Chapter 15

# The Antenatal Detection of Fetal Limb Anomalies

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Additional information is available at the end of the chapter

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**Abstract**

The etiology of fetal limb abnormalities is very complex, involving different risk factors: chromosomal abnormalities, gene disorders, intrauterine factors, maternal diseases, or exposure to different risk factors. The prevalence of fetal limb anomalies is reported to be approximately 6 in 10,000 live births, and the impairments of the upper limbs seem to present a higher incidence in comparison to the inferior limbs, more often are affected unilaterally and on the right side in comparison to the left side, some being isolate or may associate other anomalies, as a part of an underlying syndrome. According to the current guidelines, the assessment of the fetal limbs should be performed in the late first and early second trimester. Three-dimensional ultrasound provides a better understanding of the fetal anomaly for the parents and helps a better counseling, and it is used to confirm the anomalies detected by the conventional ultrasound. In cases of treatable anomalies, a multidisciplinary approach involving an obstetrician, geneticist, neonatologist, pediatrician, and pediatric orthopedic surgeon is essential to improve the postnatal outcome. Ultrasound examination and genetic counseling for the parents has an important benefit since some conditions present a genetic inheritance, and the recurrence rate in further pregnancies is very high.

**Keywords:** fetal limbs, malformations, fetal syndrome, ultrasonography, 3D ultrasound, matero-fetal medicine

## 1. Current recommendations

The evaluation of musculoskeletal system and limbs is a part of the routine fetal ultrasound (US) examination, especially during the first- and second-trimester (ST) screening.

Its assessment is significantly more difficult in the third trimester, as the fetal dimensions and movements frequently alter the visualization of some segments, situated far from the transducer or behind other fetal bony structures.

In the last decades, the 11–13 weeks +6 days of US genetic scan has become an important tool for fetal anatomy assessment. It includes almost all segments of the fetal body and also the upper and lower extremities. The second-trimester anomaly scan remained the standard morphologic evaluation, an audit for the early scan, and a baseline for future US evaluations and interpretation of the fetal development. Still, between the guidelines issued by the major societies, there is a wide variation of the parameters proposed as a minimum for limb evaluation (**Table 1**).

Systematic and careful examination of the extremities is important, at any time. Congenital anomalies may affect one or more limbs and may affect any segment.

Usually, these limb anomalies are isolated, but detection of any of them should be followed by a detailed examination of the rest of the fetal anatomy. In many cases with aneuploidy and genetic syndromes, limb defects are present.

| **Limb segments included in the protocol recommendations** | **ISUOG [1]** | **NHS (UK) [2]** | **ACOG, AIUM, ACR, SRU [3–5]** |
|---|---|---|---|
| Upper and lower limb presence | x | x | x |
| Femur diaphysis length (measurement) | x | x | x |
| Metacarpal and metatarsal bones/presence of the hands and feet | x | x | — |
| Digit count | — | — | — |
| Fetal movement | x | — | — |

ISUOG: International Society of Ultrasound in Obstetrics and Gynecology; NHS, UK: National Health Service in the United Kingdom; ACOG: American College of Obstetricians and Gynecologists; AIUM: American Institute of Ultrasound in Medicine; ACR: American College of Radiology; SRU: Society of Radiologists in Ultrasound.

**Table 1.** Recommendation for fetal limb evaluation on prenatal ultrasound.

## 2. Development

The fetal skeleton starts to develop early during gestation. The appendicular and axial skeletons undergo a programmed pattern of endochondral ossification during which a cartilage template is replaced by the bone. In contrast, the calvarium and portions of the clavicle and pubis ossify via membranous ossification, whereby mesenchymal cells differentiate directly into osteoblasts [6].

Limb buds begin to develop during the fourth to fifth gestational week (GW) as clusters of mesenchymal cells covered by the ectoderm, but before the end of the seventh GW, the anatomy

of the embryonic pole is difficult to observe. The upper limb development precedes the lower limbs in bud appearance, differentiation, individualization, movements, and final size. The process starts from proximal to distal, with the humerus and femur first, then ulna and radius, tibia and fibula, metacarpal and metatarsal bones, and lastly phalanges [7]. Then, the mandible, maxilla, and clavicles ossification centers appear at 8 weeks of gestation; appendicular skeleton, ilium, and scapula by 12 weeks; and metacarpals and metatarsals by 12–16 GW [6].

## 3. First-trimester assessment

During the so-called nuchal or genetic scan, a morphologic evaluation is recommended. Nuchal translucency (NT) assessment is more sensitive at an earlier gestation, 11–12 weeks of gestational age, but the optimal moment of the first-trimester anomaly scan is reported after 12 GW [8–11]. Regardless of scan timing, the fetus needs to be assessed in all planes: longitudinal, axial, and coronal. The examination may be performed transabdominal, and if necessary transvaginal, and a combination of the two approaches might give the best results [12]. In our experience, the completion of the basic protocol regarding the assessment of the fetal skeleton rarely requires an increased gestational age or the transvaginal approach, but we should keep in mind that the imaging of the fingers and feet was reported consistently and is achieved only after 12 GW [13]. Still, there was an important and constant technological progress in ultrasound capabilities since the respective researches that enables the operators to use modern systems and high-resolution probes for an earlier and a better visualization of fetal anatomy and especially the echogenic structures.

The exam should detect both upper limbs, which are often found in front of the fetal thorax or face, in semiflected position. The lower limbs are generally flexed at the hip at this gestation. The fingers are relatively easy to assess in the first trimester as number and position, including the thumb, because they frequently lie in the same ultrasound plane. Feet can also be identified, but the number of toes may be difficult to assess because of their small size. The tendency of the ankles to have an inward position may result in an overdiagnosis of clubfoot in the first trimester. The proximal long bones—femur and humerus—can be seen and measured at the first-trimester scan, although their dimensions are not part of the routine biometry at this developmental stage.

The performance of the routine first-trimester anomaly scan was reported satisfactory in a recent study [14], where all the examinations were performed transabdominal and the vast majority of limb abnormalities detected prenatally were identified in the first trimester (82%). In the respective group, 77.8% of the total limb abnormalities were diagnosed prenatally and 63.9% on the first-trimester scan.

