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ORIGINAL PAPER

Long Story of Short Femur: A Single-Center Study with Step-Wise Imaging Approach

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Abstract

Purpose To evaluate the possible outcomes of fetuses diagnosed with short femur length (FL) and to guide diagnosis through a step-wise imaging algorithm.

Methods This was a prospective cohort study of 42 pregnancies with fetal femur length (FL) below the 5th centile for gestational age. The cases were divided into two categories of isolated short FL & non-isolated short FL and followed up to determine the etiology.

Results There were 11 cases of non-isolated short FL with skeletal dysplasia observed in 7 and chromosomal abnormalities in 4 cases. There were 31 cases with isolated short FL in which fetal growth restriction (FGR) occurred in 14/31 (45%) cases; 13 out of 31 (42%) were constitutional (short for gestational age, SGA) whereas 4/31(13%) showed normal interval growth on follow up (false positive).

Conclusion Short femur can be isolated or non-isolated. Short femur length can be a good predictor and early sign of FGR. Serial follow up scan of the all cases of isolated short FL is important since a majority of them are normal and not require any further intervention. Cases of non-isolated short FL require step-wise approach to differentiate into dysplasia or aneuploidy.

Keywords Femur · Micromelia · Ultrasound · Skeletal dysplasia · Aneuploidy

Introduction

The fetal femur is the only fetal long bone measured during the routine antenatal scan to ascertain the gestational age. A femur length (FL) below the 5th centile or 2 standard deviation (-2SD) for gestational age is defined as short femur [1]. This could be an isolated finding or may be associated with other anomalies. An isolated short femur may be a normal variant in constitutionally small fetuses or could be due to inaccurate dating. Non isolated short femur may be associated with skeletal dysplasias and chromosomal abnormalities [2–4]. Kurtz Criteria of Femoral shortening states that if FL is 1-4 mm below the -2SD point it needs serial measurement whereas if FL is > 5 mm below the -2SD point there is high likelihood of skeletal dysplasia [2]. Considering the relative frequency of short FL, there is a real paucity of Indian data regarding the perinatal outcome associated with short femur. This study aims to study the causes of short femur and predict perinatal outcomes in Indian population to plan appropriate management and ease parents counseling.

Material and Methods

This was a prospective cohort study of 42 cases of short Femur (FL < 5th percentile) diagnosed over a period of 32 months from July 2019 to March 2022 on USG performed after 18 weeks of gestational age. Patients with multiple pregnancies, fetal demise were excluded from the study.

Femur length was measured according to the prescribed 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. A short femur was

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considered isolated when all other fetal biometry parameters were within normal limits with no other structural abnormality. All gestational age-specific biometry values were determined by standards derived by Hadlock. [5]

In case of isolated short femur length, serial follow up scan was done after 3–4 weeks with uterine artery Doppler study. In case of non-isolated short FL, presence of other soft markers for fetal aneuploidy was evaluated and background risk assessment calculator was employed to determine the final risk. High risk for aneuploidy cases were subjected to invasive testing in the form of amniocentesis and final diagnosis on the basis of karyotyping and FISH studies.

Non-isolated short FL cases with severe shortening were evaluated for possibility of skeletal dysplasia and characterized on the basis of other sonographic features. Uterine artery Dopplerwas also done to exclude the possibility of FGR. Uterine artery Doppler was done by the standard procedure where both right and left uterine arteries were identified. The sagittal section of the uterus was obtained to identify the cervical canal. The probe was tilted from side to side and color flow mapping was used to identify each uterine artery. Pulse wave Doppler was used with sampling gate of 2 mm and angle < 30°. Mean pulsatility index (PI) of both uterine arteries was calculated. If PI was above 90th percentile for gestational age then there was suspected risk of preeclampsia and subsequent FGR.

