

Prenatal diagnosis of limb abnormalities: role of fetal ultrasonography

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Summary

Fetal ultrasonography is the most important tool to provide prenatal diagnosis of fetal anomalies. The detection of limb abnormalities may be a complex problem if the correct diagnostic approach is not established. A careful description of the abnormality using the right nomenclature is the first step. Looking for other associated abnormalities is the threshold to suspect chromosomal abnormalities or single gene disorder. According to the pathogenic point of view, limb abnormalities may be the result of malformation, deformation, or disruption. The prenatal diagnosis and the management of limb abnormalities involve a multidisciplinary team of obstetrician, radiologist/sonologist, clinical geneticist, neonatologist, and orthopedic surgeons to provide the parents with the information regarding etiology of the disorder, prognosis, option related to the pregnancy and recurrence risk for future pregnancies.

KEY WORDS: *role of prenatal ultrasound in detection and diagnosis of limb abnormalities.*

The aim of this review is to describe the importance of detailed fetal ultrasonography in prenatal diagnosis of limb abnormalities.

Approximately, the prevalence of limb abnormalities is six in 10,000 live births, the incidence is higher in the upper limbs compared with the lower limbs (3.4 of 10,000

and of 10,000, respectively) (1); more commonly the limb abnormalities are unilateral instead of bilateral, and more frequently are present in the right side compared with the left. (2)

Limb formation occurs at 4-8 weeks' gestation, while primary ossification centers develop in all the long bones of the limbs by the 12th week of gestation.

The molecular regulation of limb formation is under the control of different gene families.

The positioning of the limbs along the craniocaudal axis of the embryo is regulated by the homeobox (HOX) gene family, while limb outgrowth depends on fibroblast growth factor (FGF) genes together with the bone morphogenetic proteins (BMPs). Sonic hedgehog (SHH) genes regulate patterning of the anteroposterior axis of the limb.

Patient body habitus, quality of the ultrasound machine, and operator skill have the main role in detection and diagnosis of limb abnormalities using prenatal ultrasonography (3).

Limb abnormalities can be isolated or associated with other malformation and detected as part of a known syndrome (chromosomal or single gene), in the latter case they are diagnosed more accurately than in former one (3, 4).

The etiology of limb abnormalities is very complex, it involves single gene disorders (5-7), chromosomal abnormalities (8), intrauterine factors (9), vascular events (10, 11), maternal diseases (12), and maternal exposures (13, 14), but in many case it remains unknown.

The knowledge of the etiology, and thus the prognosis, will provide the parents with possibilities for prenatal diagnosis for their future pregnancies and, if possible, options for prevention of recurrence. To this aim, it is important a multidisciplinary approach involving the obstetrician, radiologist/sonologist, clinical geneticist, neonatologist/pediatrician, and a pediatric orthopedic surgeon. Upper and lower limb abnormalities are a morphologically and etiologically heterogeneous group of abnormalities, that can be limited to one limb or part of a limb, only the upper or the lower limbs, or all the four limbs. We can classify them under the pathogenic point of view in:

- **Malformation:** A morphologic defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process (eg, phocomelia, polydactyly).
- **Deformation:** An abnormal shape or position of part of the body caused by mechanical forces (eg, clubfeet).
- **Disruption:** A morphologic defect of an organ, part of an organ, or a segment of the body caused by an extrinsic factor interfering with an originally normal developmental process (eg, amniotic band sequence).

When a limb abnormality is identified, the operator should use the correct established nomenclature to de-

scribe the defect, and this pathogenic classification to provide with the correct information regarding etiology, prognosis and recurrence risk.

According to the etiological approach, fetal limb abnormalities can be divided into six groups:

1. Chromosomal diseases (T21, T13, T18)
2. Single gene disorders
3. Multifactorial conditions (congenital dislocation of the hips, clubfeet, scoliosis)
4. Maternal diseases and teratogens (Maternal insulin-dependent diabetes mellitus, autoimmune diseases, Valproic Acid, Cocaine, etc.).

In the correct diagnostic approach, the sonologist should know the pregnancy history, if there are maternal diseases such as diabetes mellitus, hypercoagulability, systemic lupus erythematosus and other autoimmune diseases, myotonic dystrophy, presence of high blood pressure, and exposure to teratogens such as medications, infections, alcohol, and cigarette smoke.

Information regarding family members with congenital limb or other abnormalities, recurrent miscarriage, stillbirths, mental retardation, inherited conditions, and consanguinity should be obtained.

An effort is needed to define the nature of the limb abnormality by following this kind of classification:

- **Dysplasia:** An abnormal organization of cells into tissue and its morphologic result. In other words, a process (and the consequence) of dishistogenesis.
- **Sequence:** A pattern of multiple defects caused by a single known or presumed prior anomaly or mechanical factor.
- **Syndrome:** A recognized pattern of different malformations having one etiology.
- **Association:** Nonrandom concurrence of independent malformations, the etiology of which (single or multiple) is unknown. This includes the VACTERL association: Vertebral defects, Anal atresia, Cardiac abnormalities, T-E fistula, Esophageal atresia, Renal dysplasia, and Limb/radial abnormalities.

