Skeletal Dysplasias

Normal Anatomy of the Fetal Skeleton

The skeleton is one of the earliest and easiest structures to image in the fetus. Details of the normal anatomy of the cranial, facial, and spinal components of the skeleton are discussed in Chapters 1 and 2. This chapter focuses specifically on the anatomy and biometry of the limbs and other bones not previously discussed.

The fetal skeleton becomes visible with ultrasound as soon as bones are calcified. Long bones have a primary ossification center in the diaphysis and secondary ossification centers in the epiphyses. The primary ossification center is developed in early pregnancy and is the first structure imaged with ultrasound. Secondary ossification centers develop in late pregnancy and the neonatal period, and therefore, they are not hyperechogenic structures during intrauterine life. However, the cartilages of the epiphyses can be demonstrated with ultrasound as hypoechogenic structures (e.g., head of femur and humerus).

The technique for measuring long bones is quite simple, and is described in basic texts on obstetrical ultrasound. Measurements of the long bones include only the shaft. The distal and proximal epiphyses are not included. The femur is measured from the major trocanter to the distal end of the femoral shaft. For
assessments of the fetus at risk for skeletal dysplasias, identification of each bone is extremely important, since there are disorders in which only a particular bone is hypoplastic (e.g., tibia, scapula). An easy task is to identify the bones of the forearm and leg. In a longitudinal scan of the forearm, the ulna extends farther into the elbow joint than the radius. In a transverse section of the leg, the tibia is the bone with the most central location, whereas the fibula is closest to the skin. In a longitudinal section, the tibia can be distinguished from the fibula by imaging its proximal plate at the knee. Carpal bones become ossified after birth and, therefore, they are either not demonstrable or appear as hypoechogenic structures. Metacarpals and phalanges ossify in utero and are visible from the second trimester on. Talus and calcaneus begin calcifying at the 22d to 24th week of gestation. Metatarsals and phalanges of the toes are also calcified during the second trimester. The successive appearance of epiphyseal ossification centers of long bones has been used to date pregnancies. The distal femoral epiphysis appears at 32 to 35 weeks, and the proximal...
tibial epiphysis calcifies 2 to 3 weeks later. Proximal humeral epiphysis is visualized at around 40 weeks. Nomograms for the assessment of the normal length of the long bones in the upper and lower extremities are displayed in Tables 10-3 and 10-4 (see pp. 323 and 324). Figures 10-1 to 10-10 show the normal anatomy of the appendicular skeleton.

**BIRTH PREVALENCE AND CONTRIBUTION TO PERINATAL MORTALITY**

Skeletal dysplasias are a heterogeneous group of bone growth disorders resulting in abnormal shape and size of the skeleton. The birth prevalence of skeletal dysplasias recognizable in the neonatal period has been estimated to be 2.4 per 10,000 births (95 percent confidence limits: 1.8 to 3.2 per 10,000 births).
These data come from an Italian multicentric monitoring system for birth defects in which newborns (stillbirths and live births) with limb shortness or limb trunk disproportion, delivered in 90 hospitals, were radiographed and photographed. Figures are based on 217,061 deliveries (215,392 live births and 1669 stillbirths). Among the 53 cases of skeletal dysplasias, 23 percent were stillbirths and 32 percent died during the first week of life. The overall frequency of skeletal dysplasias among perinatal deaths was 9.1 per 1000.

The birth prevalence of the different skeletal dysplasias and their relative frequency among perinatal deaths is shown in Table 10-1. The four most common skeletal dysplasias were thanatophoric dysplasia, achondroplasia, osteogenesis imperfecta, and achondrogenesis. Thanatophoric dysplasia and achondrogenesis accounted for 62 percent of all lethal skeletal dysplasias.

**CLASSIFICATION OF SKELETAL DYSPLASIAS**

The existing nomenclature for skeletal dysplasias is complicated. There is a lack of uniformity about definition criteria. For example, they can be referred to by eponyms (e.g., Ellis-van Creveld syndrome, Larsen dysplasia), by Greek terms describing a salient feature of the disease (e.g., diastrophic = twisted; metatropic = changeable), or the presumed pathogenesis of the disease (e.g., osteogenesis imperfecta, achondrogenesis). The fundamental problem with any classification of skeletal dysplasias is that the patho-
### TABLE 10-2. INTERNATIONAL CLASSIFICATION FOR DYSPLASIAS

| Osteochondrodysplasias |  |  |
|-------------------------|-----------------------------|
| Abnormalities of cartilage and/or bone growth and development |  |  |
| A. Defects of growth of tubular bones and/or spine |  |  |
| a. Identifiable at birth |  |  |
| b. Usually lethal before or shortly after birth |  |  |
| 1. Achondrogenesis type I (Parenti-Fraccaro) | AR ** |  |
| 2. Achondrogenesis type II (Langer-Saldino) |  |  |
| 3. Hypochondrogenesis |  |  |
| 4. Fibrochondrogenesis | AR ** |  |
| 5. Thanatophoric dysplasia |  |  |
| 6. Thanatophoric dysplasia with cloverleaf skull |  |  |
| 7. Ateleosogenes |  |  |
| 8. Short rib syndrome (with or without polydactyly) |  |  |
| a. Type I (Saldino-Noonan) | AR ** |  |
| b. Type II (Majewski) | AR ** |  |
| c. Type III (lethal thoracic dysplasia) | AR ** |  |
| ji. Usually nonlethal dysplasia |  |  |
| 9. Chondrodysplasia punctata |  |  |
| a. Rhizomelic form autosomal recessive | AR ** |  |
| b. Dominant X-linked form; lethal in male | XLD ** |  |
| c. Common mild form (Scheffeld) |  |  |
| Exclude: symptomatic slipping (warfarin, chromosomal aberration) |  |  |
| 10. Campomelic dysplasia |  |  |
| 11. Kyphomelic dysplasia | AR ** |  |
| 12. Achondroplasia | AD ** |  |
| 13. Diastrophic dysplasia | AR ** |  |
| 14. Metatropic dysplasia (several forms) | AR, AD ** |  |
| 15. Chondrodactylomalacic dysplasia (Eliis-Van Crevel) | AR *** |  |
| 16. Asphyxiating thoracic dysplasia (Jeune) | AR ** |  |
| 17. Spondyloepiphyseal dysplasia congenita |  |  |
| a. Autosomal dominant form | AR ** |  |
| b. Autosomal recessive form | AR ** |  |
| 18. Kniest dysplasia | AD ** |  |
| 19. Dyssegmental dysplasia | AR ** |  |
| 20. Metosomelic dysplasia |  |  |
| a. Type Nievergelt | AD ** |  |
| b. Type Langer (probable homozygous dyschondrosteosis) | AR ** |  |
| c. Type Robinow | AD ** |  |
| d. Type Rheinardt | AD ** |  |
| e. Others | AD ** |  |
| 21. Acromesomelic dysplasia | AR ** |  |
| 22. Cleidocranial dysplasia | AD *** |  |
| 23. Otopalatodigital syndrome |  |  |
| a. Type I (Langer) | XLSD ** |  |
| b. Type II (Andri) | XLR ** |  |
| 24. Larsen syndrome | AR, AD ** |  |
| 25. Other multiple dislocation syndromes (Dietboveld) |  |  |
| b. Identifiable in later life |  |  |
| 1. Hypochondroplasia | AD *** |  |
| 2. Dyschondrosteosis | AD *** |  |
| 3. Metaphyseal chondrodysplasia type Jansen |  |  |
| 4. Metaphyseal chondrodysplasia type Schmid | AD ** |  |
| 5. Metaphyseal chondrodysplasia type McKusick | AR ** |  |
| 6. Metaphyseal chondrodysplasia with exocrine pancreatic insufficiency and cyclic neutropenia |  |  |
| 7. Spondylometaphyseal dysplasia |  |  |
| a. Type Kozlowski | AD ** |  |
| b. Other forms |  |  |
| 8. Multiple epiphyseal dysplasia |  |  |
| a. Type Fairbank | AD ** |  |
| b. Other forms |  |  |
| 9. Multiple epiphyseal dysplasia with early diabetes (Wolcott-Rallison) | AR ** |  |
| 10. Arthro-ophthalmopathy (Stickler) | AR ** |  |
| 11. Pseudoachondroplasia |  |  |
| a. Dominant | AD ** |  |
| b. Recessive | AR ** |  |
| 12. Spondyloepiphyseal dysplasia tarda (X-linked XLR recessive) |  |  |
| 13. Progressive pseudohematosid chondrodysplasia |  |  |
| 14. Spondylolophiphysisplasia, other forms |  |  |
| 15. Brachyolmia |  |  |
| a. Autosomal recessive | AR ** |  |
| b. Autosomal dominant | AD ** |  |
| 16. Dyggve-Melchior-Clausen dysplasia |  |  |
| 17. Spondyloepimetaphyseal dysplasia (several forms) |  |  |
| 18. Spondyloepimetaphyseal dysplasia with joint laxity | AR ** |  |
| 19. Otospondyloepigaepphyseal dysplasia (OSMED) | AR ** |  |
| 20. Myotonic chondrodysplasia (Cate-Schwartz-Jampel) | AR ** |  |
| 21. Parastemmatic dysplasia | AD ** |  |
| 22. Trichorhinophalangeal dysplasia | AD ** |  |
| 23. Acrodysplasia with retnitis pigmentosa and nephropathy (Saldino-Mainzer) | AR ** |  |

B. Disorganized development of cartilage and fibrous components of skeleton

1. Dysplasia epiphyseal hermimelica | AD ** |  |
2. Multiple cartilaginous exostoses | AD ** |  |
3. Acrodysplasia with exostoses (Giedion-Langer) | AD ** |  |
4. Enchondromatosis (Ollier) | AD ** |  |
5. Enchondromatosis with hemangima (Maffucci) | AD ** |  |
6. Metachondromatosis | AD ** |  |
7. Spondyloependochondrodysplasia | AR ** |  |
8. Osteoglyphon dysplasia | AR ** |  |
9. Fibrous dysplasia (Jaffe-Lichtenstein) | AR ** |  |
10. Fibrous dysplasia with skin pigmentation and precocious puberty (McCune-Albright) | AR ** |  |
11. Chenouih (familial fibrous dysplasia of the jaws) | AR ** |  |

C. Abnormalities of density of cortical diaphyseal structure and/or metaphyseal modeling

1. Osteogenesis imperfecta (several forms) | AR, AD ** |  |

(continued)
<table>
<thead>
<tr>
<th>TABLE 19-2. (Continued)</th>
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<tbody>
<tr>
<td>2. Juvenile idiopathic osteoporosis</td>
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<tr>
<td>3. Osteoporosis with pseudoglioma</td>
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<td>4. Osteopetrosis</td>
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<tr>
<td>a. Autosomal recessive lethal</td>
</tr>
<tr>
<td>b. Intermediate recessive</td>
</tr>
<tr>
<td>c. Autosomal dominant</td>
</tr>
<tr>
<td>d. Recessive with tubular acidosis</td>
</tr>
<tr>
<td>5. Pycnodysostosis</td>
</tr>
<tr>
<td>6. Dominant osteosclerosis type Stanescu</td>
</tr>
<tr>
<td>7. Osteomerosyndactylosis</td>
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<td>8. Osteoporosis</td>
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<tr>
<td>9. Osteopatia striata</td>
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<tr>
<td>10. Osteopatia striata with cranial sclerosis</td>
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<tr>
<td>11. Melorheostosis</td>
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<tr>
<td>12. Diaphyseal dysplasia (Camurati-Engelmann)</td>
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<tr>
<td>13. Craniodiaphyseal dysplasia</td>
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<tr>
<td>14. Endosteal hyperostosis</td>
</tr>
<tr>
<td>a. Autosomal dominant (Worth)</td>
</tr>
<tr>
<td>b. Autosomal recessive (Van Buchem)</td>
</tr>
<tr>
<td>c. Autosomal recessive (sclerosing)</td>
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<tr>
<td>15. Tubular stenosis (Kenny-Caffey)</td>
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<td>16. Pachydermoperiostosis</td>
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<tr>
<td>17. Osteodysplasia (Meilick-Needles)</td>
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<tr>
<td>18. Frontometaphyseal dysplasia</td>
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<tr>
<td>19. Craniofacial dysplasia (several forms)</td>
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<tr>
<td>20. Metaphyseal dysplasia (Pyle)</td>
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<tr>
<td>21. Dysostosclerosis</td>
</tr>
<tr>
<td>22. Osse-o-ectasia with hyperphosphatiasis</td>
</tr>
<tr>
<td>23. Oculo-dento-osseous dysplasia</td>
</tr>
<tr>
<td>a. Mild type</td>
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<tr>
<td>b. Severe type</td>
</tr>
<tr>
<td>24. Infantile cortical hyperostosis (Caffey disease, familial type)</td>
</tr>
</tbody>
</table>

Dysostoses
Malformation of individual bones, singly or in combination

<table>
<thead>
<tr>
<th>A. Dysostoses with cranial and facial involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Craniosynostosis (several forms) ***</td>
</tr>
<tr>
<td>2. Craniofacial dysostosis (Crouzon) ***</td>
</tr>
<tr>
<td>3. Acrocephalopolysyndactyly</td>
</tr>
<tr>
<td>a. Type Apert</td>
</tr>
<tr>
<td>b. Type Crouzon</td>
</tr>
<tr>
<td>c. Type Pfeiffer</td>
</tr>
<tr>
<td>d. Other types</td>
</tr>
<tr>
<td>4. Acrocephalopolysyndactyly (Carpenter and others)</td>
</tr>
<tr>
<td>5. Cephalopolysyndactyly (Gregg)</td>
</tr>
<tr>
<td>6. First and second branchial arch syndromes</td>
</tr>
<tr>
<td>a. Mandibulofacial dysostosis (Treacher Collins, Franceschetti)</td>
</tr>
<tr>
<td>b. Acrofacial dysostosis (Nager)</td>
</tr>
<tr>
<td>c. Oculo-auriculo-vertebral dysostosis (Goldenhar)</td>
</tr>
<tr>
<td>d. Hemifacial microsomia</td>
</tr>
<tr>
<td>e. Others</td>
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</tbody>
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<thead>
<tr>
<th>B. Dysostoses with predominant axial involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vertebral segmentation defects (including Klippel-Feil)</td>
</tr>
<tr>
<td>2. Cervico-oculo-acoustic syndrome (Wilder-van der)</td>
</tr>
<tr>
<td>3. Sprengel anomaly</td>
</tr>
<tr>
<td>4. Spondylocostal dysostosis</td>
</tr>
<tr>
<td>a. Dominant form</td>
</tr>
<tr>
<td>b. Recessive forms</td>
</tr>
<tr>
<td>5. Oculovertebral syndrome (Weyers)</td>
</tr>
<tr>
<td>6. Osteo-onychodysostosis</td>
</tr>
<tr>
<td>7. Cerebrocostomandibular syndrome</td>
</tr>
</tbody>
</table>