Results

From July 2019 to March 2022, 42 cases were evaluated for short femur length. Demographic characteristics of the 42 patients included in the study population are shown in Table 1. The gestational age at which the first diagnosis of short FL was made are summarized in Table 2. There were 31(74%) cases with isolated short FL and 11(26%) cases with non-isolated short FL (Table 3). Amongst 31 cases of isolated short FL 4 (9.5%) turned to be false positive, 13 cases were small for gestational age (SGA) whereas 14 cases developed growth restriction (FGR) on follow up scans. Amongst 11 cases with non-isolated short FL, 7 cases had skeletal dysplasia and the remaining 4 had chromosomal abnormalities as suggested by amniocentesis. The pregnancy outcomes of isolated and non-isolated cases of short FL are summarized in Tables 4 and 5. Case of Trisomy 21 is shown in Figs. 1 and 2. Thanatophoric dwarfism is shown in Figs. 3 and 4; Asphyxiating thoracic dystrophy is shown in Fig. 5.

Table 1 Demographic characteristics of the study population ($N=42$)

Variable	Mean
Age (years)	29.7
Gestational age at diagnosis (weeks)	21.4
Height (cms)	156.5
Weight (kgs)	62
Nulliparous	23/42 (55%)
Parous	19/42 (42%)

Table 2 Distribution of cases (N = 42) as per gestational age at diagnosis-

Gestational age (weeks)	False positive ($n=4$)	SGA ($n=13$)	FGR ($n=14$)	Aneuploidy ($n=4$)	Skeletal dysplasia ($n=7$)
18–24	4	10	0	4	0
24–28	0	3	8	0	2
28–32	0	0	6	0	3
32 –term	0	0	0	0	2

*SGA-Small for Gestational age; FGR-Fetal Growth Restriction

Discussion

The detection of short FL is a diagnostic challenge for clinicians due to different possible diagnoses, as it may be a marker of aneuploidy or may be associated with other genetic abnormalities, such as skeletal dysplasia. Detailed ultrasound examination shows associated fetal abnormalities in about one-third of cases, whereas it is an isolated finding in about two thirds of pregnancies. Non isolated short femur cases are strongly associated with aneuploidy whereas isolated cases are usually contributed by severe FGR. Early identification of SGA fetuses is crucial as it is possible to decrease the risk of adverse neonatal outcome by four-fold with a structured program of surveillance and accurate delivery [6].

Isolated Short Femur Length

Isolated short femur can be due to SGA, FGR or may be false positive. It is hypothesized that an isolated short femur may be an early marker of placental dysfunction as

Table 3 Distribution and categorization of short FL cases into 2 groups and their final outcome

Total cases of short FL ($N = 42$)		
Isolated short FL ($N = 31$; 73.8%)	Diagnosis	Frequency
	False Positive	$N = 4$; 9.5%
	SGA	$N = 13$; 30.95%
	FGR	$N = 14$; 33.33%
NON−ISOLATED SHORT FL ($N = 11$; 26.2%)	Skeletal Dysplasias	$N = 7$; 16.6%
	Aneuploidies	$N = 4$; 9.5%

Table 4 Diagnosis and outcomes of non-isolated short femur cases ($n=11$)

	Diagnosis	*N*	Outcome
Aneuploidy ($n=4$)	Trisomy 21	2	Termination
	Trisomy 18	1	Termination
	Triploidy	1	Termination
Skeletal dysplasia ($n=11$)	Achondroplasia	2	Live Birth
	Thanatophoric dwarfism	2	Neonatal death, Intrauterine death
	Asphyxiating thoracic dystrophy	2	Neonatal death
	Osteogenesis imperfecta	1	Termination

Table 5 Distribution and outcomes of isolated short femur cases ($n=31$)

Outcome	False Positive ($n=4$)	SGA ($n=13$)	FGR ($n=14$)
GA at delivery in wks (median & interquartile range)	40.3 (39.3 to 41.1)	39 (37.0 to 41.0)	32.6 (31.0 to 34.3)
Birth Weight in Kg (median & interquartile rage)	3450 (2912–3670)	2423 (2135–2710)	1261 (980–1540)
Abnormal Uterine Doppler indices (Number & percentage)	0 (0)	2 (15%)	11(79%)
Pre-Eclampsia /abruption (Number & percentage)	0 (0)	1 (7%)	6 (43%)
Live Birth (Number & percentage)	4 (100%)	12 (92%)	9 (64%)

