Refresher Course

Ultrasound Assessment of Fetal Skeletal Abnormalities

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Disturbance of the normal process of bone growth and modeling results in a heterogeneous group of skeletal abnormalities. Prior to the introduction of sonography, the prenatal detection of skeletal disorders in utero was possible only by using radiographs obtained during pregnancy. This was achieved by performing either a flat x-ray of the maternal abdomen or amniography. Currently, the diagnosis of many skeletal disorders is feasible due to improved ultrasound resolution, better sonographic skill and experience, and a more precise understanding of fetal embryology and development. With the increased utilization of ultrasound screening programmes, the rising trend in detection of skeletal malformation will continue.[1] However, this is not an easy task, especially in the prenatal diagnosis of severe abnormalities which may require difficult decision concerning terminating of pregnancy.

Normal and abnormal embryological development of the fetal skeleton

Early in the 4th week of development, somites which are condensations of the paraxial mesoderm separate into subdivisions and then develop into vertebrae. The ventral portion of the sclerotome surrounds the notochord which induces the sclerotome to form the rudiment of the vertebral body. The dorsal portion surrounds the neural tube which induces the formation of the vertebral arch.

During the 5th week, costal processes (small mesenchymal condensations) develop in association with the vertebral arches of all developing trunk vertebrae. The ribs develop as cartilagenous precursors and later ossify.

At the end of the 6th week, sternal bars form within the ventral body wall and later connect to the distal end of the developing first seven ribs.[2] Skull development is initially self-differentiating, but then becomes influenced by brain growth and prenatal movements. It develops from paraxial mesoderm, neural crest, occipital somites and mesenchyme from the prechordal plate. The face develops from the five swellings of the first pharyngeal arch and the fifth pharyngeal arch.[3] The fifth component is the frontonasal prominence.[3]

The limbs consist of 4 parts, i.e., the girdles that include several bones (clavicle and scapula, hip bone), the segment in which one bone develops (humerus, femur), the segment in which two parallel bones develop (radius/ulna, tibia/fibula), and the terminal portion containing short bones followed by a number of long bones (metacarpals, metatarsals, phalanges). Limb bud development takes place from the fifth to eighth weeks. It is formed by proliferation of the somatopleuric lateral plate of the mesoderm. Each limb bud consists of an outer ectodermal cap and an inner mesodermal core. Shortly after they are formed, the mesodermal core induces ectoderm along the apex to differentiate into a ridge-like thickening called the apical ectodermal ridge. The digits are formed by a break-down process of apoptosis. Ossification appears from 9 weeks and continues through to puberty. The limb bones and the girdles (except for the clavicle) are formed by ossification of a cartilagenous precursor. This is called endochondral ossification.

Many abnormalities of the skeletal system occur as part of embryological development. These include vertebral (spina bifida), skull (cranioschisis

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and craniosynostosis), and facial (cleft palate) defects. The most common facial abnormality is the holoprosencephalic spectrum of anomalies which occurs in both the fetal alcohol syndrome and the autosomal recessive Meckel syndrome. Abnormalities of the limbs vary greatly and may be represented by partial reduction (mesomelia) or absence (amelia) of one or more of the extremities. Specific causes of limb defects include (1) arrest of development, (2) failure of differentiation of primordial components, (3) homeotic transformations and duplication of components, (4) hyperplasia, (5) hypoplasia, (6) focal defects such as amniotic band syndrome, and (7) general skeletal abnormalities that incidentally affect the limbs. Most human limb defects appear to have a multifactorial basis.[3] In a few cases, familial associations or teratogens are involved.

Limb abnormalities also include the presence of extra fingers or toes (polydactyly). Abnormalities with an excessive number of bones are mostly bilateral, while the absence of a digit such as a thumb (ectrodactyly) is usually unilateral. Abnormal fusion is restricted to the fingers or toes (syndactyly).

