

## Original Article

# Application of two-dimensional and three-dimensional ultrasound in prenatal screening for brachydactyly deformity

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**Abstract:** This study aims to summarize the characteristics of prenatal ultrasonography of the fetus with brachydactyly. From November 2015 to December 2016, a total of 10,866 pregnant women underwent prenatal ultrasound screening at the gestational age of 17-26 weeks. Targeted ultrasonographic imaging of the fetal hands was performed. The multi-view observation of fetal fingers by ultrasound was performed at different flexions of fingers (stretching, bending and fist) to observe the ultrasonographic manifestations of metacarpals and phalanges, and the number, size, shape and arrangement of the ossification centers of metacarpals and phalanges. A comparison was performed on the prenatal sonographic findings and the results of follow-up after termination of pregnancy or birth. The prenatal ultrasound detected six cases of brachydactyly. Among these cases, five cases were bilateral and one case was unilateral. In these cases, more than one ossification center of phalanxes were invisible or significantly smaller. Furthermore, among the six cases of brachydactyly, the women of four cases chose to terminate the pregnancy, while the women of the other two cases had no other abnormalities and gave birth. In the two cases with multiple malformations, one case was complicated with osteodysplasty, cleft lip and palate, and pleural effusion, while the other case was complicated with limb body wall complex and malformation of the heart. Overall, our results suggest that the targeted two- and three-dimensional ultrasound imaging of the fetal hands in the second trimester of pregnancy can improve the detection of severe brachydactyly.

**Keywords:** Ultrasound, prenatal, brachydactyly

## Introduction

Brachydactyly literally means short digits. It refers to disproportionately short fingers and toes with absence or underdevelopment of metacarpal or phalange. Generally, the impact of hand deformity on function is higher than that of the foot deformity. Its diagnosis and typing were mainly dependent on X-ray [1]. Since fetal hand was often in the fist state, the ultrasound examination of phalanges is very difficult. In the present study, two- and three-dimensional ultrasound was used to observe the prenatal ultrasonographic features of fetuses with brachydactyly.

## Information and methods

### Subjects

From November 2015 to December 2016, a total of 10,866 pregnant women underwent

prenatal ultrasound imaging in our hospital. The age of these pregnant women ranged within 19-47 years old, with an average age of  $27.6 \pm 6.8$  years old. Furthermore, the gestational age of these fetuses ranged within 17-26 weeks, with an average of  $22.6 \pm 4.7$  weeks. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Renmin Hospital of Wuhan University. Written informed consent was obtained from all participants.

### Instruments and methods

The Voluson E8 and Voluson E10 color Doppler ultrasound diagnostic instruments (GE Healthcare) were used in the present study. The two-dimensional probe frequency was 2.5-5.0 MHz, while the three-dimensional volume probe frequency was 4.0-8.0 MHz.

## Prenatal detection of brachydactyly

The conventional two-dimensional ultrasound examination method: The pregnant woman was in the supine position or lateral position, and the fetus was initially examined by conventional prenatal ultrasound. The targets of the conventional two-dimensional ultrasound examination included the head and face, thoracic and abdominal organs, spine, limbs, placenta, umbilical cord and amniotic fluid. Furthermore, the fetal biparietal diameter, head circumference, abdomen circumference, femur and humerus length were measured to assess the growth of the fetus.

### *Ultrasound examination method for the fetal hand*

Conventional ultrasound examination method for the fetal hand: From the bilateral wrist and the distal end of the ulna and radius, the metacarpals and phalanges were continuously scanned transversely up to the fingertip. For low risk population, we carried out the conventional ultrasound examination for the fetal hand. While for fetuses with odd hand posture and shape, or suspicious abnormality of hands, or other structural abnormality revealed by conventional ultrasound examination, and for pregnant women with adverse pregnancy history and family history of malformation of bones and/or limbs, and for some other high risk patients, it was necessary to carry out targeted ultrasound imaging of the fetal hand. If necessary, the three-dimensional imaging of the hand could be used to observe the shape of the hand. All patients were examined by experienced sonographers.

