

# Prenatal limb defects

## Epidemiologic characteristics and an epidemiologic analysis of risk factors

Yue Shi, MD, MS<sup>a</sup>, Bin Zhang, MD, PhD<sup>a</sup>, Fanbin Kong, MD, PhD<sup>b,\*</sup>, Xilian Li, MD, MS<sup>a,\*</sup>

### Abstract

To analyze prenatal ultrasound data for fetal limb deformities in high-risk pregnant women and the risk factors for prenatal limb defects in high-risk pregnant women.

This was a retrospective study of high-risk pregnant women at the multidisciplinary consultation center from January 2006 to December 2015. When deformities were definitively diagnosed in the first trimester by ultrasound, patients were recommended to undergo an abortion, and fetal abnormalities were confirmed by pathological examination (both gross anatomic examinations and fetal chromosome and genetic tests). The risk factors for fetal limb deformities and other congenital malformations were analyzed by multifactor analysis.

Of the 4088 fetuses recorded, 144 (3.52%) were diagnosed with limb abnormalities. The abnormalities included 70 (48.61%) clubfoot/clubhand cases, with 5 polydactyly, 5 syndactyly, 4 flexion toe, 4 split hand/foot malformation, 3 overlapping fingers, and 49 congenital talipes equinovarus. A total of 6 (4.17%) and 13 (9.02%) fetuses had phocomelia and imperfect osteogenesis, respectively; 22 (15.28%) cases showed achondrogenesis; 19 (13.19%) and 12 (8.33%) had partial limb deletion absence and joint movement malfunction, respectively.

In the high-risk population with limb deformities (144 patients), 19 (13.19%) were  $\geq 35$  years old, 6 (4.17%) had family history of congenital malformations, 14 (9.72%) had abnormal reproductive history, 21 (14.6%) had harmful chemical exposure, 6 (4.2%) had early TORCH infections, 16 (11.1%) had gestational diabetes, 9 (6.3%) had hypertension, 3 (2.1%) took glucocorticoid, 9 (6.3%) took sedatives.

In the high-risk population with other congenital malformations except limb deformities (3766 patients), 144 pregnant women were randomly selected. In the high-risk population with other congenital malformations (144 patients), 9 (6.25%) were  $\geq 35$  years old, 7 (4.86%) had family history of congenital malformations, 10 (6.94%) had abnormal reproductive history, 22 (15.28%) had harmful chemical exposure, 5 (3.47%) had early TORCH infections, 12 (8.33%) had gestational diabetes, 11 (7.64%) had hypertension, 4 (2.78%) took glucocorticoid, 11 (7.64%) took sedatives.

Ultrasound can provide adequate evidence for fetal limb deformities evaluation in most patients. Fetal limb deformity cases showed a significantly higher rate than other congenital malformations for advanced maternal age ( $\geq 35$  years old).

**Abbreviations:** GDM = gestational diabetes mellitus, NIPT = noninvasive prenatal testing, TORCH = toxoplasmosis, other (syphilis), rubella, cytomegalovirus (CMV), herpes simplex virus (HSV).

**Keywords:** fetal limb deformity, high-risk pregnant women, screening, ultrasound

### 1. Introduction

Congenital limb abnormalities may be caused by genetic syndromes or can be isolated and sporadic events; therefore,

their prognoses are highly variable. In China, the prevalence of fetal limb abnormalities is 0.38%.<sup>[1]</sup> In Europe, it varies from 1.4 to 30 cases per 10,000 births.<sup>[2,3]</sup> In Canada, this rate is about 5.6 per 10,000 births.<sup>[4]</sup> Early detection of such abnormalities is important in providing counseling to families in the optimal time window.

First-trimester screening for fetal limb abnormalities was introduced since the 1980s and 1990s.<sup>[5-7]</sup> It is widely accepted that first-trimester screening can be performed as early as 9 weeks of gestation using transvaginal ultrasound. Recently, the increasing use of NIPT (noninvasive prenatal testing) prompted many researchers to assess the clinical value of early screening for fetal limb abnormalities.<sup>[8-17]</sup> Indeed, except fingers, most abnormalities can be observed using a combination of transabdominal and transvaginal ultrasound sessions.<sup>[13-23]</sup> Nevertheless, many of these studies were based on small sample sizes, with the scarcity of fetal abnormalities rendering their interpretations difficult. Liao et al<sup>[1]</sup> assessed 9438 fetuses and identified 36 cases (0.38%) of fetal limb abnormalities, of which 28 (78%) were detected prenatally and 23 (64%) during the first trimester of pregnancy.

Some pregnant women are considered to be at high risk for having fetuses with structural abnormalities. Maternal risk factors for structural abnormalities include age ( $\geq 35$  years old),

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<sup>a</sup>Department of Obstetrics, <sup>b</sup>Department of Ultrasound, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China.