C. Dysostoses with prominent involvement of extremities

| 1. Achondria | AR ** |
| 2. Apoplasia | AR ** |
| 3. Tetrapolomela syndrome (Roberts) (SC pseudothalidomide syndrome) | AR ** |
| 4. Ectrodactyly |
| a. Isolated | AD ** |
| b. Ectrodactyly-ectodermal dysplasia, cleft palate-syndrome | AD ** |
| c. Ectrodactyly with scalp defects | AD ** |
| 5. Oro-alveolar syndrome (aglossia syndrome, Harhart syndrome) | AD ** |
| 6. Fuchsian radicular synostosis | AD ** |
| 7. Brachydactyly, types A, B, C, D, E (Bell's classification) | AD ** |
| 8. Symphalangism | AD ** |
| 9. Polydactyly (several forms) | AD ** |
| 10. Syndactyly (several forms) | AD ** |
| 11. Polysyndactyly (several forms) | AD ** |
| 12. Camptodactyly | AD ** |
| 13. Manko syndrome | AD ** |
| 14. Poland syndrome | AD ** |
| 15. Rubinstein-Taybi syndrome | AD ** |
| 16. Coffin-Siris syndrome | AD ** |
| 17. Pancytopenia-dysmelia syndrome (Fancour) | AD ** |
| 18. Blackfan-Diamond anemia with thumb anomalies (Aase syndrome) | AD ** |
| 19. Thyrotoxico-facial dysplasia (Treacher-Collins, Franceschetti) | AD ** |
| 20. Oro-odontofacial syndrome |
| a. Type Papillon-Lejeune, lethal in males | XLD ** |
| b. Type Mohr | AD ** |
| 21. Cardiac syndromes (Holt-Oram and others) | AD ** |
| 22. Femoral focal deficiency (with or without facial anomalies) | AD ** |
| 23. Multiple synostoses (includes some forms of symphalangism) | AD ** |
| 24. Scapulo-humeral dysostosis (Kosonow-Sinios) | AD ** |
| 25. Hand-foot-genital syndrome | AD ** |
| 26. Focal dermal hypoplasia (Goltz): lethal in males | XLD ** |

Idiopathic Osteolyses

| 1. Phalangeal (several forms) | ** |
| 2. Tarsal apertur |
| a. Including Francois form and others | AD ** |
| b. With nephropathy | AD ** |
| 3. Multicentric |
| a. Hajdu-Cheney form | AD ** |
| b. Winchester form | AR ** |
| c. Torg form | AR ** |
| d. Other forms | ** |
### Table 10-2. (Continued)

<table>
<thead>
<tr>
<th>Miscellaneous Disorders with Osseous Involvement</th>
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</thead>
<tbody>
<tr>
<td>1. Early acceleration of skeletal maturation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Marshall-Smith syndrome</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>b. Weaver syndrome</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>c. Other types</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>2. Marfan syndrome</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>3. Congenital contractual arachnodactyly</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>4. Cerebrohepatorenal syndrome (Zellweger)</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>5. Coffin-Lowery syndrome</td>
<td>SLR</td>
<td></td>
</tr>
<tr>
<td>6. Cockayne syndrome</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>7. Fibrodysplasia ossificans congenita</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>8. Epidermal nervous syndrome (Solomon)</td>
<td></td>
<td></td>
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<tr>
<td>9. Nevoid basal cell carcinoma syndrome</td>
<td></td>
<td></td>
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<tr>
<td>10. Multiple hereditary fibromatosis</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>11. Neurofibromatosis</td>
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</tbody>
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### Chromosomal Aberrations

<table>
<thead>
<tr>
<th>Primary Metabolic Abnormalities</th>
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</thead>
<tbody>
<tr>
<td>A. Calcium and/or phosphorus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hypophosphatemic rickets</td>
<td>XLD</td>
<td></td>
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<tr>
<td>2. Vitamin D dependency or pseudodeficiency rickets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Type I with probable deficiency in 25-hy-AR</td>
<td></td>
<td></td>
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<tr>
<td>droy vitamin D 1α-hydroxylase</td>
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<td></td>
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<tr>
<td>b. Type II with target-organ resistance</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>3. Late rickets (McCance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Idiopathic hypercalcemia</td>
<td></td>
<td></td>
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<tr>
<td>5. Hypophosphatemia (several forms)</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>6. Pseudohypoparathyroidism (normo- and hypocalcemic forms, including acrodysostosis)</td>
<td>AD</td>
<td></td>
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</tbody>
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<thead>
<tr>
<th>B. Complex carbohydrates</th>
<th></th>
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<tbody>
<tr>
<td>1. Mucopolysaccharidosis type I (α-L-iduronidase deficiency)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Hurler form</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>b. Scheie form</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>c. Other forms</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>2. Mucopolysaccharidosis type II—Hunter (sulfatiduronate sulfatase deficiency)</td>
<td>XLR</td>
<td></td>
</tr>
<tr>
<td>3. Mucopolysaccharidosis type III—Sanfilippo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Type III A (heparin sulfatidase deficiency)</td>
<td>AR</td>
<td></td>
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</table>

- a. Type III B (N-acetyl-α-glucosaminidase deficiency)  | AR |  |
- b. Type III C (α-glucosaminidase-N-acetyl transferase deficiency)  | AR |  |
- c. Type III D (N-acetyl-glucosamine-6-sulfate sulfatase deficiency)  | AR |  |
- d. Type IV A—Morquio (N-acetyl-galactosamine-6-sulfate sulfatase deficiency)  | AR |  |
- e. Type IV B (β-galactosidase deficiency)  | AR |  |
- f. Type IV C—Morquio B (β-glucuronidase deficiency)  | AR |  |
- g. Type IV D—Morquio C (α-L-fucosidase deficiency)  | AR |  |
- h. Type IV E—Morquio D (α-L-fucosidase deficiency)  | AR |  |
- i. Type IV F—Morquio E (α-L-fucosidase deficiency)  | AR |  |
- j. Type IV G—Morquio F (α-L-fucosidase deficiency)  | AR |  |
- k. Type IV H—Morquio H (α-L-fucosidase deficiency)  | AR |  |
- l. Type IV I—Morquio I (α-L-fucosidase deficiency)  | AR |  |
- m. Type IV J—Morquio J (α-L-fucosidase deficiency)  | AR |  |
- n. Type IV K—Morquio K (α-L-fucosidase deficiency)  | AR |  |
- o. Type IV L—Morquio L (α-L-fucosidase deficiency)  | AR |  |
- p. Type IV M—Morquio M (α-L-fucosidase deficiency)  | AR |  |
- q. Type IV N—Morquio N (α-L-fucosidase deficiency)  | AR |  |
- r. Type IV O—Morquio O (α-L-fucosidase deficiency)  | AR |  |
- s. Type IV P—Morquio P (α-L-fucosidase deficiency)  | AR |  |
- t. Type IV Q—Morquio Q (α-L-fucosidase deficiency)  | AR |  |
- u. Type IV R—Morquio R (α-L-fucosidase deficiency)  | AR |  |
- v. Type IV S—Morquio S (α-L-fucosidase deficiency)  | AR |  |
- w. Type IV T—Morquio T (α-L-fucosidase deficiency)  | AR |  |
- x. Type IV U—Morquio U (α-L-fucosidase deficiency)  | AR |  |
- y. Type IV V—Morquio V (α-L-fucosidase deficiency)  | AR |  |
- z. Type IV W—Morquio W (α-L-fucosidase deficiency)  | AR |  |

<table>
<thead>
<tr>
<th>C. Lipids</th>
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<tbody>
<tr>
<td>1. Niemann-Pick disease (sphingomyelinase deficiency) (several forms)</td>
<td>AR</td>
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<tr>
<td>2. Gaucher disease (β-glucocerebrosidase deficiency) (several types)</td>
<td>AR</td>
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<tr>
<td>3. Farber disease lipogranulomatosis (ceramidase deficiency)</td>
<td>AR</td>
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<tr>
<th>D. Nucleic acids</th>
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<tbody>
<tr>
<td>1. Adenosine-deaminase deficiency and others</td>
<td>AR</td>
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<tr>
<th>E. Amino acids</th>
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<tbody>
<tr>
<td>1. Homocystinuria and others</td>
<td>AR</td>
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<tr>
<th>F. Metals</th>
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<tbody>
<tr>
<td>1. Menkes syndrome (kinky hair syndrome and others)</td>
<td>AR</td>
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</table>

* Mode of transmission.
** Frequency.
AR, autosomal recessive
XLD, X-linked dominant
AD, autosomal dominant
XLR, X-linked recessive
SLR, sex-linked recessive
***1000+ cases.
****100—1000 cases.
**20—100 cases.
* Fewer than 20 cases.

(Estimates of the relative frequency of these conditions are based on the compilers’ experience and a review of the literature.)

The statistical technique used to establish the relationship between gestational age and a biometric fetal parameter is regression analysis. This method uses an independent variable (I) to predict the value of a dependent variable (D). It is incorrect to use the dependent variable to predict the independent one. (Reproduced with permission from Jeanty, Romero: Obstetrical Ultrasound. New York, McGraw-Hill, 1983.)

genesis of these diseases is rarely known. Therefore, the current system relies on purely descriptive findings of either a clinical or radiologic nature.

In an attempt to develop a uniform terminology, a group of experts met in Paris in 1977 and proposed an International Nomenclature for Skeletal Dysplasias. This classification was subsequently revised in 1983 (Table 10-2). The system subdivides the diseases into five different groups: (1) osteocondro-dysplasias (abnormalities of cartilage or bone growth and development) (2) dysostoses (malformations of individual bones singly or in combination), (3) idiopathic osteolyses (disorders associated with multifocal resorption of bone), (4) skeletal disorders associated with chromosomal aberrations, and (5) primary metabolic disorders. A comprehensive description of these diseases is beyond the scope of this book. This section focuses primarily on the osteochondro-dysplasias that are recognizable at birth. Although more than 200 skeletal dysplasias have been described, only a few can be recognized with the use of sonography in the antepartum period. Most of these disorders result in short stature, and the term “dwarfism” has been used to refer to this clinical condition. Because this term carries a negative connotation, the term “dysplasia” has substituted it.

EMBRYOLOGY

The skeletal system develops from mesoderm. In most bones (e.g., the long bones), ossification is preceded by cartilage (endochondral ossification).
Figure 10-13. This figure represents an example of a correct graph required to assess the normality of a given biometric parameter. Note that the fetal age is the independent variable (horizontal axis).

Figure 10-14. Growth of the humerus across gestational age.
**Figure 10-15.** Growth of the radius across gestational age.

**Figure 10-16.** Growth of the ulna across gestational age.
Figure 10-17. Growth of the clavicle across gestational age.

Figure 10-18. Growth of the femur across gestational age.
Figure 10-19. Growth of the tibia across gestational age.

Figure 10-20. Growth of the fibula across gestational age.
However, cartilage does not become bone but rather is destroyed and bone is formed in its place. In other cases, such as flat bones, ossification develops directly in the mesenchyme without cartilage formation (intramembranous ossification).

In long bones, ossification proceeds in an orderly fashion. It first begins in the shaft, or diaphysis, and extends from the middle toward both ends (epiphyses), where two areas of cartilage remain. During the last weeks of gestation and the first weeks of neonatal life, ossification centers appear in the epiphyses and lead to bone formation. The area of cartilage between the diaphysis and the epiphyses is called the metaphysis and represents the growing portion of the bone. Once adult size is achieved, this area ossifies, and the diaphysis joins permanently to the epiphyses.

**BIOMETRY OF THE FETAL SKELETON IN THE DIAGNOSIS OF BONE DYSPLASIAS**

Long bone biometry has been used extensively in the prediction of gestational age. Nomograms available for this purpose use the long bone as the independent variable and the estimated fetal age as the dependent variable (Figs. 10-11, 10-12). However, the type of nomogram required to assess the normality of bone dimensions uses the gestational age as the independent variable and the long bone as the dependent variable (Fig. 10-13). For the proper use of these nomograms the clinician must know accurately the gestational age of the fetus (Figs. 10-14 through 10-20, Tables 10-3, 10-4). Therefore, patients at risk for skeletal dysplasias should be advised to seek prenatal care early to assess all clinical estimators of gestational age. For those patients with uncertain gestational age, we have provided a set of nomograms that use the head perimeter as the independent variable (Figs. 10-21, 10-22). Other authors have used the biparietal diameter, but the head perimeter has the advantage of being shape independent. A limitation of this approach is the assumption that the cranium is not involved in the dysplastic process. The nomograms provide the mean, 5th, and 95th percentile for a given parameter. The 5th and 95th confidence limits are arbitrary statistical definitions of

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**TABLE 10-3. NORMAL VALUES FOR THE ARM**

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<th>Ulna (mm)</th>
<th>Radius (mm)</th>
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TABLE 10-4. NORMAL VALUES FOR THE LEG

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<th>Femur (mm)</th>
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Figure 10-21. Relationship between the head perimeter and the femur.
abnormality. A small proportion (2.5 percent) of the general population will have shortened long bones if these nomograms are employed. This point is illustrated in Figures 10-21, 10-22, 10-24, and 10-25. The crosses in these figures are measurements taken from fetuses subsequently born without short limb skeletal dysplasias. It may be better to use the 1st and 99th confidence limits because with this threshold, only 0.5 percent of the general population would be considered to have abnormally short bones. Larger studies are required for these boundaries to be established with accuracy. Our experience in the prenatal diagnosis of infants with skeletal dysplasias indicates that affected fetuses have dramatic deviations from the 5th and 95th confidence limits. An exception to this is heterozygous achondroplasia (see p. 359).

**TERMINOLOGY FREQUENTLY USED IN DESCRIPTION OF BONE DYSPLASIAS**

Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the intermediate segment (mesomelia), or the distal segment (acromelia) (Fig. 10-23). The diagnosis of rhizomelia and mesomelia requires comparison between the bone dimensions of the leg and
Figure 10-24. Relationship between the ulna and the humerus.

Figure 10-25. Relationship between the tibia and the femur.
forearm and of the thigh and arm. Figures 10-24 and 10-25 illustrate the relationship between these bones.

Several skeletal dysplasias feature alteration of hands and feet. Polydactyly refers to the presence of more than five digits (Fig. 10-26). It is classified as postaxial if the extra digits are on the ulnar or fibular side and preaxial if they are located on the radial or tibial side. Syndactyly refers to soft tissue or bony fusion of adjacent digits (Figs. 10-27, 10-28). Clinodactyly is a deviation of one or more fingers (Figs. 10-29, 10-30).

The most common spinal abnormality in skeletal dysplasias is platyspondyly, a flattening of the vertebral bodies. The antenatal detection of this abnormality has not been reported. Scoliosis can be identified in utero (Fig. 10-31).

**CLINICAL PRESENTATION**

The challenge of the antenatal diagnosis of skeletal dysplasias will generally occur in one of two ways: (1) a patient who has delivered an infant with a skeletal dysplasia and desires antenatal assessment of a subsequent pregnancy or (2) the incidental finding of a shortened, bowed, or anomalous extremity during a
Figure 10-29. Clinodactyly. Note the overlapping fingers (black arrow) in this midtrimester fetus.

Figure 10-30. Sonogram of a fetus with clinodactyly. (Reproduced with permission from Jeanty et al.: J Ultrasound Med 4:595, 1985.)

Figure 10-31. Coronal scan demonstrating severe scoliosis (curved arrow). IW, iliac wings.
routine monographic examination. The task is easier when looking for a particular phenotype in a patient at risk. The inability to obtain reliable information about skeletal mineralization and the involvement of other systems (e.g., skin) with sonography is a limiting factor for an accurate diagnosis after identification of an incidental finding. Another limitation is the paucity of information about the in utero natural history of skeletal dysplasias.

Despite these difficulties and limitations there are good medical reasons for attempting an accurate prenatal diagnosis of skeletal dysplasias. A number of these disorders are uniformly lethal, and a confident antenatal diagnosis would allow options for the pregnancy termination to be considered. Table 10-5 lists such disorders.

**APPROACH TO THE DIAGNOSIS OF SKELETAL DYSPLASIAS**

Our approach to diagnosing skeletal dysplasias follows an organized examination of the fetal skeleton.

**Long Bones**

All long bones should be measured in all extremities. Comparisons with other segments should be made to establish if the limb shortening is predominantly rhizomelic, mesomelic, or involves all segments. A detailed examination of each bone is necessary for an accurate diagnosis of skeletal dysplasias. A number of these disorders are uniformly lethal, and a confident antenatal diagnosis would allow options for the pregnancy termination to be considered. Table 10-5 lists such disorders.

**Figure 10-32.** Demineralization of the skull in a case of congenital hypophosphatasia.

**Figure 10-33.** In utero fracture in a case of osteogenesis imperfecta. F, femur. The large arrow corresponds to the fracture site. The small arrows outline the decreased shadowing cast by the bone.

**Figure 10-34.** Potential pitfall. Shadowing from an upper extremity (arrows) creates the false image of a femur fracture (open arrow).
example of skull demineralization is depicted in Figure 10-32. The pitfall is depicted in Fig. 10-65.