Targeted ultrasound examination method of the fetal hand: The palms and fingers of both hands were scanned. From the wrist, the coronal sections of the fetus's palm and fingers were continuously scanned until the fingertip. Next, shifting to the transverse section, from the distal end of the wrist's ulna and radius, the metacarpals and phalanges were continuously scanned up to the fingertip. Finally, turning to the sagittal section, the longitudinal axis of each single finger was scanned. If the hands were shielded or compressed, the fetus was properly pushed with the probe, or the pregnant woman was instructed to move outside for 10-20 minutes.

Three-dimensional ultrasound examination method of the fetal hand: The fetal hands were scanned by three-dimensional ultrasound. Then, three-dimensional volume data were acquired and preserved, and the surface imaging was performed. The posture, shape of the hand, and finger shape were observed.

Observation items of the targeted ultrasound examination of the fetal hand: Different manifestations of metacarpal and phalangeal bones in different fingers' flexion states (stretching, bending and fist gripping) were observed on transverse, coronal and sagittal views. The number, size, shape and arrangement of ossification centers in metacarpals and phalanges were observed.

(1) The number of metacarpals and phalanges: No ossification of the fetal carpal bone occurred. There are five metacarpal bones. From the radial side to the ulnar side, they are called the 1<sup>st</sup> to the 5<sup>th</sup> metacarpal. There are 14 phalanges. The thumb has two phalanges, called proximal phalanges and distal phalanges. The 2<sup>nd</sup> to 5<sup>th</sup> fingers have three phalanges, and from the proximal side to the distal side they are called proximal phalanx, middle phalanx and distal phalanx. The ossification centers that were not displayed were recorded.

(2) The size and shape of metacarpals and phalanges: The ossification centers of the metacarpal and phalangeal bones are in the shape of short rod. The metacarpals are longer than the phalanges. And the proximal phalanx is relatively longer than middle and distal phalanx. The size of metacarpals or phalanges of both hands were compared with the contralateral and ipsilateral adjacent metacarpals or phalanges. The sites of significantly smaller ossification centers were recorded and the sizes were measured.

(3) The detection of the crossing and overlapping of metacarpals and phalanges: Under normal conditions, the 2<sup>nd</sup> to 5<sup>th</sup> metacarpals can be displayed on the same coronal or transverse plane. After the probe moves slightly toward the radial side, the first metacarpal bone can be observed. The metacarpals are roughly in a fan-shaped arrangement without crossing. There is no persistent overlap among the 2<sup>nd</sup> to 5<sup>th</sup> fingers. These overlapping sites were recorded.

## Prenatal detection of brachydactyly

**Table 1.** The age, gestational age, concomitant abnormalities, family history and pregnancy outcome of six pregnant women with brachydactyly

No.	Age (years)	Gestational age (weeks)	Concomitant abnormalities	Family history of brachydactyly	Pregnancy outcome
1	25	19	None	+	TOP
2	26	24	None	+	TOP
3	23	17	Multiple abnormal	-	TOP
4	25	22	None	-	birth
5	26	23	Multiple abnormal	-	TOP
6*	25	22	None	+	birth

\*Case 1 and 6 were from two pregnancies for the same woman; + have family history of brachydactyly; TOP, termination of pregnancy.

### *Diagnostic criteria of brachydactyly*

Some phalangeal ossification centers are not displayed. Or some phalangeal ossification centers are spotty or patchy and significantly smaller in size than that of the ipsilateral adjacent phalanx, or that of the contralateral phalanx. The ossification centers of metacarpal bones sometimes invisible or significantly smaller. And the fingers look short.

### *Follow-up*

The results of prenatal ultrasound examination were compared with those of the X-ray examination of the fetal hand after termination of pregnancy. Those who terminated the pregnancy or gave birth in other hospital were followed-up by telephone.

### **Results**

10,866 pregnant women underwent conventional ultrasound examination, of which 532 patients underwent targeted hand examinations. Conventional ultrasound examination for the fetal hand took about half a minute to a minute. Targeted hand examinations took about 1-3 minutes. Three-dimensional hand examination was more dependent on proper fetal position, so it took more time and about 5-15 minutes.