\*Correspondence: Xilian Li and Fanbin Kong, Obstetrics and Gynecology Hospital of Fudan University, No. 419, Fangxie Road, Shanghai, 200011, PR China (e-mails: xilianli@aliyun.com [XL]; drli1973@hotmail.com [FK]).

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maternal gestational diseases (gestational diabetes mellitus (GDM) and hypertension), early TORCH infections, harmful chemical exposure, history of abnormal delivery, family history of congenital, taking glucocorticoid, taking sedatives, and abnormal genetic examination.<sup>[24–27]</sup> Nevertheless, few studies were done to identify which factors were more closely and specifically associated with prenatal limb defects, compared with the incidence of the risk factors for other congenital malformations. Therefore, the present study aimed to analyze prenatal ultrasound data for fetal limb deformities in high-risk pregnant women and the incidence of risk factors with prenatal limb defects in high-risk pregnant women.

## 2. Materials and methods

### 2.1. Subjects

This was a retrospective study of pregnant women and fetuses with fetal limb abnormality detected or confirmed with ultrasound scan at the multidisciplinary consultation center of the Obstetrics and Gynecology Hospital of Fudan University (Huangpu District, Shanghai, China) from January 2006 to December 2015.

Patients with fetal limb deformities diagnosed with ultrasound were reviewed. High-risk pregnancy was defined as with at least one of the following factors: maternal age  $\geq 35$  years old; family history of congenital; abnormal reproductive history; maternal gestational complications (GDM, pregnancy-induced hypertension, hypothyroidism, subclinical hypothyroidism, chronic renal disease, etc.); early TORCH infections; harmful chemical exposure; taking glucocorticoid or sedatives. High-risk patients were included and a total of 3910 high-risk pregnant women with suspicious congenital fetal malformations were reviewed.

All the included clinical cases consulted physicians at the prenatal Multidisciplinary Consultation Center. Our team consists of obstetricians, pediatricians, pediatric surgeons, radiologists, and researchers from biochemistry and genetic laboratories. The study complied with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University. The need for informed consent was waived because of the retrospective nature of the study.

### 2.2. Ultrasound examination

Routine ultrasonography included fetal head, face, spine, thoracoabdominal wall, thoracoabdominal organs, limbs, placenta, amniotic fluid, and umbilical cord. The fetal biparietal diameter, head circumference, abdominal circumference, femur length, humerus length, transverse cerebellar diameter, amniotic fluid depth, and systolic and diastolic peak velocity ratios were also measured in addition to resistance and pulse indexes of the umbilical artery. Ultrasound examinations were performed on an E8 color Doppler ultrasonic diagnostic system (GE Healthcare, Waukesha, WI) with a probe of 3.5 to 5.0 MHz.

A continuous track scan was successively performed on fetal limbs from the proximal region to the distal side along the longitudinal axis. Both longitudinal and horizontal axis sections were scanned, including humerus, ulna and radius, femur, tibia, and fibula. The number, length, shape, structure, posture, position, and activity of every long bone in each limb were recorded.

In cases for which the limbs could not be shown clearly due to fetal posture, the patients were asked to walk for 15 to

30 minutes, and then ultrasound was repeated. The initial ultrasound examinations were performed at 12 to 14 weeks of gestation. For fetuses with suspicious abnormalities, ultrasound was repeated at 22 to 26 weeks of gestation.

### 2.3. Data collection

Clinical information, including age, reproductive history, delivery method, gestational week, and high-risk pregnancy risk factors were collected.

### 2.4. Follow-up

When deformities were definitively diagnosed in the first trimester by ultrasound, patients were recommended to undergo an abortion, and fetal abnormalities were confirmed by pathological examination (both gross anatomic examinations and fetal chromosome and genetic tests). In cases of suspicious fetal limb deformities, a second-trimester ultrasound examination was performed at 18 to 24 weeks of gestation. Ultrasound examination assessed fetal position, upper limbs (upper arms, forearms, and hands), lower limbs (thighs, calves, and feet), and morphology and number of fingers and toes. Fetal limb abnormalities detected again in the second examination prompted the team to recommend pregnancy termination, while fetuses with strephenopodia alone were recommended to get corrective therapy later; these patients were followed-up till delivery, with limb abnormalities assessed definitively for confirmation.

### 2.5. Statistical analysis

Excel was used to establish the database of the risk factors of fetal congenital malformation. SPSS 22.0 software was applied to perform the multi-factor non-conditional logistic regression analysis of fetal limb deformity and other congenital malformation.

## 3. Results

### 3.1. Patient characteristics

A total of 3910 high-risk pregnant women with suspicious congenital fetal malformations who underwent prenatal multidisciplinary consultation were included. The mean maternal age was  $29.1 \pm 4.5$  years (range, 20–43 years). A total of 4088 fetuses from 3910 women (178 twin pairs) were subjected for analysis.