The degree of long bone curvature should be examined. At present, there is no objective means for this assessment; only by experience can an operator discern the boundary between normality and abnormality. Campomelia (excessive bowing) is characteristic of certain disorders (e.g., campomelic syndrome, osteogenesis imperfecta, etc.; see Table 10-6).

Finally, the possibility of fractures should be considered. They can be detected in conditions like osteogenesis imperfecta and hypophosphatasia. The fractures may be extremely subtle or may lead to angulation and separation of the segments of the affected bone (Figs. 10-33, 10-34).

**Evaluation of Thoracic Dimensions**

Several skeletal dysplasias are associated with a hypoplastic thorax (Table 10-6). Chest restriction may lead to pulmonary hypoplasia, a frequent cause of death in these conditions. Thoracic dimensions can be assessed by measuring the thoracic circumference at the level of the four chamber view of the heart. Figure 10-35 illustrates the relationship between the gestational age and thoracic circumference.

**Evaluation of Hands and Feet**

Hands and feet should be examined to exclude polydactyly and syndactyly, and extreme postural deformities as those seen in diastrophic dysplasia.

**Evaluation of the Fetal Cranium**

Several skeletal dysplasias are associated with defects of membranous ossification and, therefore, affect skull bones. Orbits should be measured to exclude hypertelorism. Other findings that should be investigated are micrognathia, short upper lip, abnormally shaped ear, frontal bossing, and cloverleaf skull deformity. Table 10-6 illustrates the conditions associated with these findings.

**Postnatal Workup**

Despite all efforts to establish an accurate prenatal diagnosis, a careful study of the newborn is required in all instances. The evaluation should include a detailed physical examination performed by a geneticist or an individual with experience in the field of skeletal dysplasias and radiograms of the skeleton. The latter should include anterior, posterior, lateral, and Towne views of the skull and anteroposterior views of the spine and extremities, with separate films of the hands and feet. Examination of the skeletal radiographs will permit precise diagnoses in the majority of cases, since the classification of skeletal dysplasias is largely based on radiographic findings. Histologic examination of the chondro-osseous tissue should be considered. Chromosomal studies should also be considered because there is a specific group of constitutional bone disorders associated with cytogenetic abnormalities. Biochemical studies are helpful in rare instances (e.g., hypophosphatasia). DNA studies and enzymatic activity assays should be considered in patients whose
<table>
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<th>Extreme micromelia</th>
<th>Normal long bones</th>
<th>Vertebral disorganization</th>
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<tr>
<td>Depressed nasal bridge</td>
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<td>Ateleostogenesis</td>
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<tr>
<td>Achondrogenesis</td>
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<tr>
<td>Achondroplasia</td>
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<tr>
<td>Campomelic dysplasia</td>
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<tr>
<td>Kniest syndrome</td>
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<tr>
<td>Larsen syndrome</td>
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<tr>
<td>Chondrodysplasia punctata nonrhizomelic variety</td>
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<tr>
<td>Osteogenesis imperfecta type II</td>
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<tr>
<td>Cleft palate</td>
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<tr>
<td>Roberts syndrome</td>
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<tr>
<td>Larsen syndrome</td>
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<td>Otopalatodigital syndrome</td>
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<td>Kniest syndrome</td>
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<td>Larsen syndrome</td>
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<tr>
<td>Chondrodysplasia punctata</td>
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<tr>
<td>Spondyloepiphyseal dysplasia</td>
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<tr>
<td>Campomelic syndrome</td>
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<td></td>
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<tr>
<td>Short upper lip</td>
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<tr>
<td>Chondroectodermal dysplasia</td>
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<tr>
<td>Micrognathia</td>
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<tr>
<td>Campomelic dysplasia</td>
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<tr>
<td>Diastrophic dysplasia</td>
<td></td>
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<tr>
<td>Weissenbacher-Zweymuller syndrome</td>
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<tr>
<td>Otopalatodigital syndrome</td>
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<tr>
<td>Achondrogenesis</td>
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<td></td>
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<tr>
<td>Mesomelic dysplasia, Langer's type</td>
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<tr>
<td>Pena-Shokeir syndrome types I and II</td>
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<td></td>
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<tr>
<td>Hypophonia</td>
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<tr>
<td>Pena-Shokeir syndrome</td>
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</table>
phenotype suggests a metabolic disorder, such as a mucopolysaccharidosis. Although a full discussion of such disorders is beyond the scope of this text, they are well-known causes of constitutional bone disease.

REFERENCES


Achondrogenesis

Synonym
Anosteogenesis.

Definition
Lethal chondrodystrophy characterized by extreme micromelia, short trunk, and a disproportionately large cranium (Fig. 10-36).

Incidence
This condition has been recognized only in the last 15 years, and not all of the 100 cases reported in the literature fit the diagnostic criteria for achondrogenesis. The birth prevalence is 0.23 in 10,000 births (see Table 10-1).

Etiology
The disease is inherited with an autosomal recessive pattern.

Pathology
Two types exist, with distinct histologic and radiologic features. Type I, Parenti-Fraccaro type, is a disorder of both endochondral and membranous ossification characterized by partial or complete lack of ossification of the calvarium and spine as well as extremely short long bones and, frequently, multiple rib fractures (Fig. 10-37). Type II, Langer-Saldino type, is a disorder of endochondral ossification only, is less severe than type 1, and shows varied calcification of the calvarium and spine, as well as absence of rib fractures. Table 10-7 describes the main characteristics of the classic subdivision of achondrogenesis. At least two different authors have proposed a subdivision of type II into different groups. Whitley and Gorlin have proposed a reclassification of the disease into four types. Table

Figure 10-36. Newborn with type I achondrogenesis. Note the short limbs (micromelia), short trunk, and large head. There is redundancy of soft tissue, giving the image of hydrops fetalis. (Reproduced with permission from Johnson et al.: J Ultrasound Med 3:223, 1984.)
Figure 10-37. Radiograph of infant shown in Figure 10-36. Note the poor ossification of the calvarium (C) and spine (large arrows). Ribs are short, and fractures are visible (small arrows). Femurs (F) are extremely shortened. (Reproduced with permission from Johnson et al: J Ultrasound Med 3:223, 1984.)

10-8 illustrates the diagnostic criteria. In essence, type I remains unchanged, and the classic type II is subdivided into three prototypes that have the absence of rib fractures in common. There is progression from type II to IV toward a lesser involvement of the long bones. An index of endochondral bone growth, the femoral cylinder index, (CI femur) has been proposed for the classification (Fig. 10-38). It is calculated by dividing the femoral length by the femoral width and the midshaft in an anteroposterior projection. Whitley and Gorlin have presented evi-

dence to suggest that achondrogenesis tends to recur in a type-specific fashion.12

Histopathologically, achondrogenesis is characterized by a failure of cartilaginous matrix formation. At present, histologic studies have been described in the two classic types. In type I, there is increased cellular density in the resting cartilages with

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**SKELETAL DYSPLASIAS**

vacuolated PAS-positive inclusions inside the chondrocytes, as well as adequate cartilaginous matrix.\(^2\) Large channels are visualized within the cartilage. Electron microscopy shows that the inclusion bodies correspond to an enlargement of the rough endoplasmic reticulum, which contains amorphous electron-opaque material.\(^10\) In type II, the hypercellular cartilage is accompanied by a markedly deficient cartilaginous matrix and primitive mesenchymal chondrocytes with abundant, clear cytoplasm.\(^2\) However, the distinction between the two entities is mainly based on radiologic criteria.\(^2\)

**Diagnosis**

The prenatal diagnosis of this condition has been reported by several authors\(^1,4,5,7,9,11\) and should be suspected by demonstration of the triad: (1) severe short limb dwarfism (Figs. 10-39, 10-40), (2) lack of vertebral ossification (Fig. 10-41), and (3) large head with normal to slightly decreased ossification of the calvarium. Although these findings are quite specific for achondrogenesis, the spectrum of the disease is broad (Table 10-8). Some patients will have vertebral ossification (mild forms of type II), and others will have calvarium demineralization (type I). Polyhydramnios and hydrops have been reported in association with achondrogenesis.\(^1,2\) However, the association with hydrops has been questioned recently by the suggestion that these infants have a hydropic appearance because of an excess of soft tissue mass over a limited skeletal frame.\(^9\) A definitive diagnosis is usually made radiographically, although a correct diagnosis has been made with prenatal sonography.\(^1,7,9\)

**Prognosis**

The disease is uniformly lethal. Infants are either stillborn or die in the neonatal period.
Obstetrical Management
The option of pregnancy termination could be offered any time a definitive diagnosis is made (e.g., a pregnant patient carrying a fetus with a short limb dysplasia and who delivered an infant with achondrogenesis).

REFERENCES

Thanatophoric Dysplasia

Synonym
Thanatophoric dwarfism.

Definition
Thanatophoric dysplasia is a lethal skeletal dysplasia characterized by extreme rhizomelia, bowed long bones, normal trunk length but narrow thorax, and a relatively large head (Fig. 10-42).

Incidence
0.69 per 10,000 births. It is the most common skeletal dysplasia (see Table 10-1).

Etiology
Unknown. Most cases of thanatophoric dysplasia are sporadic. Some cases in the same sibship have been reported, and therefore an autosomal recessive pattern of inheritance has been suggested. Alternatively, some authors have suggested a polygenic transmission with a 2 percent recurrence risk. Familial cases of thanatophoric dysplasia may represent a separate type of lethal short limb dysplasia (i.e., fibrochondrogenesis).

Pathology
The limbs show rhizomelic shortening. The femurs are extremely short and bowed, and, in the most severe forms, may be shaped like a telephone receiver. The thorax is narrow in the anteroposterior dimension, with short ribs. However, the trunk is of normal length. The spine shows flattened vertebral bodies with wide intervertebral spaces giving a typical radiologic appearance similar to an "H" (Fig. 10-43). The cranium has a short base, and, frequently, the foramen magnum is decreased in size. The forehead is prominent, and hypertelorism and a saddle nose may be present. Hands and feet are normal, but the fingers are short and sausage-shaped.

Thanatophoric dysplasia is a disorder of endochondral ossification characterized by a very...
abnormal histology of the growth plate. There is decreased or absent proliferation and maturation of chondrocytes, which are not arranged in columns but distributed irregularly. The bony trabeculae are oriented vertically and horizontally (under normal circumstances, the trabecula should be oriented only vertically). Metachromatic inclusions can be seen in the chondrocytes.

**Associated Anomalies**

Thanatophoric dysplasia is associated with a form of craniosynostosis called "cloverleaf skull" in 14 percent of cases. The cloverleaf skull results from premature closure of the coronal and lambdoid sutures. If hydrocephaly occurs, the rostral expansion of the cortex and of the ventricular system results in an enlarged anterior fontanel and separation and depression of the temporal bones. The term "cloverleaf" refers to the three leaves formed by the prominent vertex of the calvarium in the middle and the two temporal bones on the sides. The mechanism responsible for this skull anomaly is poorly understood. A defect of endochondral ossification resulting in a short skull base and a defect of membranous ossification producing premature synostosis of some cranial sutures has been suggested as the pathogenesis.

Horseshoe kidney, hydronephrosis, atrial septal defect, defective tricuspid valve, imperforate anus, and radioulnar synostosis have been described.

**Diagnosis**

The sonographic antenatal diagnosis can be made in the presence of short-limbed dwarfism (Fig. 10-44), hypoplastic thorax (Fig. 10-45) and cloverleaf skull (Figs. 10-46, 10-47). Frontal bossing can also be detected (Figs. 10-48, 10-49). Femur bowing, narrow thorax, large head size even without ventriculomegaly, and redundant soft tissues are features that become more pronounced with advancing gestation, but may not be present in midtrimester. In 71 percent of cases, thanatophoric dysplasia is associated with polyhydramnios, which may be massive and lead to premature labor. Fetal movements do not seem to be affected by the disease, but a decrease in motion during the third trimester has been reported. A specific diagnosis of thanatophoric dysplasia seems possible only when severe micromelia is associated with cloverleaf skull. On two occasions the temporal bulges of the cloverleaf skull were mistaken for encephalocele, but an intact calvarium can be visualized.

In the absence of cloverleaf skull, the disease should be suspected when severe rhizomelic dwarfism and a narrow thorax are detected. The differential diagnosis should include Ellis-van Creveld syndrome (chondroectodermal dysplasia), asphyxiating thoracic dysplasia, short rib-polydactyly syndrome, and homozygous achondroplasia.

Homozygous achondroplasia may be differentiated because it is an autosomal dominant disease, and therefore, both parents must be affected. In the heterozygous form, the long bones are only mildly shortened and not bowed. Kurtz et al. have recently shown that none of seven fetuses affected with heterozygous achondroplasia had an abnormal short femur in the early second trimester. The relationship between femur and BPD became abnormal after the 21st and 27th weeks (see p. 359). On the other hand, the micromelia of thanatophoric dysplasia may be so severe that it can be observed in some cases even at the 19th week.

Asphyxiating thoracic dysplasia can be distin-
Figure 10-44. Sonographic comparison of long bones of a fetus affected with thanatophoric dysplasia (right) and a normal fetus of the same gestational age (left). Top to bottom, femur, humerus, tibia, and radius. (Courtesy of Dr. Burrows.)

Figure 10-45. Longitudinal section of a fetus affected with thanatophoric dysplasia. Note the significant disproportion between the chest and the abdomen. Sp, spine. (Reproduced with permission from Jeanty, Romero: Obstetrical Ultrasound. New York, McGraw-Hill. 1983.)

Thanatophoric dysplasia is characterized by an H configuration to the vertebral bodies. In chondroectodermal dysplasia, the presence of a well-formed postaxial extra digit is rather typical and the short limb dysplasia is acromesomelic (p. 349). Fibrochondrogenesis is characterized by dumbbell-shaped metaphyses (p. 339).

Prognosis
This disease is uniformly fatal shortly after birth. The cause of death is cardiorespiratory failure probably related to restrictive respiratory disease.
Obstetrical Management

When a confident diagnosis is made, the option of pregnancy termination can be offered at any time during gestation because the condition is uniformly fatal. The hydrocephaly associated with cloverleaf skull may result in significant macrocrania and lead to
Fibrochondrogenesis

**Definition**
Fibrochondrogenesis is a lethal short limb skeletal dysplasia inherited with an autosomal recessive pattern. The disorder is characterized by rhizomelic limb shortening, with broad, dumbbell-shaped metaphyses, pear-shaped vertebral bodies, and short and distally cupped ribs. Histopathologically, there is disorganization of the growth plate, with unique interwoven fibrous septae and fibroblastic dysplasia of chondrocytes.1

**Incidence**
A total of five cases have been reported in the literature.1-3

**Etiology**
Autosomal recessive.

**Pathology**
The condition was first described by Lazzaroni-Fossati et al.2 in an infant who manifested many of the same characteristics of thanatophoric dysplasia. However, marked metaphyseal flaring of long bones, clefting of the vertebral bodies, and a distinctive morphologic lesion of the growth plate distinguish fibrochondrogenesis from thanatophoric dysplasia.

Infants are afflicted with moderate to severe micromelia (shortening of all segments of an extremity). Tubular bones are short and broad, with wide metaphyses. The fibula may be disproportionately short. The ribs are short and cupped, vertebral bodies are flat and clefted, clavicles are long and thin, and pelvic bones are hypoplastic. Hand and foot contractures have also been observed. The face is round and flat with protuberant eyes. Other features include frontal bossing, wide flat nasal bridge, small palpebral fissures with antimongoloid obliquity, low set abnormally formed ears, small mouth, cleft palate, and hypertelorism. An omphalocele has been described in one patient.1 Light microscopy demonstrates a grossly disorganized growth plate. Chondrocytes are large and round, and the intercellular matrix shows interwoven fibrous septae. However, both diaphyseal and metaphyseal bone formations are normal.
**Diagnosis**
A specific prenatal diagnosis of fibrochondrogenesis has not been reported. However, in one fetus, severe micromelia was detected prenatally. The differential diagnosis should include conditions associated with significant metaphyseal flaring, such as metatropic dysplasia, Kniest dysplasia, and spondyloepiphyseal dysplasia congenita. Thanatophoric dysplasia should also be considered.

