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Prenatal Diagnosis and Treatment of Congenital Differences of the Hand and Upper Limb

By Donald S. Bae, MD, Carol E. Barnewolt, MD, and Russell W. Jennings, MD

Prenatal detection of congenital abnormalities is increasing, along with the evolving technology and widespread use of ultrasonography in prenatal screening. Musculoskeletal anomalies are noted during prenatal ultrasonography in approximately six of every 1000 pregnancies (0.6%), although approximately 1% to 2% of all newborns have some type of congenital difference and the musculoskeletal system is affected in 10% to 20% of these infants (0.1% to 0.4% of newborns)\(^1,2\). The prevalence of skeletal dysplasia is 2.4 per 10,000 live births (0.02%), and the prevalence of limb deficiency is 0.49 per 10,000 births (<0.01%)\(^1,3-5\).

The discrepancies between the prevalence of musculoskeletal anomalies seen during prenatal screening and the observed rate of congenital differences in the general population of newborns are likely due to a combination of factors, including selection bias (higher risk patients are more likely to be screened), the fact that many musculoskeletal anomalies are associated with systemic conditions that result in fetal demise or early death, and elective termination of the pregnancy. Evidence that supports these factors includes an estimate that 23% of patients with skeletal dysplasia are stillborn and another 32% die within the first week of life\(^6\) as well as the observation that, in nations in which ultrasound screening during the second trimester is commonplace and therapeutic abortion is legal, high rates of pregnancy termination have been reported in association with a diagnosis of congenital differences\(^7\).

Since congenital musculoskeletal anomalies are likely to be diagnosed during prenatal screening, orthopaedic surgeons are now consulted by anxious expectant parents during this stressful, emotionally charged time\(^8\). In the Advanced Fetal Care Center at our institution, we provide comprehensive, multidisciplinary care for patients and families whose unborn child has been noted to have congenital anomalies on prenatal testing. Through the combined efforts of radiologists, geneticists, obstetricians, perinatologists, and surgeons of all specialties, patients and families are offered critical prenatal counseling and timely, often lifesaving, care.

This review of prenatal diagnosis and treatment includes current guidelines for prenatal screening for musculoskeletal anomalies, the state of the art and future directions for prenatal interventions, and some of the ethical considerations engendered by prenatal diagnosis and treatment.

Current Recommendations Regarding Prenatal Imaging Screening

Ultrasound evaluations are currently utilized to monitor fetal development, assist with prenatal care, and identify fetal abnormalities\(^9,10\). While the utility of prenatal ultrasonography is well established, there is a lack of consensus regarding the optimal timing of screening ultrasonography\(^11-13\). Furthermore, the recommendations regarding musculoskeletal examination are limited; the routine second-trimester screening standards of both the American College of Radiology and American Institute of Ultrasound in Medicine require only basic documentation that all four extremities are present, and even for level-2 (“targeted”) ultrasound studies, further detailed assessment of the extremities is “encouraged” but no formalized standards exist\(^14,15\).

In the United States, second-trimester ultrasonography is generally performed between eighteen and twenty-two weeks of gestation to confirm dates, evaluate intrauterine development, and screen for congenital anomalies or malformations. Earlier ultrasonographic evaluation may be performed to confirm dates, evaluate for possible ectopic or molar pregnancies, confirm cardiac activity, and assess for some structural anomalies. For some high-risk groups, early ultrasound risk assessment is performed between eleven and fourteen weeks of gestation; in this time period, initial limb development can be assessed with use of transvaginal techniques. High-risk pregnancies may be further evaluated during the third trimester with serial ultrasound studies. The use of ultrasound for early risk assessment or serial studies is not standardized. The utility of additional ultrasonographic screening in low-risk populations and the effect, if any, on perinatal outcomes remains controversial\(^16\).

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Although it is likely that serial ultrasound examinations, particularly in experienced centers, increase the ability to detect congenital abnormalities during the prenatal period, because of the lack of standardized screening indications for ultrasonography, this technique does not currently provide an accurate estimate of the incidence and prevalence of fetal anomalies of the hand and upper limb. In addition, further investigation regarding the frequency and utility of serial prenatal screening ultrasonography in low-risk populations is needed.

**Current Prenatal Imaging Technology**

Currently, conventional ultrasound examination may be performed with transabdominal or transvaginal techniques. Owing to the greater proximity of the ultrasound probe to the developing fetus, transvaginal ultrasound theoretically may provide for earlier detection of congenital anomalies. When the anatomy of interest is near the cervix, endovaginal techniques provide increased anatomic detail throughout pregnancy.