These encouraging results followed a previous large screening study regarding the results of routine fetal anomaly evaluation at the time of genetic scan [15], where only one third of the skeletal abnormalities were diagnosed (34.12%). In the respective group, all cases of body stalk anomaly were diagnosed, but none of those with unilateral or bilateral talipes,

club or claw hand, and digital defects. The correct diagnosis was made in the majority of cases of a missing hand or foot (77.8%), or polydactyly (60%), and half of the lethal skeletal dysplasia (50%) and isolated shortening of one of the long bones (50%). The only case of ectrodactyly was missed, and arthrogryposis was not suspected during the first-trimester scan.

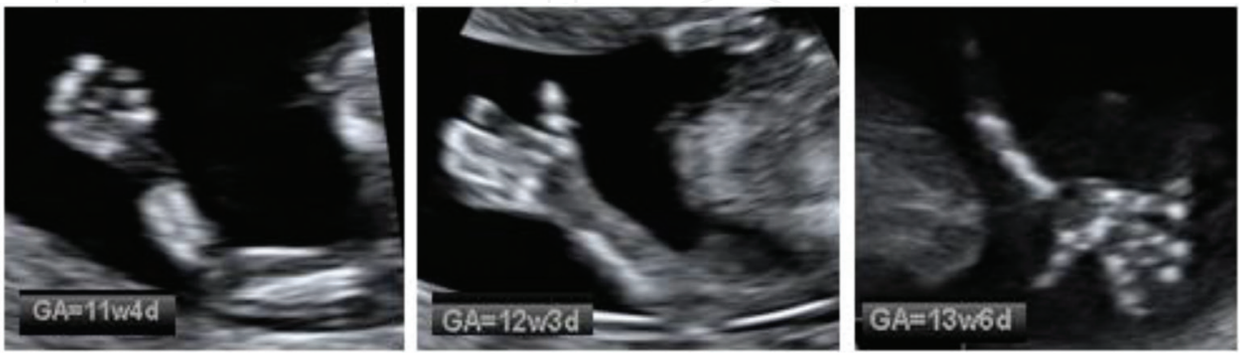


**Figure 1.** Normal aspects of fetal hand in the late first trimester.

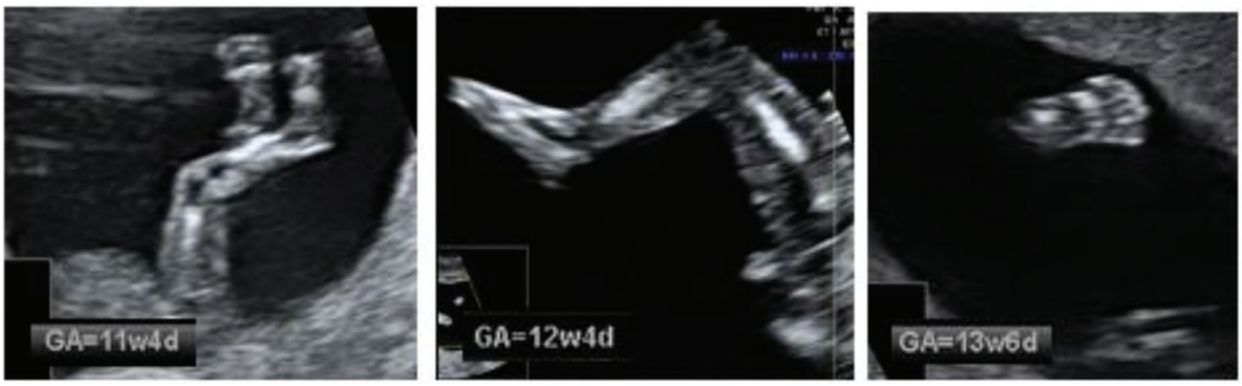


**Figure 2.** Normal aspects of fetal foot in the late first trimester.

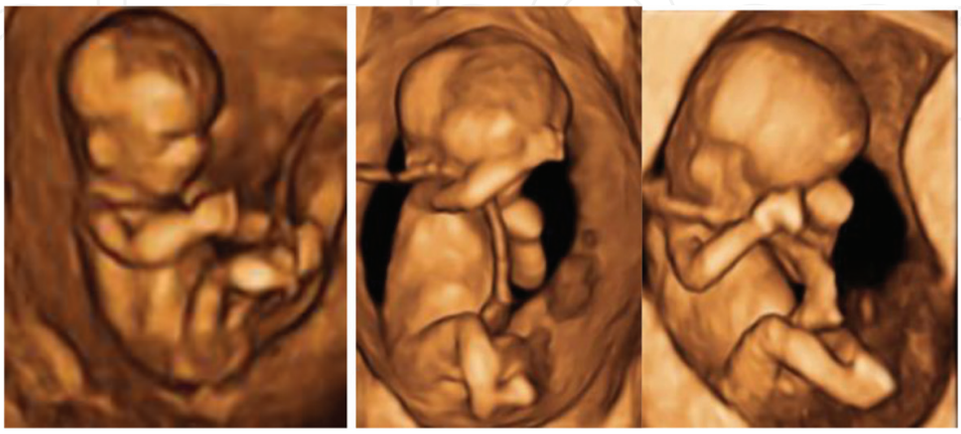

**Figure 3.** The whole fetus, imaged by 3D static ultrasound (surface rendering mode). The harmonious development and relationship between limbs' segments are easy to asses.

It was suggested that a systemic sequential approach scanning from proximal to distal until the entire limb is observed, and the strict operational training and audit and the use of high-resolution ultrasound machines may improve the early diagnosis of limb defects [14].

As for the most frequent limb anomalies diagnosed early in pregnancy, not only transverse limb reduction defects [14] but also radial aplasia and club hand [16] were proposed in different studies.