**Prognosis**
All of the reported cases of fibrochondrogenesis either have been stillborn or have died shortly after birth. The longest survivor lived 3 weeks and required mechanical ventilation.

**Obstetrical Management**
A certain diagnosis of fibrochondrogenesis can be made if there has been a previously affected child.

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**Atelosteogenesis**

**Synonyms**
Spondylohumerofemoral hypoplasia and giant cell chondrodysplasia.

**Definition**
Atelosteogenesis is a lethal chondrodysplasia featuring deficient ossification of various bones, particularly the thoracic spine, humerus, femur, and hand bones, resulting clinically in a form of micromelic dwarfism. It is characterized by hypoplasia of the distal segment of the humerus and femur with enlargement of the proximal portion.

**Incidence**
Atelosteogenesis was first recognized as a distinct entity in 1983. The original report described six cases and identified four previous cases in the literature as fitting the description of the disease. Subsequently, isolated cases have been reported.

**Etiology**
Unknown. Neither parental consanguinity nor familial cases have been reported. Both sexes can be affected.

**Pathology**
The disorder is characterized by micromelia with severe shortening of the proximal segment of the extremities. Bowing of the long bones, dislocation of the elbow or knee, clubfeet, and hyperlaxity of the ligaments may be present. There is no pathognomonic facies; however, a depressed nasal bridge, cleft palate and a frontal cephalocele have also been reported.

The diagnosis is based primarily on the radiographic appearance of the spine, long bones, and hand. There is coronal clefting of the lumbar and lower thoracic vertebral bodies and hypoplasia of the upper thoracic bodies and ribs in that area. The humerus and femur are hypoplastic, with the distal segment thinned and the proximal portion enlarged, resulting in a club-shaped appearance. The ulna may be hypoplastic, and the fibulae are generally absent. Femoral and tibial epiphyses are not ossified, whereas the proximal humeral epiphysis may be prematurely ossified. There is a lack of ossification in some metacarpals and phalanges, although others may demonstrate near normal development.

Histologically, degenerating chondrocytes surrounded by fibrous material are found in degenerative areas of the matrix of the cartilage and growth plate.

**Diagnosis**
The prenatal recognition of an affected infant with shortened long bones has been documented in one case. The specific diagnosis of atelosteogenesis was...
not made until postmortem examination. Although the ultrasonic diagnosis of micromelia is easy, the specific diagnosis of atelosteogenesis is unlikely because of its sporadic occurrence. Differential diagnosis includes all disorders manifested by micromelic dwarfism such as achondrogenesis, thanatophoric dysplasia, and fibrochondrogenesis.

**Prognosis**

Atelosteogenesis is a lethal condition. Patients either have been stillborn or have died shortly after birth.

**Obstetrical Management**

Although the condition is lethal, it is doubtful that a precise prenatal diagnosis can be made.

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**REFERENCES**


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**SKELETAL DYSPLASIAS ASSOCIATED WITH A SMALL THORAX**

A group of skeletal dysplasias is characterized by a narrow thorax, which may lead to respiratory failure and death in the newborn period or shortly thereafter (Fig. 10-50). These conditions include asphyxiating thoracic dysplasia, the short rib-polydactyly syndromes, campomelic dysplasia, and chondroectodermal dysplasia. Prenatal diagnoses of these conditions have been reported. A precise diagnosis of the specific entity responsible for the narrow chest is extremely difficult even after neonatal examination and radiography. A specific identification of a disease entity in a relative makes diagnosis much simpler, since all these conditions are inherited with an autosomal recessive pattern. In the absence of this family history, the sonographer's task is to recognize the small thorax and the most commonly associated anomalies, with the realization that a specific antenatal diagnosis is extremely difficult. A specific prenatal diagnosis is probably not critical, since severe thoracic constriction seems to be associated with an extremely poor prognosis. Table 10-9 illustrates the criteria used by Cremin and Beighton for the differential diagnosis of some of these conditions. The radiologic features are not always discernible in utero with ultrasound. It should be stressed that other skeletal dysplasias may feature a hypoplastic thorax, but this finding is not the main characteristic of the disease (e.g., thanatophoric dysplasia (p. 335), atelosteogenesis (p. 340), fibrochondrogenesis (p. 339), achondrogenesis (p. 332), and Jarcho-Levin syndrome (p. 382)).

![Figure 10-50. Marked thoracic hypoplasia in an infant with short rib-polydactyly syndrome.](image)
Asphyxiating Thoracic Dysplasia

Synonyms
Jeune syndrome, Jeune thoracic dystrophy syndrome, infantile thoracic dystrophy, and thoracopelvic-phalangeal dystrophy.

Incidence
Rare. Approximately 100 cases of asphyxiating thoracic dysplasia (ATD) have been reported in the literature.2

Etiology
It is accepted that the disorder is transmitted in an autosomal recessive pattern. Minor manifestations have been recognized in parents of affected children, and, therefore, the possibility of a heterozygous expression has been suggested.1,17

Pathology
The most prominent feature is a narrow and bellshaped thorax, with short and horizontal ribs. The clavicles may be inverted, with a high handlebar appearance. Tubular bones are either normal or mildly shortened and not bowed. The ilia are small and flattened.

The disease has a wide spectrum of manifestations. A dramatic reduction in chest dimensions leads to pulmonary hypoplasia and respiratory insufficiency.2 In very rare instances, the disease is diagnosed because of an incidental chest x-ray that demonstrates the typical findings.10

Associated Anomalies
Visceral abnormalities include involvement of kidneys (tubular dysplasia, cystic dilatation of the collecting ducts, periglomerular fibrosis),2,3,6,7,17 liver (polycystic liver disease, periportal fibrosis, hyperplasia of the bile ducts),2,17 and pancreas (interstitial fibrosis).2 Dental and nail defects,13 polydactyly,16,18 and cleft lip and palate9 have been reported in some patients. However, these anomalies are more common in Ellis-van Creveld syndrome or chondroectodermal dysplasia (p. 349).

Diagnosis
Several prenatal diagnoses have been made.2,11,15,16 One was made at 18 weeks in a fetus at risk because of an affected sibling.2 In this case, serial scans performed before the 18th week failed to demonstrate the abnormality, and the condition was diagnosed by the presence of a narrow thorax and long bones in the third percentile for gestational age.

The most important diagnostic criterion is a hypoplastic thorax (Fig. 10-51). In most reports, recognition of a hypoplastic chest was based on the sonographer’s subjective impression, since these cases predated the availability of thoracic fetal

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**TABLE 10-9. DISORDERS WITH THORACIC DYSPLASIA AND POLYDACTYLY**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Asphyxiating Thoracic Dysplasia (Jeune)</th>
<th>Chondroectodermal Dysplasia (Ellis-van Creveld)</th>
<th>Short Rib–Polydactyly Syndrome Type I (Saldino-Noonan)</th>
<th>Short Rib–Polydactyly Syndrome Type II (Majewski)</th>
<th>Short Rib–Polydactyly Syndrome Type III (Naumoff)</th>
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<tbody>
<tr>
<td>Relative prevalence</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Clinical Features</td>
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<tr>
<td>Thoracic constriction</td>
<td>+</td>
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<tr>
<td>Polydactyly</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Limb shortening</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Congenital heart disease</td>
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<td>+</td>
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<td>Other abnormalities</td>
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<tr>
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<tr>
<td>Ectodermal dysplasia</td>
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<td>Radiographic features</td>
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<tr>
<td>Tubular bone shortening</td>
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<tr>
<td>Distinctive features in femora</td>
<td>+</td>
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<tr>
<td>Short, horizontal ribs</td>
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<tr>
<td>Vertical shortening of ilia and flat acetabula</td>
<td>+</td>
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<tr>
<td>Defective ossification of vertebral bodies</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Shortening of skull base</td>
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<td>+</td>
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biometric nomograms. In one case, the chest was narrow only in the anteroposterior diameter, whereas the transverse diameter was normal. In all cases prenatally diagnosed with ultrasound, there was short limb dwarfism, with long bones that were two standard deviations below the mean for gestational age. This probably represents ascertainment biases since this condition may be present with only mild limb shortening. The differential diagnosis between ATD and Ellis-van Creveld syndrome is impossible in atypical cases. Typically, ATD lacks polydactyly, ectodermal abnormalities, and congenital heart disease. Polyhydramnios has been associated frequently with this condition.

**Prognosis**

Eighty percent of affected infants die in the neonatal period from respiratory failure and infections. Long-term survivors have been reported, but they seem to have the milder form of the disease. However, with time, visceral involvement may lead to renal failure or hepatic cirrhosis. Of the four cases prenatally diagnosed (three with ultrasound and one with radiography), three underwent termination of pregnancy before viability, and one survived. The survivor developed hepatomegaly and mild jaundice.

**Obstetrical Management**

The option of pregnancy termination should be offered if the diagnosis is made in the second trimester. There is a paucity of data on which to base the management of cases diagnosed in the third trimester. Until the predictive value of sonographically diagnosed thoracic hypoplasia for neonatal death is established, it seems that traditional obstetrical management should not be altered.

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3. Bernstein J, Brough Al, McAdams AJ: The renal lesions
Short Rib-Polydactyly Syndromes

Short rib-polydactyly syndromes (SRPS) are a group of lethal disorders characterized by short limb dysplasia, constricted thorax, and postaxial polydactyly. Classically, three different types have been described, but some other variants have been recognized subsequently. It is likely that SRPS types I and III represent different manifestations of a single entity. Varying expressivity could be due to different alleles at a single locus. Although SRPS are ascertained on the basis of the skeletal abnormality, it is becoming clearer that generalized abnormalities of other organ systems are present. Therefore, the disorder may represent a fundamental defect of cellular differentiation during early embryogenesis. The different phenotypes could be the result of interaction with other intrauterine factors. For example, hydrops may be due to associated cardiovascular defects. The differential diagnosis of the three classic forms of SRPS with asphyxiating thoracic dysplasia and Ellis-van Creveld syndrome is outlined in Table 10-9.

The view that SRPS require the presence of polydactyly has been challenged by a number of authors who have reported cases that fit the morphologic description of SRPS but without polydactyly. The term "short rib syndrome" has, therefore, been proposed to refer to entities in which this bone abnormality is responsible for a narrow thorax. Confusion results from the fact that there are no specific biochemical or histopathologic markers for these diseases. Also, the small number of cases reported in the literature precludes a rigorous statistical analysis of the different phenotypic variants.

An interesting feature of SRPS is the female sex preponderance. Recent data indicate that such preponderance may be artifactual and that failure of development of secondary sexual characteristics can occur. Indeed, in some cases, although the chromosomal constitution is XY, and the gonads are testes, the phenotype is female or ambiguous. The other skeletal dysplasia in which this type of sex discrepancy has been documented is campomelic syndrome.

REFERENCES


TYPE I OR SALDINO-NOONAN SYNDROME

Etiology
Autosomal recessive.

Pathology
There is severe micromelia with hypoplastic tubular bones. The femurs are typically pointed at both ends. The thorax is narrowed, and the ribs are extremely short. Vertebral bodies are distorted, with deficient ossification and incomplete coronal clefts.

Associated Anomalies
Associated anomalies of the heart (transposition of the great vessels, double outlet right ventricle, endocardial cushion defect), gastrointestinal tract (imperforate anus, agenesis of the gallbladder, intes-
tinal atresia), and genitourinary system (hypoplastic or polycystic kidneys) have been reported.\textsuperscript{1,3,5,6}

**Diagnosis**

This condition has been identified antenatally with ultrasound in fetuses at risk.\textsuperscript{2,4} The first fetus was identified with the combination of radiography and ultrasound. In the second fetus, oligohydramnios prevented the evaluation of the fetal long bones. The condition was suspected because of ascites in a fetus at risk. Figures 10-52 through 10-55 illustrate the sonographic findings in this condition in one of our prenatally diagnosed cases.

In the absence of a positive family history, a specific diagnosis of type I SRPS seems impossible. It should be suspected in fetuses with short limb dysplasia, narrow thorax, and polydactyly.

**Prognosis**

The disease is uniformly fatal.

**Obstetrical Management**

The option of pregnancy termination could be offered any time the diagnosis is made during gestation in a pregnancy at risk.

**REFERENCES**


**TYPE II OR MAJEWSKI TYPE**

**Etiology**

Autosomal recessive.

**Pathology**

Distinctive features of this type of SRPS are less severe micromelia, cleft lip or palate, markedly short tibia with an ovoid shape, and normal pelvis and spine.
Associated Anomalies
Associated anomalies include hypoplasia of the epiglottis, larynx, ambiguous genitalia, polycystic kidneys, pancreatic fibrosis, and cardiovascular and gastrointestinal (malrotation) anomalies.1-3,5,6

Diagnosis
The prenatal diagnosis has been made in fetuses at risk by identification of short tibia, polydactyly, and cleft lip at fetoscopy,7 or severe micromelia, short ribs with narrow thorax, and polydactyly at ultrasound.4,6 The earliest diagnosis has been made at the 16th week of gestation.5

Cases resembling the Majewski type of SRPS but without polydactyly and with bowing of the long bones 8 are more consistent with a newly described short rib syndrome.

The diagnosis should be suspected whenever a hypoplastic thorax, polydactyly, short limb dysplasia (with short tibia), and cleft lip or palate are visualized. The differential diagnosis with other conditions is outlined in Table 10-9. In the absence of a positive family history, a specific differential diagnosis is difficult even after birth.

Prognosis
The disease is uniformly fatal.

Obstetrical Management
The option of pregnancy termination can be offered any time the diagnosis is made during gestation in a pregnancy at risk.

REFERENCES

TYPE III OR NAUMOFF TYPE
Although originally considered a different entity, growing evidence supports the view that type I and type III are similar disorders.1

Etiology
Autosomal recessive.

Pathology
This type is characterized by vertebral hypoplasia, long bones with widened metaphyses and marginal spurs, short base of the skull, bulging forehead, and depressed nasal bridge. Urogenital abnormalities are frequently associated.2,3,5

Diagnosis
The diagnosis of this variety has been described in a fetus scanned because of the clinical suspicion of polyhydramnios. The fetus showed hydrops, a narrow chest, short limbs, polydactyly, hypoplastic vertebrae, and widened metaphyses of the femurs.7

It has been proposed that the differential diagnosis between type I and type III SRPS can be made on the basis of the appearance of the extremities of the long bones. Sharp ends are seen in type I, whereas widened metaphyses are seen in type III.8 As stated before, it is possible that types I and III SRPS be different expressions of the same disorder.1 Some authors have suggested the name "non-Majewski SRPS" for these two conditions.1

Prognosis
The disease is uniformly fatal.

Obstetrical Management
The option of pregnancy termination can be offered any time the diagnosis is made during gestation in a pregnancy at risk.

REFERENCES
Campomelic Dysplasia

Synonyms
Campomelic dwarfism and campomelic syndrome.

Definition
Campomelic dysplasia (campomelic means bent limb) is a condition characterized by bowing of the long bones (particularly lower extremities), hypoplastic scapulae, and a wide variety of associated abnormalities, including hydrocephalus, congenital heart disease, and hydronephrosis. In a significant number of cases the phenotype is female, but the chromosomal constitution is XY and the gonads are testes.2

Incidence
Campomelic dysplasia has been reported in 0.05 per 10,000 births (see Table 10-1).

Etiology
Although the pattern of inheritance is not clearly defined, the frequency of parental consanguinity suggests an autosomal recessive transmission.3,11,12 Many cases are sporadic.3

Pathology
The most prominent and invariable feature is bowing of the tibiae and femurs. Tubular bones are either normal in length or shortened.8 Craniofacial anomalies, such as macrocephaly, cleft palate, and micrognathia, are seen in 90 to 99 percent of cases. Hypoplastic scapulae have been reported in 92 percent of patients.7 The chest is narrow and bellshaped. The vertebral bodies are frequently hypoplastic, and the pedicles are nonmineralized. The iliac wings are vertically narrow in 98 percent of patients, and hip dislocation is a frequent finding.