### 3.2. Fetal limb abnormalities

Deformities occurred in 2496 (61.6%) fetuses, and included 1168 (46.8%) cardiac, 847 (33.9%) renal, and 720 (28.8%) bone deformities. Among the 4088 fetuses, 144 (3.5%) were diagnosed with limb abnormalities; all were singlet (Table 1). Of these, 70 (48.6%) had clubhand/clubfoot (Figs. 1–3), including 5 polydactyly, 5 syndactyly, 4 flexion toe, 4 split hand/foot malformation, 3 overlapping finger, and 49 congenital talipes-equinovarus cases; 13 (9.0%) had imperfect osteogenesis (Fig. 4); 22 (15.3%) cases with achondrogenesis (Figs. 5–7) were found, including 7 and 15 with fatal dysplasia and cartilage hypoplasia, respectively; 19 (13.2%) and 12 (8.3%) cases had partial deletion limb (Fig. 8) and joint movement malfunction, respectively; 6 (4.2%) fetuses had phocomelia.

<b>Table 1</b>	
<b>Characteristics of the fetuses with limb abnormalities.</b>	
	<b>n=144</b>
Clubhand/clubfoot	
Polydactyly	5 (3.47%)
Syndactyly	5 (3.47%)
Flexion toe	4 (2.78%)
Split hand/foot malformation	4 (2.78%)
Overlapping finger	3 (2.08%)
Congenital talipesequinovarus	51 (35.41%)
Phocomelia	6 (4.16%)
Imperfect osteogenesis	13 (9.02%)
Achondrogenesis	
Fatal dysplasia	7 (4.86%)
Cartilage hypoplasia	15 (10.41%)
Limb partial deletion	19 (13.19%)
Joint movement malfunction	12 (8.33%)

### 3.3. An epidemiologic analysis of risk factors

The frequency of prenatal limb deformities is significantly elevated in high-risk pregnant women compared with the low-risk population.<sup>[24-27]</sup> As it is obvious that congenital malformations are associated with these risk factors, more analyses were done to identify which factors are more closely associated with fetal limb deformities compared with other congenital malformations this time.

In the high-risk population with limb deformities (144 patients), 19 (13.19%) were  $\geq 35$  years old, 6 (4.17%) had family history of congenital malformations, 14 (9.72%) had abnormal reproductive history, 21 (14.6%) had harmful chemical exposure, 6 (4.2%) had early TORCH infections, 16 (11.1%) had gestational diabetes, 9 (6.3%) had hypertension, 3 (2.1%) used glucocorticoid, 9 (6.3%) used sedatives.

In the high-risk population with other congenital malformations except limb deformities (3766 patients), 144 pregnant women were randomly selected. In the high-risk population with other congenital malformations (144 patients), 9 (6.25%) were  $\geq 35$  years old, 7 (4.86%) had family history of congenital

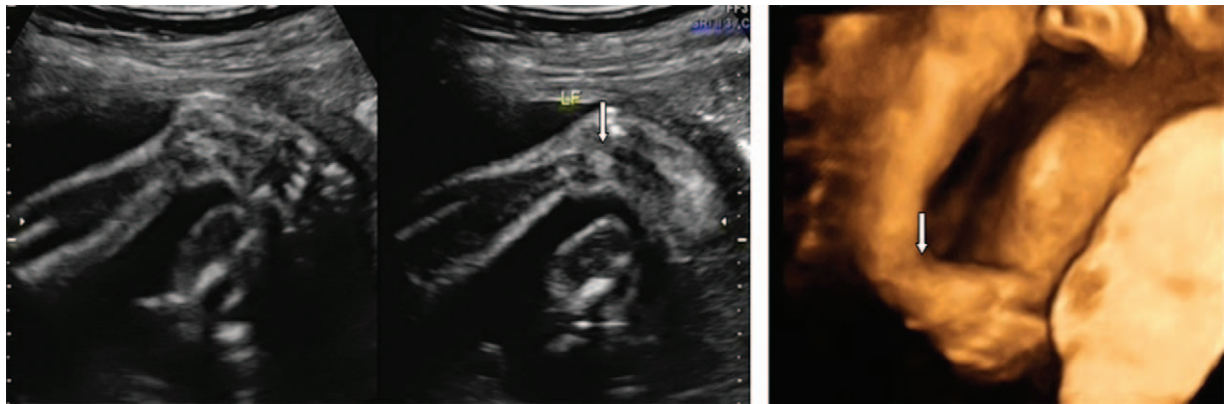


Figure 1. Representative strephenopodia images. The arrows indicate that the left (left panel) and right (right panel) feet are inverted.