An abnormal nuchal translucency may accompany major skeletal abnormalities [17] and sometimes may be the only early sign in conditions with discrete if any early features [18–20]. Narrowing of the thorax with secondary mediastinal compression and abnormal cutaneous collagen deposition were discussed as possible causes (**Figures 1**–**3**).

## 4. Second-trimester assessment

Most of the authors agree that the fetal anatomy may readily be assessed at 20–24 WG, because:

- The pregnant uterus is completely lifted up in the maternal abdomen.
- The fetus may present favorable positions and axis for scan.
- The fetus is also enough developed to be seen, leading to good results if scanning for anomalies.

Some important studies underlined a statistically significant difference being able to perform a complete fetal morphology scan if US is performed at 18 to 19 + 6 (in 76% of cases) versus 20 to 22 + 6 weeks of gestation (in 90% of cases) [21–24]. However, with the improved technological capabilities of the ultrasound equipment, the gestational age for confidently assessment is constantly lowering. On the other hand, due to absorption of sound phenomenon, the visualization of the skeleton is easier than for other fetal systems (e.g., the cardiovascular system). Also, the skeletal system is already completely developed, unlike other structures (e.g., central nervous system components, as the corpus callosum or vermis). Therefore, the fetal skeletal evaluation may be proposed and successfully performed in the routine early second-trimester scan (**Figures 4**–**7**).

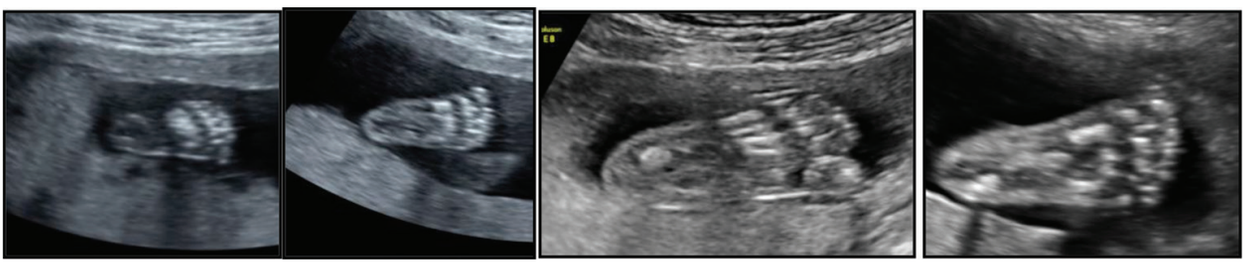

**Figure 4.** 2D conventional US images of normal feet at 17 weeks of amenorrhea (WA) and at 23 WA. The normal position of the toe is readily observed. In many cases, numbering the digits is possible.

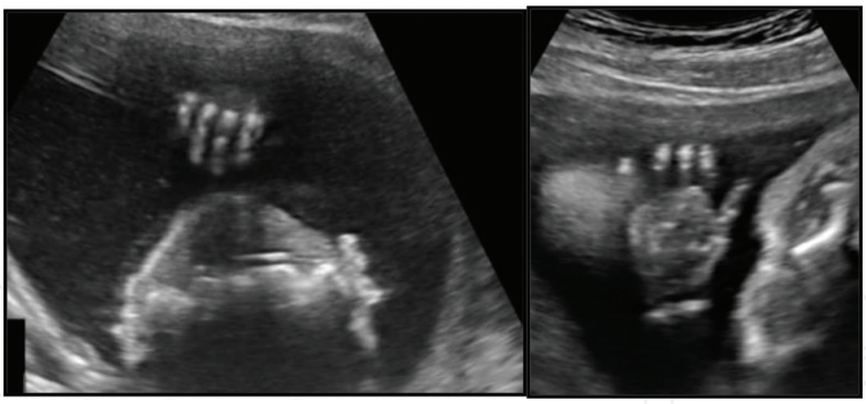

**Figure 5.** 2D conventional US images of normal fetal hands in midtrimester. Similarly, numbering the fingers is possible and, in certain cases, even the phalanges. As seen, in most cases, the thumb lies in a different plane than the other four fingers. Due to hand anatomy, thumb visualization may not be simultaneous than the other fingers. Yet, confirming the presence of the opposable finger is considered important, due to the prehension function of the hand.

**Figure 6.** Hands and foot, imaged by 3D static ultrasound (surface rendering mode). Using this technique, the demonstration of the extremities is easier, despite the different spatial arrangement of the thumb.

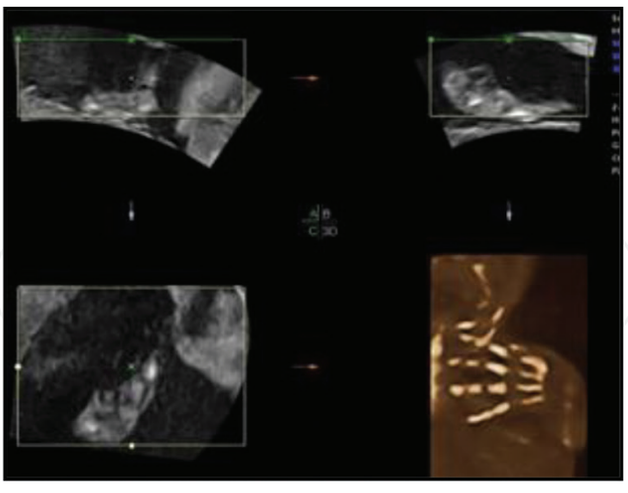

**Figure 7.** Hand imaged by 3D static ultrasound (skeletal mode). The technique makes the confirmation of the normal number of phalanges of each finger easier.

## 5. Third-trimester assessment

Later in the second trimester and in the third trimester, despite the increase in the size of the fetus, morphological examination of the limbs is more difficult because:

- the fetal position is maintained for longer periods, due to the reduced mobility;
- the limb's segments have a complete flexion, and the proximal limb's position is maintained toward the fetal axis;
- the amniotic fluid volume decreases, especially at term; and
- the bone ossification increases, impairing the visualization of the underlying structures.

