Musculoskeletal anomalies are not uncommon in prenatal life. They can be either sporadic or part of chromosomal syndromes causing prenatal morbidity and mortality. The prenatal diagnosis of musculoskeletal anomalies is based on information assembled from various imaging modalities and from biochemical and genetic workups. The prenatal diagnosis can serve as a prognostic tool and in counseling the parents. Among the imaging methods, ultrasonography is the most popular and cost effective in observing and following fetal development from the very early stages of gestation. Transvaginal sonography can detect and identify most of the normal and the specific pathologic changes very close to the stage of their embryogenic development. From a practical point of view, early detailed transvaginal sonography screening at 14 to 15 weeks of gestation is very useful while late detection at 20 to 23 weeks of gestation may provide some additional information in low-risk pregnancies. Very early screening, even during the ninth week, may be indicated in high-risk pregnancies. Additional genetic counseling is recommended when abnormal findings are suspected. We summarize the diagnostic approach and the information available for the most common musculoskeletal anomalies.

It is estimated that congenital defects (including those of the skeleton) are found in 0.02% of healthy fetuses, and that 80% of them occur in so-called “low-risk” pregnancies.15,23

The prenatal diagnosis of skeletal anomalies needs the assembling of the following data: family and pregnancy history (including exposure to teratogens and medications), serial measurements (including those of the head, the abdomen, and the thorax and the lengths of the femoral and long bones), and a thorough examination of the spine, hands, and feet, calvarial and facial features, the presence of bowing, shortening or angulation of the long bones and the degree of mineralization (ie, healthy or reduced; Table 1). Of a myriad of anomalies and developmental conditions, there are about 400 syndromes with involvement of the musculoskeletal system.

Our purpose is to review the current and novel techniques that are relevant to prenatal diagnosis and to succinctly present the most commonly found musculoskeletal anomalies.

Prenatal diagnosis is essential in identifying and isolating specific pathologic expressions and for detecting abnormal developmental patterns and events. It enables establishment of the prognostic importance of the various findings and provides the information needed for appropriate parental reassurance (98% of ultrasound examinations are normal) as well as the information essential for genetic, orthopaedic, and obstetric counseling. In addition, it has a crucial role in extending the current knowledge with the aim of generating the development of different in-utero or postnatal treatment options in fetal or postnatal life. Ideally, fetal screening for malformations should be understood as an ongoing process of decision making (Fig 1).

Early prenatal detection of most of the fetal anomalies has been made possible by the ever-expanding knowledge and better understanding of the relevant genetic and pathologic mechanisms together with enhanced molecular diagnostic tools, examiners’ skills and the quality of imaging technology and equipment. It was postulated that between 93 and 96%15,20 of all fetal anomalies are detectable by ultrasonography before the seventeenth week of gestation. Some skeletal defects,17 however, cannot be detected at the early scanning and should be followed with an additional detailed ultrasonographic scanning between 18 and 24 weeks of pregnancy, even when there is no reason to suspect the existence of an abnormality. Some ultrasonographic markers of chromosomal aberrations are transient and may disappear at more advanced stages, stressing the importance of early screening during 14 to 15 weeks of gestation.15,24,66

The impressive amount of accumulated data on the prenatal recognition and detection of skeletal dysplasias and
musculoskeletal anomalies allows the early involvement of a medical team, which also includes a pediatric orthopaedic surgeon, in comprehensive prenatal parental counseling. Early diagnosis also paves the way for possible fetal surgery, although the place of fetal surgery for non-lethal conditions is controversial, given the possible jeopardy to the fetus, the mother, and future reproductive potential.5,18,51

Table 2 lists the important milestones in the musculoskeletal embryonic development that can be detected by ultrasonography. The upper limbs mature and develop more rapidly than the lower limbs. The movements of all four limbs can be detected by the ninth postmenstrual week. A long bone’s length increases in a relative constant and linear pace throughout intrauterine life and maturity. The fingers can be detected and counted through the tenth week of gestation in many of the fetuses.61