Now, we can describe the more common types of limb abnormalities that we may detect on the daily fetal ultrasound scan.

Malformation-Deformation: Positional Abnormalities

Positional abnormalities can be considered as a deformation or a malformation. Thus, clubfeet can result from oligohydramnios condition or uterine septum and can also be the result of an abnormality in the formation of the feet. The most common positional abnormalities detected on fetal ultrasound scan are clubbed hands/feet, clinodactyly, camptodactyly, and clenched fingers.

Clubfeet

Clubfoot or talipes equinovarus is a condition characterized by a foot fixed in adduction, supination, and varus position. There is subluxation of the talo-calcaneonavicular joint, with underdevelopment of the soft tissues on the medial side of the foot and frequently of the calf and peroneal muscles (15). As a result, the foot

typically is turned inward, and it has clublike appearance.

This is one of the most common congenital birth defects and has been diagnosed as early as 13 weeks' gestation by transvaginal sonography (16, 17) and at 16 weeks by transabdominal ultrasound scan (18). Approximately one third of cases are isolated; however, many are associated with other abnormalities such as central nervous system defects and chromosome abnormalities. Thus, it is important to perform a thorough fetal ultrasound examination, as well as fetal karyotyping should be offered (19-22).

Clinodactyly

Clinodactyly is a fixed deviation of the digit. Clinodactyly of the fingers may be detected on fetal ultrasound scan, on the other hand clinodactyly of the toes is difficult to be seen. This abnormality affects each of the fingers but commonly it is seen as fifth finger clinodactyly. This abnormality results from asymmetrical hypoplasia of the mid-phalanx with the medial part being shorter than the lateral part, resulting in radial angulation of the distal phalanx.

In many cases, the clinodactyly is familiar and isolated and has an autosomal dominant mode of inheritance with incomplete penetrance (23). It should be known that clinodactyly exists in 18% of the normal population and has been reported in up to 60% of infants with Down syndrome, but it is not a reliable sign for the detection of Down syndrome on fetal ultrasound scan when isolated (24). However, when seen, other ultrasound markers suggestive of trisomy 21 should be looked for (thickened nuchal fold, heart defect, ventriculomegaly, hypoplastic nasal bone, short humerus and femur, and renal pelvis dilatation).

Clenched hand

In clenched hand the second and fifth fingers overlap the third and fourth with an adducted thumb, it is important to evaluate, on ultrasound scan, if it is a persistent or a temporary finding. When constant, it suggests the possibility of chromosomal abnormalities, particularly trisomy 18, as well as other causes of fetal akinesia sequence/arthrogryposis multiplex congenita. Both conditions are associated with poor prognosis (25, 26).

Camptodactyly

Camptodactyly is a flexion contracture of one of the interphalangeal joints. It may be associated with chromosomal abnormalities, particularly when multiple fingers are affected (trisomy 18 and 13) as well as with inherited conditions such as Tel-Hashomer camptodactyly syndrome (27). In many cases, it is associated with arthrogryposis multiplex congenita, which can be a noninherited as in amyoplasia, or a variety of inherited conditions such as Larsen syndrome (autosomal recessive or dominant) (28) and geleophysic dysplasia (autosomal recessive) (29).

Malformation-Disruption: Abnormalities of size and number

They are abnormalities of length or width. Abnormalities in width, such as macrodactyly, are known to be associated with conditions such as Proteus syndrome and are difficult

to detect using fetal ultrasound scan. Length abnormalities are seen in different skeletal dysplasia and can be rhizomelic (short femurs or humeri), mesomelic (short forearms or calves), or acromelic (involving the hands or the feet). These abnormalities can be caused by disruption, as in amniotic band sequence, or malformation, such as thalidomide teratogenicity.

Clubhand

This condition is divided into radial and ulnar form. Radial and ulnar clubhand are frequently associated with radial ray and ulnar ray abnormalities, respectively (30-31). Radial clubhand is more commonly detected prenatally and very often is associated with other abnormalities, many of them inherited.

Ulnar clubhand is secondary to ulnar ray deficiency. This is a rare anomaly and is usually isolated, although it can be in association with Larsen syndrome or TAU syndrome (thrombocytopenia and absent ulna with mental retardation and facial dysmorphism) (32). The condition may be associated with skeletal dysplasia and arthrogryposis. Prenatal differentiation between ulnar clubhand and radial clubhand is difficult, and in many cases ulnar clubhand is associated with a radial ray defect also.