The association of hypoplastic scapulae, nonmineralized thoracic pedicles, and vertically narrowed iliac bones is quite unique for campomelic syndrome.4 Khajavi et al.8 have suggested that the campomelic syndrome is a heterogeneous group of disorders that include two forms: (1) long-limbed campomelic syndrome with bent bones of normal width, only slightly shortened, and rarely involving the upper limbs and (2) short-limbed campomelic syndrome, in which the bent bones are short and

Figure 10-56. Bowing of the femur in a fetus with campomelic syndrome.

Figure 10-57. Bowing of a long bone in a fetus with campomelic syndrome.
wide. This variety can be classified into a craniosynostotic type with cloverleaf skull and a normocephalic type.

Associated Anomalies
Hydrocephalus has been reported in 23 percent of patients, congenital heart disease (VSD, ASD, Tetralogy of Fallot, aortic stenosis) in 30 percent, and hydronephrosis, frequently unilateral, in 30 percent. Fifty percent of the affected females have an XY chromosomal constitution.²

Diagnosis
Prenatal diagnosis of this condition has been reported in patients at risk.⁴,⁶,⁷,¹³ In two reports, the condition was visualized antenatally, but a correct diagnosis was made only in the newborn.¹,¹⁰ The condition should be suspected any time there is a skeletal dysplasia with bowing of long bones, particularly if it is associated with other anomalies, such as congenital heart disease or hydronephrosis.

Some physiologic bowing can be seen in normal fetuses. There are no objective means available to differentiate pathologic from physiologic bowing. Experience is needed to make this assessment. All the patients we have seen had marked bowing (Figs. 10-56, 10-57); however it is not specific for campomelic syndrome. Other skeletal dysplasias associated with this finding include osteogenesis imperfecta, hypophosphatasia, thanatophoric dysplasia, and mesomelic dysplasia Reinhart variety. In addition, congenital bowing of the long bones could be a benign condition with no other metabolic disorder. Long bone curvilinear deformation in campomelic syndrome may be limited to the proximal segment of the limbs (Fig. 10-58).

Prognosis
Beluffi and Fraccaro reviewed all the reported cases of campomelic dysplasia.⁵ They found that of 92 infants for whom follow-up was available, 89 died within the first 10 months of life. At the time of their report, the age of the three survivors was 7 months, 19 months, and 17 years. The main cause of death was respiratory failure. Despite this gloomy overall prognosis, some patients may have reasonably normal psychomotor development. Long-term survivors can develop hearing loss and severe kyphosis.⁹

Obstetrical Management
The option of pregnancy termination should be offered before viability. After viability, standard obstetrical management is not altered.

REFERENCES
Chondroectodermal Dysplasia

Synonyms
Ellis-van Creveld syndrome, mesodermal dysplasia, and six-fingered dwarfism.

Incidence
More than 120 cases have been reported. In the United States, the disorder is prevalent in the inbred Amish communities in Pennsylvania.

Etiology
It is inherited in an autosomal recessive pattern.

Pathology
The typical findings are shortening of the forearm and lower leg (acromesomelic dwarfism), postaxial polydactyly (generally of fingers but occasionally of the toes), and dysplasia of ectodermal derivates (hypoplastic or absent nails, neonatal teeth, partial anodontia, scant or fine hair). The thorax is long and narrow. In 50 percent of patients, a congenital heart defect (typically atrial septal defect) is found. The spine is normal. Rarer anomalies are hypoplasia of the tibia, talipes equinovarus, and cryptorchidism.

Diagnosis
Prenatal diagnosis of this condition has been reported. The first prenatal diagnosis of chondroectodermal dysplasia was made with fetoscopy by demonstrating the presence of polydactyly in a fetus at risk. Fetoscopy was used before the development of high-resolution ultrasound. More recently, an infant with short limb skeletal dysplasia, narrow thorax, ectodermal dysplasia, polydactyly, and cardiac defects was identified antenatally with ultrasound. Sonography demonstrated the short limb dysplasia and the narrow thorax. Although the authors did not label the condition as chondroectodermal dysplasia, their description fits the disorder. An important diagnostic consideration is that polydactyly is a constant finding. The supernumerary finger usually has well formed metacarpal and phalangeal bones.

Chondrodysplasia Punctata

Synonyms
Stippled epiphyses, chondrodystrophia calcificans congenital and dysplasia epiphysealis punctata.

Definition
Chondrodysplasia punctata includes two different disorders: a rhizomelic, potentially lethal variety, and
a nonrhizomelic variety (Conradi-Hünermann syndrome), which is more common and generally benign. These two conditions have different clinical, genetic, and radiologic characteristics.

**Incidence**
Chondrodysplasia punctata occurs in 0.09 per 10,000 births (see Table 10-1).

**Etiology**
The rhizomelic type of chondrodysplasia punctata is inherited with an autosomal recessive pattern. The nonrhizomelic type is heterogeneous. An autosomal dominant, X-linked dominant, and recessive transmission pattern has been postulated for this type.

**Pathology**
The rhizomelic type is characterized by marked limb shortening that is maximal in the arms. Contractions may occur, and the fingers are fixed in flexion. The face is flat, with a depressed nasal bridge, and hypertelorism may occur. Some patients have ichthyosiform skin dysplasia and cataract. Radiographically there is calcific stippling of the epiphysis. This finding is not pathognomonic for chondrodysplasia punctata, since it may occur with other conditions (multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia, hypothyroidism, trisomy 18, trisomy 21, warfarin embryopathy, and the Zellweger cerebrohepatorenal syndrome). Metaphyseal spraying is seen, particularly at the level of the knee. The spine has coronal clefts in the lumbar and lower thoracic region.

The nonrhizomelic, or Conradi-Hünermann, type is a milder form of the disease. The limb shortening is mild or absent. Metaphyses are not splayed. Stippling is very fine and may be limited to the tarsal or carpal bones. Joint contractures can be present. Ascites and polyhydramnios have been reported.

**Diagnosis**
An antenatal sonographic diagnosis of chondrodysplasia punctata has not been reported. Prenatal diagnosis of the rhizomelic variety with radiography has been made. The findings included stippling of pubic, ischium, and femoral epiphyses and abnormal epiphyseal centers of the joints of the knees and ankles. The radiographic changes, however, are not sufficiently specific to permit recognition and separation of the two types in all cases. Figures 10-24 and 10-25 permit the diagnosis of rhizomelia by comparing the length of the humerus or femur to that of the ulna or tibia, respectively. Stippling has not been reported with ultrasound.

**Prognosis**
The rhizomelic type is frequently fatal. Infants generally die before 1 or 2 years of age because of respiratory failure. Severe mental deficiency and psychomotor retardation with spastic tetraplegia are present in most of the late survivors. The nonrhizomelic type is compatible with life. Complications include failure to thrive, orthopedic problems, such as scoliosis, cataracts, retinal detachment, and recurrent infections.

**Obstetrical Management**
The option of pregnancy termination should be offered if diagnosis is made prior to viability. After viability, standard obstetrical management is not altered.

**REFERENCES**

Diastrophic Dysplasia

**Synonyms**
Diastrophic nanism syndrome and diastrophic dwarfism.

**Definition**
Diastrophic dysplasia is characterized by micromelia, clubfoot, hand deformities, multiple joint flexion contractures, and scoliosis. The term “diastrophic” means twisted and refers to the twisted habitus present in this condition.

**Etiology**
The disorder is inherited as an autosomal recessive trait.3,5,9,11

**Pathology**
The disease may be recognized at birth, but milder cases are diagnosed later.1,2,12 The clinical features at birth include short stature, micromelia (predominantly of the rhizomelic type), multiple joint flexion contractures (notably of the major joints), hand deformities, with short and widely spaced fingers and abducted position of the thumbs (hitchhiker thumb) (Fig. 10-59) and severe talipes equinovarus. The head and skull are normal. Micrognathia and cleft palate are frequently observed.11

With time, the affected infants develop progressive kyphoscoliosis with a potential for respiratory compromise. The gait is characterized by a twisting motion because of hip dislocation and genu varum deformities of the knee. Inflammation of the pinna of the ear results in a typical deformation known as "cauliflower ear." 1,11

Diastrophic dysplasia is a generalized disorder of cartilage. There is a destructive process of chondrocytes and cartilage matrix. This is followed by the formation of fibrous scar tissue and ossification. The latter process is responsible for the contractures. Growth plates are also affected.10 No known biochemical defects have been demonstrated.12

**Diagnosis**
Antenatal diagnoses of diastrophic dysplasia have been reported in fetuses at risk for the disorder.4,8,13

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Figure 10-59. Abortus with hitchhiker thumbs.
We have made this diagnosis by ultrasound, demonstrating rhizomelic dwarfism at 20 weeks' gestation.6 (Figs. 10-60, 10-61). O'Brien et al. made the diagnosis at 16 weeks with a combination of ultrasound and fetoscopy.8 Sonography demonstrated shortening of the long bones, and fetoscopy showed a cleft palate and micrognathia. Wladimiroff et al. diagnosed the condition at 17 weeks by visualizing with ultrasound the severe shortening and bowing of all long bones.15 Kaitila et al. reported a diagnosis at 18 weeks by demonstrating shortening of the limbs and lateral projection of the thumb with ultrasound in a patient at risk.4 They also reported the exclusion of the diagnosis in three fetuses at risk who were examined between 15 and 16 weeks of gestation.

The spectrum of the disease is wide,2 and some cases of diastrophic dysplasia may not be diagnosable in utero. Besides short limb dysplasia, the most characteristic feature of diastrophic dysplasia is the presence of multiple contractures in the upper and lower extremities. However, this finding can occur in other disorders, such as arthrogryposis multiplex congenita (p. 380), and the Nievergelt type of mesomelic dysplasia (p. 361). A skeletal dysplasia that should be considered as part of the differential diagnosis is Weissenbacher-Zweymuller syndrome, which consists of the association of short limb dysplasia and micrognathia (other facial features of the syndrome may include cleft palate, hypertelorism, and a depressed nasal bridge). In this condition, contracture deformities are not expected.7,14

**Prognosis**

Increased neonatal mortality has been reported in these patients. Respiratory distress and aspiration pneumonia are the leading causes.1,13 The disorder is nonlethal, and intellect is not affected. The progressive kyphoscoliosis and arthropathy lead to severe physical handicap and, in extreme cases, to restrictive respiratory distress.13

**Obstetrical Management**

The option of pregnancy termination can be offered when diagnosis is made before viability. After viability, diagnosis of diastrophic dysplasia does not alter standard obstetrical management.

**REFERENCES**


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**Figure 10-60.** Fetus with diastrophic dysplasia. The prenatal diagnosis was based on the detection of shortened limbs. (Reproduced with permission from Mantagos et al.: Am J Obstet Gynecol 139:11 1, 1981.)

**Figure 10-61.** A comparison between the normal femur (left) and those of a fetus with diastrophic dysplasia (right) for the same gestational age.
Metatropic Dysplasia

Synonyms
Hyperplastic achondroplasia and metatropic dwarfism.

Definition
Metatropic dysplasia is a short limb skeletal dysplasia characterized by dumbbell-like configuration of the long bones, a narrow but normal length thorax, and, occasionally, a coccygeal appendage similar to a tail.

Etiology
Some familial cases have been reported, suggesting an autosomal recessive pattern of inheritance. However, most cases occur sporadically.

Pathology
The term "metatropic" means changeable and was suggested by Maroteaux et al. to indicate the change in proportions of the trunk to the limbs that occurs over time.

The newborns have a normal trunk length with a restricted thorax and short limb dwarfism. The long bones have a characteristic broadening of their metaphyses (trumpet-shaped long bones). With time, the pelvis develops a typical battle-axe configuration. The intervertebral disk spaces are widened, and a typical tail-like appendage can be seen at the level of the coccyx. Although inconstant, this finding is very characteristic of the disorder.

In childhood there is growth retardation of the spine and kyphoscoliosis develops, resulting in a trunk shorter than the limbs.

Cleft palate has been reported in association with metatropic dysplasia.

Diagnosis
Not all cases are identifiable at birth. The diagnosis should be suspected when shortening of the limbs is associated with a trumpet-shaped widening of the metaphyses. A prenatal diagnosis of this condition has not been reported.

Another disorder associated with a dumbbell configuration of long bones is the Weisenbacher-Zweymuller syndrome characterized by severe micromelia, micrognathia, and coronal cleft in the vertebrae. Other disorders with metaphyseal flaring include fibrochondrogenesis (p. 339), Kniest syndrome (p. 364), and dyssegmental dysplasia (p. 365).

Prognosis
This disorder is compatible with life. However, with age, there is increased disability because of progressive kyphoscoliosis. In some patients, death occurs during infancy.

Obstetrical Management
If the diagnosis is made before viability, the option of pregnancy termination should be offered to the parents. Diagnosis after viability does not change standard obstetrical management.

REFERENCES

Skeletal Dysplasias Characterized by Bone Demineralization

OSTEOGENESIS IMPERFECTA

Synonyms
Van der Hoeve syndrome, trias fragilitas osseum, Eddowes's syndrome, osteopsathyrosis idiopathica of Lobstein, and Ekman-Lobstein disease.

Definition
Osteogenesis imperfecta (OI) is a heterogeneous group of collagen disorders characterized by bone fragility, blue sclerae, and dentinogenesis imperfecta.

Incidence
The overall incidence of OI is 1 in 28,500 live births.\(^{19}\) The most frequent variety ascertained in newborns is OI type II, with an incidence of 1 in 54,000 births.\(^{4}\)

Etiology
OI is a heterogeneous disorder of production, secretion, or function of collagen. A detailed discussion of the nature of the biochemical alterations is beyond the scope of this text. The interested reader is referred to other reviews on the subject.\(^{3}\)

Pathology
Several classifications of OI have been proposed, but the most widely accepted is one based on phenotype suggested by Sillence et al.\(^{19}\) and subsequently modified.\(^{3}\)

**OI Type I.** This type is inherited in an autosomal dominant pattern. Patients have blue sclerae and bone fragility and are deaf or have a family history of presenile deafness. Infants are of normal weight and length at birth and do not have multiple fractures. Vertebral malalignment and deformation of tubular bones are uncommon complications. OI type I is subdivided into type A and type B according to the presence or absence of abnormal dentinogenesis, respectively.

**OI Type II.** This form is the lethal variety of OI. It is claimed to be inherited as an autosomal recessive trait, but the lack of affected siblings in different series suggests, in some cases, a new mutation of a dominant gene or a nongenetic etiology.\(^{22}\) Therefore, the empiric recurrence risk should be somewhat below the expected 25 percent. Infants are either stillborn or die during the neonatal period. Multiple fractures occur in utero, and the long bones are shortened, broad, and crumpled. The thorax is short but not narrowed. The skull is poorly ossified, and blue sclerae are present. Infants are frequently small for gestational age. Sillence et al.\(^{20}\) proposed a subdivision of type II OI into three varieties based on radiologic criterion. The first variety is characterized by short, broad, "crumpled" long bones, angulation of tibiae and beaded ribs, the second type by broad, "crumpled" femora but minimal or no rib fractures, and the third by narrow fractured femora and thin, beaded ribs.

**OI Type III.** Type III can be transmitted as an autosomal recessive or an autosomal dominant disorder. Patients have bluish sclerae during infancy and normal or pale blue sclerae later in life. Long bones are shortened and bowed, and multiple fractures are present at birth in most patients. The skull has decreased ossification. The disease is characterized by progressive deformity of the long bones and spine.