Among the 10,866 pregnant women, prenatal ultrasound revealed that brachydactyly were detected in six cases, while other hand abnormalities were detected in 32 cases. Among these six cases with brachydactyly, case No. 1 and No. 6 were from two pregnancies of the same woman with the family history of brachydactyly, and case No. 2 also had the family history of brachydactyly. The age of these preg-

nant women, gestational age, and family history of brachydactyly were presented in **Table 1**.

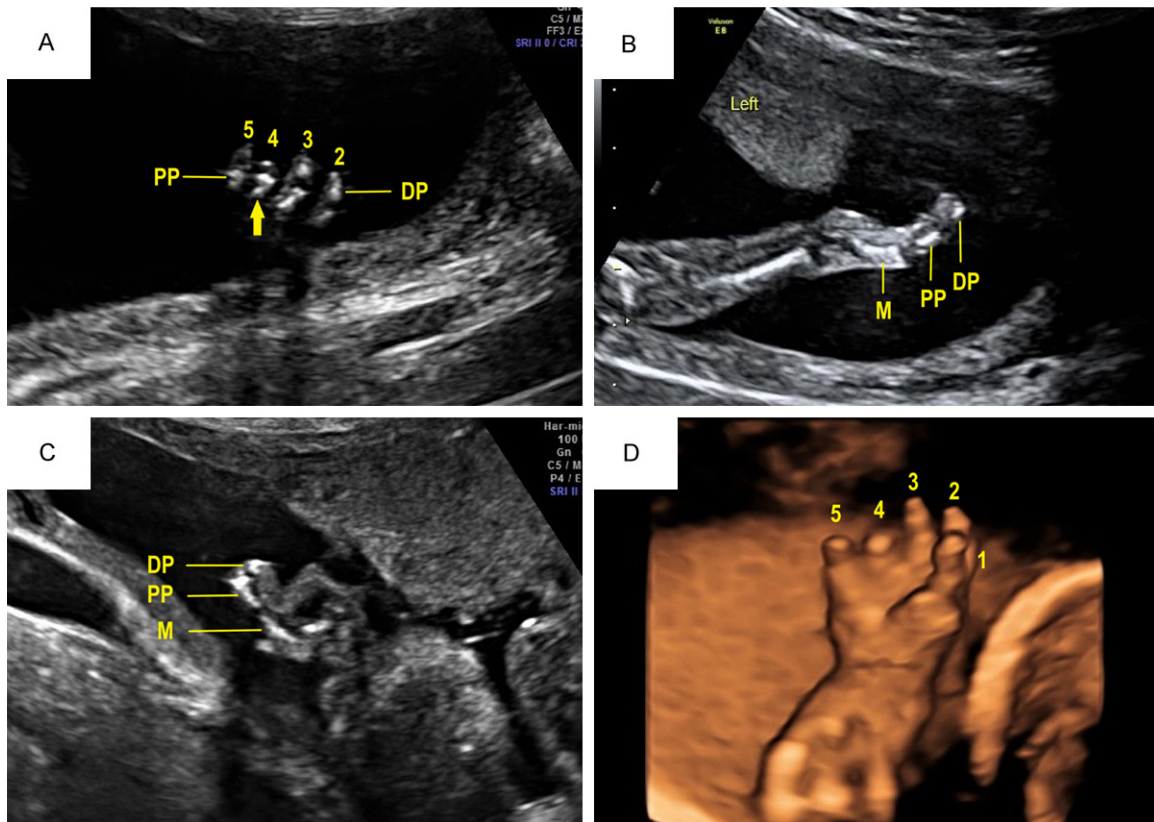
### *Characteristics of the sonogram*

Among the six cases with brachydactyly, the ossification centers of bilateral multiple phalanges were not displayed or significantly smaller in five cases (**Figure 1A**), while the ossification centers of the middle phalanx of the unilateral 2<sup>nd</sup>-5<sup>th</sup> fingers were not displayed in case No. 4. The prenatal lesion sites of ossification centers of the hand were presented in **Table 2**. When the fingers were stretching, the fingers on the sagittal sections were I-shaped (**Figure 1B**). When the fingers were bending, the fingers were L-shaped (**Figure 1C**). All these fetuses did not have a clenched fist. Three-dimensional ultrasound revealed that some fingers were significantly shorter than the adjacent fingers (**Figure 1D**), or the length of some fingers was equal to or shorter than the thumb (**Figures 1D, 2A**). In two cases, the duplicated distal phalanges of the bilateral thumbs were detected (**Figure 2B, 2C**), and it was observed that the thumb was wide (**Figure 2A**). In one patient, the ossification centers of the bilateral third metacarpal bones were not displayed or significantly smaller.

