Int J Clin Exp Med 2018;11(11):12225-12231
www.ijcem.com /ISSN:1940-5901/IJCEM0072936

Original Article

Clinical study of real-time three-dimensional ultrasonography in diagnosis of fetal limb deformities

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Received January 17, 2018; Accepted June 25, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Objective: The aim of this study was to investigate the clinical value of real-time dynamic three-dimensional ultrasonography (3D US) in prenatal diagnosis of fetal limb deformities. Methods: A total of 272 consecutive high-risk pregnant women were examined by two-dimensional ultrasonography (2D US) and 3D US during pregnancy. Ultrasonographic results were compared with those of induced abortions and full-term deliveries. Two-dimensional US examinations were directly followed by dynamic 3D US data acquisition. A physician, blinded to 2D US results, independently analyzed dynamic 3D US images, making a diagnosis. Results of 2D US and 3D US were statistically compared. Results: There were 30 fetuses with limb deformities in this study. Prenatal 3D US diagnosed limb deformities in 27 fetuses while missing the diagnosis in 3 fetuses. Sensitivity, specificity, accuracy, and positive and negative predictive values of real-time 3D US in diagnosis of fetal limb deformities were 90.0%, 99.1%, 98.1%, 93.1%, and 98.7%, respectively. Sensitivity and positive predictive values were significantly better in 3D US than in 2D US ($P<0.05$). Conclusion: Real-time dynamic 3D US can significantly improve sensitivity and positive predictive values of prenatal diagnosis of fetal limb deformities. The acquired images are lively and vivid, helping clinicians and patients comprehensively and systematically understand the anatomic malformation of fetal limbs. These images can provide objective evidence for a clinical regimen and demonstrate the diagnostic value of 3D US.

Keywords: Dynamic, three-dimensional ultrasonography, limb, fetal deformity

Introduction

Fetal limb deformity is a skeletal deformity, with an incidence of approximately 0.2% in domestic and international literature. Multiple deformities and affected segments have been reported but the underlying causes remain complex [1]. Post-natal survival and quality of life are seriously compromised in fetuses with severe congenital malformations. The infants and their families suffer from terrible pain. Moreover, infants with limb deformities may have accompanying cardiac, urinary, neurological, and chromosomal abnormalities. To this end, fetal limb prenatal ultrasonography examinations have drawn more and more attention. In the past, 2D US was a major modality for prenatal diagnosis of limb deformities, with detection rates ranging from 23% to 50%. Its accuracy is highly associated with the sonographer's clinical experience and technical skills. Furthermore, 2D US captures planar images. These have certain limitations for diagnosis and can be easily affected by fetal posture, amniotic fluid amount, and maternal conditions [2, 3]. It is a great challenge to detect all fetal limb deformities by means of prenatal ultrasonography, particularly distal fetal limb deformities. There remains a high rate of missed diagnosis. Compared with 2D US imaging, 3D US imaging can provide richer information in 3D images, offsetting the drawbacks of two-dimensional ultrasound images. Three-dimensional US has become a completely new modality for diagnosis of fetal limb deformities and an important complement of 2D US. The purpose of this work was to investigate the clinical value of real-time dynamic 3D US in prenatal diagnosis of fetal limb deformities.

Materials and methods

Patients

Between September 2016 and November 2017, 272 pregnant women undergoing prenatal ultrasonography in the Department of Ultrasonography were recruited for this study. Their mean age was 28.5 ± 5.1 years (range: 21 to 40 years). Mean fetal gestational age was 25.0 ± 4.1 weeks (range: 21 to 32 weeks). All study subjects had one of the following high-risk factors: suspected fetal abnormalities during two-dimensional ultrasonography or prenatal examination, abnormal delivery history, exposure to X-rays, history of intrauterine infection, and medication administration during pregnancy. All subjects in this study voluntarily signed consent to receive two-dimensional and dynamic three-dimensional ultrasonography and to share the results of induced abortion or full-term delivery. All subjects volunteered to participate and signed an informed consent form prepared by the Ethics Committee.