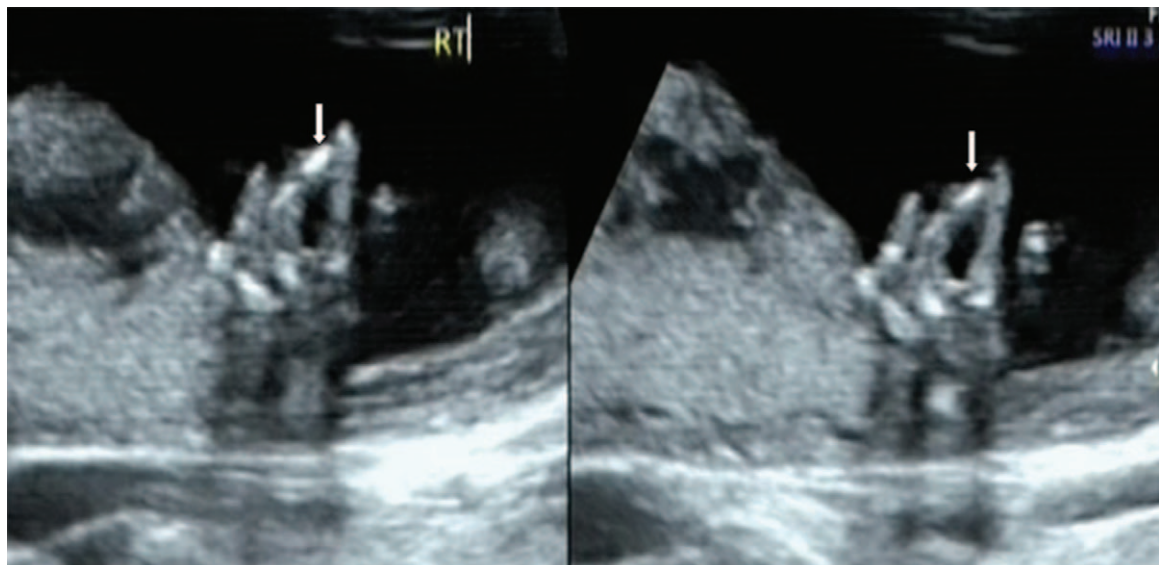
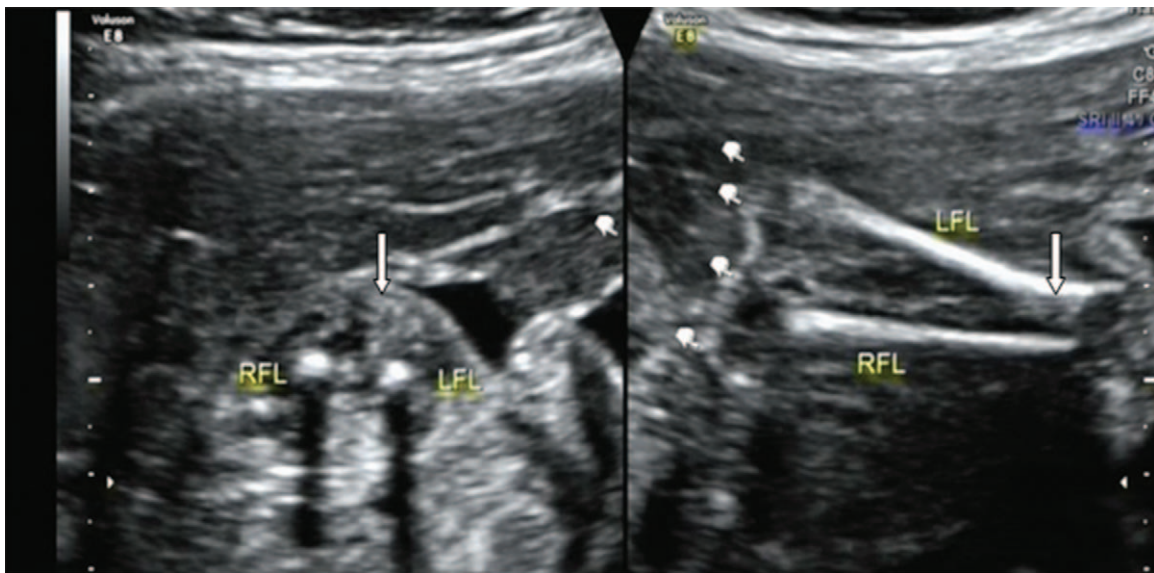


Figure 2. Representative image showing a bent right finger (arrow) with no activity.





**Figure 3.** Representative sirenomelia image. This suggested lower limb fusion. LEF= left femur, RFL=right femur.

malformations, 10 (6.94%) had abnormal reproductive history, 22 (15.28%) had harmful chemical exposure, 5 (3.47%) had early TORCH infections, 12 (8.33%) had gestational diabetes, 11 (7.64%) had hypertension, 4 (2.78%) took glucocorticoid, 11 (7.64%) took sedatives.