Ultrasonography has become the method of choice for routine antenatal diagnosis because of its low cost, availability, safety, accuracy and real-time capability. A systematic detailed sonographic survey enables the detection of most possible skeletal anomalies (Table 1). Transvaginal scanning (TVS) is considered to be the most advanced sonographic technique available to date.15 Transvaginal scanning is best done at the end of the first trimester and the beginning of the second one when it is possible to observe fetal organs with high accuracy. Unlike transabdominal sonography (TAS), TVS can detect the fetus through various scanning planes without being affected by

**TABLE 1. Sonographic Evaluation of the Skeleton**

<table>
<thead>
<tr>
<th>Anatomic Structure</th>
<th>Sonographic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long bones and joints</td>
<td>Degree of limb shortening</td>
</tr>
<tr>
<td></td>
<td>Pattern of limb shortening</td>
</tr>
<tr>
<td></td>
<td>Degree of mineralization</td>
</tr>
<tr>
<td></td>
<td>Presence of fractures, bowing or angulation (continuity)</td>
</tr>
<tr>
<td></td>
<td>Abnormal shape or contour</td>
</tr>
<tr>
<td></td>
<td>Limb-reduction anomalies</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic or aplastic bones</td>
</tr>
<tr>
<td></td>
<td>Spontaneous motion of major and small joints</td>
</tr>
<tr>
<td></td>
<td>Contractures</td>
</tr>
<tr>
<td>Spine</td>
<td>Degree and pattern of demineralization</td>
</tr>
<tr>
<td></td>
<td>Continuity (scoliosis, kyphosis, diastematomyelia, spina bifida)</td>
</tr>
<tr>
<td></td>
<td>Perispinal soft tissue masses</td>
</tr>
<tr>
<td>Thorax</td>
<td>Hypoplastic versus normal</td>
</tr>
<tr>
<td></td>
<td>(hypoplastic ribs, bell-shaped thorax, pulmonary hypoplasia)</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>Postural deformities</td>
</tr>
<tr>
<td></td>
<td>Abnormal number of digits</td>
</tr>
<tr>
<td></td>
<td>Sydactyly</td>
</tr>
<tr>
<td>Skull</td>
<td>Macrocranium</td>
</tr>
<tr>
<td></td>
<td>Frontal bossing</td>
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<tr>
<td></td>
<td>Craniosynostosis</td>
</tr>
<tr>
<td></td>
<td>Compressibility/abnormal degree of mineralization</td>
</tr>
<tr>
<td></td>
<td>“Banana sign”</td>
</tr>
</tbody>
</table>

**TABLE 2. Milestones in the Sonographic Appearance of the Developing Embryo**

<table>
<thead>
<tr>
<th>Week(s) of Gestation</th>
<th>Sonographic Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Lower limb buds (mainly)</td>
</tr>
<tr>
<td>9</td>
<td>Upper limb buds, separation of fingers and initial movements</td>
</tr>
<tr>
<td>10</td>
<td>Entire length of long bones in the upper and lower limbs</td>
</tr>
<tr>
<td>11</td>
<td>Opposing thumbs</td>
</tr>
<tr>
<td>10–12</td>
<td>Skull and calcified spinal column</td>
</tr>
<tr>
<td>11–12</td>
<td>Foot position 90° in relation to tibia/fibula</td>
</tr>
<tr>
<td>12–13</td>
<td>Metacarpal and phalangeal bones</td>
</tr>
<tr>
<td>12–17</td>
<td>Spreading of fingers</td>
</tr>
<tr>
<td>13</td>
<td>Feet and toes</td>
</tr>
<tr>
<td>Third trimester</td>
<td>Hip joint (the relation of the acetabulum and femoral head)</td>
</tr>
</tbody>
</table>

**Fig 1.** This flowchart shows the ideal approach to fetal screening for malformations, which is seen as dynamic process throughout the pregnancy. (Note: there is a 2-week discrepancy between the gestational age and the embryologic age.)
maternal obesity, abdominal scars or uterine myomas. The high resolution of the most advanced ultrasound technology enables TVS detection capacity up to 4 weeks earlier than TAS. This advantage makes TVS even more favored because most fetal anomalies already are present in the first trimester. Although TVS enables a higher rate of early detection than TAS, TVS has a limited use because of its short focal distance; the upper limit of its reliability is at 17 to 18 weeks of gestation. TAS represents the routine and traditional imaging method. It is the method of choice for scanning starting from 17 to 18 weeks of gestation. Observation of the limbs by ultrasound is limited in the third trimester when there is less amniotic fluid relative to fetal size and the fetus is less mobile. The technology of multidimensional, three-dimensional (3D) or four-dimensional (“real-time” or 4D), ultrasound has been clinically studied over the last few years. Finally, color Doppler ultrasound is useful for assessing blood flow, for example in a limb with constriction bands.