Equipment

GE-Voluson E8 and GE-Voluson 730 Expert ultrasound systems (GE Medical Systems/Kretztechnik GmbH, Zipf, Austria), equipped with a two-dimensional convex vibration transducer (3 and 5 MHz) and a RAB4-8-D volumetric transducer (2 and 8 MHz), were used in this study.

Two- and three-dimensional ultrasonography

The pregnant women laid down in a supine position. Two-dimensional US was performed on the fetus, including scans of the fetal head, face, spine, chest, abdominal organs, umbilical cord, placenta, and amniotic fluid. Measured data and acquired images were saved. Sequential ultrasound scans along the long axes of the fetal limbs from the proximal end to the distal end were used to examine long- and short-axis planes of the limbs to determine the presence or absence, length, number, shape, structure, posture, positional relationship, and movement of limbs or long bones. Entire limb images included long bones, joints, palms, plantar sole, fingers, and toes. Two-dimensional US examination was directly followed by dynamic 3D US data acquisition. A physician, blinded to 2D US results, independently collected the data from dynamic 3D US. The 3D/4D (dynamic three-dimensional) program was initiated under the selection of surface mode, maximum transparent imaging mode, focus adjustment, capture frame size, and capture line slope to scan any fetal anomalies. If 3D mode was selected for three-dimensional reconstruction, the image was rotated and cropped on the X, Y, and Z axes to display a three-dimensional image in multiple views. Surface imaging mode was selected to display the external structural features of regions of interest, including contour, edge, shape, superficial attachments, and surface defects. Maximum transparent imaging mode displays the reconstruction of the structure with transparent view and three-dimensional texture. As with a radiograph, this mode can examine the internal features of bone structure. Four-dimensional mode can perform real-time scanning, showing real-time three-dimensional fetal dynamic images. Finally, the acquired images were stored on a hard disk and diagnostic results were documented.

Followup

Follow up examinations were performed for fetuses with prenatally diagnosed limb deformities. Fetal visual inspections after childbirth or autopsies after induced abortion and radiography were used to confirm whether limb deformities were present. Some fetuses with multiple limb deformities were accompanied by other abnormalities. Postpartum results were compared with prenatal ultrasound findings.

Statistical analysis

Statistical analyses were performed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA) software package. Continuous variables are expressed as mean ± standard deviation (SD). Pearson's x^2 or Fisher's exact test were applied for comparison of 3D US with 2D US in diagnosis of fetal limb deformities. Statistical examinations were performed by matched McNemar x^2 tests to compare results of fetal 2D US and 3D US examinations. $P<0.05$ was considered statistically significant. $P<0.01$ was considered a statistically significant difference while $P>0.05$ was considered to be indicative of no statistical differences.

Results

Ultrasound examination

Experimental data from induced abortions or full-term deliveries were available from the 272 pregnant women. A total of 30 cases of limb

Table 1. Category and number (cases) of deformities diagnosed by 3D US

Limb deformity (categories)	N (cases)	Upper limb deformity (sites)	Lower limb deformity (sites)
Short limb	4	Bilateral upper short limbs (8)	Bilateral lower short limbs (8)
Absence of the radius	2	Absence of the right radius (2)	
Absence of metacarpal bones	2	Absence of the right metacarpal bones (2)	
Polydactyly (finger)	3	Polydactyly of the right hand (3)	
Ectrodactyly (finger)	2	Ectrodactyly of the left hand (2)	
Syndactyly (finger)	1	Syndactyly of the left hand (1)	
Split hand	2	Left split hands (2)	
Abnormal hand posturing	2	Bilateral clawhand (4)	
Clubfoot	4		Bilateral clubfoot (8)
Polydactyly (toe)	2		Polydactyly of the right foot (2)
Ectrodactyly (toe)	2		Ectrodactyly of the right foot (2)
Syndactyly (toe)	1		Syndactyly of the right foot (1)
Total 12	27	24	21

3D US, three-dimensional ultrasonography; N, number.