### *Pregnancy outcomes*

Among the six cases with brachydactyly, two cases were accompanied by multiple malformations (**Table 1**), while no other abnormalities were found in the remaining four patients. In the two patients with multiple malformations, one patient was complicated with osteodysplasty, cleft lip and palate, and pleural effusion, while the other was complicated with limb-body wall syndrome and cardiac malformation.

## Prenatal detection of brachydactyly



**Figure 1.** Prenatal two-dimensional and three-dimensional ultrasound images of brachydactyly. A. The coronal section of the 2<sup>nd</sup>-5<sup>th</sup> fingers of the right hand of the brachydactyly fetus was revealed. The 4<sup>th</sup> finger (arrow) was obviously shorter than the 3<sup>rd</sup> and 5<sup>th</sup> fingers. The numbers of ossification centers of phalanxes in the 4<sup>th</sup> and 5<sup>th</sup> fingers looked obviously fewer than the adjacent fingers. B. The sagittal section of the stretching short finger was shown. Only proximal and distal phalanges could be observed. The longitudinal axis of the two phalanges formed an I-shaped line. C. The sagittal section of the bending short finger was observed. Only two phalanges could also be observed. The longitudinal axis of the two phalanges formed a L-shape. D. The three-dimensional ultrasonic imaging of the right hand was shown. The 4<sup>th</sup> and 5<sup>th</sup> fingers looked obviously shorter than the other fingers, and the 4<sup>th</sup> finger was the shortest one. PP: proximal phalanx, DP: distal phalanx, M: metacarpal bone.

Among the six cases with brachydactyly, four cases elected to terminate the pregnancy, while the pregnancy of two fetuses continued to birth. Among the four cases terminating of pregnancy, two patients were accompanied by multiple malformations, while the other two patients were with family history of brachydactyly and detected to have only brachydactyly. The patient No. 4 had no family history of brachydactyly and no other malformations, so she continued pregnancy to birth. Although having the family history of brachydactyly, the case No. 6 continued pregnancy to birth too, that was the second pregnancy of the woman of the case No. 1.

The gross specimen of these four abortus revealed that the fingers were significantly short (Figure 2D), and the results of the hand X-ray

examination were consistent with those of the prenatal ultrasound examination. However, in one patient, the duplication of the distal phalanges of the thumbs was neglected prenatally. No other abnormalities were found during the follow-ups for the two patients after birth. Only the appearance of the hands was smaller, but no impairment of hand function was found. The follow-up of the woman of the case No. 2 revealed that she bore a normal baby without short digits at the next pregnancy.

### Discussion

#### *Characteristics of the development of ossification of the hand bones*

At the 8<sup>th</sup>-9<sup>th</sup> gestational week, the early ossification centers of the long bones of all limbs