Magnetic Resonance Imaging (MRI) is a noninvasive important adjunct tool in the assessment and prenatal diagnosis of congenital anomalies. Because it provides an excellent spatial and tissue resolution with multiphasic display, it is recommended from the second trimester onward and when ultrasound analysis of congenital fetal defects is not conclusive. It is especially effective in better assessing the critical features of the central nervous system (CNS) where the traditional prenatal ultrasonography fails.

Plain radiographs taken in the third trimester may be used as an additional tool for detecting skeletal dysplasias only.

Genetic screening tests are used for mutation analysis and the detection of different chromosomal aberrations. Screening tests for specific genetic skeletal anomalies are not yet available. An intrauterine sampling of the fetal cells is taken for subsequent DNA analysis by doing chorionic villus sampling (CVS), usually around 11 to 13 weeks of pregnancy, and/or amniocentesis between 16 and 20 weeks. The recent advances in molecular diagnosis of fetal pathology are based on using circulating embryonic cells after they have been isolated from the mother’s blood. Neural tube defects can be detected with the use of alpha-feto-protein (AFP) in maternal serum, which is preferred whenever possible because of a reported risk of limb deficiency after CVS in the period of limb morphogenesis and slightly beyond.

For prenatal screening purposes, musculoskeletal anomalies can be divided into three main groups. The first group consists of primary anomalies, which are detectable from 8 to 9 weeks of gestation, and are characterized either by absence or reduction of a structure (aplasia and hypoplasia) and/or by an additional (hypertrophy and supernumeral) structure. The second group consists of growth anomalies (abnormal length and width of tubular bones). Nonlethal syndromes with severe length and shape abnormalities can be detected after 23 weeks of gestation (eg, achondroplasia) whereas minor anomalies that appear very similar to normal structures (eg, congenital simple short femur, focal femoral dysplasia) may be missed. The third group is comprised of contractures that include clubfoot, arthrogryposis, Larsen syndrome and others. Fetal dyskinesia is a long-standing lack of motion that causes molding and postural deformities of the limbs and spine, and it can be found in many conditions involving severe neurologic damage.

Transvaginal scanning and TAS provide detailed information on upper and lower extremity fetal anatomy. The anomalies of the hands may present a broad spectrum of defects ranging from a focal involvement of a single distal ray to a global whole limb involvement. Therefore, when a finger or hand anomaly is detected antenatally, a thorough survey and search for associated malformations is mandatory.

Syndactyly is considered to be a result of a failure of differentiation. The complex type is much easier to diagnose prenatally than simple syndactyly. Polydactyly presents two distinctive subgroups: the isolated form, which is usually detected in fetuses with a normal karyotype and is associated with a favorable outcome, and the second form that has associated abnormalities. There are associated malformations and/or chromosomal disorders in 59 to 60% of cases with fetal fingers of upper and lower extremity abnormalities.

Most of the length anomalies of bone are caused by failures of formation during the embryo’s development. Long-bone abnormalities are usually of nongenetic etiology. When moderate shortening of long bones is the only early sonographic finding, followup scans are mandatory in order to exclude a false positive diagnosis of bone dysplasias. The prenatal detection of bone length anomalies can be divided into three groups according to the extent of the delay in length compared with normal values in intrauterine growth charts. The first group includes those cases with severe shortening of bone where there is a delay of more than 3 to 4 weeks in bone length in early pregnancy. These anomalies, almost always lethal, are usually detected in the first trimester and may be seen in achondrogenesis, osteogenesis imperfecta Type II and thanatophoric dwarfism. The second group is comprised of moderate shortening (estimated as a delay of 2 to 3 weeks in the size of bones) in which the diagnosis of long bone shortening is possible as early as the twelfth week of gestation. The last group consists of late onset cases in which the bones ap-
pear within the normal range in early pregnancy and their shortening is only obvious after 23 weeks of gestation.