**OI Type IV.** This type is the mildest form of the disease and is inherited as an autosomal dominant disorder. Patients' sclerae are blue at birth, but with time they become white. Tubular bones are normal in length, but mild femoral bowing may occur. According to the presence or absence of dentinogenesis imperfecta, the disease is subclassified into subtype A or B, respectively. Although this classification encompasses most cases of the disease, some do not fit the proposed subdivisions.

Diagnosis
The diagnosis of OI type II has been reported several times with ultrasound.\(^{11-14,24,25}\) This condition has been diagnosed before 20 weeks' gestation,\(^{6,7,9,15,18,23}\) and no false negative diagnoses have been reported. The sonographic findings may be present in all skeletal districts. Long bones may show fractures (Fig.)
SKELETAL DYSPLASIAS CHARACTERIZED BY BONE DEMINERALIZATION

Figure 10-62. Fracture (large white arrow) of a femur (F) in a fetus with osteogenesis imperfecta.

Figure 10-63. Left femur at 18 weeks of gestation is 1.9 cm in length. Note the marked bowing and shortening of the shaft and breakage (arrow). (Reproduced with permission from Ghosh et al.: Prenat Diagn 4: 235, 1984.)

Figure 10-64. Bowing of the femur at 24 weeks of gestation in a fetus with osteogenesis imperfecta. (Reproduced with permission from Chervenak et al.: Am J Obstet Gynecol 143: 228, 1982.)

10-62), angulations, shortening (Fig. 10-63), localized thickening secondary to callous formation, and bowing and demineralization (Fig. 10-64). These findings are usually more evident in the femurs but have been described in the upper limbs as well. In rare instances, the limbs are so shorted that they become impossible to measure.\textsuperscript{13} The skull may be thinner than usual, and the weight of the ultrasound probe may deform the head quite easily. In severe cases, the cranial vault has a wavy outline and is easily compressible. Multiple fractures of the ribs result in a bell-shaped or narrow chest. Seldom does the spine show decreased echogenicity. Fetal movements are decreased.\textsuperscript{7,9}

Type I OI diagnosis has been attempted as well.\textsuperscript{5,10,17} An early diagnosis was possible in some fetuses,\textsuperscript{10,17} but in others, even serial monographic scans failed to diagnose the condition with certainty.\textsuperscript{5} Type III OI was diagnosed once in a fetus at risk because of a previous affected sibling.\textsuperscript{1} At 15 ½ weeks of gestation, the long bones were normal in length, but a fracture was suspected. At 19 weeks, long bones of the lower extremities were shortened, whereas bones of the upper extremities were within normal limits.\textsuperscript{*}

There are limitations to the evaluation of bone mineralization with sonography (Figs. 10-65 and 10-66). Although a biochemical approach to the diagnosis by measuring pyrophosphate concentration in amniotic fluid has been proposed,\textsuperscript{21} this method has been reported to be unreliable.\textsuperscript{8} As molecular defects are identified, prenatal diagnosis is likely to shift to molecular biology techniques.

**Prognosis**

There is limited information available on the prognosis of OI diagnosed in utero, since most of these pregnancies have been electively terminated. Of the 16 fetuses diagnosed in utero, 12 were type II (the lethal form), 3 were type I, and 1 was type III. OI is a disease with a wide range of clinical presentations. Multiple fractures and intracranial bleeding may lead to intracranial hemorrhage and

\*A similar case has been reported.\textsuperscript{16}
death in utero or during the neonatal period. The quality of life of survivors is extremely variable. Multiple fractures may require repeated surgery and lead to serious handicaps. Spinal deformities, otosclerosis, and deafness can occur in long-term survivors.2

The classification proposed by Sillence does not have a reliable prognostic significance. Spranger et al. have proposed a radiographic scoring system based on the severity of underossification and bone deformities and fractures.22 The scoring system should be used during the neonatal period to predict prospective mortality. Infants with a score of more than 2.6 have an 88 percent mortality rate, whereas those with a score of 2.6 or less have a 90 percent chance of survival.

Type II OI is lethal. Type I and type III are compatible with life, but affected individuals may suffer significant handicaps because of multiple and recurring fractures and deformities. Type IV has the best prognosis, since fractures and deformities are uncommon.

Obstetrical Management

The option of pregnancy termination can be offered any time a type II OI is diagnosed. For other varieties, the option of pregnancy termination should be offered before viability. After viability, consideration should be given to the mode of delivery. Theoretically, skull fractures could occur during the passage of the infant through the birth canal. Therefore, delivery by cesarean section has been proposed.23 This view seems reasonable, although there are no empirical data to prove the benefit of this approach.

REFERENCES


**HYPOPHOSPHATASIA**

**Definition**

Hypophosphatasia is a congenital disease usually inherited in an autosomal recessive pattern and characterized by demineralization of bones and low activity of serum and other tissue alkaline phosphatase.

**Incidence**

The incidence of hypophosphatasia is 1 in 100,000.2

**Etiology**

Autosomal recessive. Some familial cases of the mild form have been attributed to an autosomal dominant trait.10

**Pathology**

There are four clinical forms of the disease depending on the age of onset: neonatal, juvenile, adult, and latent. The neonatal (also known as "congenital" or "lethal") variety is associated with a high incidence of intrauterine fetal demise or early neonatal death. In the juvenile or severe variety, the onset of symptoms takes place within weeks or months. The adult or mild form is recognized later in childhood, adolescence, or even during adulthood. It seems to be inherited with an autosomal dominant pattern with variable expressivity and penetrance.10 The latent form (heterozygote state) is characterized by normal or borderline levels of alkaline phosphatase and no other pathologic features. It is unclear whether these clinical varieties represent different forms of the same genetic defect or rather different diseases. It has been suggested that recurrences within a family are type specific.7

The mechanism for the development of bone fragility in hypophosphatasia is not clearly understood. Alkaline phosphatase normally acts on pyrophosphates and other phosphate esters and leads to the accumulation of inorganic phosphates, which are critical for the formation of bone crystals. A deficiency in alkaline phosphatase leads to deficient generation of bone crystals.

**Diagnosis**

The variety relevant to antenatal diagnosis is the congenital form. It is characterized by marked demineralization of the calvarium.14,7,9,11 The skull appears soft and is called "caput membranaceum" (Fig. 10-67). An increased echogenicity of the falx cerebri has been attributed to enhanced sound transmission through a poorly mineralized skull.7 Tubular bones are short, bowed, and demineralized, and multiple fractures can be present. Amniotic fluid volume is characteristically increased.6,8

The amniotic fluid alpha-fetoprotein concentra-
Prognosis
The congenital variety of hypophosphatasia is uniformly fatal.

Obstetrical Management
When a confident diagnosis of the lethal variety is made, the option of pregnancy termination can be offered any time during gestation.

REFERENCES
Heterozygous Achondroplasia

Definition
The term "achondroplasia" was used in the past for defining all short limb dysplasias. With recognition of the heterogeneity of these disorders, this term is used currently to describe a specific disease characterized by predominantly rhizomelic dwarfism, limb bowing, lordotic spine, bulky head, and depressed nasal bridge. The disorder is compatible with normal life.

Incidence
A birth prevalence of 1 in 66,000 in the United States has been reported. These figures probably represent an overestimate of the real incidence of the condition because other skeletal dysplasias were probably confused with achondroplasia and included in the calculations.

Etiology
Achondroplasia is transmitted with an autosomal dominant pattern with invariable penetrance. However, in 80 percent of cases, the parents are not affected, suggesting the occurrence of a new mutation. Achondroplasia is one of the few diseases in which advanced paternal age probably plays a role. The disease is lethal in the homozygous state.

Pathology
The disease was regarded as the result of anomalous growth of cartilage (hence the term "achondroplasia"), followed by abnormal endochondral ossification, but it has been demonstrated that the disorder is not qualitative but quantitative. Defective endochondral bone formation is responsible for the shortness of long bones, whereas normal periosteal bone formation gives the impression of abnormally thickened long bones. Moreover, long bones are enlarged at the end and frequently bowed. The bones of the hands and feet are short (brachydactyly). The fingers are divergent, and the infants are unable to approximate the third and fourth fingers (trident hand) (Fig. 10-68). Progressive narrowing of the interpedicular space in the anteroposterior x-ray projection is a typical finding in the spine. Marked lordosis in the lumbar area results in a prominent buttocks (Fig. 10-69). The head is large with a shortened cranial base and frequently a small foramen magnum. Facial features include a flattened nasal bridge, frontal bossing, and a broad mandible (Fig. 10-70). The chest shows decreased dimensions, and the pelvic bones appear square-shaped with a tombstone configuration.

Associated Anomalies
Hydrocephalus has been reported in some patients and may be related to a narrowed foramen magnum.

Diagnosis
Prenatal diagnosis of achondroplasia has been reported by several authors. The diagnosis has relied on identification of shortened long bones, particularly the femur. An extremely important observation is that alterations in long bone growth may not be observed until the third trimester, and, therefore, a diagnosis before viability may only be possible in the most severe cases. Kurtz et al. recently reviewed their experience with seven cases of prenatal diagnosis of heterozygous achondroplasia. None had an abnormally short femur in early second trimester. Using the relationship between femur and biparietal diameter, all fetuses with serial examinations (six) fell below the 1st percentile between 20.9 and 27 weeks of gestation. The shape of long bones

Figure 10-68. Hand of an achondroplastic child, showing the typical trident appearance and stubby fingers.
was normal. Spine and head abnormalities were not identified in utero.

**Prognosis**

Achondroplasia may be compatible with a normal life span. However, affected individuals experience significant morbidity. Recurrent ear infections during early childhood are attributed to poor development of the facial bones, with constriction and inadequate drainage of the eustachian tube. Unrecognized or incompletely treated infections are probably responsible for hearing loss. Orthodontic care may be required to alleviate crowded dentition and problems of malocclusion. The mean adult height for men is 52 inches and for women 49 inches. Obesity is frequent. Hydrocephalus as well as syringomyelia may result from a small foramen magnum. However, hydrocephaly is rarely a serious problem and is generally managed conservatively. Sudden infant death and respiratory compromise have been attributed to compression of the upper cervical spine. Indeed, a recent study using somatosensory evoked potentials showed that up to 44 percent of asymptomatic achondroplasts had abnormal findings secondary to spinal compressions. The most significant handicaps suffered by achondroplastic patients are neurologic complications secondary to spinal cord compression, which may range from paresthesias to complete paraplegia. Genu varum and tibia vara are more frequent with advancing age.

**Obstetrical Management**

At present, it is doubtful whether a confident diagnosis can be made before viability. In the third trimester, fetal head growth should be monitored because of the possible development of macrocrania. The method of choice for delivery of achondroplastic mothers is elective cesarean section.

**REFERENCES**


Mesomelic Dysplasia

Definition
The term "mesomelic dysplasia" refers to a group of disorders in which limb shortening is most pronounced in the middle segment (forearm and leg) of the extremities. It includes dyschondrosteosis, Nievergelt mesomelic dysplasia, Langer mesomelic dysplasia, Robinow (fetal face syndrome) mesomelic dysplasia, Reinhardt mesomelic dysplasia, and Werner mesomelic dysplasia.

Incidence
Rare.

Etiology
Mesomelic dysplasias are inherited with an autosomal dominant pattern, with the exception of the Langer variety which is inherited as an autosomal recessive trait.1,5

Pathology
The most prominent findings of the different varieties are described as follows.3,13

Langer Mesomelic Dysplasia. Hypoplastic ulna, fibula, and mandible; the mesomelia is more marked in the lower extremities. The ulna is shorter than the radius. The degree of mandibular hypoplasia is variable and can be mild. There is marked ulnar deviation of the hand. Some authors have considered the Langer type as the homozygous state of dyschondrosteosis, a mesomelic dysplasia that is not recognized until late childhood and is characterized by mesomelic dwarfism and Madelung deformity or dinner fork deformity of the forearm (short radius with lateral and dorsal bowing).4,6,8

Robinow Mesomelic Dysplasia. Acromelicbrachymelia (short hands and feet with stubby fingers and toes), mesomelic shortening predominantly of the upper extremities, abnormal facies resembling that of an 8-week fetus (with macrocephaly, prominent forehead, hypertelorism, hypoplastic mandible), and mental retardation. Additional features include hemivertebra formation and fusion anomalies of the spine and ribs. Small genitalia are present.7,12,15,16

Nievergelt Mesomelic Dysplasia. Besides mesomelia, it is characterized by clubfeet, flexion deformities of the fingers and elbows, and genu valgum. The tibia

Figure 10-71. Mesomelic shortening of the upper extremity. Note the normal humerus, extremely short forearm bones, and deformed hand.
may be flattened and rhomboid. Although the disease was originally described in a man and his three affected sons (from different mothers), the disorder has also been reported in a nonfamilial case.\(^1\)

**Reinhardt Mesomelic Dysplasia.** This disorder is characterized by mesomelic shortening of the upper extremities, bowing of the forearm bones, and ulnar deviation of the arm. The fibula is hypoplastic, and there is synostosis of the carpus and tarsus.\(^1\)

**Werner Mesomelic Dysplasia.** This is characterized by extreme bilateral hypoplasia of the tibia, polydactyly, absence of the thumbs, and frequently webbing of the fingers.\(^10\)

**Diagnosis**

Of the mesomelic dysplasias, dyschondrosteosis is generally recognized late in childhood and may not be detected prenatally. The other varieties are recognized at birth and are, therefore, amenable to prenatal diagnosis. However, a prenatal diagnosis of any of the mesomelic dysplasias has not been reported. Diagnosis is feasible by comparing the dimensions of the long bones of the leg with the femur and the long bones of the forearm with the humerus (see Figs. 10-24, 10-25; Fig. 10-71). Table 10-10 shows the major characteristics of the mesomelic dysplasias. Some of these findings are identifiable with ultrasound (e.g., hemivertebra, tibial hypoplasia). Figure 10-72 illustrates a prenatal diagnosis of hemivertebrae.\(^2\)

**Prognosis**

With the exception of the Robinow type, these disorders are usually associated with normal intelligence. Some orthopedic problems could result from the associated skeletal deformities and stress in the affected bones.

**Obstetrical Management**

It is unknown whether the diagnosis of mesomelic dysplasia can be made before viability. A diagnosis after viability does not alter standard obstetrical management.

**REFERENCES**

9. Nievergelt K: Positiver aterschaftsnachweis auf
Spondyloepiphyseal Dysplasia

Definition
"Spondyloepiphyseal dysplasia" refers to a heterogeneous group of disorders involving the spine and the epiphyses. Two varieties have been described: congenita and tarda. Only the congenital variety is apparent at birth.

Etiology
The congenital form is inherited with an autosomal dominant pattern with considerable variability of expression.3,4

Pathology
The disease is characterized by ovoid vertebral bodies and severe platyspondyly (flattened vertebral bodies). There is also hypoplasia of the odontoid process, which may cause cervical myelopathy with significant neurologic compromise. The limbs may or may not be shortened, but severe dwarfism is not seen. The thorax is bell-shaped in the anteroposterior projection.2 Morphologic and histochemical studies suggest an unknown disorder of metabolism of mucopolysaccharide in the chondrocytes.4,5

Diagnosis
Antenatal diagnosis of spondyloepiphyseal dysplasia congenita has not been reported. Even at birth, a diagnosis may be difficult because the radiographic changes can be subtle. Therefore, the condition seems very difficult to diagnose antenatally with ultrasound but should probably be suspected when mild shortening of the limbs, flattened vertebral bodies, and bell-shaped thorax are seen in a patient at risk.

Prognosis
The disease is often compatible with life. Adults are usually less than 140 cm tall. Secondary arthritis develops in weightbearing joints. Ophthalmologic problems occur in 50 percent of patients,4 and retinal detachment and myopia can seriously impair vision.2 The progressive spinal deformities lead to kyphoscoliosis and eventually to cardiorespiratory compromise.

Obstetrical Management
It is unclear if the diagnosis can be made in the second trimester. If the diagnosis is made after viability, standard obstetrical management should not be altered.