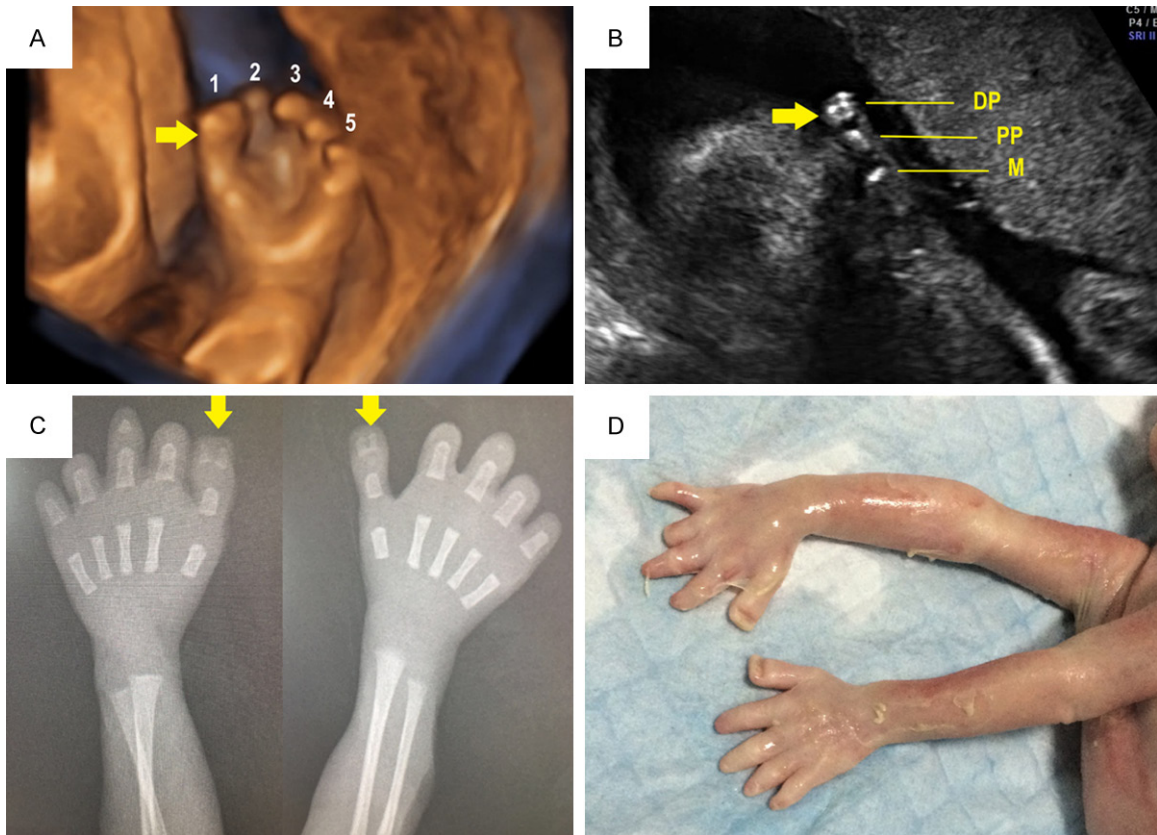
## Prenatal detection of brachydactyly

**Table 2.** The prenatal lesion sites of ossification centers of the hand in six patients with brachydactyly

NO.	Lesion sites									
	L1	L2	L3	L4	L5	R1	R2	R3	R4	R5
1	Duplication of distal phalanx	Middle phalanx absent, distal phalanx small	Middle phalanx absent, distal phalanx small	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Duplication of distal phalanx	Middle phalanx absent, distal phalanx small	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Middle, distal phalanx absent
2	Duplication of distal phalanx	Middle, distal phalanx absent	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Middle, distal phalanx absent	Duplication of distal phalanx	Middle, distal phalanx absent	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Middle, distal phalanx absent
3	(-)	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent	(-)	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent
4	(-)	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent	Middle phalanx absent	(-)	(-)	(-)	(-)	(-)
5	(-)	Middle phalanx absent	Middle phalanx absent, metacarpals small	Middle phalanx absent	Middle phalanx absent	(-)	Middle phalanx absent	Middle phalanx absent, metacarpals absent	Middle phalanx absent	Middle phalanx absent
6	(-)	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Middle, distal phalanx absent	Middle, distal phalanx absent	(-)	Middle phalanx absent, distal phalanx small	Middle, distal phalanx absent	Middle, distal phalanx absent	Middle, distal phalanx absent

L1: Left thumb; L2: Left index finger; L3: Left middle finger; L4: Left ring finger; L5: Left little finger; R1: Right thumb; R2: Right index finger; R3: Right middle finger; R4: Right ring finger; R5: Right little finger; (-): no abnormalities.

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**Figure 2.** Prenatal two-dimensional and three-dimensional ultrasound images of the wide thumb of brachydactyly fetus. A. The wide thumb (arrow) was shown by the three-dimensional ultrasound. B. The coronary section of the wide thumb was shown. The distal phalanx of the fetal thumb is duplicated (arrow). C. X-ray examination of fetal short fingers after termination of pregnancy was shown. Multiple phalanges were invisible and some phalanges were obviously smaller. Especially, duplicated distal phalanges of bilateral thumbs could be observed (arrow). D. The gross examination of fetal hand after termination of pregnancy was shown. The thumb was wide and the other fingers were short. PP: proximal phalanx, DP: distal phalanx, M: metacarpal bone.