Classification of skeletal abnormalities (Table 1)

The prenatal detection of skeletal abnormalities are of various forms and sonography has been applied to the detection of anomalies as early as the first trimester of pregnancy.[4]

One of the most serious skeletal defects particularly amenable to prenatal sonographic diagnosis, is the result of imperfect fusion of the vertebral bodies (spina bifida) which may involve only the bony vertebral arches, leaving the spinal cord intact. Vertebral abnormalities and hypoplasia of the lower limbs affect individuals with caudal dysgenesis, a syndrome in which there is insufficient development in the caudal most region of the embryo. Pregnancies in diabetic mothers are at significantly increased risk of this kind of skeletal malformation when there is poor control in the early stages of organogenesis.[5]

Skeletal abnormalities can be a feature of multiple abnormalities including the autosomal recessive Baller-Gerold syndrome, VATER (Vertebral, Anal, Tracheo-Esophageal and Renal anomalies) association, Cornelia de Lange or non-syndromic dysmorphic fetuses.[6]

Benecerraf (1986)[7] recommended fetal karyotyping of fetuses with talipes due to the high association with chromosomal aberration, e.g. trisomy 18. Polydactyly and a relatively short femur are soft sonographic markers associated with a higher risk of trisomy 13 and trisomy 21 respectively.[8]

Bone growth manifested in the upper and lower limbs can be impaired as a result of placental insufficiency and fetal growth retardation.[9] Infections like parvovirus or cytomegalovirus can produce generalized fetal growth restriction with various other bone abnormalities.[10]

Positional deformities include talipes, rocker-bottom feet and a heterogenous group of disorders known as arthrogryposis multiplex congenita. The latter can result from intrauterine crowding as with oligohydramnios, or defective development of the central nervous system.[11]

Malformation of individual bones can occur singly or in combination with other bones. This can vary from isolated cases of absence or shortage of long bones to complete amputation of the limb resulting from an amniotic band.[12]

Polysyndactyly and other abnormalities of the fingers can be familial in origin or caused by various syndromes. Therefore a detailed search for other fetal abnormalities is essential before coming to a diagnosis.[13]

Skeletal dysplasia are subdivided into those demonstrating defective growth and development of tubular bones like achondroplasia, thanatophoric dysplasia, etc., and skeletal disorders with disorganized development of cartilage and fibrous skeletal components like achondrogenesis. A third group of skeletal disorders involves multifocal resorption of bone, e.g. osteogenesis imperfecta.[14]

Incidence of skeletal abnormality

A population-based register of congenital anomalies,[15] demonstrates a prevalence rate of skeletal malformation of 3.22 per 10,000 live births. However, this figure may not be a true representation of all skeletal anomalies because of their coexistence with various other syndromes. In addition many pregnancies terminate before reaching the registering stage.

Table 1. Classification of skeletal abnormalities.

Class	Type
A	Neural tube defects associated with skeletal abnormalities
B	Multiple fetal abnormalities including skeletal anomalies with normal karyotype
C	Skeletal disorders associated with abnormal karyotype
D	Defects in bone growth
E	Positional abnormalities
F	Malformation of individual bones
G	Digital abnormalities
H	Skeletal dysplasias
I	Unidentified

Neural tube defects occur 1 in 1,000 births and many cases are prevented by providing mothers with folic acid prior to conception. Up to 5% of neural tube defects occur as a part of the autosomal recessive Meckel syndrome which is a multiple malformation syndrome associated with neural tube defects, consisting of hydrocephalus and polydactyly, as well as a variety of other defects.[16] 25% of all conceptuses have a major chromosomal defect and 6% of all malformed infants are due to a chromosomal abnormality.[17]

Intrauterine growth retardation complicates 5% of pregnancies due to placental insufficiency. However defective bone growth is not always an adverse effect of these conditions. Isolated talipes occurs in about 1 in 1,200 pregnancies but it may be an integral part of a genetic syndrome.[1]

Not infrequently (1 in 2,000 births) abnormal fusion of the fingers or toes (syndactyly) occurs and in some cases this leads to fusion of the bones.[19] A multi-hospital birth defects register, the Latin American Collaborative Study of congenital malformation (ECLAMC), reported a birth prevalence of skeletal dysplasia as 2.3/10,000 births.[20]

Aetiology

There is a known molecular basis for various skeletal malformations,[21] however, not all developmental defects are necessarily genetic in origin and various aetiological categories can be recognized.