In certain cases, in the late second and third trimester, the secondary anatomy changes due to functional disturbances (some forms of skeletal dysplasia, fetal tumors, segmental deformations secondary to compression in oligohydramnios, multiple pregnancies, or other pathologies) become evident. Thus, even in cases with a normal morphological examination in the second trimester, the examination of the upper and lower members should be attempted in the third trimester. The commendation is stronger if such conditions are suspected.

In the third trimester, the evaluation of the fetal well-being includes the limbs and hand movements, as part of the Manning classical biophysical profile.

## 6. Literature

Historically, the sensitivity of prenatal ultrasound for detection of musculoskeletal and limb anomalies has been low. In 1991, Levi published a series of 16,072 pregnant women with prenatal ultrasound and found a 45.32% sensitivity for detection of any type of anomaly, with a 23.26% sensitivity for detection of limb and skeletal anomalies [25]. In 1992, Stoll found a 15% sensitivity for isolated anomalies and 48% sensitivity for multiple anomalies for the second-trimester prenatal ultrasounds [26]. The most meaningful result of these early studies is the high specificity of scanning in terms of skeletal abnormalities [25, 26]. This is important, because conditions with high false-positive rates can mislead parents and clinicians in their decisions and recommendations.

Detection of major anomalies has improved over time as a result of improvements in technology and skills, although detection of limb anomalies remained low. The Eurofetus study, in 1999, showed an overall sensitivity for detection of any anomaly to be 61%, with identification of musculoskeletal anomalies much lower and similar to the findings of Levi et al. at 18% [27].

It seems that detection of proximal limb reduction defects is better (23–50%) than detection of hand or finger limb reduction defects (0–8%) [28]. The 2005 EUROCAT study of 4366 fetuses with different anomalies reported a prenatal detection rate for both upper and lower limb reduction defects of 34% [29]. In a more recent study, a higher prenatal detection rate was found for limb reduction defects with associated malformations (49%), if compared to isolated limb reduction defects (25%) [30]. Pajkrt et al. also found a high detection rate for fetuses with short or absent radii and/or ulnae associated with aneuploidy or genetic syndromes (70%) [31]. In another large study, Gray et al. found that 31% of upper extremity anomalies were detected prenatally; however, only 18% were correctly diagnosed [32]. The missed malformations were also located distally (hand and fingers).

The difficulties in detection of upper extremity anomalies may be related to the current guidelines. They mandate only a cursory examination of the upper and lower limbs during the standard second-trimester (ST) examination. This may contribute to the high false-negative rate [33].

## 7. Technique

The standard examination includes measurements of fetal biometry, in order to estimate the gestational age and fetal weight. It includes the biparietal diameter (BPD), the head circumference (HC), the abdominal circumference (AC), and the femur length (FL) [34]. The measurements of the humerus length (HL) and the transcerebellar diameter (TCD) are optional in many settings. Yet, the fetal biometry may be completed with other segment measurements, as Jeanty proposed over three decades ago [35]. Benefits of such an approach are investigated recently [36]. For almost all fetal structures, nomograms were created, in order to accurately estimate the gestational age.

For limbs examination is recommended to start the sweep proximally. The long bones must be measured in their entirety ("end to end") in a parallel plane to the probe. The examination aims to confirm the normal mineralization and the absence of fractures. The "shortening" diagnosis is allowed only if a previous scan certifies gestational age (preferably, a first-trimester scan).

The forearm and lower leg contain two long bones. In routine examination their presence and normality should be confirmed. If differences between them are suspected or in the presence of other anomalies, all measurements and comparison with the standard data for the gestational age should be done. At the elbow, the ulna is located medially to the radius and has a much higher extremity in relation with humerus. At the wrist, its position depends on the degree of rotation of the forearm.

The image of the foot is obtained in a transverse section to show the heel, the sole, and toes. The position of the big toe with respect to the other toes can be evaluated readily. The length of the foot is not a part of the routine examination, but is important in assessment of skeletal dysplasias and in cases of short femur. If the dimensions of foot remain in normal range for the gestational age and the femur is short, the femur/foot length ratio will be significantly decreased (0.9). In fetuses with constitutionally short femur, this ratio will remain normal.

The ideal window for visualizing the fetal hands is at the late first and early second trimester, when the fingers tend to be extended and abducted. US examinations will be less accurate later in pregnancy, due to fetal position and flexed digits [37]. By some authors, the use of three-dimensional (3D) and 4D US, as well as fetal MRI, improves detection of hand anomalies [32, 37–42]. However, the technique is not currently recommended for routine use by The American College of Obstetricians and Gynecologists [3, 33].

## 8. Types of limb abnormalities

The most common types of limb anomalies include abnormal number of digits (the higher frequency having polydactyly), abnormal hand/foot position, limb reduction defects, and arthrogryposis. It seems that unilateral limb defects are rarer.

Abnormal hand position is defined as clenched hands or overlapping digits. Arthrogryposis is defined as fetal joint contractures and rigidity.

Counting the fingers is not part of routine scan. Polydactyly is more common in some ethnic groups, such as African Americans. It may occur isolated or may affect both hands and feet.

In amniotic band syndrome, fingers can be missing. This is due to the arrest in development and not as a primary defect in the blastulation process.

In some rare syndromes such as ectrodactyly-ectodermal dysplasia-cleft syndrome (EEC syndrome), missing fingers occur in association with complex malformations. EEC syndrome is a rare form of ectodermal dysplasia. It is an autosomal dominant disorder, inherited as a genetic trait. EEC includes also vesicoureteral reflux, recurrent urinary tract infections, obstruction of the nasolacrimal duct, decreased pigmentation of the hair and skin, missing or abnormal teeth, enamel hypoplasia, absent punctae in the lower eyelids, and photophobia. Occasional, cognitive impairment, kidney anomalies, and conductive hearing loss may appear.

In the development of fetal limbs the free movement itself has a very important role. This is favored by the proximity of fluid in the uterine cavity. The limbs should move freely within each joint. Normal movement assures the normal positions of the hip, knee, elbow, ankle, and wrist joints.