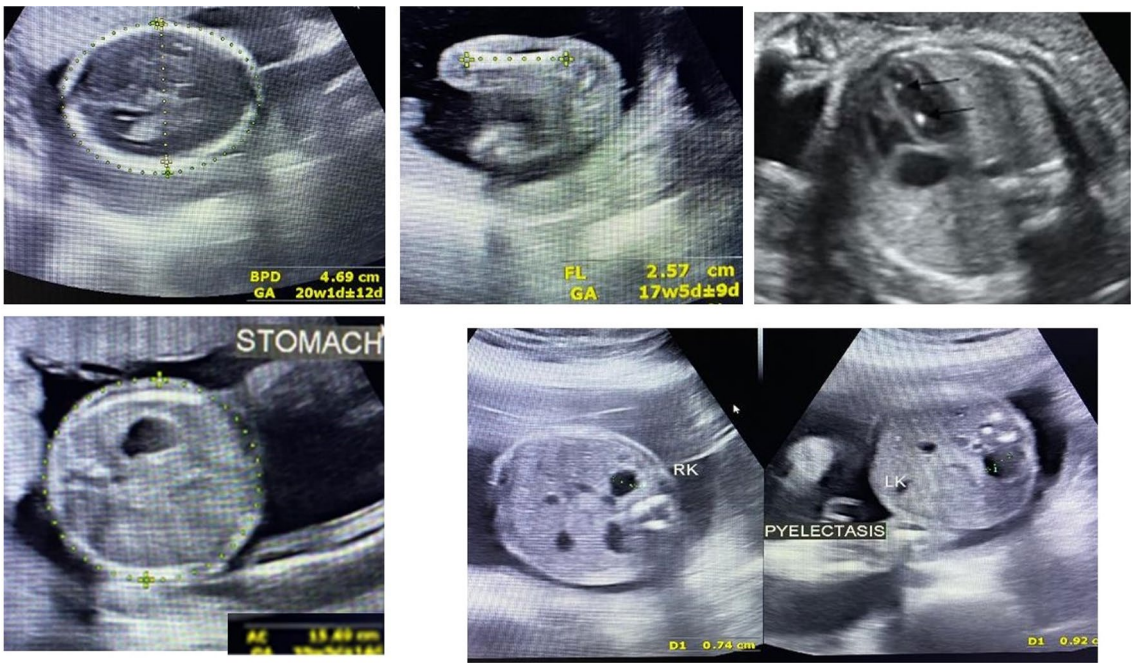

Fig. 1 Axial USG images of fetus at 20 weeks of gestation showing short femur (corresponding to 17.5 weeks) with presence of echogenic intracardiac focus and pyelectasis as soft markers

oxygenated fetal blood is preferentially shunted towards vital organs at the expense of the extremities [7]. One potential mechanism for short femur in FGR 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 [8, 9].

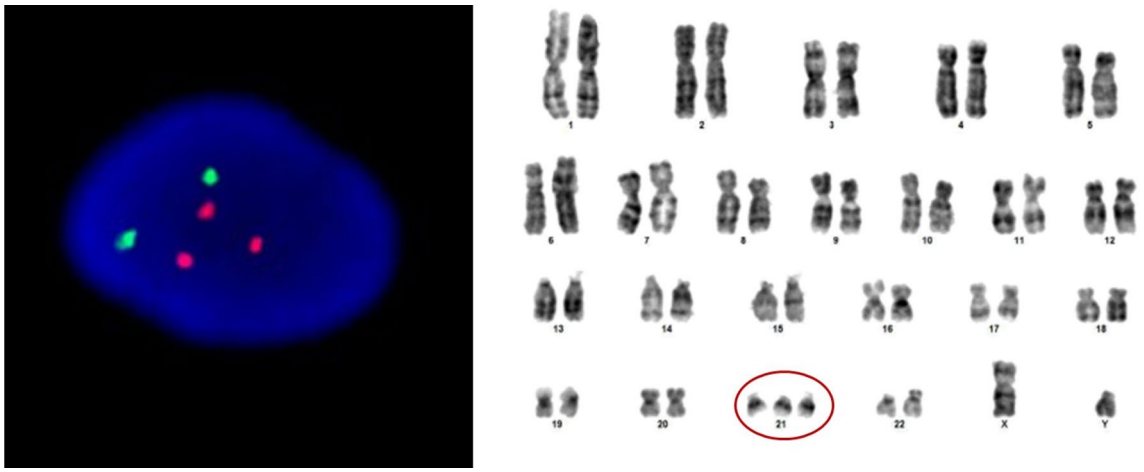

Fig. 2 FISH (Fluorescent in-situ hybridization) & karyotyping of amniocentesis sample confirming Trisomy 21