A severe asymmetrical appearance of limb and unilateral shortening of bones can be detected at the end of the first and in the early part of the second trimester.3-38,40 The most common anomaly is proximal femoral deficiency/hypoplasia or congenital short femur (Fig. 2), and its intrauterine sonographic detection is possible by the observation of a discrepancy in length between the two femoral bones.38 When congenital shortening of the femur is part of other syndromes, the diagnosis of femoral shortening is possible as early as the fourteenth week of gestation.16,58

Limb reduction deficiencies (LRD) include the absence of a limb or the lack of the formation of a segment of a limb. They are usually sporadic and nongenetic. From 30 to 45% of LRD cases are associated with other malformations.35,56 There are very few reports on antenatal diagnosis of fibular hemimelia (also known as fibular agenesis or hypoplasia), and it usually is found in association with other anomalies.63 Tibial hemimelia often is associated with polydactyly of the feet and deficiency of the medial rays of the foot. Amelia represents the most severe form of LRD with an incidence of 0.4 to 1.5 per 100,000 births43; it is generally associated with other malformations.

Clubfoot is a relatively common anomaly, with a prevalence ranging from 0.09% in the newborn population22 to 0.43% when detected by ultrasound in the intrauterine phase.49 It presents a wide variation among the different races. Clubfoot is bilateral in 40 to 50% of the affected fetuses. Most clubfoot cases are idiopathic, but the condition may be associated with other structural anomalies, including hydrocephalus, neural tube defects, cleft lip/palate and heart defects, and/or chromosomal abnormalities.8,36,52

Identifying an isolated clubfoot on antenatal ultrasound should alert the examiner to look for other associated anomalies. The wide difference in the rate of false positive diagnosis of clubfoot (from 0–40%) may be related to variations in the scanned populations41,55,60,62 or missed diagnosis of positional clubfoot and clubfoot-like feet. The improvements of ultrasonographic equipment and in the sonographers’ skills have led to a continuous increase of antenatal detection of clubfoot over the years (Fig. 3). In a previous study,37 the earliest weeks of gestation in which the condition was diagnosed with a high degree of confidence were the twelfth and thirteenth, and the latest was week 32. Not all patients were diagnosed at an early stage. The first ultrasound examination failed to detect the deformity that subsequently became obvious at a later examination in 29% of fetuses. Therefore, it can be considered to be an early event in gestation (45% identified by week 17), a late event (45% detected between 18 and 24 weeks), or a very late event (10% recognized between 25 and 32 weeks). We cannot, however, exclude the possibility that the late-onset groups may have been diagnosed late because earlier scans yielded false-negative results. There was no significant relationship between the prenatal diagnosis and the postnatal therapeutic approach (conservative or surgical), or the degree of rigidity of the affected foot.6,15 It should be borne in mind that transient findings of clubfoot in early pregnancy may turn into a normal foot position after 10 to 20 minutes of scanning.6,15

Partial or complete absence of toes and/or fused toes may be detected in ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome and in fetuses with femur-fibula-ulna syndrome (FFU) or amniotic band syndrome. Hypoplasia or aplasia of the lateral part of the feet and toes are common in cases of fibular hypoplasia. The incidence of “missing” toes in the prenatal scanning is quite high, but such a finding is usually a false positive one.

Any asymmetrical or abnormal appearance of toes can be a clue for other associated anomalies. Severe contrac-

Fig 2A–B. Proximal femoral deficiency is shown. The right lower limb is affected. (A) The diagnosis was made at the sixteenth week of gestation by measuring both femoral bones. (B) The autopsy findings correlate with the early sonographic detection.
tures of the toes, as in metatarsus primus varus, are ob-
served in the form of a “sandal foot” which can be either
a transient finding or a clue for additional associated skel-
etal or chromosomal anomalies when it persists.