Apparition of abnormal angulation of the ankle joint (ankle clubbing, talipes equinovarus) is frequent, with a prevalence of 1 in 100 live births. The best image is to get a coronal section of the ankle, in which the extended ankle straight along is seen, in a normal spatial relationship with the lower leg. In ankle clubbing, the ankle deviates medially. In the third trimester, especially when the amniotic fluid decreases, a slight subjective angulation of the ankle is common. The key feature for ruling out a true clubbing is the normal shape of the foot. Unilateral ankle clubbing is usually an isolated defect. Bilateral clubbing should be investigated for chromosomal anomalies and genetic syndromes.

The wrist is very flexible and the position of the fingers is also variable. Thus, the examination can find them in a wide variety of positions. In late second trimester and third trimester, the resting position is fisting. The hand can be stimulated to open, showing all four fingers and the thumb. Due to the anatomy of the hand, the thumb is visible in a different plane from the rest of the fingers. Due to this particular context, the diagnosis of abnormal hand position is more difficult than in distal limb.

## 9. Rationale of screening

All limb anomalies, other than isolated polydactyly, have an increased risk for associated nonskeletal malformations, aneuploidy, stillbirth, neonatal neurodevelopmental delay, and pregnancy termination [43]. This information influences the guiding of evaluation and management, the counseling of parents, and the delivery planning.

The abnormal number of fingers or abnormal position of fingers (Campylodactyly or clinodactyly) is associated with an increased risk of an underlying fetal syndrome.

An image of "sandal gap" anomaly has a weak association with trisomy 21.

The shortening of the humerus seems to have a slightly better predictive value than shortening of the femur in screening for aneuploidies, especially for trisomy 21.

In skeletal dysplasias, the shortening or fracture of long bones is a criterion for diagnosis. The site and the type of shortening are important in establishing an accurate diagnosis (**Table 2**).

| Limbs segments | Proximal | Midsegments | Distal segments |
|---|---|---|---|
| Term* | (Humerus/femur) | (Radius and ulna/tibia and Fibula) | (Hand and foot) |
| Normal (N)** | N | N | N |
| Rhizomelia | Short | N | N |
| Mesomelia | N | Short | N |
| Acromelia | N | N | Short |
| Micromelia | Short | Short | Short |

*The term does not include the malformation, fractures, or absence of the bones.
**Normal measurements is related to an accurate gestational age, ideally established in the first trimester of pregnancy.

**Table 2.** Terminology in long bone abnormalities.

The upper limb anomalies (and especially radial hypoplasia or aplasia) are phenotypical features of a number of syndromes.

The primary advantage of prenatal diagnosis of upper extremity anomalies is the opportunity for more refined prenatal counseling [44]. Parents are given the chance to discuss their child's diagnosis with a variety of specialists and to receive genetic counseling. For treatable anomalies, a team may be assembled to prepare for postnatal care. Some families will consider pregnancy termination for major untreatable anomalies, and several studies have shown higher rates of pregnancy termination after early prenatal diagnosis of major untreatable anomalies [25, 28, 29, 45].

## 10. Personal experience

We selected from our archive several suggestive cases of limb abnormalities (**Figures 8–19**):

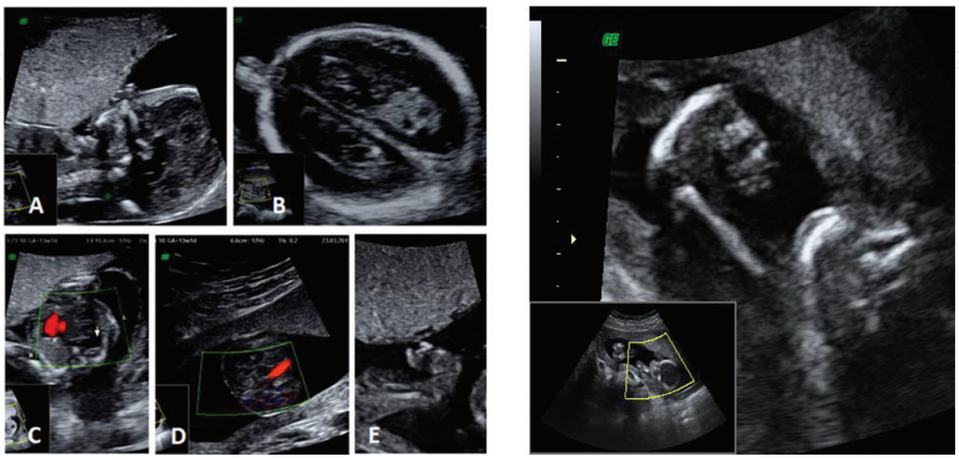


**Figure 8.** Trisomy 18, diagnosed in early pregnancy. The left image composite shows (A) the abnormal facial profile, the nuchal edema, and the absent nasal bone; (B) multiple choroid plexus cysts; (C) axial plane of the fetal thorax with dextroposition of the fetal heart and presence of the stomach in the thorax, both suggesting diaphragmatic hernia; (D) single umbilical artery crossing lateral to the fetal bladder; and (E) skeletal abnormality and persistent malposition of the fetal arm. In the right-hand image—a detail: the radial aplasia, very characteristic for the syndrome.

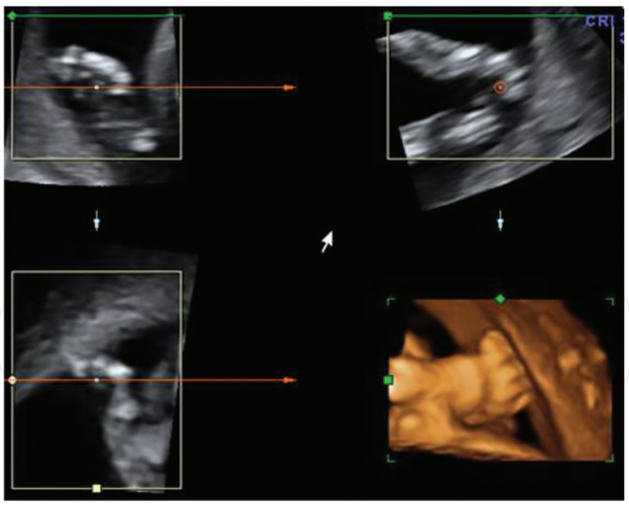

**Figure 9.** 3D ultrasound images (surface rendering mode), applied in a case of polydactyly. The case was scanned in the first trimester, and the volume was acquired by means of transvaginal scan.