1. Chromosomal anomalies (e.g. trisomies, translocations).
2. Polygenic disorders (e.g. short stature)
3. Single gene mutation (e.g. achondroplasia, cleft palate).
4. Environmental/teratogenic factors (e.g. phenytoin, warfarin).
5. Multifactorial aetiology (e.g. neural tube defects).
6. Unknown aetiology.

The phenotype is determined by the product of the combined effects of genetic and environmental influence,[22] but the relative contributions of each can differ for each aspect of the phenotype. In some instances, genetic or environmental contributions are tissue type-specific. For example, achondroplasia, an autosomal dominant mutation affecting the function of the epiphyseal growth plates in the long bones, also affects the function of the synchondroses in the cranial base, resulting in a reduced growth of the mid-face.[23]

Limb defects associated with other abnormalities are often hereditary. As the most important events in limb development occur between the fourth and eighth week post-fertilisation, this is also the period of higher susceptibility to teratogens or defective expression of developmentally regulated genes.[24] However, limb defects can also occur as a consequence of trauma, once development of all the limb structures has been accomplished. For example, secondary disruption, so called intrauterine

amputation, is thought to be caused by constriction of the developing limb due to exogenous pressure or disturbance of blood supply.[25]

Diagnosis of skeletal abnormalities by real-time ultrasound

Routine ultrasonography in a low-risk population of pregnant women has led to increased identification of fetuses affected with a skeletal abnormality in the second trimester.[26] However, establishing a specific diagnosis in utero is often difficult since sonographic findings are not necessarily pathognomonic of a postnatal diagnosis.[27]

First trimester ultrasound scan has limited usefulness in the early detection of skeletal abnormalities apart from the diagnosis of neural tube defects and early dating of the pregnancy. Hewitt (1993)[28] reported a case of skeletal dysplasia in the second trimester who had increased thickness of nuchal fold in the first trimester and a normal karyotype. A larger series of first trimester scans[29] suggested the possibility of increased finding of skeletal anomalies in eukaryotype fetuses with increased nuchal translucency.

Most skeletal abnormalities are diagnosed between 18 and 20 weeks, when most women attend for a fetal anomaly scan.[30] The other cluster of cases is found in the third trimester as a result of ultrasound diagnosis performed for the investigation of polyhydramnios, intrauterine growth retardation, premature labour, or intrauterine fetal death.

Most routine screening examinations have included measurements of the head, abdomen and femora.[31] At this time the ultrasonographer may detect a skeletal abnormality. The long bones may be abnormal not only in size but also in shape. An abnormal screening ultrasound should result in a more intensive study (e.g., if the femoral measurements are abnormal) progressing to a detailed examination that includes all the long bones: humerus, radius and ulna as well as the femur, tibia and fibula.[32] A special linear chart is prepared for future sonographic assessment and growth.[33] An attempt should be made to assess the degree of mineralisation by examining the acoustic shadowing behind the bone; the echogenicity of the bone itself and the possibility of fractures should be considered (Figure 1).