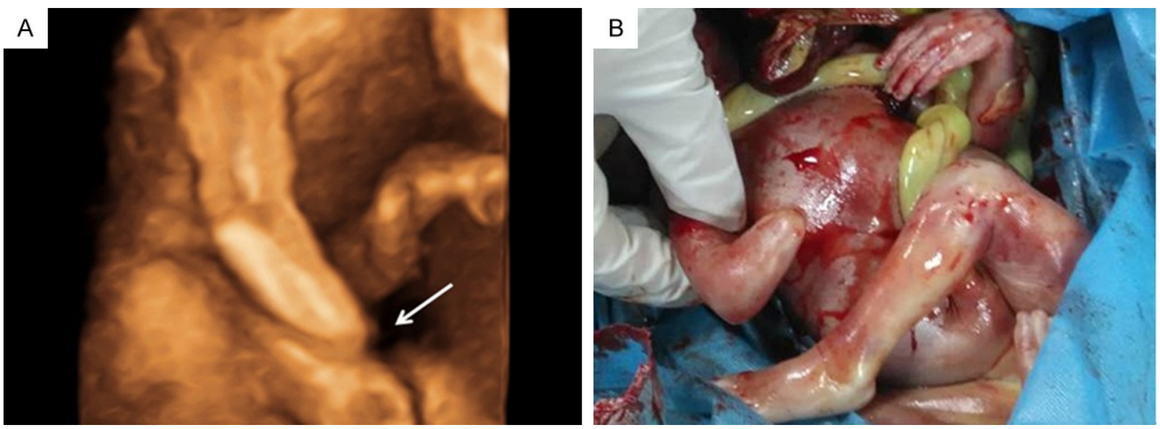

Figure 1. Absence of right metacarpal and phalangeal bones in a fetus at 21 weeks gestation. A. Three-dimensional ultrasonographic image showing the absence of the right metacarpal and phalangeal bones (arrows); B. Diagnosis was confirmed by specimens from the induced abortion.

deformities were identified. Of the 30 cases, 27 cases of limb deformities were diagnosed by 3D US, including 45 deformities in the 12 categories of deformities (**Table 1**). Upper limb deformities were divided into 8 categories with 24 deformities, including short limbs, absence of the radius, absence of metacarpal bones (**Figure 1**), polydactyly (finger) (**Figure 2**), ectrodactyly (finger), syndactyly (finger), split hand, and abnormal hand posturing (**Figure 3**). Lower limb deformities were divided into 5 categories at 21 sites, including short limbs, clubfoot, polydactyly (toe), ectrodactyly (toe) (**Figure 4**), and syndactyly (toe). Most of these deformities were accompanied by other deformities including hydrocephalus, cleft lip and palate, spina bifida, ventricular septal defect, endocardial cushion defect, double-outlet right ventricle, pleural effusion, renal agenesis, acromphalus, and single umbilical artery. Missed diagnoses by 3D US included abnormal hand posturing (1 case) and absence of partial phalanges (2 cases).

Comparison of diagnoses of fetal limb deformities

Results of 2D US and 3D US are shown in **Table 2**. Compared with 2D US, 3D US showed significantly higher sensitivity and positive predictive values in diagnosis of fetal limb deformities ($P<0.05$) (**Table 3**).