The spine can be seen at 7 to 8 weeks of gestation and
its calcification is well defined at 10 to 12 weeks of ges-
tation.44 Meticulous comparison of each of the ossification
centers in the each line to its parallel one is important for
the detection of hemivertebra, fused vertebra, absence of
vertebra, widening of the spinal canal or kyphoscoliosis.
Transverse scanning enables the detection of neural tube
defects and isolated skin defects. Intact skin posterior to
the spine is crucial for ruling out the presence of a menin-
gocele or myelomeningocele.

Congenital malformations of the vertebrae can be di-
vided into two groups. The first includes anomalies that
are caused by a failure of formation, a morphogenetic
event that may result in hemivertebra, fused vertebra, absence of
vertebra (as in caudal regression syndrome). The real inci-
dence of isolated asymptomatic hemivertebrae is unknown
since most of them are diagnosed postnatailly by incidental
x-rays.15 The second group consists of malformations
caused by a failure of segmentation, such as fused verte-
brae and unsegmented bar, which is the cause of congen-
itai scoliosis or kyphosis (Fig 4).

The earliest reported age at which abnormal spinal cur-
vatures were detected was the fourteenth week of gesta-
tion. A final prenatal diagnosis of spinal curvatures re-
quires a persistent finding on different planes of scan-
ning.15

Spina bifida is a common malformation of the vertebral
column. A posterior midline defect is associated with ex-
posure of the neural canal. The prenatal ultrasonographic
detection of spina bifida (Fig 5) is possible if one or more
of the following findings is present: skin defects posterior
to the vertebral column, a cystic lesion protruding from the
spinal canal, a U-shaped appearance of the vertebra, or the
“banana sign,” which represents the shape of the cerebel-
lum herniating through the foramen magnum (this is the
Chiari II manifestation which is the typical sign of spina
bifida). More than 90% of these signs can be seen in early
pregnancies.

Fig 3. Prenatal detection of clubfoot with the use of two-dimensional (2D) provides less information of the pathological features compared with the three-dimensional (3D) transvaginal ultrasonography.

Fig 4A–B. (A) Failure of vertebral segmentation (arrow) diagnosed by transvaginal sonography at the thirteenth week of gestation and (B) a postnatal radiograph that confirmed the fused vertebrae are shown.
Our experience is that most cases of spina bifida can be detected at 12 to 17 weeks of gestation; however Olde Scholtenhuis et al reported diagnosing most of their cases after the 24th week of gestation. It should be noted that there are still some unique unusual echogenic structures in the lower spine that are present in early pregnancy and that can become sacrococcygeal teratoma or even pilonidal sinus or scar tissue in the sacral region. Some of these echogenic plaques can disappear at the followup examinations, such as the “fetal tail” which on subsequent ultrasounds around 22 to 23 weeks of gestation always disappears but turns into a postnatal pilonidal sinus or a dimple.

Caudal regression syndrome (CRS) is a rare fetal complication of diabetic pregnancy. Its spectrum of presentation ranges from mild incomplete development of the sacrum to severe agenesis of the lumbosacral spine, including disruption of the distal spinal cord and lack of growth of the caudal region. The associated anomalies include neurologic, urologic, and orthopedic manifestations. High-resolution TVS may diagnose caudal regression syndrome as early as the ninth or eleventh week of gestation, but most cases are diagnosed during the second trimester. The ultrasonographic diagnosis of shortened spine and missing vertebrae is made with certainty by the fourteenth week of gestation.

Fetal tumors are being diagnosed with increasing frequency and great accuracy by antenatal ultrasound. The most common tumor in newborns is sacrococcygeal teratoma with a 22% incidence of malignancy. The most common mass site and is external followed by the sacrum and perineal region. Two-dimensional ultrasound is able to detect a teratoma by the end of the first trimester, but 3D scanning can be used for the definitive diagnosis and for defining the degree of involvement of the sacrum, the pelvic structures and the vascular bed for prognostic purposes. Other masses that were reported to be antenatally diagnosed are: infantile myofibromatosis (a common soft tissue tumor), congenital fibrosarcoma, and intraspinal lipoma.

Diastematomyelia is a rare expression of spinal dysraphism that can be associated with other spinal anomalies, such as spina bifida, hemivertebra and butterfly vertebra. The anomaly usually is occult and its antenatal sonographic detection is usually possible only in the third trimester. The detection of these typical findings mandate extensive scanning and, if possible, MRI in order to exclude posterior defects in the spine, lack of skin integrity or a soft tissue mass which might be associated with the more serious neural tube defects.