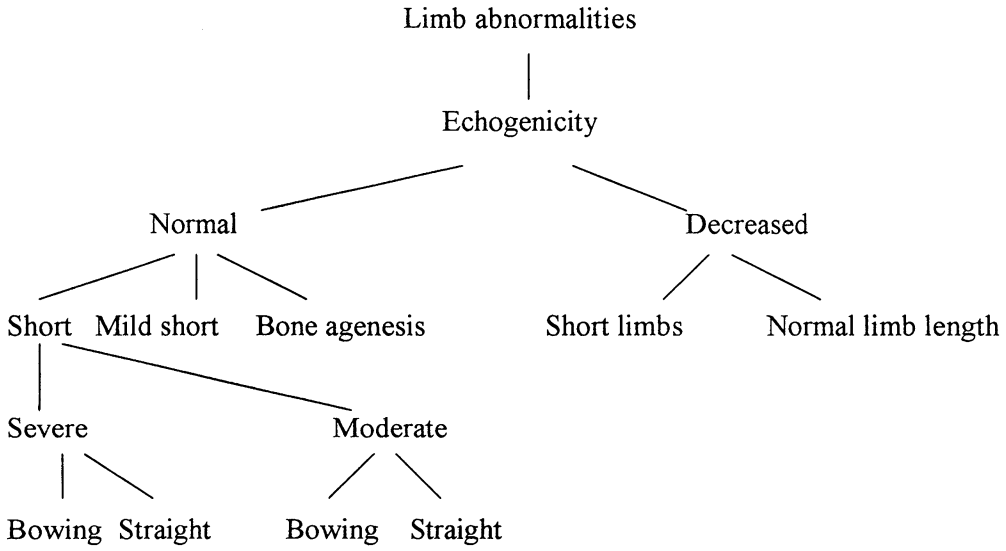

Figure 1. Scheme for assessing fetal limbs.

The terminology used for shortening of the proximal long bones (humerus, femur) is rhizomelia. Mesomelia is shortening of the distal long bones while rhizomelia is shortening of both proximal and distal parts of the limb.

A careful thoracic evaluation represents one of the most important parts of the prenatal examination (Figure 2).

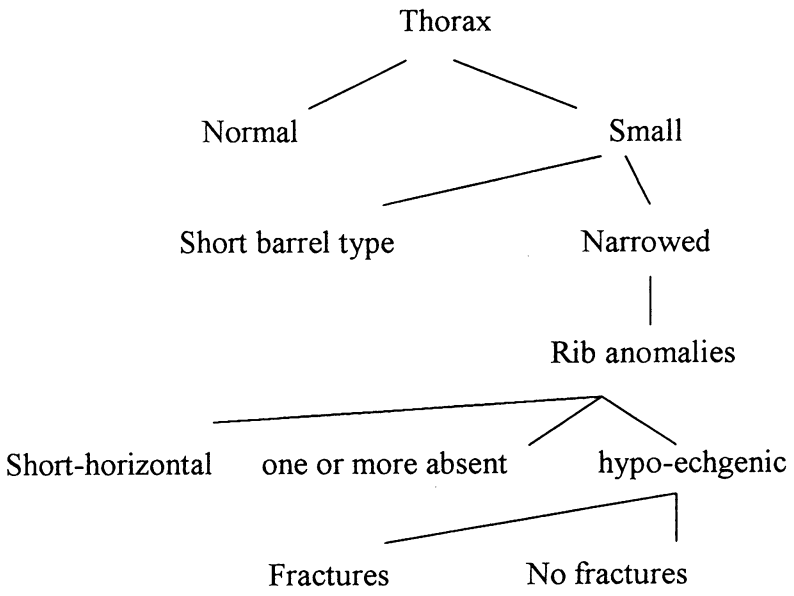

Figure 2. Scheme for assessing the fetal thorax.

A small or constricted thorax often leads to neonatal death because of respiratory difficulties. Thoracic dimensions can be assessed by measuring the thoracic circumference at the level of the four chamber view of the heart.[34] Special note should be made of the shape and integrity of the thorax.[35]

A sagittal view of the head permits the determination of midface hypoplasia[36] which occurs in several bone disorders (Figure 3).

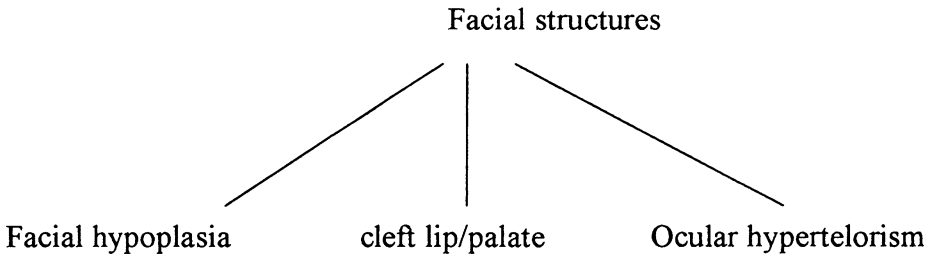

Figure 3. Scheme for assessing the fetal face.