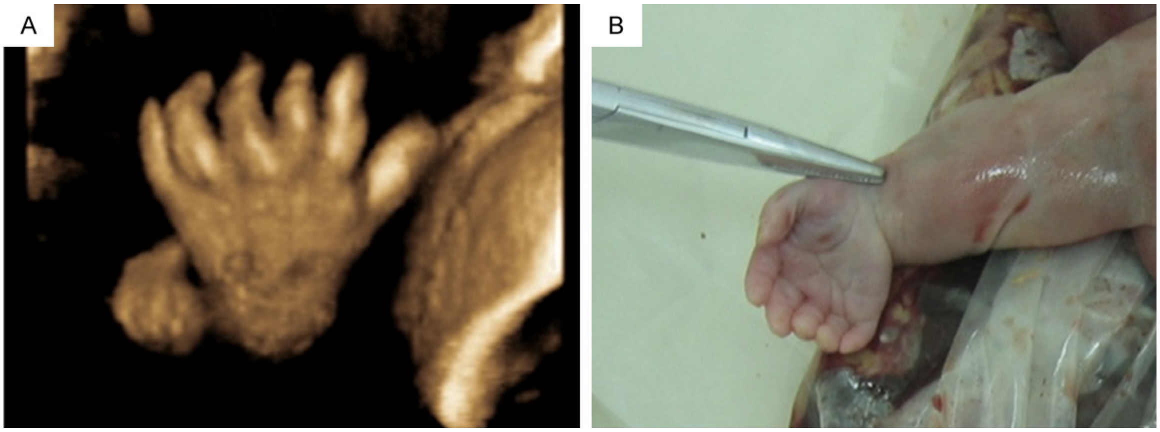

Figure 2. Polydactyly of the right hand in a fetus at 23 weeks gestation. A. Three-dimensional ultrasonographic image showing polydactyly of the right hand; B. Diagnosis was confirmed by specimens from the induced abortion.

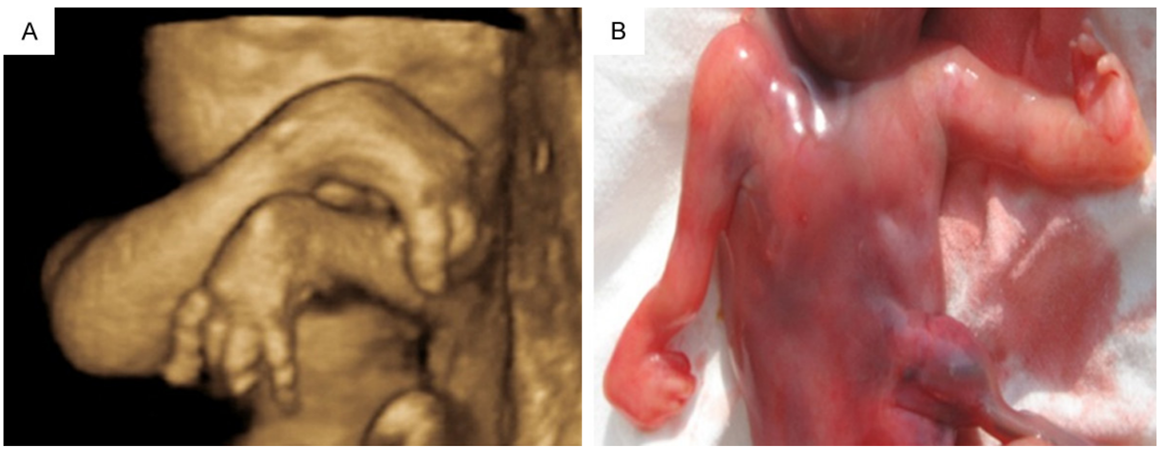

Figure 3. Abnormal hand posturing in a fetus at 18 weeks gestation. A. Three-dimensional ultrasonographic image showing bilateral clawhand; B. Diagnosis was confirmed by specimens from the induced abortion.

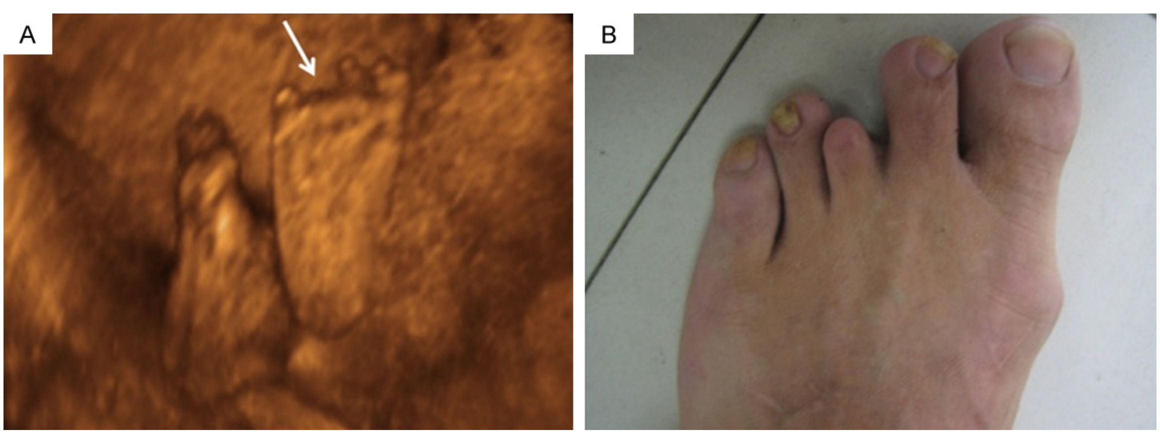

Figure 4. Ectrodactyly in a fetus at 26 weeks gestation. A. Three-dimensional ultrasonographic image showing ectrodactyly (arrows); B. The presence of ectrodactyly in the fetus' father.