REFERENCES
Kniest Syndrome

Synonyms
Metatropic dwarfism type II,10 and pseudometatropic dwarfism.11

Definition
Kniest syndrome is a skeletal dysplasia characterized by involvement of the spine (platyspondyly and coronal cleft) and the tubular bones (shortened and metaphyseal flaring), with a broad and short thorax. The entity has been confused with metatropic dysplasia because both entities share dumbbell-shaped, short, tubular bones and platyspondyly.

Etiology
The original cases reported by Kniest were sporadic,7 but an autosomal dominant inheritance has been suggested by other authors.5,8

Pathology
The disorder affects tubular bones and the spine. Long bones are short and demonstrate metaphyseal enlargement. The thorax is broad and short. Platyspondyly and vertical clefting of the vertebral bodies are present. With time, the spinal involvement may lead to scoliosis. A deep posterior fossa of the skull can also be present. Facial features include a flat midface, flat nasal bridge, wide-set and prominent eyes, and cleft palate.1,4,7,13

Associated Anomalies
Inguinal hernia, deafness, myopia, and retinal detachment.

Diagnosis
Prenatal diagnosis of Kniest syndrome has not been reported. The disease should be considered as part of the differential diagnosis of skeletal dysplasias associated with metaphyseal flaring (metatrophic dysplasia, fibrochondrogenesis, Weissenbacher-Zweymuller syndrome). In metatrophic dysplasia, the thorax is long and narrow and is not associated with the facial features of Kniest syndrome. Weissenbacher-Zweymuller syndrome consists of micromelia with dumbbell configuration of long bones, micrognathia, and coronal clefting of the vertebrae rather than platyspondyly. Another condition that is virtually identical to Kniest dysplasia is dyssegmental dysplasia. This disorder is inherited with an autosomal recessive pattern and has similar radiologic and histologic findings as Kniest dysplasia.1,4,9,12 Some authors have suggested that Kniest syndrome and dyssegmental dysplasia represent different manifestations of the same disorder.2

Prognosis
This disorder is compatible with life. However, progressive disability develops mainly because of kyphoscoliosis. Deafness and ophthalmologic complications are major incapacitating complications.

Obstetrical Management
It is not clear if this diagnosis can be made before viability. After viability, a diagnosis would not alter standard obstetrical management.

REFERENCES
Dyssegmental Dysplasia

Synonyms
Rolland-Langer-Dinno syndrome,¹,⁶,⁸ Rolland-Des-quois syndrome,⁸ and dyssegmental dwarfism.

Definition
Dyssegmental dysplasia is a lethal short limb dysplasia characterized by micromelia, marked disorganization of the vertebral bodies and, frequently, an occipital cephalocele.

Incidence
The disorder was first recognized as a distinct entity in 1977, when four cases (one new and three from the literature) were discussed.⁴ Since then, occasional cases have been reported.²,⁵

Etiology
Autosomal recessive.

Pathology
Dyssegmental dysplasia is characterized by severe micromelia with bowing and metaphyseal flaring of long bones, narrow thorax, vertebral segmentation defects, and variable limited mobility at the elbow, wrist, knee, and ankle joints. The hallmark of the condition is the disorganization of the vertebral bodies, with varying vertebral body size and vertical clefts. The frequent encephalocele is probably the result of defective segmentation at the level of the occiput.

Associated Anomalies
Inguinal hernia, hydronephrosis, hydrocephalus, patent ductus arteriosus, and cleft palate.⁴

Diagnosis
Prenatal identification of dyssegmental dysplasia has been reported once in a patient at risk.³ The disorder should be suspected when micromelia with metaphyseal flaring is associated with a cephalocele and there is an abnormal spine. The differential diagnosis includes other causes of micromelia and metaphyseal flaring, such as Weissenbacher-Zweymuller syndrome and fibrochondrogenesis.³ Some authors have suggested that dyssegmental dysplasia is a variety of the Kniest syndrome.³ Other conditions associated with vertebral disorganization are Jarcho-Levin syndrome (p. 382) and mesomelic dysplasia (p. 361).

Prognosis
This is a uniformly lethal disorder.

Obstetrical Management
A certain diagnosis of dyssegmental dysplasia can be made if there has been a previously affected child. The option of pregnancy termination should be offered to the parents before viability. As dyssegmental dysplasia is considered a lethal disorder, the option of pregnancy termination after viability could be offered. Only a few cases of this disorder have been reported in the literature, however.

REFERENCES
Larsen Syndrome

**Definition**
Larsen syndrome is a skeletal dysplasia characterized by a flat face, multiple joint laxities, and a supernumerary ossification center of the calcaneous.

**Etiology**
Although the original report included six sporadic cases, subsequent communications suggest both autosomal recessive and dominant patterns of inheritance. The severe type (associated with cardiac and vertebral abnormalities) seems to be inherited with an autosomal recessive pattern, whereas the mild form is probably an autosomal dominant disease.1

**Pathology**
Infants have a flat face, with a depressed nasal bridge, and joint laxity with multiple dislocations. Hypertelorism and clubfoot are frequently present. Cleft palate has been reported. A supernumerary ossification center in the calcaneous is pathognomonic of the disease, but it does not appear until the end of the first year of life. Scoliosis may develop with time. Tubular bones are not shortened.3,5

**Diagnosis**
A prenatal diagnosis has not been reported. The diagnosis could be suspected by the combination of hypertelorism and joint dislocation in patients with a positive family history. Since the syndrome is characterized by joint laxity and these deformations are present at birth, Larsen syndrome is potentially identifiable in patients at risk.

**Prognosis**
The autosomal dominant type is relatively benign. The recessive type is potentially lethal. Prognosis is generally related to the presence of cardiac lesions and spinal cord compression. An insufficient number of cases have been reported to permit adequate counseling of parents about the long-term prognosis of the disease.

**Obstetrical Management**
It is unclear if a prenatal diagnosis could be made before viability. In this case, the option of pregnancy termination should be offered to the parents. After viability, a diagnosis does not demand a change in standard obstetrical management.

**REFERENCES**

Otopalatodigital Syndrome Type II

**Definition**
This is a syndrome characterized by the combination of cleft palate, hearing loss, and skeletal abnormalities, including polydactyly, syndactyly, and bowed long bones.

**Incidence**
At least eight cases have been reported in the literature.2,3

**Etiology**
This disease seems to be transmitted as an X-linked recessive trait, but an autosomal dominant pattern with variable expressivity has not been ruled out.4

**Pathology**
This syndrome has been recognized at birth in three infants. The most prominent features include cleft palate, microstomia, micrognathia, flattened bridge of the nose, hypertelorism, flexed overlapping fingers, finger syndactyly and polydactyly, toe syndactyly, and short thumbs and short big toes. The bones of forearms and legs are curved, and the fibula is frequently either absent or hypoplastic. The ribs are short and wavy. Some of the findings may change with growth (e.g., the curved long bones may disappear).
Diagnosis
A prenatal diagnosis of this condition has not been reported. The disorder should be suspected in the presence of micrognathia, polydactyly, syndactyly, clinodactyly, and curved long bones. The differential diagnosis should include campomelic syndrome, which may affect both males and females and has hypoplastic or absent scapulae, nonmineralized thoracic pedicles, and vertically narrow ilial bones.

Prognosis
Six of the eight affected infants died shortly after birth. Of the survivors, one is mentally retarded, and the other developed aseptic meningitis, multiple respiratory tract infections, and profound hearing loss but is reported to have normal psychomotor development and intelligence for his age.

Obstetrical Management
The option of pregnancy termination should be offered if diagnosis is made before viability in a family at risk. After viability, no change in standard obstetrical management seems warranted.

REFERENCES

Cleidocranial Dysplasia

Synonyms
Cleidocranial dysostosis, mutational dysostosis.

Definition
This disorder is characterized mainly by absence or hypoplasia of the clavicles and by skull abnormalities.

Etiology
The disease is inherited as an autosomal dominant trait, although some authors have suggested an autosomal recessive transmission.

Pathology
Cleidocranial dysplasia is characterized by varying degrees of clavicular hypoplasia and skull abnormalities. Absence of the clavicle occurs in only 10 percent of affected infants. The thorax may be narrow, which could lead to respiratory distress. Other thoracic findings include supernumerary ribs and incompletely ossified sternum. The pubic bones are characteristically not ossified. Iliac bones are generally hypoplastic, and long bones are of normal length.
SKELETAL DYSPLASIAS

The skull shows wide sutures and multiple wormian bones (small and irregular bones in the course of the cranial sutures). The foramen magnum is enlarged, and paranasal sinuses are absent. The anterior fontanel remains open. Scoliosis is a rare but serious complication.

Diagnosis

Although a prenatal diagnosis of cleidocranial dysplasia has not been reported, its identification seems feasible, since the clavicles are easily imaged with ultrasound (see Fig. 10-1). The diagnosis does not depend on absence of the clavicles. In fact, in most instances, clavicles are hypoplastic. Figure 10-17 displays the growth of the clavicle during gestation. Table 10-11 is a nomogram for the assessment of clavicular size. Hypoplastic or absent clavicles are not pathognomonic of cleidocranial dysplasia, and other entities with such findings are listed in Table 10-12.

Prognosis

This condition does not seriously affect the individual and frequently goes unrecognized. Problems associated with the disease include occasional luxation of the shoulder and hip and scoliosis.

Obstetrical Management

Standard obstetrical management is not altered by diagnosis of this condition.

REFERENCES


Dysostoses

Dysostoses refer to malformations or absence of individual bones singly or in combination. Any bone can be affected. Table 10-2 shows the classification of dysostosis of the International Nomenclature Group of Skeletal Dysplasias. There are three main groups, depending on the most affected part of the skeleton:
dysostosis with craniofacial involvement, dysostosis with predominant axial involvement, and dysostosis with predominant involvement of the extremities.

**Diagnosis**

Some of the listed conditions have been diagnosed in utero by fetoscopy or ultrasound or are amenable to prenatal detection. A definitive diagnosis is possible in cases at risk. The most frequent conditions are discussed in subsequent sections.

**REFERENCES**

Craniosynostoses

Synonym
Craniostenoses.

Definition
Craniosynostosis is an abnormal shape or dimension of the skull caused by premature closure of one or more skull sutures. It includes scaphocephaly, brachycephaly, oxycephaly, plagiocephaly, trigonocephaly, turricephaly, and cloverleaf skull.

Incidence
Since craniosynostoses are not lethal or always diagnosed at birth, a birth prevalence cannot be provided. Neurosurgical files provide an incidence of 1 in 4000 births.

Etiology
Craniosynostoses can be due to an idiopathic developmental error (primary craniosynostoses) or part of other syndromes that involve other abnormalities, such as chromosomal, metabolic, inherited mendelian disorders, teratogenic (e.g., aminopterin), or infectious. Table 10-13 provides a list of conditions associated with craniosynostoses. For further details' references 1 and 2 are excellent texts on the subject.

Pathogenesis and Pathology
The names and locations of skull sutures are shown in Figure 10-73. All sutures close anatomically after the fourth decade of life, with the exception of the frontal or metopic suture that closes during infancy in 90 percent of people (in the remaining 10 percent, it never closes). Premature closure of skull sutures results in alteration of the shape of the skull, but, more importantly, craniosynostosis prohibits normal growth of the brain and leads to intracranial hypertension, brain dysfunction, and visual impairment. The brain increases in weight by 85 percent during the first 6 months after birth and by 135 percent during the first year. Visual symptoms are attributed to traction and distortion of the optic nerve. During intrauterine life, the skull bones are separated by fibrous tissue that remains from the original membranous constitution of the calvarium. The mechanisms responsible for the physiologic closure of the skull sutures are not known. Several hypotheses have been proposed to explain the occurrence of craniosynostosis: (1) hypoplasia of the fibrous tissue normally interposed between the bones, (2) primary decrease in intracranial pressure, (3) anomalous ossification process, and (4) primary anomaly in the base of the skull interfering with venous outflow or the architectural growth of the vault.

When craniosynostosis occurs, growth of adjacent bones is inhibited in a direction perpendicular to the closed suture. This results in a compensatory growth of the vault in the direction of the open sutures and fontanelles. The nomenclature of craniosynostoses refers to the shape of the head. Craniosynostoses are commonly classified according to the involved suture (Fig. 10-74).

Diagnosis
Physiologic molding of the fetal head occurs frequently due to changes in intrauterine pressure, position, intrauterine tumors, and oligohydramnios. The two most frequent types are dolicocephaly and brachycephaly. Diagnosis of these conditions is made by the cephalic index, which describes the relationship between the biparietal and the occipitofrontal diameters. The normal range is 75 to 85 percent when an outer-to-inner biparietal diameter and a midecho-to-midecho occipitofrontal diameter are used. The cranial sutures can be imaged with ultrasound (Fig. 10-75). Dolicocephaly is diagnosed when the cephalic index is below 75 percent, and brachycephaly is diagnosed when the index is above 85 percent. In either case, biparietal diameter should not be used for

Figure 10-73. Schematic arrangement of the bones, sutures, and fontanelles. The fontanelles are: 1, sphenoidal, 2, mastoid, 3, occipital, 4, frontal. (Reproduced with permission from David et aL: The Craniosynostoses. Causes, Natural History, and Management. Berlin, Springer-Verlag, 1982.)
gestational age prediction. Since the head perimeter does not change with molding, this parameter can be used to assess gestational age when an abnormal cephalic index is present.

A specific diagnosis of craniosynostosis in utero is extremely difficult (except for cloverleaf skull and trigonocephaly). There is no information about the natural history of craniostenoses in utero. Antenatal diagnosis of these conditions has barely been discussed in the literature. Some practical diagnostic guidelines follow.

Premature closure of the sagittal suture (scaphocephaly) is characterized by a disproportionately large occipitofrontal and short biparietal diameter. Premature closure of the coronal suture (brachycephaly) is characterized by a cephalic index above 85 percent. Still, the differential diagnosis with molding appears difficult. A sagittal scan of the fetal face can be helpful by demonstrating a very prominent forehead. Hypertelorism is sometimes associated with this type of craniosynostosis.

Premature closure of the metopic or frontal suture (trigonocephaly) is characterized by a triangular or egg-shaped head (oeecephaly) (Figs. 10-76, 10-77).
Since the upper portion of the orbits are formed by the frontal bone, premature closure of the metopic suture frequently leads to hypotelorism.

Oxycephaly is a craniosynostosis that results from fusion of multiple sutures and leads to a high, conical, pointed head (Fig. 10-78). Different head shapes can result depending on the involved sutures. If the main involved suture is the sagittal, a form of scaphocephaly will result. A variety of turricephaly occurs if the coronal suture is primarily affected. Cloverleaf skull is a variety of oxycephaly.

Cloverleaf skull syndrome, or Kleeblattschadel, is characterized by the association of premature closure of the coronal, lambdoid, and sagittal sutures and hydrocephalus (usually a communicating type or aqueductal stenosis). As a consequence of this craniosynostosis, grotesque bulging of the temporal, occipital, and frontal bones occurs (Figs. 10-42, 10-43, 10-46, 10-47). This diagnosis can be made easily with ultrasound.

Turricephaly is an abnormally broad head with a high forehead and is due to premature closure of the coronal suture. Plagiocephaly is due to asymmetrical synostosis of a suture-the coronal suture (frontal plagiocephaly), the lambdoid suture (occipital plagiocephaly)-or more than one suture (hemicranial plagiocephaly).

Associated Anomalies
Craniosynostoses are frequently associated with other anomalies (Table 10-13). Therefore, the sonographer must perform a thorough fetal examination.

Prognosis
The prognosis is dependent primarily on the presence of associated anomalies. Secondarily, there are some differences in neurologic and intellectual performance according to the type of craniosynostosis.

Scaphocephaly is not usually associated with
symptoms of intracranial pressure, and its relationship with mental retardation is unclear. Most infants seem to do well, but ocular problems have been reported. Prognosis is, however, different for those patients with associated Apert, Cruzon, and Carpenter syndromes.

Brachycephaly is frequently associated with symptoms of elevated intracranial pressure and ophthalmologic problems, including exophthalmos, strabismus, and optic nerve atrophy.