Polydactyly

Polydactyly consist in the presence of extra digit/s in the upper or lower extremities. The extra digits may vary in their developmental maturity. The extra digit can appear on the radial side (preaxial) or on the ulnar side (postaxial) polydactyly. Postaxial polydactyly is more frequent than preaxial polydactyly, particularly among Africans. Meso-axial polydactyly is less frequent than pre-/postaxial polydactyly. The incidence of polydactyly is one in 700 pregnancies (33). Postaxial polydactyly can be an isolated finding, usually with an autosomal dominant mode of inheritance with incomplete penetrance or part of a syndrome. Preaxial polydactyly is a highly variable condition ranging from broad thumb to duplication of the thumb and can be isolated (autosomal dominant) or part of a syndrome. In some families with isolated preaxial polydactyly, mutations of regulatory genes affecting the SHH pathway (34) have been reported.

Thumb Anomalies

The prenatal diagnosis of thumb abnormalities includes thumb hypoplasia, triphalangeal thumb, broad thumb, and hitchhiker thumb. Thumb abnormalities may be isolated but in many cases are associated with other body organ or limb abnormalities. The extremely rare hitchhiker thumb deformation corresponds to the abnormally

abducted position of a more proximally inserted thumb (30, 35, 36). This constant malposition is suggestive of diastrophic dysplasia, a rare skeletal dysplasia with an autosomal recessive mode of inheritance easily to be controlled by using ultrasonography (30, 35, 36).

Terminal Transverse Limb Defects

Generally, terminal transverse defects are more common in the upper limbs than the lower limbs; they may be isolated or associated with other abnormalities. A vascular injury is thought to be the cause of this condition, moreover this defect has been found in association with coagulation defects (11) as well as conditions causing fetal hypoxemia, such as α -thalassemia homozygous state (37), or after chorionic villus sampling (38).

In many cases the condition is caused by constriction band sequence/amniotic band sequence, created by early rupture of the amnion and formation of fibrous bands that can trap and disrupt fetal parts. The possible situations can vary from a simple circumferential groove to ring constriction, amputation of part of a finger resulting in whole-limb amputation, or severe malformations including syndactyly, pterygium, and lethal craniofacial or thoraco-abdominal destructive possesses. Disruptions caused by amniotic bands are characteristically asymmetrical and are amenable to ultrasound detection, but the wide range of abnormalities makes the diagnosis challenging. The differential diagnosis of this condition includes Adams-Oliver syndrome (aplasia cutis congenita, limb defects) (39) with an autosomal dominant mode of inheritance.

Ectrodactyly (Split Hand/Split Foot)

Split hand/foot deformity, also known as lobate claw hand/foot, results from the absence of the central digits/toes with a deep V- or U-shaped central cleft. The main pathogenic mechanism is most probably a failure of the median apical ectodermal ridge in the developing limb bud (40). It may be isolated or associated with other abnormalities such as in EEC syndrome (ectrodactyly, ectodermal dysplasia, cleft lip/palate) and syndactyly, absence, or hypoplasia of the residual phalanges; metacarpals/metatarsals can also be seen. The severity of the malformation is variable, and the inheritance can be autosomal recessive, autosomal dominant, or X-linked (41).

Syndactyly

In syndactyly two or more digits are fused together. It is the most common congenital malformation of the limbs, with an incidence of 1 in 2000 to 3000 live births (42, 43). The condition is the result of failure of separation of the fingers or toes into individual appendages, which usually occurs between the sixth and seventh week postconception. Syndactyly is simple when it involves soft tissue only or complex when it involves the bone or nail of the adjacent fingers or toes that are joined side by side. It can be complete when the fusion extends to the tip of the finger or toe or incomplete when the soft-tissue

union does not extend to the fingertips. Complex syndactyly occurs when fingers are joined by bone or cartilaginous union, usually in a side-to-side fashion at the distal phalanges. The most severe form is complicated syndactyly which refers to fingers joined by bony fusion other than a side-to-side and can include bony abnormalities such as extra, missing, or duplicated phalanges and abnormally shaped bones such as delta phalanges. The complex syndactyly may be associated with other digitis abnormalities including polydactyly, oligodactyly, or duplicated phalanges as well as abnormally shaped bones.

The condition can be isolated or associated with other abnormalities, in fact more than 30 syndromes with syndactyly have been reported, including Poland, Apert, Fraser and Holt-Oram syndrome. Simple syndactyly is more common between the third and fourth fingers and the second and third toes. In 50% of the cases it is bilateral.

Prenatal diagnosis of simple toe syndactyly is almost impossible, whereas prenatal diagnosis of finger simple syndactyly is possible but very difficult.

The diagnosis is easier when the syndactyly is complete and complex because it is

associated with bony changes in shape and results in synchronous movements of the affected digits. In cases of mitten hand deformity as seen in Apert syndrome, the fingers and toes cannot be seen individually, which makes the prenatal diagnosis easier.

Phocomelia

In phocomelia, the arms/forearms and thighs/calves are missing or foreshortened, the hands/feet may be normal or abnormal. The condition can be sporadic as well as associated with single gene disorders such as Robert syndrome, TAR (thrombocytopenia absent radius) syndrome, Grebe syndrome and teratogens such as thalidomide (30).

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