The hand and digits are best visualized with use of ultrasound during the late part of the first and early part of the second trimesters. During this period, the fingers are large enough to be visualized and characteristically are extended and abducted, providing the examiner with the ability to discern anatomic differences. Later in gestation, the hands may be clasped and the digits flexed, making detection much more challenging. Additionally, the upper extremities may be being held in a position that is obscured by the growing fetus, and the relative decrease in intruterine space and amniotic fluid limits fetal motion and hence the likelihood that the fetus will soon move into a position that allows for a more detailed ultrasound assessment.

Three-dimensional ultrasound provides improved diagnostic potential, allowing for identification and characterization of clinical features and phenotypes that may not be seen with conventional imaging. In particular, three-dimensional ultrasound allows for improved visualization in the coronal plane, volumetric analysis of organs, and more detailed analysis of complex anatomic structures, possibly providing confirmation of normal anatomy after suspected anomalies have been identified on two-dimensional ultrasonography. Indeed, some have advocated three-dimensional ultrasound as the imaging modality of choice for analysis of the limbs and, in particular, the hand.

As experience with prenatal ultrasound increases, the ability to identify normal and abnormal musculoskeletal structures also increases (Table I). With use of advanced ultrasonographic techniques, exquisite static and dynamic detail can be observed. For example, Katz et al. recently reported on the normal range of fetal finger movement during the second and third trimesters on the basis of an ultrasonographic evaluation of 260 consecutive fetuses between sixteen and forty-one weeks of gestation. Normative information such as this is helpful in identifying conditions such as arthrogyrosis, symphalangism, camptodactyly, and other conditions that affect digit range of motion.

### Table I. Ultrasonographic Visualization of the Developing Musculoskeletal System

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Visible Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>Lower limb buds</td>
</tr>
<tr>
<td>9 weeks</td>
<td>Upper limb buds, initial motion</td>
</tr>
<tr>
<td>10 weeks</td>
<td>Entire upper and lower limbs</td>
</tr>
<tr>
<td>11 weeks</td>
<td>Opposing thumbs</td>
</tr>
<tr>
<td>11-12 weeks</td>
<td>Plantigrade foot position</td>
</tr>
<tr>
<td>12-13 weeks</td>
<td>Metacarpals, phalanges</td>
</tr>
<tr>
<td>11-13 weeks</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>12-17 weeks</td>
<td>Individual separated phalanges</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Developing hip joint</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging offers several theoretical advantages in comparison with conventional sonography. Imaging of the fetus is less dependent on the presence of normal amniotic fluid volume, fetal position, and maternal body habitus. However, fetal motion produces artifacts on magnetic resonance imaging, and the fetus typically moves the extremities more than the head or torso, causing technical challenges to the application of fetal magnetic resonance imaging in the assessment of extremity anatomy. While fetal magnetic resonance imaging has demonstrated particular advantages in the evaluation of neural axis, thoracic, and head or neck abnormalities, its usefulness in the accurate evaluation of the hand and upper limb has not yet been determined. The extraordinarily rapid advances in magnetic resonance imaging hardware and software promise that technical limitations associated with movement will be overcome; high-detail delineation of fetal musculoskeletal anatomy with use of magnetic resonance imaging technology is on the horizon.

**Prenatal Diagnosis of Musculoskeletal Conditions**

Isolated musculoskeletal abnormalities may be identified with use of prenatal ultrasound imaging; the hand and upper-limb conditions that can be visualized include transverse and longitudinal deficiencies, polydactyly, syndactyly, clinodactyly, and clasped thumbs (Figs. 1-A through 2-C). Similarly, many spinal and lower-limb differences may be seen, including congenital scoliosis due to failures of vertebral formation and segmentation, neural tube defects, clubfoot, proximal femoral deficiency, fibular and tibial deficiencies, and congenital vertical talus (Figs. 3-A, 3-B, and 3-C). Skeletal dysplasias and other systemic conditions affecting the musculoskeletal system are often first recognized on the basis of screening ultrasound findings, such as short limbs, diminished fetal movement, and/or absent skeletal structures. However, a precise diagnosis of skeletal dysplasia is difficult to make because of phenotypic variability, variations in timing of the appearance of skeletal manifestations, overlapping features, and the inability of current imaging technologies to provide an
encompassing or integrative view. Advances in genetics, specifically the increasing knowledge of the specifics of gene localization and microarray techniques, are improving the accuracy of prenatal diagnosis.