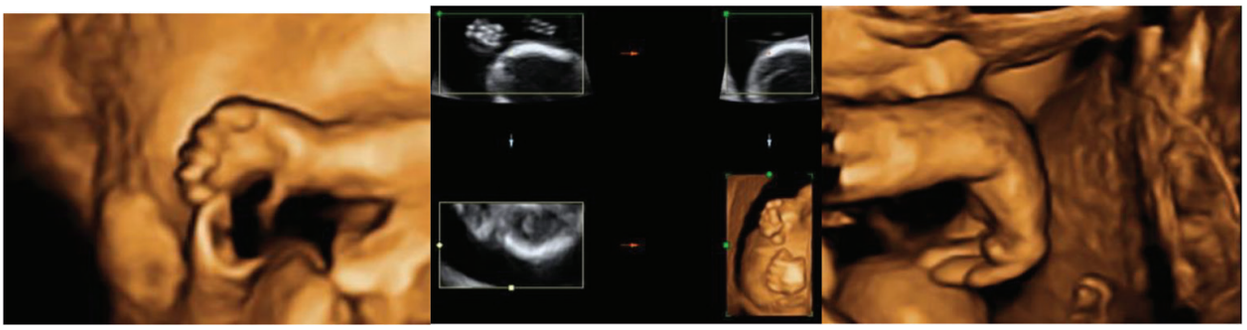

**Figure 10.** 3D ultrasound images (surface rendering mode), applied in cases of polydactyly in the second trimester; the volume datasets were acquired by means of transabdominal scan. The images were used in the parental counseling process.

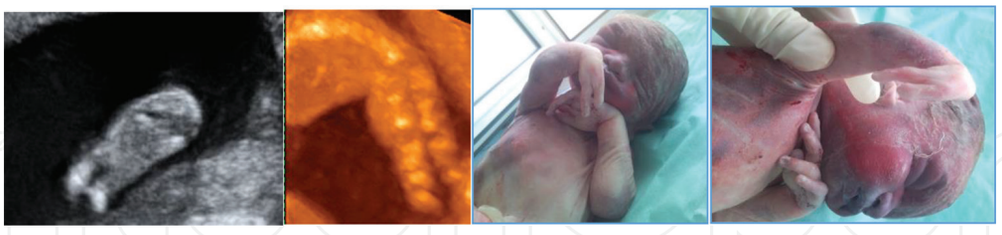

**Figure 11.** Ectrodactyly: conventional 2D ultrasound, 3D ultrasound skeletal mode, and pathological specimen correlated.

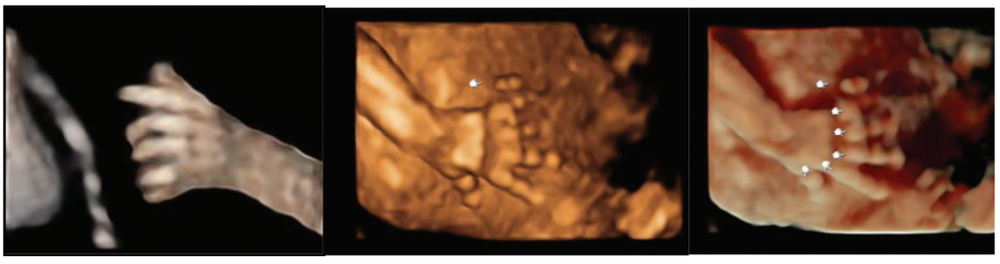

**Figure 12.** Unilateral postaxial polydactyly type I. Different techniques for acquiring the 3D volume datasets: surface rendering, skeletal mode, and HD life. The case evolved with spontaneous amputation in utero (reproduced with permission of authors) [39].