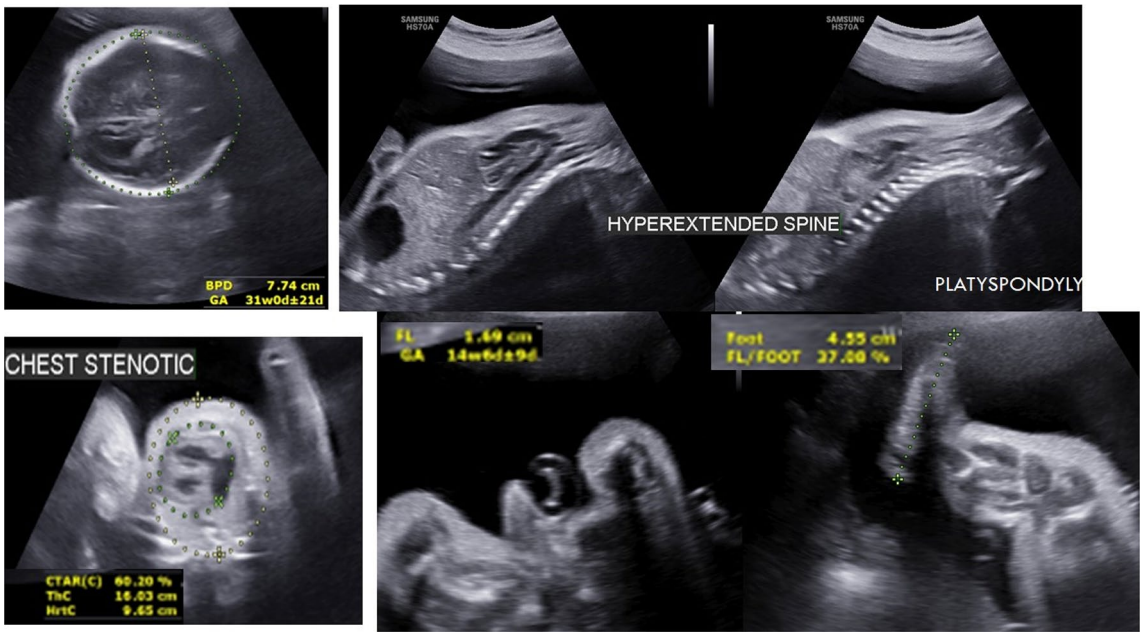

Fig. 3 Case of severe micromelia (non-isolated short FL) with chest stenosis and platyspondyly consistent with all features of thanatophoric dwarfism

In our study there were 14(33.33%) cases among 42 cases of short FGR with abnormal uterine artery- Doppler whereas 13(31%) cases were SGA which is also supported by previous studies. Todros et al. reviewed 86 consecutive referrals for short femur and investigated that 21% of the patients delivered structurally normal, euploid SGA neonates. Diagnosis of SGA was made about 9 weeks after the finding of a short femur [10]. Weisz et al., Ventura et al. and Goetzinger et al. similarly demonstrated an increased risk of fetal growth retardation, showing SGA rates of 19%, 19.7% and 21.5% respectively [7, 11, 12].

In cases where the diagnosis of FGR is confirmed, the prognosis is guarded, as it may require preterm birth and may be accompanied with pre-eclampsia or abruption (Table 4). As placental insufficiency is the most common cause of growth retardation it seems likely that FGR and short FL might be linked to hypertensive disorders and preeclampsia as depicted in a study done by Zalel et al. where 77% cases with an isolated short FL developed hypertension [8]. Similar finding is reported in our study where 43% cases had hypertensive disorders.

