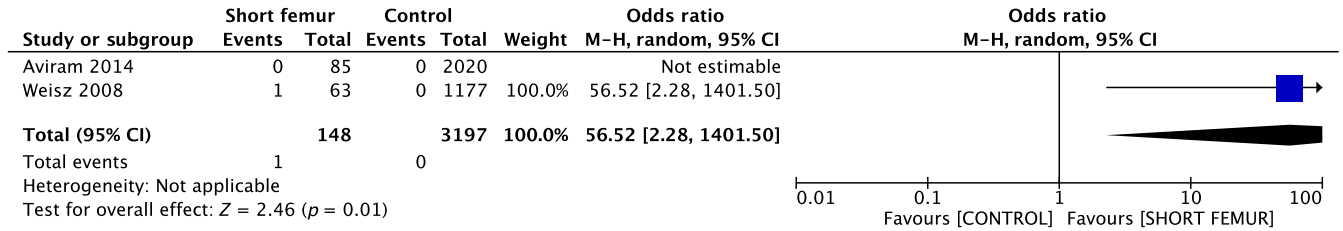

FIGURE 8 Meta-analyses for neonatal death [Color figure can be viewed at wileyonlinelibrary.com]

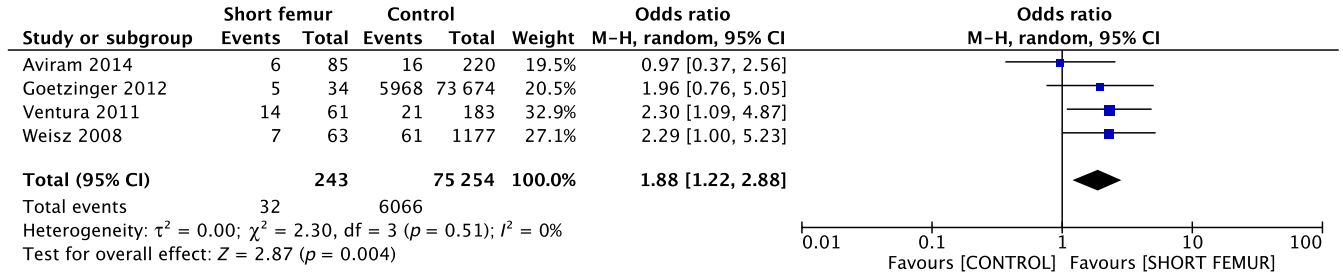

FIGURE 9 Meta-analyses for hypertensive disorders [Color figure can be viewed at wileyonlinelibrary.com]

5 minutes, hypertensive disorders and neonatal death for fetuses with short FL.

It should be underlined that in the case of isolated short femur, conservative counseling should be given to prospective parents because an uncomplicated pregnancy with a normal neonate at term has been reported in 61% of cases.[25] On the other hand, our meta-analytic data demonstrated that obstetricians should use a more careful approach to the management of these fetuses in order to prevent perinatal adverse outcomes, monitoring these pregnancies in a tertiary center,[8,9,19-21] with a structured program of sonographic surveillance and accurate delivery[28]; when malformations are excluded, serial ultrasound studies of fetal growth and frequent monitoring of maternal blood pressure are indicated.

To our knowledge, no prior meta-analysis evaluated the association between short FL and IUGR or SGA fetuses and no systematic review is as large, up to date or comprehensive as the present analysis. The population included is sufficiently large (3078 fetuses with short FL), and the statistical heterogeneity within the studies was low for all outcomes analyzed, apart from NICU admission.

This meta-analysis has some limitations. First, the overall sample sizes might be unbalanced, with 1.4% in the study group and 98.6% in the control group. Furthermore, in some of the included studies, short FL was probably not the only indication for referral to a tertiary center. Heterogeneity of IUGR and SGA definitions also represents a limitation, as well as the small number of cases in some of the included studies and their nonrandomized design. Even when authors of selected studies used the same definition for short FL (<5th percentile for gestational age), they referred to different growth charts and this could represent another potential limitation.

5 | CONCLUSION

In summary, this study shows that there is a significant association between an isolated short FL, IUGR or SGA and poor perinatal outcome, as supported by recent literature. Abnormal Doppler measurements of the uterine and umbilical arteries may help to differentiate between inherently small FL and those at risk for IUGR, since short FL may be an early sign of placental dysfunction; however, further large, prospective, multicenter studies investigating this correlation are needed.

CONFLICT OF INTEREST

The authors report no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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