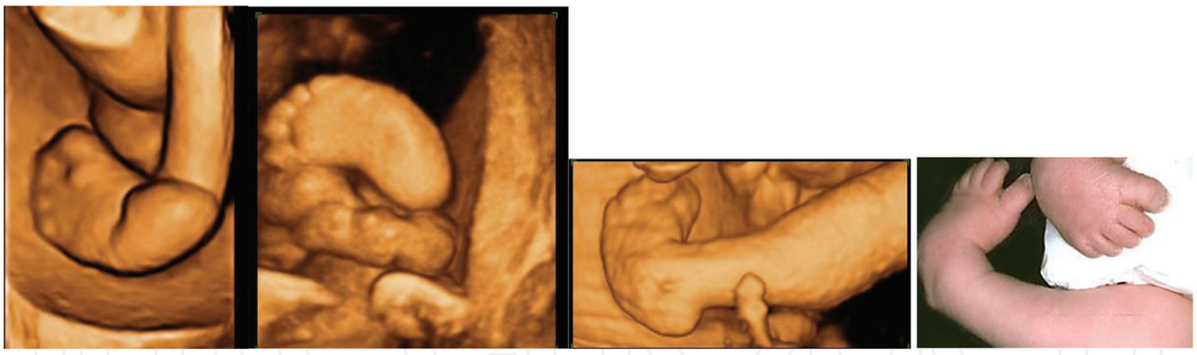

**Figure 13.** Different cases of clubfoot.

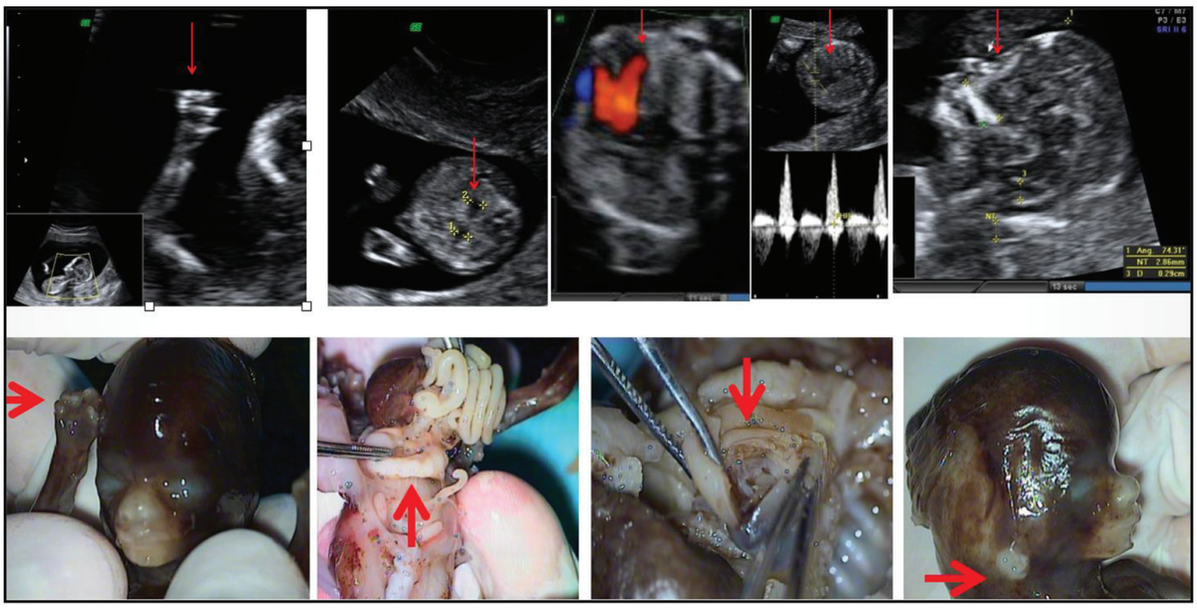

**Figure 14.** A paucisymptomatic case of trisomy 18, diagnosed in the late first trimester. The upper row demonstrated the ultrasound features: club hand, bilateral pyelectasis, atrioventricular defect, abnormal spectral Doppler at the tricuspid valve interrogation, and unremarkable profile. All these features were compared with the pathological specimen details. The added information were horseshoe kidneys and low set years.

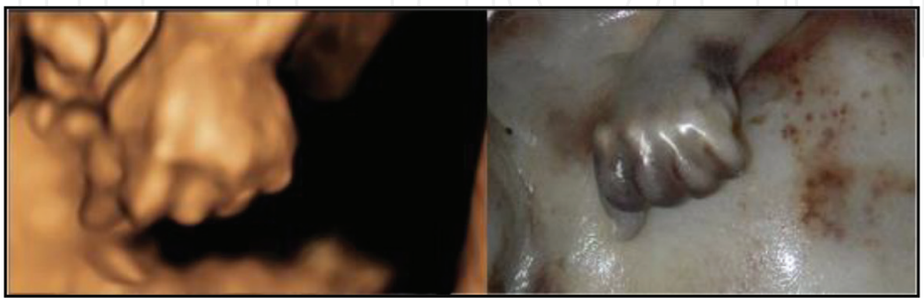

**Figure 15.** Persistent abnormal hand position. The ultrasound and pathologic data are displayed (the thumb overlapping finger 2). In this case trisomy 13 was diagnosed. The fetus had multiple-associated congenital malformations.