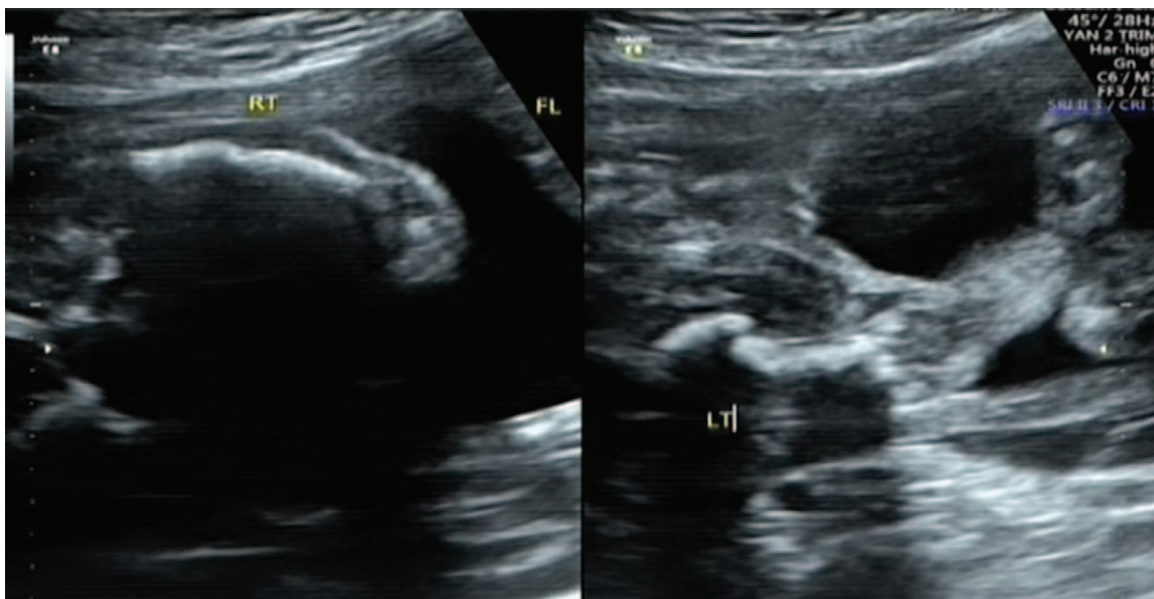
### 3.4. Multi-variant analysis

Fetal limb deformities cases had a significantly higher rate than other congenital malformations for advanced maternal age  $\geq 35$  years old ( $P < .05$ ,  $OR = 2.774$ ), but there were no significant difference between the incidence of family history of congenital

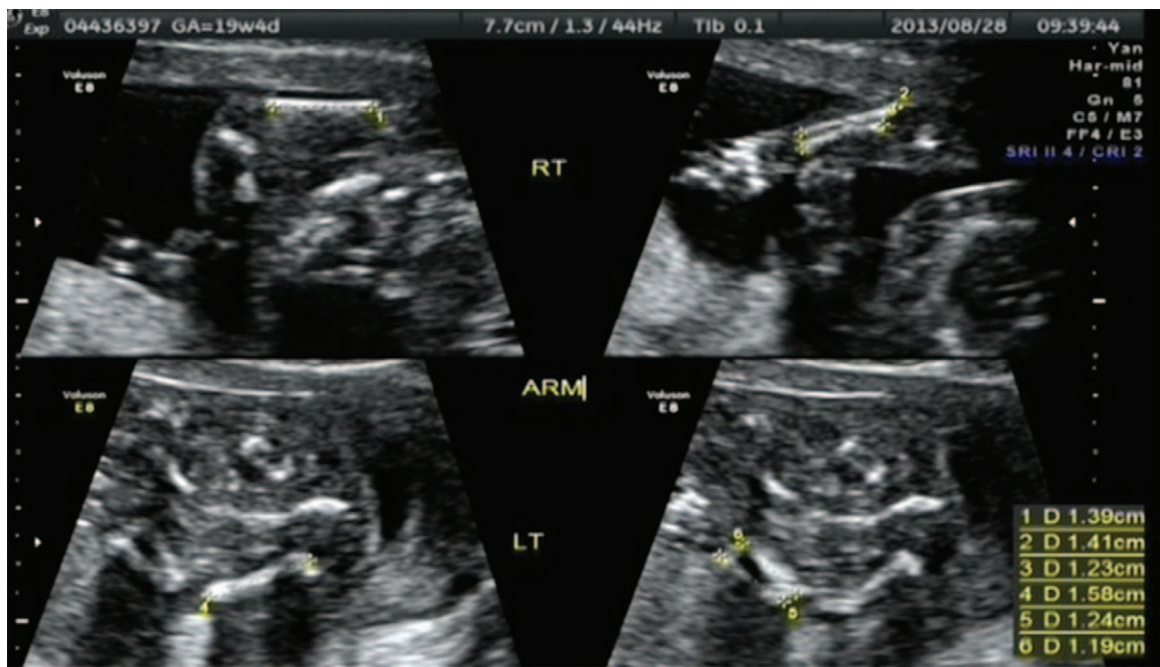
malformations, abnormal reproductive history, harmful chemical exposure, early TORCH infections, gestational diabetes, hypertension, taking glucocorticoid and taking sedatives in the fetal limb deformities population compared with other congenital malformations (Table 2).