Finally the skull shape, mineralisation and degree of ossification should be evaluated (Figure 4) to obtain as much information as possible for a specific diagnosis.[31] In addition, non-skeletal abnormalities, such as cardiac defects and kidney malformation may be helpful clues to the diagnosis of a specific skeletal dysplasia. Besides a specific diagnosis, which is often very difficult, a probably lethal condition can often be detected with this detailed examination.

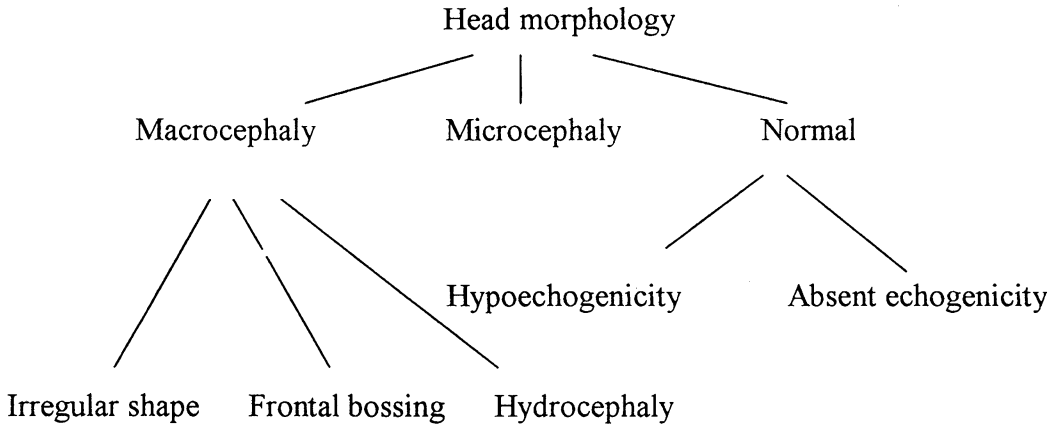

Figure 4. Scheme for assessing the fetal head.

Other techniques for fetal diagnosis

Three-dimensional ultrasound

Three dimensional ultrasound (3D) has been introduced as a potential breakthrough in ultrasound imaging in the past four years. Only recently, 3D technology became advanced enough to be used in clinical practice. The transparent or translucency mode of 3D ultrasound provides imaging of structures with high echogenicity. Thus, the long structures of the fetal skeleton can be viewed in a way that resembles x-ray images.[37] This enables detailed analysis of both normal and abnormal skeletal malformations, e.g. severe scoliosis.[38] Anomalies characterized by angular deformity (e.g. talipes) can be demonstrated by the surface mode of three-dimensional ultrasound. Fingers and toes are well recognized.[39] With further development, 3D imaging may be used in routine clinical practice particularly in assessing facial abnormalities.

Fetoscopy

This was first described by Hobbins and Maloney in 1974 for fetal blood sampling for haemoglobinopathies. In 1997 they published data of performing 34 fetoscopies in 28 continuing pregnancies, without evident harm to the fetus. Benzie et al (1976)[40] described the use of the fetoscope for the detection of skeletal abnormalities; however, two pregnancies continued normally to term, but one miscarried with evidence that the fetus died from the direct effect of the procedure.

An improvement of the technique was reported in 1978 by Rodeck and Campbell[41] but the risk to the fetus remained 5-6% when data were accumulated from different centres[42] (International Fetoscopy Group 1984). At present it is not used in routine practice in view of its invasive nature and visualisation can be impaired by cloudy amniotic fluid.