Despite advances in prenatal imaging capabilities, many challenges and limitations remain. Controversy exists regarding the timing and technique of imaging. Diagnostic capabilities are still inherently constrained by the operator-dependency of
image acquisition and experience of the imager or clinical consultant interpreting the examination. Rates of detection of cleft palate, for example, range from 16% to 94%.

Even with regard to congenital clubfoot deformity, prenatal assessment is accurate in only 80% to 90% of patients. Awareness of the current imaging limitations and the potential for false-negative and false-positive results is critical for the consulting orthopaedic provider.

**Prenatal Intervention**

Prenatal interventions include genetic counseling, prenatal specialist consultation, and fetal surgical treatment.

**Genetic Counseling**

Currently, genetic counseling is highly individualized according to the fetal abnormality in question and the institution in which the fetus and mother are being treated. While some have advocated formal genetic analysis in the evaluation of fetal abnormalities, particularly when multiple anomalies have been identified, these recommendations are tempered by the inherent risks of obtaining a fetal tissue sample by amniocentesis or chorionic villus sampling and the infrequency with which chromosomal analysis affects prenatal or postnatal care.

However, a timely prenatal consultation with a geneticist provides an informed and thorough discussion of the prenatal findings and potential implications prior to delivery.

**Prenatal Specialist Consultation**

In addition to genetic counseling, prenatal consultation with the medical and surgical specialists who are knowledgeable about the diagnosis and prognosis is very valuable to expectant parents. The etiology, natural history, and potential treatment

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**Figs. 2-A, 2-B, and 2-C** Conventional two-dimensional (Figs. 2-A and 2-B) and three-dimensional (Fig. 2-C) ultrasound images of a fetus at twenty-six weeks of gestation with a congenital amputation at the distal end of the left forearm and a single rudimentary digit. With a conventional probe, the truncated nature of the distal part of the forearm is observed (Fig. 2-A) but, with a higher-detail linear transducer (Fig. 2-B), the hypoechoic cartilage of the distal part of the radius and ulna is visible (arrow). The three-dimensional surface rendering (Fig. 2-C) shows the fetus holding the digit in front of his nose and lips (Courtesy of Children’s Hospital, Boston, Massachusetts).
Figs. 3-A, 3-B, and 3-C Single-shot fast-spin-echo T2-weighted magnetic resonance imaging examples of three different fetuses, all showing abnormal position and contour of the extremities. These include a fetus at twenty-one weeks of gestation with the spondylothoracic variety of Jarcho-Levin syndrome, including a short trunk and bilateral clubfoot (Fig. 3-A); a fetus at thirty-five weeks of gestation with a lumbosacral myelomeningocele, bilateral clubfoot, and genu recurvatum (Fig. 3-B); and a fetus at nineteen weeks of gestation with arthrogryposis and a strikingly abnormal holding position of the left upper and right lower extremity (Fig. 3-C) (Courtesy of Children’s Hospital, Boston, Massachusetts).
options, including possible postnatal surgical reconstruction, may be discussed prior to the birth. Decisions may be made regarding the timing and order of medical and surgical interventions, and the interventions planned by various specialists can be coordinated. Finally, the prenatal establishment of relationships between families and care providers may help ease the stress of the neonatal period.

Fetal Surgery
Fetal surgery is the ultimate prenatal intervention. To date, the vast majority of fetal surgery has been performed for life-threatening conditions. Established indications for fetal surgery include twin-twin transfusion syndrome, twin reversed arterial perfusion (TRAP) sequence, fetal airway obstruction, obstructive uropathy, sacrococcygeal teratoma, and thoracic congenital anomalies, such as primary hydrothorax and congenital cystic adenomatoid malformations. Relative or investigational indications include congenital diaphragmatic hernia, aortic valve stenosis, and neural tube defects such as myelomeningocele. These procedures may be performed open, percutaneously, or with use of transabdominal fetoscopic techniques.

With the development of improved diagnostic imaging capabilities and fetoscopic techniques, the potential for fetal surgery on nonlethal congenital hand and upper-limb differences exists. Among the nonlethal conditions most amenable to fetal intervention is congenital constrictive band syndrome. Release or excision of constricting bands may theoretically prevent hand and upper-limb deformation and, in extreme situations, tissue loss. Keswani et al. previously reported on the successful fetoscopic release of constriction bands of the upper limb in two fetuses at twenty-three and twenty weeks of gestation, respectively, with use of a neodymium-yttrium aluminum garnet (Nd-YAG) laser; Doppler ultrasound evaluation demonstrated improved blood flow to the threatened distal limb following band release in both fetuses. Similar strategies have been used successfully in congenital constriction band syndrome involving the lower extremities.