(humerus, femur, radius, ulna, tibia and fibula) appear. After the 11<sup>th</sup> gestational week, all of these can be stably displayed and accurately measured by ultrasound [2]. At the 13<sup>th</sup> gestational week, the metacarpal bones, the two phalanges of the thumb, and the proximal and distal phalangeal bones of the remaining fingers are all ossified. At the 14<sup>th</sup> gestational week, the middle phalanx of the second and third fingers becomes completely ossified. At the 15<sup>th</sup> gestational week, the middle phalanx of the fourth finger becomes completely ossified. At the 17<sup>th</sup> gestational week, the middle phalanx of the fifth finger becomes completely ossified. Then, the carpal bones are ossified after birth [2, 3]. After the appearance of the ossification centers of the fetal hands, these can be clearly displayed by ultrasound. Therefore, serious abnormalities in the upper extremities and hands can be found by ultra-

sound during the first and second trimester [4-6].

### *Brachydactyly*

Brachydactyly is a congenital abnormality that is characterized by disproportionately short digits. It is due to absent, rudimentary metacarpals, metatarsals, and/or phalanges, or a combination of them. Brachydactyly can appear alone, or be accompanied by other hand malformations, such as reduction defects, polydactyly, syndactyly, or symphalangism, or serve as one of the clinical manifestations of complex syndromes [7], such as Albright hereditary osteodystrophy [8], Feingold syndrome [9], 2q37 microdeletion [10], 6p25 microduplication [11], Robinow syndrome [12] and Rubinstein-Taybi syndrome [13]. In the present study, two fetuses with multiple malformation

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chose to terminate the pregnancy. In addition to the impact of appearance and psychological injury, isolated brachydactyly has no lethality. A part of patients with isolated brachydactyly can be accompanied by hypoplastic nails. In the present study, one patient with isolated brachydactyly without the family history of brachydactyly determined to continue pregnancy after fully counselling. After birth, merely one hand had a smaller size, and no impaired hand function was found in the newborn.

Brachydactyly has obvious family genetic tendencies. Most solitary brachydactyly are autosomal dominant inheritance. Studies have revealed that a series of pathogenic gene loci PDE3A [14], PTHLH [15], PRMT7 [16], GDF5 [17] and IHH [18] were correlated to brachydactyly. In the present study, among the six cases, isolated brachydactyly were found in both the first pregnancy (case No. 1) and the second pregnancy (case No. 6) of the same woman, while a patient with family history of brachydactyly gave birth to a normal baby after the termination of pregnancy of the first fetus of isolated brachydactyly (case No. 2). It implied the recurrence risk of brachydactyly is uncertain.

Brachydactyly has many types, and its typing mainly depends on the anatomical basis. Bell first classified brachydactyly in 1951. In 1978, Temtamy and McKusick further perfected the classification of brachydactyly [19], and divided it into five different types: types A to E. All these types have multiple subtypes. However, the above classifications are based on children, adolescents and even adults, making it not entirely suitable for fetuses. Furthermore, it is difficult to examine fetal fingers, which can be easier detected only when multiple phalanges are abnormal. In the present study, all six patients had multiple phalangeal abnormalities.

### *Prenatal ultrasound imaging for brachydactyly*

The fingers of fetuses in early pregnancy tend to keep stretching, while they are mostly bending or fist gripping in the second and third trimester, and are easily sheltered by other parts of the fetal body. These reduce the possibility and improve the difficulty of examining fetal fingers by ultrasound. Therefore, the sensitivity of prenatal ultrasound for detection of isolated finger abnormalities is low. The ideal window for

visualizing the fetal hands is thought to be at the late first and early second trimester [20]. The present study revealed that all the six patients with brachydactyly were detected at the 17<sup>th</sup>-24<sup>th</sup> gestational week.