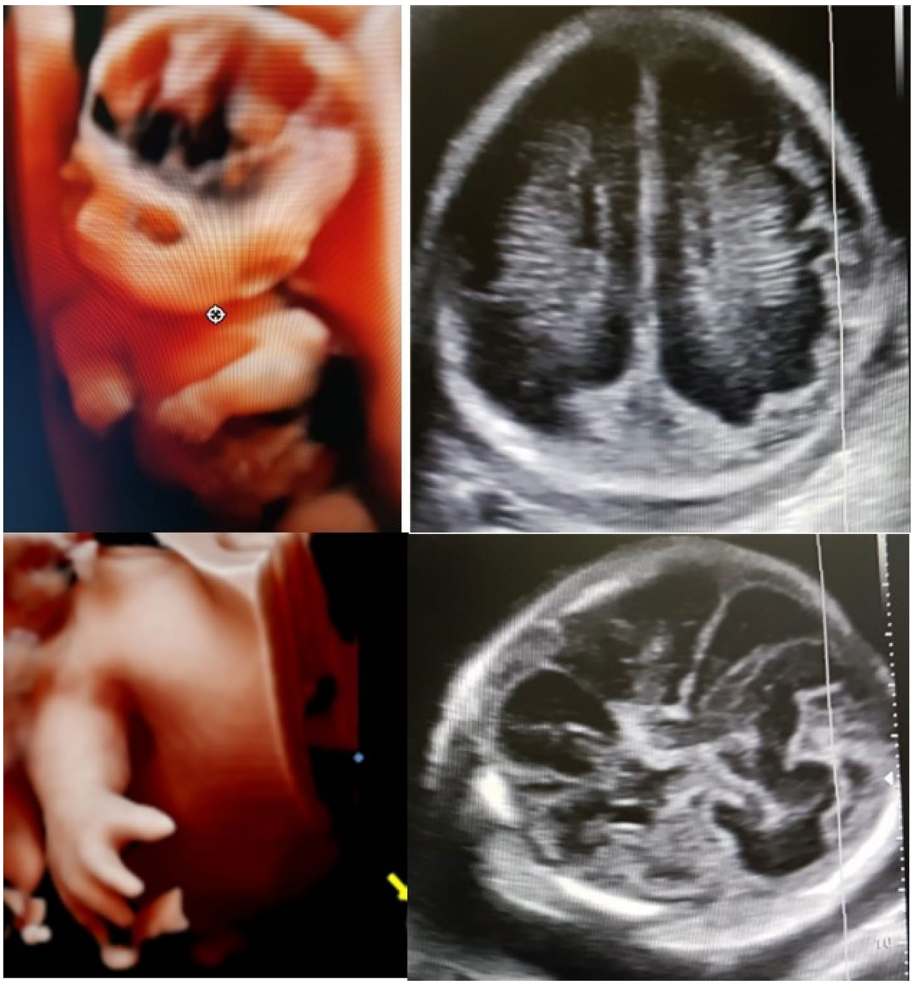

Fig. 4 3D image of case of thanatophoric dwarfism showing short limbs with axial image of fetal head showing temporal lobe dysplasia and laminar heterotopia

Non-Isolated Short Femur Length

Short femur length has been associated with an increased risk of Down syndrome [4]. However, a meta-analysis of 1,32,295 fetuses suggested that given a positive likelihood ratio of 2.7, isolated short femur was not a useful tool to exclude or confirm Down syndrome [13]. In patients with previously normal fetal NT thickness the finding of short femur at later scans is unlikely to be due to aneuploidy [14].

Role of soft marker risk assessment is crucial while evaluating the cases of mild shortening of femur. This standard assessment calculates the final risk of aneuploidy above the age-related risk and give the probability of aneuploidy.

In our study population, there were 11 cases with non-isolated short femur, where other ultrasonographic abnormalities coexisted. Amongst them there were 4 cases of chromosomal abnormalities with amniocentesis suggestive of trisomy 21 in 2 patients, trisomy 18 in 1 patient, triploidy in 1 patient. They were all offered termination of pregnancy. In study by Papageorghiou et al., no single case of trisomy 21 was found which may be due to low prevalence of Down syndrome in the population under study [14]

There were 7 cases of skeletal dysplasia with all of them showing moderate to severe shortening of FL. Only 2 had nonlethal dysplasia (achondroplasia) with mild to moderate rhizomelia and were live born. 5 out of 7 cases were lethal types of dysplasia in the form of severe micromelia and reduced thoracic circumference. Imaging features of Thanatophoric dwarfism were seen in 2 cases, Asphyxiating thoracic dystrophy (Jeune's syndrome) in 2 cases and Osteogenesis imperfecta in 1 case. The fetal outcome was poor with intrauterine death or early neonatal death reported in all 5 cases. A standardized imaging approach of severe micromelia was employed using a reference algorithm put forward by Agarwal et al. [15].