Table 2. Results of fetal 2D US and 3D US examinations

Examining method	Postpartum Result: Deformity	Postpartum Result: Normal	Total	*P*-value
3D US				
Deformity	27	2	29	<0.001
Normal	3	240	243	
2D US				
Deformity	10	17	27	<0.001
Normal	20	225	245	

3D US, three-dimensional ultrasonography; 2D US, two-dimensional ultrasonography.

Chromosomal testing

Of the 30 cases of fetal limb deformities, 4 cases received prenatal chromosomal examination, which was unremarkable. Two cases of fetal limb deformities manifested as short limbs, clubfoot, polydactyly, cleft lip, endocardial cushion defect, low-set ears, narrow sternum, and lung dysplasia. The latter two fetuses were from different gravidities in the same woman. Postnatal chromosome examination indicated Trisomy 18 syndrome.

Discussion

Fetal congenital limb deformity refers to fetal limb skeletal and soft tissue morphological abnormalities caused by various endogenous and exogenous factors, including genetic and non-genetic factors present during fetal development [4-6]. The incidence rate reported in domestic and international literature is approximately 0.2% [7, 8]. Fetal limb deformity is often associated with chromosomal abnormalities, such as Trisomy 13 syndrome, often associated with polydactyly, and Trisomy 18 syndrome, often complicated by short limbs, clubfoot, abnormal finger posturing, and overriding fingers. A higher correlation between Trisomy 18 syndrome and overriding fingers has been shown [9-11]. One study by Spencnck et al. has shown that multiple fetal malformations are significantly associated with chromosomal abnormalities [12]. A high number of malformations is correlated with greater possibility of chromosomal abnormalities, especially in the presence of central nervous system malformations. The presence of abnormal limbs is considered an important indication for screening for chromosomal abnormalities.

In recent years, dynamic 3D US has emerged as a completely new modality for diagnosis of fetal limb deformities and as an important complement to two-dimensional ultrasonography [13-15]. Compared with 2D US imaging, 3D US imaging can visualize the superficial structure of the fetus, observe images from all angles, accurately assess the degree of defects, and reconstruct the most easily understood image, making it useful for diagnosis of some deformities. Merz reported two- and three-dimensional ultrasonographic findings of 216 cases of congenital fetal deformities, confirming that in most cases, 3D US was superior to 2D US [16].

It is difficult to diagnose polydactyly (finger) or ectrodactyly (finger) by 2D US alone, but 3D US can accurately accomplish this task [17, 18]. In this study, a case of polydactyly (toe) was missed by 2D US but diagnosed by 3D US in the surface imaging mode. Another case with ectrodactyly (toe) was not diagnosed by 2D US but was diagnosed by 3D US. Moreover, the presence of ectrodactyly in the father indicated that congenital genetic factors may have contributed. The use of three-dimensional surface imaging can show the three-dimensional morphology of the hands, feet, and distal limbs to improve the accuracy of prenatal diagnosis. Therefore, this study demonstrated that, compared with 2D US, 3D US in diagnosis of fetal limb deformities has the following advantages: (1) Dynamic 3D US can quickly and accurately provide vivid three-dimensional volumetric images of fetal limbs. It can visually show the superficial morphology, posture, movement, and relative relationships among various parts of the limbs and the number and arrangement of limb bones. These findings help the sonographer to understand the fetal anatomical structure and spatial orientation, providing a completely new observation mode for diagnosis of fetal limb deformities [19, 20]; (2) It can reduce misdiagnosis rates of ectrodactyly (toes), polydactyly (toes), and abnormal finger posturing present in 2D US examinations and more accurately identify local deformities of fetal limbs [21, 22]. For instance, 2D US showed a smaller right palm, compared with the left palm, and vague metacarpophalangeal bones in a fetus, considering the right-hand developmental abnormalities to be a diagnosis. In contrast, 3D US showed a comprehensive three-dimensional image, displaying a small protruding struc-