Constriction band syndrome (or amniotic band syndrome) is a sporadic rare condition that mainly refers to constriction and amputation of fingers, toes, and limbs, and is associated with a wider spectrum of craniofacial, visceral and limb anomalies. Authors of few studies using real-time prenatal sonography were able to show intrauterine amputation with surrounding fibrous strands or bands originating from the amniotic membrane and floating freely in the amniotic fluid. The earliest reported detection of the syndrome was at the 18th week of gestation.

There is one report of antenatal intrauterine lysis of the amniotic constriction bands.

Prenatal diagnosis of skeletal dysplasias remains problematic. The lethal forms can be diagnosed towards the end of the first trimester whereas the nonlethal forms can be diagnosed between 22 and 23 weeks of gestation. Advances in molecular genetics (eg, the use of mutation analysis) have contributed to prenatal diagnosis of many skeletal dysplasias, such as the identification of the muta-
tion of the fibroblast growth factor receptor (FGFR3) gene that is associated with achondroplasia, hypochondroplasia, and thanatophoric dysplasia.

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited disorders that are characterized by bone fragility and connective tissue abnormalities.24,54 There are case reports of ultrasonographic antenatal detection of OI (Type II; the lethal form) as early as the first trimester29,33,36 or at 14 weeks of gestation (Type III; the progressive form).12,56 The mild form of OI (Type IV) is not diagnosable until after 20 weeks of gestation, when the sensitivity of the ultrasound is sufficient to detect femoral bowing and limb shortening, or only post-delivery. Recent biochemical studies of collagen, procollagen and fibroblasts obtained from chorionic villus sampling and amniocentesis can provide an antenatal diagnosis by 13 to 14 weeks gestation.24

Congenital multiple arthrogryposis is a collective term used to clinically describe multiple joint contractures of variable and heterogeneous etiologies with a prenatal onset. There are several types of this condition that differ in clinical presentation, severity and inheritance. The contractures may be either isolated (classic), or associated with other malformations and syndromes. The prenatal sonographic diagnosis is usually based on the detection of persistently reduced/absent fetal movements, deformed long bones, joint contractures, clubhand (severe flexed hands), absent muscles or markedly reduced soft tissue, clubfoot, subcutaneous edema with skin creases, abnormal joint positioning and the “Buddha” position. The latter finding can be detected in 95% of the cases.1,12,28 Reduced spontaneous intrauterine movements of joints can be noted during sonographic examination. One must keep in mind that prenatal diagnosis of clubfoot may be the first sign for arthrogryposis, and a thorough followup is indicated. Fixed articular contractures and abnormal positioning of the extremities are difficult to detect during the first trimester. For this reason, the prenatal diagnosis mainly is made during the early second trimester of pregnancy.28

The basic timing of intrauterine bone mineralization (ossification) still is not altogether clear.3 There is a good correlation between sonographic and x-ray imaging findings with regard to the appearance of the skeletal ossification centers.54

Hypophosphatemia presents a spectrum of clinical findings that ranges from the lethal form to the mildest adult form. The prenatal diagnosis can be arrived at by corroborating ultrasonographic findings with the measurement of alkaline phosphatase in cultured amniotic fluid cells after 16 weeks of gestation.45

There is a consensus that early systematic ultrasonographic screening at the fourteenth and fifteenth weeks of gestation followed by a late scan at week 20 is essential in the detection of musculoskeletal anomalies that were described above. The contribution of 3D and 4D ultrasound in the diagnosing process has not yet been established. Magnetic resonance imaging and plain radiographs have inherent limitations, and their overall disadvantages outweigh the benefits. Genetics together with molecular biology, either by itself or as an adjuvant to imaging modalities, plays a more and more important diagnostic role. Therefore, a geneticist with knowledge in musculoskeletal abnormalities must be involved in making the conclusive diagnosis.

It is an ethical responsibility to provide future parents with appropriate information regarding any unusual finding together with its known implications for the child’s health and quality of life.

References