Computer Database

A number of computer systems have been dedicated to some aspects of dysmorphology. Some of these systems are purely database applications designed to take advantage of computer technology in order to provide up to date syndrome information. On the other hand, a number of projects have endeavoured to build an intelligent system that can formulate a diagnosis, either through its own knowledge-base, or through interaction with an expert user.[43]

Ultrafast magnetic resonance

Although magnetic resonance has been used in prenatal imaging with success due to poor resolution, recent development of ultrafast technique produced pictures complementary to real-time ultrasound. This is useful in certain cases where scanning is hampered by the patients' habitus or due to reduced amniotic fluid or oligohydramnios.[44]

Current management of prenatally diagnosed skeletal abnormality

The initial management following the diagnosis of a suspected skeletal abnormality is to arrange for a detailed fetal scan to look carefully for other abnormalities which may influence the prognosis and future follow up. Karyotyping should be discussed with potential parents as various chromosome disorders have skeletal abnormalities as discussed earlier. This is carried out using cytogenetic culture and sometimes the more urgent FISH (Fluorescence In Situ Hybridisation) technique for the detection of trisomy 13, 18, 21 and sex chromosomes.[45] Establishment of fetal sex is important in the diagnosis of campomelic dysplasia.

Close examination of both parents for signs of skeletal disorder is of value in the rare possibility of autosomal dominant inheritance. Some families may be faced with the 25% recurrence risk associated with autosomal recessive inheritance. It is usually impossible to designate these families, although consanguinity or a previously affected child may be suggestive.[46]

The important of serial examinations by ultrasound scan should be borne in mind and algorithms and growth charts are used for assessing fetal development.[33] A second look assessment is carried out for solitary and minor abnormalities like clubfoot which are managed expectantly.

Counseling

The increasing use of routine ultrasound in recent years has allowed for optimal prenatal care for fetal malformation.[47] In addition there has been a greater understanding of the natural history of skeletal abnormalities in recent years due to advances in ultrasound imaging. Some parents will take the decision to interrupt the pregnancy whilst others will opt to continue in the hope of a more favourable perinatal outcome. Identification of prenatal factors that are useful in counseling will help parents make these difficult decisions. In all cases the parents should be offered the opportunity to discuss the diagnosis, prognosis and subsequent management with a paediatrician, orthopaedic surgeon and/or a geneticist.

Diagnosis and risk assessment

Without an exact diagnosis precise risk assessment is not possible. A diagnosis adequate for management is not always sufficient for genetic counseling. This emphasizes the need for the geneticist to be involved in the diagnostic process especially where opportunities for further examination may not exist. This occurs, for example, after termination of a fetus as a result of prenatal diagnosis or in the case of very sick newborn infants.[48]

Termination of pregnancy (TOP)

At present, termination performed on pregnancies up to fourteen weeks gestation is by uterine aspiration as a one stage procedure. Between fifteen weeks and twenty three weeks local application of prostaglandin is the preferred mode of termination.[49] Live fetuses of more than twenty three weeks require fetocide to prevent a live birth. Cardiac asystole with the injection of potassium chloride into the heart prior to the induction of labour is performed. Patients should be informed of this procedure if they are considering late TOP.

Postmortem examination

The purpose of fetal examination follow-

ing termination of pregnancy after detection of fetal anomaly is vital for postnatal parental counseling for recurrence risk. It is also important to establish the accuracy of prenatal diagnosis.[50] This procedure should be explained to the parents to permit calculation of recurrence risks of the disorder for that particular family. Basic fetal examination comprises naked-eye examination including careful measurement and recording of anomalies, radiographic examination followed by visceral dissection and histological examination of the major organs.[51] A photographic record of all external dysmorphic features as well as any visceral anomalies provides a permanent record of the abnormalities, particularly important for a future consultation in usual cases. Tissue culture, chromosome analysis, DNA analysis may be necessary depending on the type of anomaly found. Macerated fetuses create difficulty in reaching a diagnosis particularly in assessing the central nervous system (CNS) abnormality. Postmortem axial skeletal radiography can reveal fetal CNS malformation otherwise missed by routine autopsy.[52]

Conclusion

Diagnosis of fetal anomalies with ultrasound has improved since the first reported termination of pregnancy after ultrasound prenatal diagnosis.[53] This is due to the improvement in machine resolution and the specialist's skill and expertise. However, there is still a big gap that is needed to bridge before the time arrives when prenatal diagnosis is easily reached in at least 80% of cases. Newer technologies like molecular biology or 3D scan may alter the prediction rate in the prenatal diagnosis of skeletal abnormality in the future. Care in the meantime should be exercised until more fetuses have been studied and followed to delivery.

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