Table 3. Comparison of 3D US with 2D US in diagnosis of fetal limb deformities

Examining method	Sensitivity	Specificity	PPV	NPV	Accuracy
3D US	90.0% (27/30)	99.1% (240/242)	93.1% (27/29)	98.7% (240/243)	98.1% (267/272)
2D US	33.3% (10/30)	92.9% (225/242)	37.0% (10/27)	91.8% (225/245)	86.3% (235/272)
χ^2	4.985	0.247	4.175	0.315	1.062
P-value	0.034	0.649	0.041	0.604	0.322

3D US, three-dimensional ultrasonography; 2D US, two-dimensional ultrasonography; NPV, negative predictive value; PPV, positive predictive value.

ture in the distal right forearm and absence of normal metacarpal and phalangeal bony structures. Thus, absence of the right metacarpal and phalangeal bones was diagnosed.

Dynamic three-dimensional ultrasonography for screening of fetal limb deformities has some limitations [23-25]. For instance, oligohydramnios may affect the diagnostic accuracy of fetal malformations. During late gestation, unmovable fetal position, fetal body interference, and frequent limb movement will affect the diagnostic accuracy of 3D US. In this study, a case of hand posture abnormalities was overlooked by 3D US because wrist posture and hand movements were not carefully observed. When abnormal hand posturing is suspected, repeated observation of hand posture in different views is recommended. Reasons for the missed diagnoses in 2 cases of ectrodactyly may be related to poor fetal positioning and less amniotic fluid in late gestation.

In summary, dynamic 3D US can view fetal limbs in three-dimensional images. These are better than the cross-sectional images offered by 2D US. Its advantages include offline analysis, multiple imaging methods, speedy imaging, direct imaging, detailed dynamic volumetric imaging, and clear imaging of anatomical relationships. Thus, 3D US is considered a nice complement to traditional 2D US for viewing limbs and improving sensitivity of prenatal diagnosis of fetal limb deformities, thereby minimizing deformed births and playing an important role in improving the quality of fetal screening.

Acknowledgements

This work was supported financially by Jiangxi Provincial Department of Science and Technology (NO: 20161BBI90053).

Disclosure of conflict of interest

None.

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References

[1] Gramellini D, Fieni S and Vadora E. Prenatal diagnosis of isolated limb defects: an updated review. Fetal Diagn Ther 2005; 20: 96-101.

[2] Nemec SF, Nemec U, Brugger PC, Bettelheim D, Rotmensch S, Graham JM Jr, Rimoin DL and Prayer D. MR imaging of the fetal musculoskeletal system. Prenat Diagn 2012; 32: 205-213.

[3] Dicke JM, Piper SL and Goldfarb CA. The utility of ultrasound for the detection of fetal limb abnormalities--a 20-year single-center experience. Prenat Diagn 2015; 35: 348-353.

[4] Dyson RL, Pretorius DH, Budorick NE, Johnson DD, Sklansky MS, Cantrell CJ, Lai S and Nelson TR. Three-dimensional ultrasound in the evaluation of fetal anomalies. Ultrasound Obstet Gynecol 2000; 16: 321-328.

[5] Garjian KV, Pretorius DH, Budorick NE, Cantrell CJ, Johnson DD and Nelson TR. Fetal skeletal dysplasia: three-dimensional US--initial experience. Radiology 2000; 214: 717-723.

[6] Pooh RK, Nakagawa Y, Pooh KH, Nakagawa Y and Nagamachi N. Fetal craniofacial structure and intracranial morphology in a case of apert syndrome. Ultrasound Obstet Gynecol 1999; 13: 274-280.

[7] Lu J, Vaidya N, Meng H, Dai Q, Romine LE, Jones MC and Pretorius DH. Prenatally diagnosed fetal split-hand/foot malformations often accompany a spectrum of anomalies. J Ultrasound Med 2014; 33: 167-176.