The limitation of our study was small sample size and thus it is difficult to extrapolate the results on general population. Genomic sequencing of all cases of skeletal dysplasia could not be performed due to financial constraints. The strength of our study is its prospective nature and is the only Indian study in terms of fetal outcome of cases of short FL. This study may be considered as a pilot study on Indian population with short FL and further studies with larger population may be carried out. Based on available literature

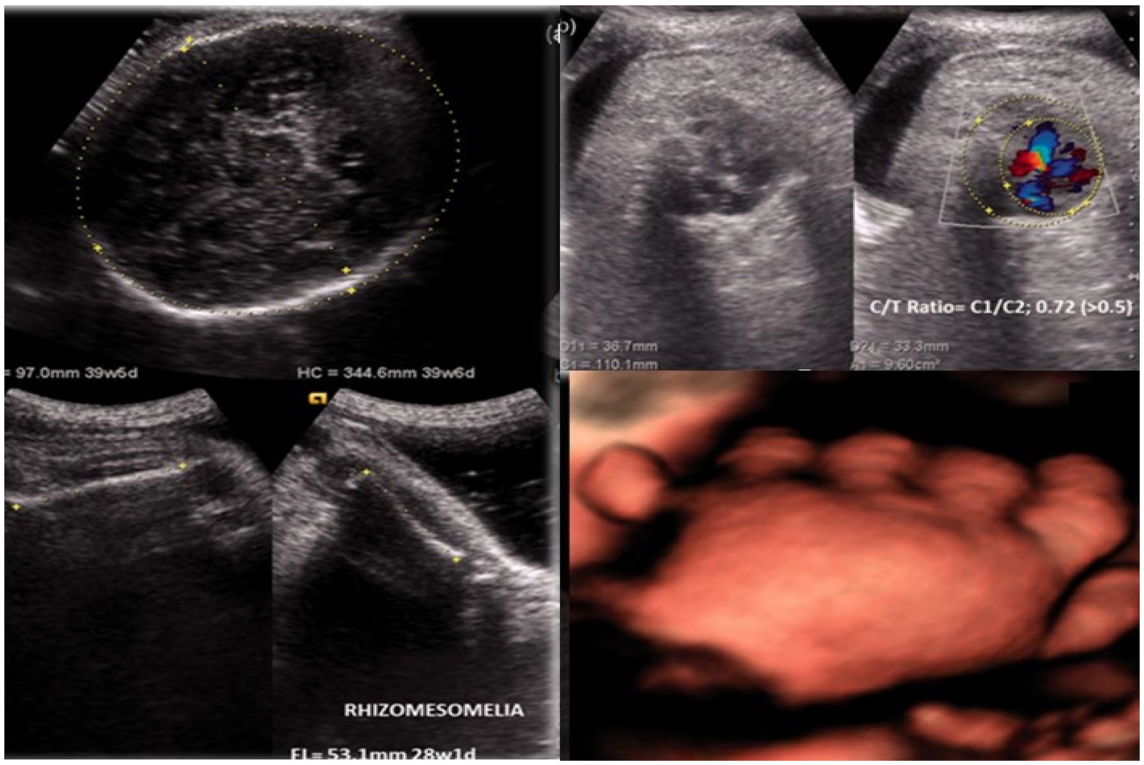

Fig. 5 Case of asphyxiating thoracic dystrophy (ATD, Jeune's syndrome) with micromelia (short long bones), normal sized fetal head, stenotic chest and post-axial polydactyly (3D image)

and study outcome; a step-wise algorithm/approach is also suggested for cases of short FL by dividing them into in two broad categories -i.e. isolated short FL and non-isolated short FL (Figs. 6, 7).

This study also shows that there is a significant association between an isolated short FL, FGR or SGA and poor perinatal outcome, as supported by recent literature. Abnormal Doppler measurements may help to differentiate between SGA and FGR, since short FL may be an early sign of placental dysfunction; however, further large, multicenter studies are required for standardization of protocol.