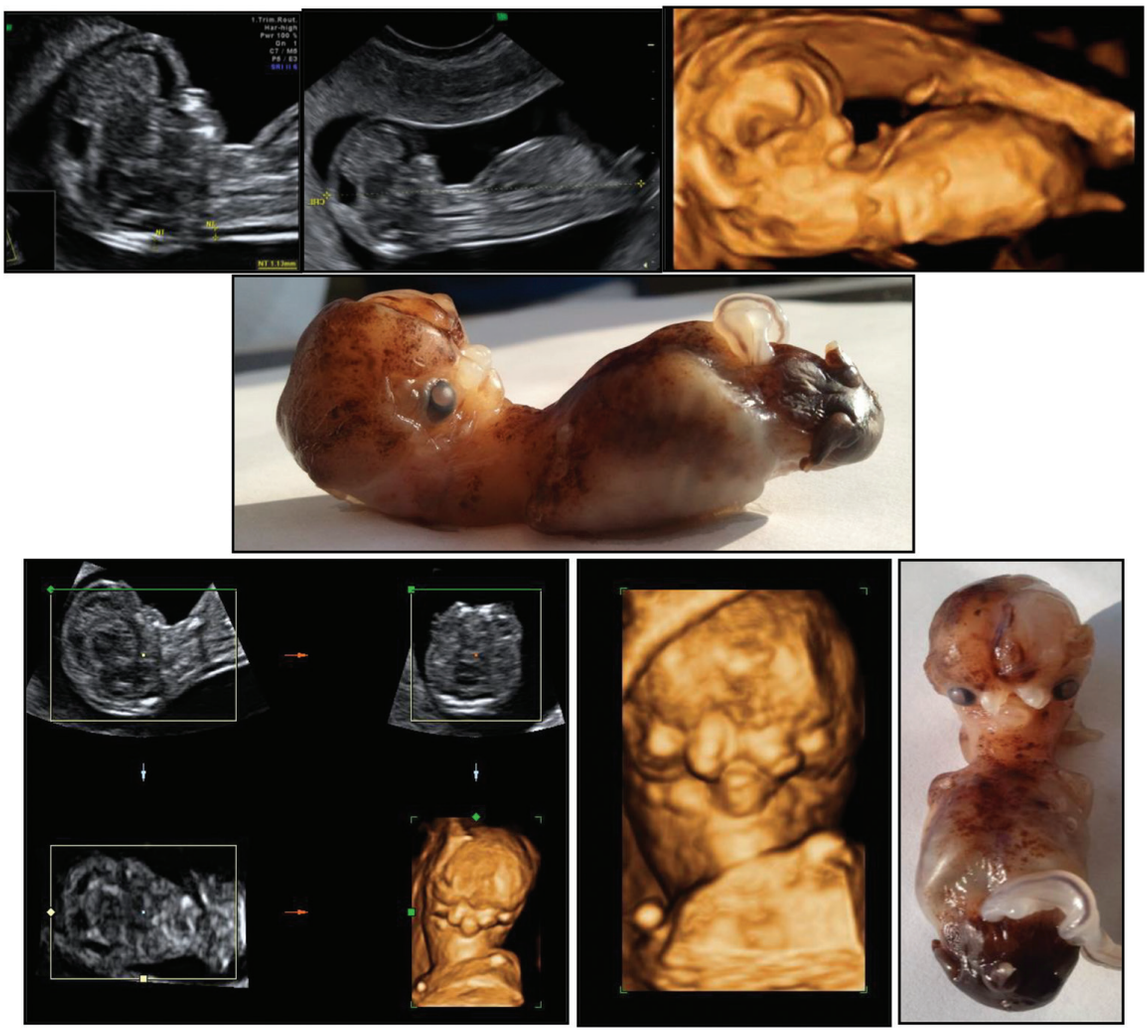

**Figure 16.** A rare case of complex severe facial malformation, in association with tetraamelia. The 2D conventional ultrasound, the 3D static surface rendering mode, and the pathologic data are correlated.

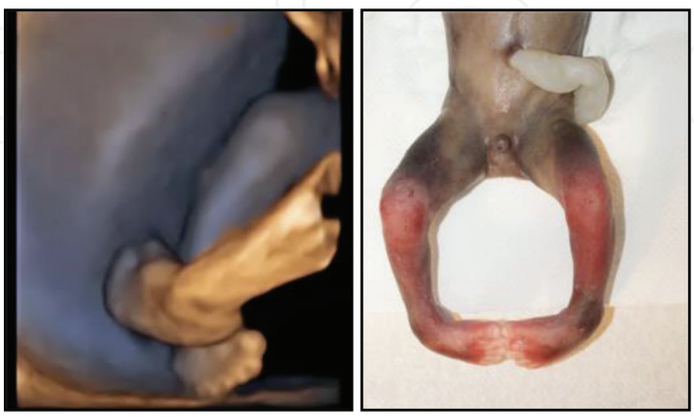

**Figure 17.** Bilateral clubfoot (genu varum), seen prenatally and post abortion.

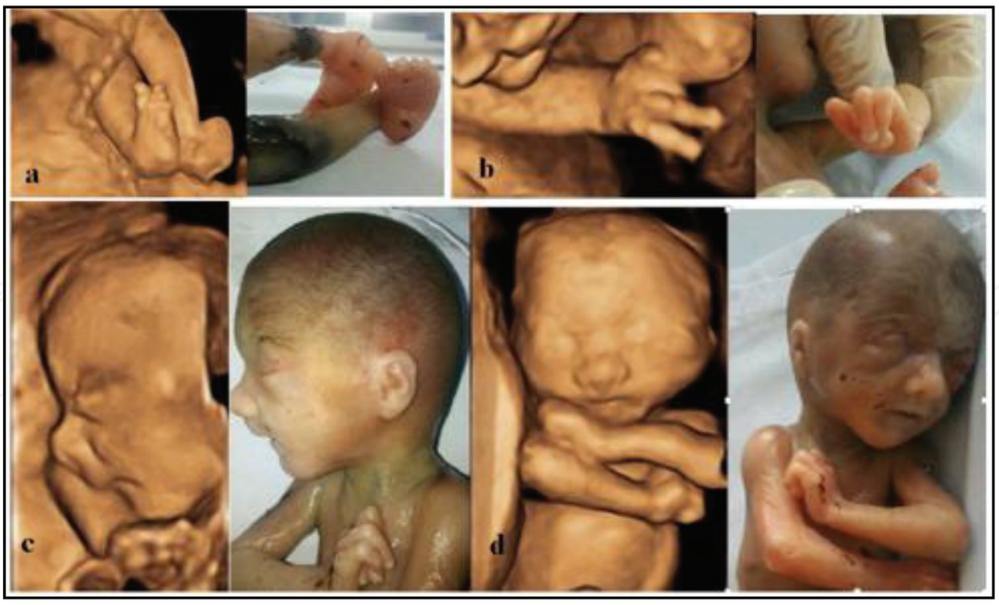


**Figure 18.** A case of fetal akinesia deformation sequence. The fetus had a complete normal 12 weeks of scan. The mother self-presented for decreased active fetal movements. The matching details obtained by means of volumetric ultrasound and pathology can be observed: Abnormal feet position[a], campylodactyly [b], ulnar deviation of the hands [c], multiple joints contracture (arthrogryposis) [b, c, d], short neck, facial anomalies, hypertelorism, telecanthus, posterior angulation of the ears, and small mouth [c, d].

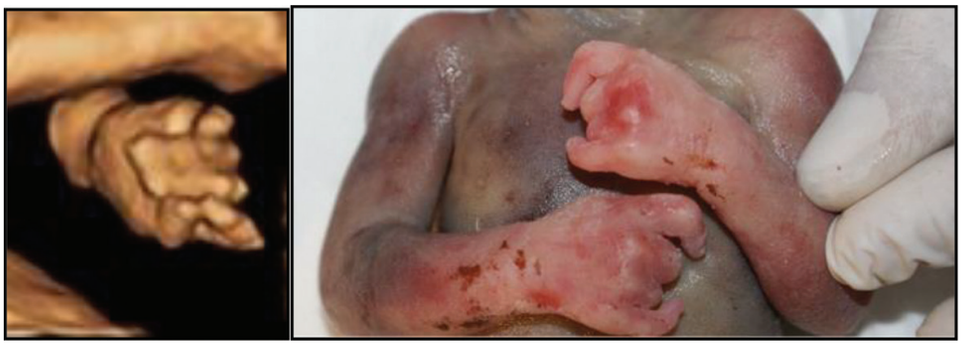

**Figure 19.** Abnormal position of the hand, with camptodactyly and overlapping fingers.

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