[8] Andrikopoulou M, Vahanian SA, Chavez MR, Murphy J, Hanna N and Vintzileos AM. Improving the ultrasound detection of isolated fetal limb abnormalities. J Matern Fetal Neonatal Med 2017; 30: 46-49.

[9] Wong WS, Filly RA. Polyhydramnios associated with fetal limb abnormalities. AJR Am J Roentgenol 1983; 140: 1001-1003.

[10] Lu J, Vaidya N, Meng H, Dai Q, Romine LE, Jones MC and Pretorius DH. Prenatally diagnosed fetal split-hand/foot malformations of-

ten accompany a spectrum of anomalies. J Ultrasound Med 2014; 33: 167-176.
[11] Rice KJ, Ballas J, Lai E, Hartney C, Jones MC and Pretorius DH. Diagnosis of fetal limb abnormalities before 15 weeks: cause for concern. J Ultrasound Med 2011; 30: 1009-1019.
[12] Spencer K, Spencer CE, Power M, Dawson C and Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003; 110: 281-286.
[13] Ermito S, Dinatale A, Carrara S, Cavaliere A, Imbruglia L and Recupero S. Prenatal diagnosis of limb abnormalities: role of fetal ultrasonography. J Prenat Med 2009; 3: 18-22.
[14] Noguera-Morel L, Hernández-Ostiz S, Casas-Fernández L, Hernández-Martín A, Rodríguez-Blanco I, Requena L, Hotz A, Fischer J and Torrelo A. CHILD syndrome with minimal limb abnormalities. J Eur Acad Dermatol Venereol 2016; 30: e201-e202.
[15] Stoll C, Wiesel A, Queisser-Luft A, Froster U, Bianca S and Clementi M. Evaluation of the prenatal diagnosis of limb reduction deficiencies. EUROSCAN study group. Prenat Diagn 2000; 20: 811-818.
[16] Merz E. Three-dimensional ultrasound--a requirement for prenatal diagnosis? Ultrasound Obstet Gynecol 1998; 12: 225-226.
[17] Rosa RF, Rosa RC, Lorenzen MB, Zen PR, Oliveira CA, Graziadio C and Paskulin GA. Limb abnormalities on trisomy 18: evidence for early diagnosis. J Pediatr (Rio J) 2012; 88: 401-405.
[18] Alvi F, Alonso A and Brewood AF. Upper limb abnormalities in mosaic trisomy 8 syndrome. Arch Orthop Trauma Surg 2004; 124: 718-719.
[19] Kevern L, Warwick D, Wellesley D, Senbaga R and Clarke NM. Prenatal ultrasound: detection and diagnosis of limb abnormalities. J Pediatr Orthop 2003; 23: 251-253.
[20] Gray BL, Calfee RP, Dicke JM, Steffen J and Goldfarb CA. The utility of prenatal ultrasound as a screening tool for upper extremity congenital anomalies. J Hand Surg Am 2013; 38: 2106-2111.
[21] Stoll C, Alembik Y, Dott B and Roth MP. Associated malformations in patients with limb reduction deficiencies. Eur J Med Genet 2010; 53: 286-290.
[22] Zheng Y, Zhou XD, Zhu YL, Wang XL, Qian YQ, Lei XY, Chen BL, Yu M and Xin XY. Three- and 4-dimensional ultrasonography in the prenatal evaluation of fetal anomalies associated with trisomy 18. J Ultrasound Med 2008; 27: 1041-51.
[23] David AL, Turnbull C, Scott R, Freeman J, Bilardo CM, van Maarle M and Chitty LS. Diagnosis of apert syndrome in the second-trimester using 2D and 3D ultrasound. Prenat Diagn 2007; 27: 629-632.
[24] Zheng LP, Gong LL, Guo FC, Chang HB and Liu GH. Application research on three-dimensional ultrasonic skeletal imaging mode in detecting fetal upper jaw bone. Int J Clin Exp Med 2015; 8: 12219-12225.
[25] Liao YM, Li SL, Luo GY, Wen HX, Ouyang SY, Chen CY, Yao Y, Bi JR and Tian XX. Routine screening for fetal limb abnormalities in the first trimester. Prenat Diagn 2016; 36: 117-126.