### 3.5. Combined abnormalities

Table 3 presents combined deformities with abnormality. Cardiac deformities were found in 41 fetuses (27.5%), urinary tract abnormalities in 11 (7.4%), neurological disorders in 20 (13.4%), and digestive system deformities in 28 (18.8%).



**Figure 4.** Representative images showing imperfect osteogenesis. The right femur was bent to angle (arrow in the left image) and the left femur was discontinuous (arrow in the right image).

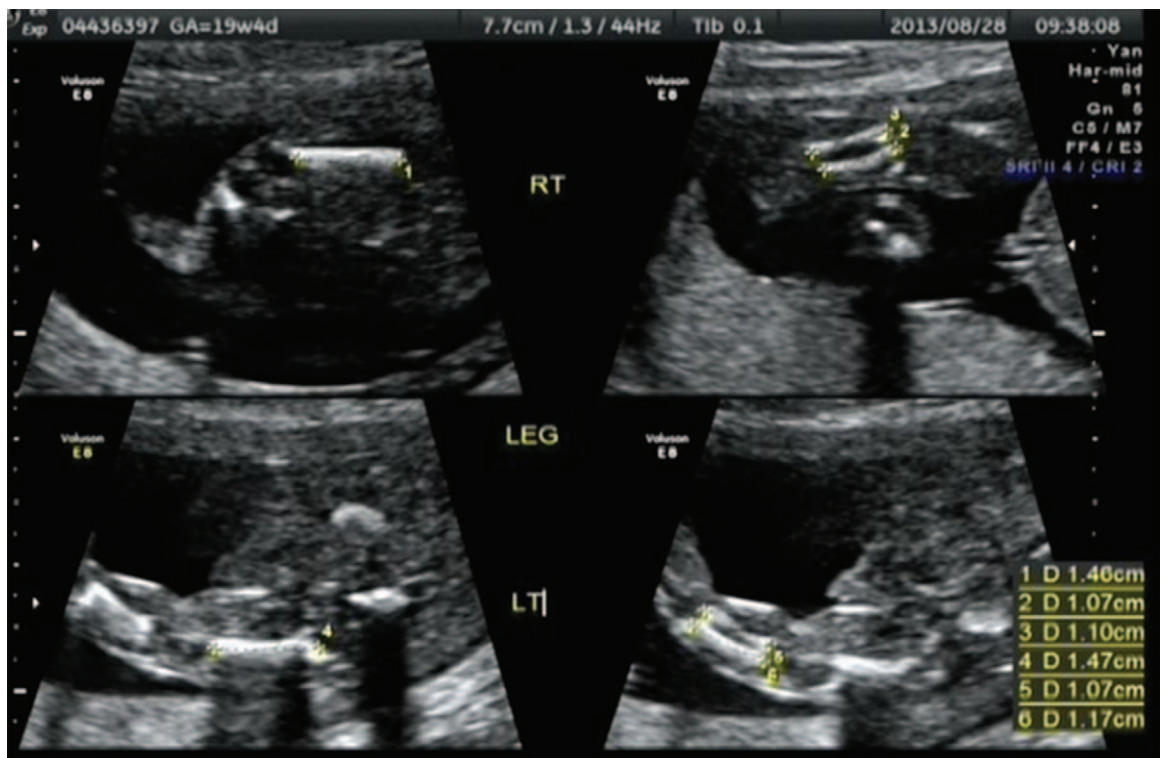


**Figure 5.** Representative achondroplasia images. The fetus was 19 weeks and 4 days, with short upper limbs. 1, length of right humerus; 2, length of right ulna; 3, length of right radius; 4, length of left humerus; 5, length of left ulna; length of left radius.

Moreover, genetic abnormalities were recorded in 4 (14.8%) of 27 patients tested. These results suggested that limb abnormalities are frequently accompanied with other deformities and present as genetic syndromes.