A potential advantage afforded by fetal hand and upper-limb surgery is based on the observation that fetal tissues heal without scar formation. This observation has been supported by a number of animal-model studies in which fetal wound-healing free from scar tissue has been documented. Efforts to further characterize this phenomenon are ongoing; wound-healing without scar formation is especially desirable in the hand, as excessive scar formation can have a deleterious effect on function following surgical reconstruction of congenital hand abnormalities.

In the future, prenatal intervention may provide the congenitally deficient hand and upper limb with new tissue and structure. While this possibility is beyond our current capabilities, inroads have been made in other surgical fields in this regard. For example, neural stem cells have been delivered to the spine in animal models of spina bifida. The Management of Myelomeningocele Study (a multicenter randomized controlled trial for the study of fetal intervention as compared with postnatal repair of spina bifida) is underway to address potential clinical applications of advanced technologies.

Many obstacles to fetal surgery remain. Since its inception, in utero surgery has been limited by difficulties in fetal monitoring and access to fetal structures (e.g., intravenous access). Preterm labor and the resultant complications to both fetus and mother remain considerable risks following prenatal interventions. Furthermore, every fetal intervention inherently places two patients, the fetus and the mother, at risk, for the benefit of only one patient, the fetus. Finally, the indications for fetal surgery remain very narrow, particularly given the advances in neonatal care and the expertise with which preterm delivery and perinatal and/or postnatal surgery may be provided. Until the outcomes of prenatal surgery are demonstrated to be safe, efficacious, reproducible, and superior to postnatal intervention, fetal surgery for nonlethal conditions of the hand and upper limb remains investigational.

Ethical Considerations
While a comprehensive evaluation of all of the ethical implications of prenatal diagnosis and treatment is beyond the scope of this review, a number of central issues merit discussion.

First, despite technological advances, improved diagnostic capabilities, and increasing expertise, the prenatal diagnosis of congenital anomalies may be inaccurate, and many congenital differences are not diagnosed prenatally. A recent investigation comparing prenatal ultrasound findings to autopsy findings following termination of pregnancy in the second trimester found full agreement in only 58% of cases, and in 10% of cases, observations made by ultrasound were not confirmed at autopsy. Another investigation documented a 40% false-positive rate for isolated clubfoot deformity seen on third-trimester ultrasound studies. Any discussion regarding prenatal or postnatal care of a congenital anomaly must include recognition of the imperfect rates of detection and characterization of fetal anomalies.

Second, the impact of prenatal diagnosis on decisions regarding pregnancy termination must be weighed. In settings in which women have the choice to terminate pregnancy, rates of pregnancy termination appear to increase when the rates of prenatal diagnosis of congenital anomalies increase. Stoll et al. reported similar increases in both the prenatal diagnosis of congenital anomalies and pregnancy termination rates over a twenty-year period (1979 to 1999) in a well-defined population. The implications of prenatal findings on pregnancy-termination decisions are particularly pertinent with regard to offering appropriate prenatal counseling and prenatal surgical consultations so that the full extent of the anomaly can be understood and neither overestimated nor underestimated. This is particularly important with regard to nonlethal musculoskeletal conditions, such as those involving the hand and upper limb. Finally, care providers offering prenatal diagnosis should provide consistent resources and information to expectant parents after identification of a congenital difference, including access to genetic counseling and, if appropriate, prenatal surgical consultation. Genetic counseling should always be offered following the detection of any fetal anomaly.
and indications for additional imaging or testing should be standardized to confirm the diagnosis and to ensure that counseling will be provided regarding the risk of recurrence in future pregnancies".

Conclusions

At present, the major benefit of prenatal diagnosis lies in the opportunity to counsel families with regard to the implications of the fetal anomaly that has been identified. Continued efforts to improve the accuracy of prenatal diagnostic imaging are needed, as is an improved understanding regarding the emotional impact of these prenatal diagnoses on expectant families. While great advances have been made in prenatal treatment for some lethal conditions, the role of fetal intervention for isolated congenital anomalies of the hand and upper limb remains unclear; further investigation regarding the risks, benefits, and potential outcomes of fetal surgery for nonlethal anomalies of the musculoskeletal system is needed. Involvement of orthopaedic specialists, including the pediatric hand and upper-limb surgeon, is paramount in the counseling of families and the provision of prenatal musculoskeletal care.

References