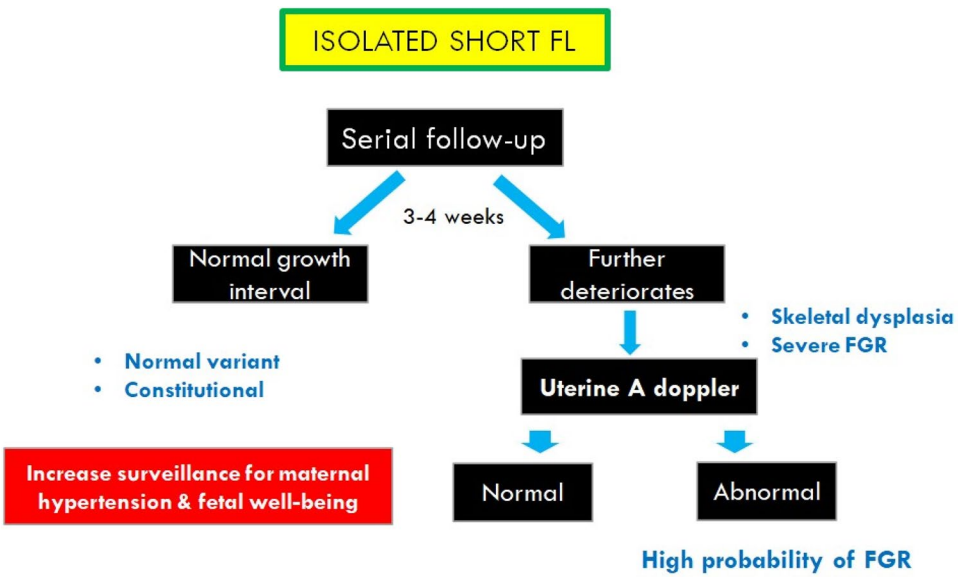

Fig. 6 Step-wise diagnostic imaging approach of cases of Isolated Short FL

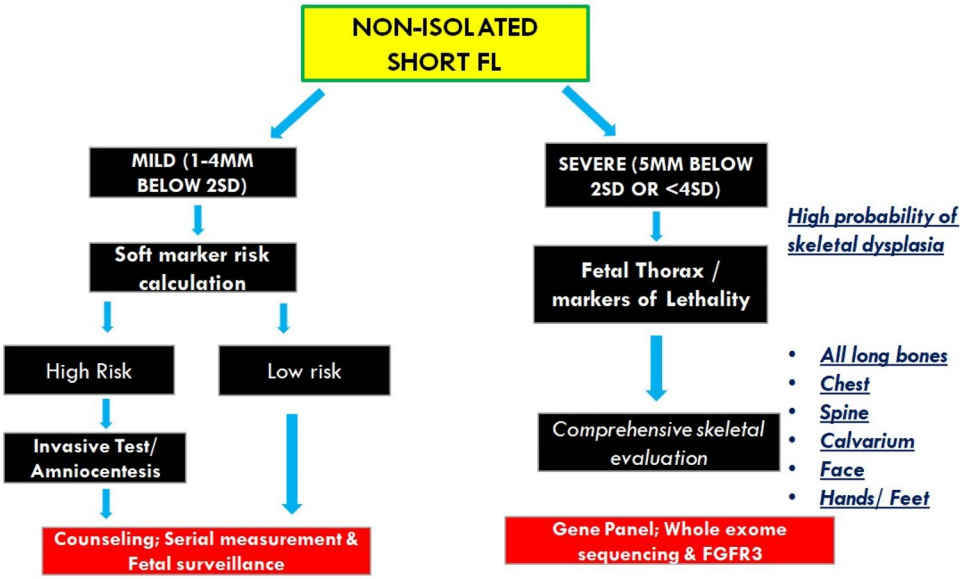

Fig. 7 Step-wise diagnostic approach of cases of Non-isolated Short FL

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Arjit Agarwal], [Shruti Chandak]. The first draft of the manuscript was written by [Shubhra Agarwal] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This is an observational study. The Institute Research Ethics Committee has confirmed that no ethical approval is required.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1 to 6.

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