The number of fingers of most brachydactyly fetuses was normal. Therefore, in addition to observing the number of fetal fingers, there was a need to carefully examine each metacarpal and phalangeal bone, in order to avoid missed diagnosis. In particular, the high risk patients should be given the targeted ultrasound examination of the fetal hand, such as for fetuses with abnormal odd hand posture and shape, or suspicious abnormality of fingers, or other structural abnormality revealed by conventional examination, and for pregnant women with adverse pregnancy history and family history of malformation of bones and/or limbs. In these conditions, simple scanning transversely of conventional ultrasound examination of fetal hand is not enough. Multiple views scanning of the targeted ultrasound examination is much better. Prenatal two-dimensional ultrasound examination is mainly conducted on the transverse and coronal sections of the fingers, which can reveal the abnormal number of fingers, and even can reveal the abnormal number of phalanges when the hand is entirely open. But when only parts of fingers can be displayed in coronal section, it is difficult to distinguish between brachydactyly and the clenched fist. At this time, the sagittal sections of the fingers become much more important. The fingers of brachydactyly fetuses would be difficult to undergo clenching of the fist, and can only be stretched, slightly curved, or undergo half of a clenching fist. So the short fingers can be observed in sagittal section to be I-shaped or L-shaped. And it was easy to detect abnormalities of the number and/or size of ossification centers in sagittal section of the fingers.

Patients with brachydactyly need to focus on thumb examination, because the absence or severe dysplasia of the thumb would affect hand function. When the hand is curved or at a clenching fist, the thumb and the other four fingers would not always be in the same plane. In addition, the thumb sometimes is encased by the clenching fist of the four fingers. Therefore, it is difficult to display the thumb by ultrasound.

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Thumb scanning is mainly conducted on the longitudinal plane. It displays the ossification centers of one metacarpal and two phalangeal bones. But a need for multi-view scanning still remains. In the present study, we lacked the understanding of the duplicated distal phalange of the thumb at first, which led to a missed diagnosis of duplicated phalanges in one patient of brachydactyly. Afterwards, the thumb was scanned on multiple views, and the duplication of thumb phalanges was found in another patient.

Although three-dimensional ultrasound is helpful for observing the shape of the hand, it is difficult to distinguish phalanges from the surrounding tissues and bones. In the present study, the short phalanges were more difficult to distinguish, so we chose the surface imaging mode to show the shape of the hands, but not the skeletal mode. Furthermore, the three-dimensional imaging of the hand is difficult to perform, and can be easily disturbed by surrounding structures. Indeed, it took long time to obtain the 3D ultrasound figure of hand in order to get proper initial plane. Therefore, prenatal screening for hand abnormalities mainly depends on two-dimensional ultrasound imaging. In case of suspected abnormality, three-dimensional ultrasound can be used to get more information about the shape of the hand. 3D ultrasound is not currently recommended for routine use detection of hand anomalies by the American College of Obstetrics and Gynecology [20].

### *Limitations of prenatal ultrasound imaging for brachydactyly*

In the present study, all patients had multiple phalanges dysplasia, but none of these patients had dysplasia of a single phalange. It is extremely difficult to identify and diagnose the dysplasia of a single or few phalanges before birth. In addition, compared with the radiographic study of brachydactyly which is based on comparison with the standard values of tubular bone lengths, the prenatal ultrasound examination still lacked normal reference values for all phalanges at different gestational weeks, even if there are a few of studies of prenatal ultrasound about the visualization of some phalanges [3]. Therefore, in the present study, we can only distinguish the presence of

ossification centers and seek for significantly smaller phalanges by comparing the size of the ossification centers of the contralateral or ipsilateral metacarpals and phalanges. In addition, the development of fingernails cannot be observed during the fetal period, the skeleton continues to develop after birth, and very few cases can be followed-up up to childhood or even adolescence. Therefore, we can't know the difference of the ossification of hand bones of brachydactyly between the fetal period and childhood.

At present, the sensitivity of prenatal ultrasound detection for those affecting the digits alone is lower [20]. However, the conventional ultrasound examination of fetal hands can be a screening method of hand abnormality in low risk population, because of its less time consuming and the relative simplicity of implement, while the targeted hand two-dimensional ultrasound examination for high risk pregnant women, supplemented by three-dimensional ultrasound, can help to detect severe brachydactyly.

### **Disclosure of conflict of interest**

None.

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