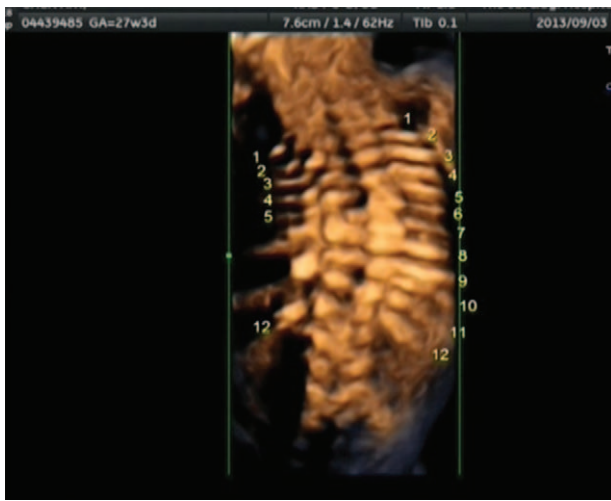
#### 4. Discussion

So far, few reports have assessed prenatal limb deformity and investigated the associated risk factors in a real-life setting. Therefore, this study aimed to retrospectively review the



**Figure 6.** Representative achondroplasia images. The fetus was 19 weeks and 4 days, with short lower limbs. 1, length of right femur; 2, length of right tibia; length of right fibula; length of left femur; 5, length of left tibia; 6, length of left fibula.





**Figure 7.** Fatal dysplasia. Cartilage formation was incomplete in this fetus (27 weeks and 3 days). The left side of the first 6 to 11 thoracic vertebrae and rib fusion were missing, and short limbs could be observed.

epidemiologic characteristics of prenatal limb defects and also investigate the gestational risk factors associated with fetal limb deformities.

A Chinese study reported a prevalence of fetal limb abnormalities of 0.38%.<sup>[1]</sup> Previous studies in Europe and Northern America found that such defects occur in 1.4 to 30 cases per 10,000 births.<sup>[2–4]</sup> In the present study, the prevalence of fetal limb abnormalities was substantially higher (3.7%),

**Table 3**

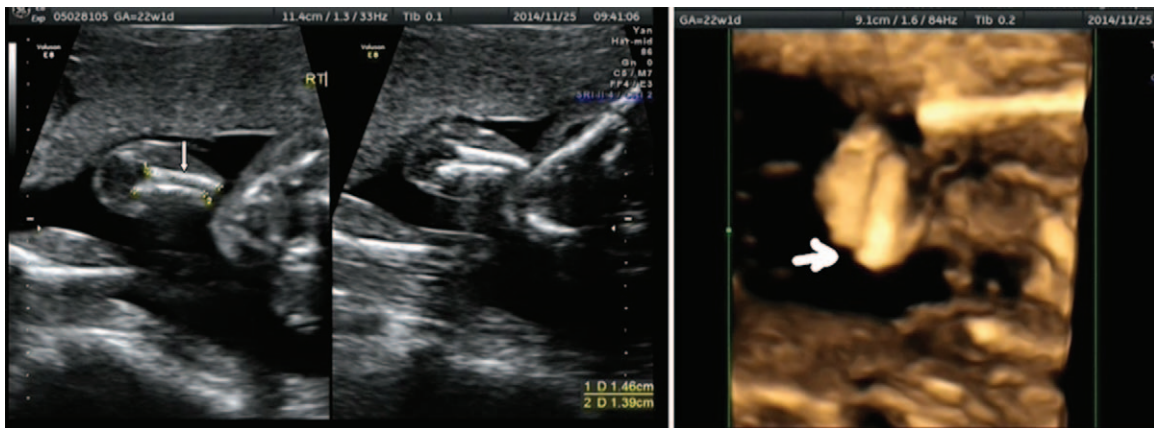
**Combined deformity.**

Combined deformity	n (%)
Cardiac deformities	41 (28.7%)
Urinary tract anomalies	11 (7.7%)
Neurological disorders	20 (14.0%)
Others	28 (19.6%)
Chromosome abnormality	4/27 (14.8%)

which is probably because only high-risk pregnant women were included. Indeed, maternal risk factors for congenital malformations include age ( $\geq 35$  years old), family history of congenital malformations, abnormal reproductive history, harmful chemical exposure, pregnancy TORCH virus infection, diabetes, hypertension, pregnancy taking glucocorticoid, sedative.<sup>[24–27]</sup>

As shown above, clubfoot/clubhand was the most frequent abnormality, followed by limp dysplasia. A previous study showed that radial aplasia and clubhand are the most frequent abnormalities found in the first trimester,<sup>[19]</sup> corroborating our findings. On the other hand, Liao et al<sup>[11]</sup> showed in a Chinese population that transverse limb reduction defects were the most frequent. Meanwhile, a study from The Netherlands indicated that polydactyly was the most frequent defect.<sup>[2]</sup> Discrepancies among studies could be due to small sample size and population differences.

The present study showed that fetal limb abnormalities were often found in combination with other bone and cardiac abnormalities, which in themselves could be fatal or result in



**Figure 8.** Partial limb deletion. In this fetus (22 weeks and 1 day), the right forearm ulnar was short, and the right hand was missing.

**Table 2**

**Correlation univariate analysis of mother characteristics between fetal limb deformities and other congenital malformations.**

Risk factors	$\beta$	S.E.	Wald	P value	OR value (95% CI)
Age	1.02	0.508	4.04	.044	2.774 (1.026–7.504)
Family history of congenital malformations	−0.057	0.588	0.01	.922	0.944 (0.298–2.990)
Abnormal reproductive history	0.454	0.44	1.068	.301	1.575 (0.665–3.729)
Harmful chemical exposure	−0.01	0.337	0.001	.977	0.990 (0.511–1.918)
TORCH infections	−0.053	0.657	0.007	.935	0.948 (0.262–3.435)
GDM	0.372	0.412	0.813	.367	1.150 (0.646–3.254)
Hypertension	−0.641	0.538	1.42	.223	0.527 (0.184–1.512)
Taking glucocorticoid	−0.317	0.811	0.153	.695	0.728 (0.149–3.566)
Taking sedatives	−0.093	0.478	0.038	.846	0.911 (0.357–2.324)

GDM=gestational diabetes mellitus, TORCH=toxoplasmosis, other (syphilis), rubella, cytomegalovirus (CMV), herpes simplex virus (HSV).

poor prognosis. Indeed, multiple limb abnormalities are associated with vascular factors,<sup>[28]</sup> which can be related to other developmental defects. Nevertheless, our findings indicated that ultrasound could be used to guide the next step of pregnancy management. Indeed, the presence of fetal limb abnormalities could lead to the recommendation of pregnancy termination. It should be stressed that counseling should be tailored to each specific case; for example, in case of strephenopodia, medical treatment could be suggested. Of course, the parents have the final call.

Additional analyses were done to identify which factors were more closely associated with fetal limb deformities compared with other congenital malformations. Fetal limb deformity cases had a significantly higher rate than other congenital malformations for advanced maternal age ( $\geq 35$  years old), but there was no significant difference between the incidence of congenital malformation, abnormal reproductive history, harmful chemical exposure, pregnancy TORCH virus infection, diabetes, hypertension, pregnancy taking hormones, and sedatives in fetal limb deformities compared with other congenital malformations.

Two early studies of prenatal limb defects did not examine the pattern of occurrence according to maternal age,<sup>[29,30]</sup> while another study<sup>[31]</sup> demonstrated a positive relation between maternal age and increasing birth prevalence of fetal limb deformities. Here, we also reached similar conclusion that advanced maternal age ( $\geq 35$  years old) should also be a risk factor more related to fetal limb deformities amongst gestational risk factors leading to congenital malformations, for which more elaborate and frequent examinations during the pregnancy should be done for them to screen for potential limb deformities.

Ultrasound for structural abnormality screening is a convenient, inexpensive, and highly accepted procedure, making it one of the most common diagnostic procedures for prenatal evaluation performed in an office setting without anesthesia.<sup>[28]</sup> It can provide adequate evidence for prenatal structural abnormality evaluation in most patients.<sup>[2]</sup> The high sensitivity and specificity of ultrasound for the detection of structural abnormalities are widely accepted.<sup>[1,8,10,15,19,32]</sup>

The present study had some limitations. First, the sample size was relatively small, with the subjects being from a single center. Secondly, its retrospective nature limited data availability. In particular, no data were available regarding folic acid supplementation or pollutant exposure. Additional studies are required to refine and supplement the present results. In addition, more investigations need to be done for further analysis on risk factors such as abnormal reproductive history, harmful chemical exposure, pregnancy TORCH virus infection, diabetes, hypertension, pregnancy taking glucocorticoid, sedative. An additional problem, so far not evaluated, is that parental age may be a confounder.

In conclusion, fetal limb deformity cases showed a significantly higher rate than other congenital malformations for advanced maternal age ( $\geq 35$  year old).

### Author contributions

YS and XL contributed to the acquisition of data, or analysis and interpretation of data; FK and XL contributed to conception and design; XL, YS, BZ and FK have been involved in drafting the manuscript or revising it critically for important intellectual content; all authors have given final approval of the version to be published.

**Data curation:** XiLian Li.

**Formal analysis:** XiLian Li.

**Funding acquisition:** FanBin Kong.

**Investigation:** XiLian Li.

**Project administration:** FanBin Kong.

**Resources:** Bin Zhang, XiLian Li.

**Software:** Yue Shi.

**Supervision:** FanBin Kong.

**Validation:** Bin Zhang.

**Writing – original draft:** XiLian Li.

**Writing – review & editing:** Yue Shi.

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