Trigonocephaly is associated with a higher incidence of mental retardation than the other types. In addition, other congenital anomalies are frequently associated with this syndrome (holoprosencephaly, cleft palate, microphthalmos).

Surgical procedures to accomplish decompression of the intracranial content and cosmetic changes are available. Their value in altering the course of neurologic impairment in these syndromes seems promising.

**Obstetrical Management**

Detection of an abnormally shaped head is an indication for a careful search for associated anomalies. Amniocentesis to look for chromosomal anomalies is indicated. The diagnosis of craniosynostosis per se does not change obstetrical management. However, the etiology of the disorder may alter obstetrical management (e.g., a chromosomal disorder).

**REFERENCES**


**LIMB REDUCTION ABNORMALITIES**

The term "limb reduction abnormalities" refers to the absence of a limb or a segment of a limb. These defects are usually nongenetic in origin except for a few rare syndromes.

Terms frequently used to refer to limb reduction abnormalities include:

- Abelima: absence of a limb or limbs
- Hemimelia: absence of a longitudinal segment of a limb (e.g., radial aplasia, radial hypoplasia)
- Phocomelia: hypoplasia of the limbs, with hands and feet attached to the shoulder and hips
- Acheira: absence of a hand or hands
- Apodia: absence of a foot or feet
- Acheiropodia: absence of hands and feet

The prenatal diagnosis of isolated limb reduction abnormalities is technically simple. It is our opinion that identification of all segments of both extremities should be an integral part of a routine sonographic examination. This approach must be taken because limb reduction abnormalities are by and large a nongenetic group of disorders.

We will discuss only three entities with important genetic and diagnostic value that we have encountered in our prenatal diagnostic practice: Roberts syndrome, Holt-Oram syndrome, and thrombocytopenia with absent radius.
**Roberts Syndrome**

**Synonyms**
Tetraphocomelia with cleft lip and palate, AppeltGerken syndrome, hypomelia-hypotrichosis-facial hemangioma syndrome.

**Definition**
This disorder is characterized by the association of tetraphocomelia with midfacial clefting or hypoplastic nasal alae.2,3

**Etiology**
Autosomal recessive.

**Pathology**
The most important finding is the reduction deformity of the four limbs. Reduction is more prominent in the upper than lower extremities and may consist of absence or severe micromelia. Toes and fingers may be absent or reduced in number. Other limb abnormalities include bowing of long bones, flexion contractures of knees and elbows, and clubfoot deformities.1,4 Severe growth retardation is a prevalent feature.

Facial abnormalities are also prominent and include hypertelorism and cleft lip or palate, which may be bilateral or in the midline. Polyhydramnios has been described. Other findings are hypoplasia of the alae nasi, ocular proptosis, and microcephaly. The phallus or clitoris can be prominent.3

**Associated Anomalies**
Hydrocephaly, encephalocoele, spina bifida, and polycystic and horseshoe kidneys.

**Diagnosis**
The diagnosis can be made in patients at risk by demonstrating the severe limb reduction abnormalities and the described facial features. Specific diagnosis of a sporadic case would be extremely difficult.

**Prognosis**
The condition is associated with a high perinatal mortality. The syndrome has been reviewed by Freeman et al., who found that 15 of 19 patients were either stillborn or died within the first month of life. Survivors have a short life span, and mental retardation is common.

**Obstetrical Management**
The option of pregnancy termination should be offered before viability.

**REFERENCES**

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**Holt-Oram Syndrome**

**Synonyms**
Atriodigital dysplasia, cardiac limb syndrome, upper limb cardiovascular syndrome, cardiomeic syndrome, and heart upper limb syndrome.

**Definition**
The Holt-Oram syndrome is characterized by the association of aplasia or hypoplasia of the radial structures and congenital heart disease, mainly atrial septal defect secundum type.1,3

**Etiology**
The disorder is inherited with an autosomal dominant pattern with variable degree of penetrance.2

**Pathology**
The skeletal abnormalities encompass a wide spectrum of defects. Basically, they affect the radial structures, which include the thumb, the first metacarpal, the carpal bones, and the radius. The defects range...
from absence, hypoplasia, or triphalangism of the thumb to upper limb hemimelia.

The most common cardiac abnormality is an atrial septal defect secundum type. Other reported cardiac anomalies include ventricular septal defect, tetralogy of Fallot, and coarctation of the aorta. In some family members, only the cardiac or skeletal abnormalities are present.\(^3\)

**Diagnosis**
The diagnosis can be made in a patient at risk by demonstrating the skeletal anomaly. It is doubtful that a small ostium secundum defect can be recognized by ultrasound. A specific diagnosis of Holt-Oram syndrome in fresh mutations seems extremely difficult.

**Prognosis**
The prognosis depends on the severity of the cardiac congenital abnormality. Functional impairment depends on the extent of the skeletal defect.

**Obstetrical Management**
The option of pregnancy termination should be offered before viability. After viability standard obstetrical management is not altered.

**REFERENCES**

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**Thrombocytopenia with Absent Radius**

**Synonyms**
TAR syndrome, amegakaryocytic thrombocytopenia and bilateral absence of the radii, and phocomelia with congenital thrombocytopenia.

**Definition**
This syndrome is characterized by thrombocytopenia (platelet count of less than 100,000/mm\(^3\)) and bilateral absence of the radius.

**Etiology**
The disease is inherited with an autosomal recessive pattern.

**Pathology**
The radius is absent bilaterally in all cases. The ulna and humerus may be unilaterally or bilaterally absent or hypoplastic.Clubfoot and hand deformations have been described.\(^4\)

Thrombocytopenia is present in all patients. It is due to a decreased production of platelets by bone marrow. The platelet count fluctuates and can be sometimes within normal range. Stress associated with surgery or infections can induce thrombocytopenia.

**Associated Anomalies**
Cardiac anomalies are found in 33 percent of patients.\(^2\) The most common defects are tetralogy of Fallot and atrial septal defects. Other anomalies include renal malformations, spina bifida, brachycephaly, micrognathia, and syndactyly.\(^1,5\)

**Diagnosis**
The diagnosis can be made in a patient at risk in whom radial aplasia is detected with ultrasound.\(^1,3\) Thrombocytopenia may be absent at presentation.

**Prognosis**
The disease is associated with a high fatality rate within the first months of life. Ten of 40 patients reviewed by Hall et al. died in that period of time.\(^2\) After 1 year, prognosis improves considerably. Mental retardation is present in 8 percent of the patients, and it is usually mild.\(^5\) Intracranial bleeding associated with thrombocytopenia is the proposed mechanism. Long-term disability is related to the skeletal deformity. Some patients develop nerve compression and arthritis because of the hand deformations.

**Obstetrical Management**
Diagnosis before viability would make elective termination of pregnancy possible. After viability, the most important consideration is to avoid the intracranial hemorrhage that could be associated with a traumatic delivery. Therefore, an elective cesarean section can be performed or, alternatively, a percutaneous umbilical cord puncture may be used to assess
the fetal platelet count. In the presence of a normal value, labor may be allowed.

REFERENCES

Polydactyly

Definition
Presence of extra digits.

Epidemiology
The incidence varies in different ethnic groups.

Etiology
Polydactyly is a feature of many genetic syndromes. Table 10-14 shows the most common associations. Isolated postaxial polydactyly, polydactyly of the index finger, and polydactyly of the triphalangeal thumb are inherited as autosomal dominant traits with variable penetrance.1

Pathology
Polydactyly can be classified as preaxial and postaxial, depending on the presence of the extra digit on the ulnar side (postaxial) or on the radial side (preaxial) of the hand. The same concept applies to the foot. The former is more common than the latter. In some cases, the extra digit is a simple cutaneous appendage, whereas in others, it contains a full bony complement.2

Diagnosis
Diagnosis of polydactyly can be made with ultrasound provided the extra digit contains bony structures (Fig. 10-79). The ideal means for imaging the hands is in a coronal view where all the fingers can be counted. The same approach can be used with the feet.

Prognosis
The prognosis is dependent on the presence or absence of associated congenital anomalies. A careful search for other defects is necessary both prenatally and postnatally.

Obstetrical Management
Management is dependent on the associated disorder.

REFERENCES

![TABLE 10-14. SYNDROMES FEATURING POLYDACTYLY](image)

![Figure 10-79. Scan of the hand of a fetus with short rib-polydactyly syndrome. Six digits are clearly identified.](image)
Congenital Contractures: Clubfoot

**Synonyms**
Equinovarus and talipes.

**Definition**
This defect is characterized by medial deviation and inversion of the sole of the foot.

**Epidemiology**
The overall incidence is reported to be 1.2 in 1000. The male to female ratio is 2:1. When the mild forms of postural clubfoot are considered, the ratio is reversed.

**Etiology**
Clubfoot can be caused by genetic or environmental causes. There may be a genetic predisposition to laxity of the joint ligaments. Indeed, a tendency toward dislocation of hips and shoulders has been documented in first degree relatives. Other congenital diseases, such as skeletal dysplasias (e.g., diast-
trophic dysplasia), limb deficiencies, or neurologic disorders (e.g., spina bifida), are associated with this condition.

Environmental causes are those associated with intrauterine constraint (oligohydramnios, amniotic band syndrome, and uterine tumors).

Clubfoot is a feature of many genetic syndromes, which are listed in Table 10-15.

**Pathology**
The basic pathology is inversion of the foot and flexion of the sole. The navicular bone comes closer to the medial portion of the calcaneous.

**Diagnosis**
Diagnosis is based on knowledge of the relative orientation of the leg bones and the heel of the foot. When a normal lower extremity is scanned in the lateral axis, the two bones of the leg and the heel are imaged (Figs. 10-80, 10-81). In clubfoot, a similar view will demonstrate the leg bones and both the heel and forefoot (Figs. 10-82 through 10-85).

Another approach to the diagnosis is to use the anteroposterior view of the leg, which allows visualization of both the leg and the entire foot. In a fetus with clubfoot deformity, only the heel will be seen. The diagnosis of clubfoot in the presence of oligohy
Recognition of a clubfoot deformity should prompt a careful search for associated anomalies, particularly a neural tube defect.

**Prognosis**
The prognosis is dependent on the etiology of the equinovarus. Cases secondary to intrauterine constraint have a better prognosis than those associated with true malformations.5

**Obstetrical Management**
This defect does not alter obstetrical management at any time in gestation.

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**Rocker-Bottom Foot**

**Definition**
This defect is characterized by a prominent heel with a convex sole.

**Etiology**
This anomaly is associated with trisomy 18, 18q-syndrome, and cerebrooculofacioskeletal syndrome.1

**Epidemiology**
Unknown.

**Pathology**
The defect is due to a prominent calcaneus. The sole adopts a rounded or convex shape.

**Diagnosis**
Sonographic imaging of the foot and leg in the anteroposterior axis may allow the diagnosis. Figure 10-86 shows an image of a rocker-bottom foot.2

Identification of this deformity should prompt a careful search for associated congenital anomalies. An amniocentesis to exclude chromosomal abnormalities should be considered.

**Prognosis**
Prognosis depends on the presence and severity of associated anomalies.

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**REFERENCES**
Arthrogryposis Multiplex Congenita

Synonyms
Classic arthrogryposis, myodystrophia fetalis deiformans, multiple congenital rigidities, congenital arthromyodysplasia, myophagism congenital and amyoplasia congenita.

Definition
The term "arthrogryposis multiplex congenita" (AMC) refers to multiple joint contractures present at birth. AMC is not a specific disorder but is the consequence of neurologic, muscular, connective tissue, and skeletal abnormalities or intrauterine crowding, which may lead to limitation of fetal joint mobility and the development of contractures (Fig. 10-87).

Incidence
The incidence of AMC varies widely because different definitions and heterogeneous conditions have been grouped under the term AMC, and the accuracy of these figures is open to question.

Etiology
Normal intrauterine movement is essential for the development of fetal joints, which occurs during the 3d month of gestation. Any process that impairs fetal motion around this critical time leads to congenital contractures. Administration of curare to chick embryos or fixation of the ankle joint has resulted in the development of contractures. In the human, prolonged administration of curare to a mother with tetanus has been reported to lead to AMC. The role of timing and duration of immobilization in the pathogenesis of AMC has not been clearly established. Table 10-16 illustrates the different conditions that have been reported to cause limitation of movement in the fetus and AMC.

Cases of AMC are sporadic. However, some cases suggesting an autosomal dominant and recessive pattern of inheritance have been reported. The multiple etiology of AMC is responsible for this heterogeneity.

Pathology
In most cases of AMC, all four limbs are involved. However, patients with bimelic or asymmetrical involvement have been reported. Knees and elbows are the joints most frequently involved. The typical deformities are flexure contractures of hips, knees, and elbows, adduction of the scapulohumeral joint, pronated clubhands and equinovarus. Among the causes of AMC, neurologic disorders are the most common (e.g., loss of anterior horn cells and amyoplasia congenita). Pathologic examination may
allow differentiation between neurogenic and myopathic forms of AMC.

**Associated Anomalies**

Table 10-17 shows some of the anomalies associated with AMC. Ten percent of patients with AMC have associated anomalies of the CNS, including hydrocephaly, porencephaly, lissencephaly, cortical atrophy, micropolygyria, cerebellar vermal agenesis, and agenesis of the corpus callosum.

**Diagnosis**

The prenatal diagnosis of AMC with ultrasound has been reported twice. The first fetus was examined with fetoscopy at 16 weeks of gestation because a previous infant was affected with the condition. During endoscopic visualization, fetal motion was seen, and the extremities looked normal. Subsequently, real-time examinations at 18 weeks also showed normal motion of the extremities. However, serial scans at 23, 28, and 35 weeks failed to show any fetal movement. The infant died shortly after birth, and autopsy showed dropout of anterior horn cells. The muscles demonstrated findings consistent with neurogenic atrophy. This case suggests that the diagnosis of AMC due to a neurologic lesion may not be possible before 20 weeks. The other prenatal diagnosis was reported in a fetus examined because of preterm labor. At 30 weeks, the fetus showed significant limb shortening and flexion and crossing of lower extremities. The elbow joints and one hand were also flexed. No movement was seen during a 1-hour examination. Polyhydramnios has been reported in association with AMC.

Although real-time examination permits the detection of joint contracture (see the section on clubfoot) and the assessment of fetal motion, its sensitivity for early diagnosis of AMC remains to be established (Fig. 10-87).

The Pena-Shokeir syndrome can present with manifestations of AMC. This condition is inherited with an autosomal recessive pattern and is characterized by intruterine growth retardation, polyhydramnios, absent breathing movement, pulmonary hypoplasia, hypertelorism, low-set ears, depressed nasal bridge, micrognathia, camptodactyly, and clubfoot or rocker-bottom foot. We have diagnosed this condition in a fetus at risk who failed to show any breathing or body movement and had typical contracture deformities of the upper and lower extremities. The syndrome is usually lethal within a few days of birth. The cause of death is pulmonary hypoplasia, which is probably caused by lack of chest wall movement during intruterine life.

**Prognosis**

The prognosis for AMC is related to the specific etiology. In some severe cases, the disease is lethal, and death occurs shortly after birth. In other cases, musculoskeletal impairment is minimal, and intelligence is normal. Between these extremes, affected infants may have handicaps of different severity. Treatment should begin shortly after birth, and surgery may be required to correct incapacitating deformities.

**Obstetrical Management**

If a diagnosis is made before viability, the option of pregnancy termination should be offered to the parents. The optimal mode of delivery has not been established. Infants with AMC are at risk for severe birth trauma because of fixed joints. Cesarean section seems to be the best method of delivery.

**REFERENCES**

Jarcho-Levin Syndrome

Synonyms
Occipitofacial-cervicothoracic-abdominodigital dysplasia, spondylocostal dysplasia, costovertebral dysplasia, spondylothoracic dysostosis, spondylocostal dysostosis, and spondylothoracic dysplasia.

Definition
Jarcho-Levin syndrome is a congenital disorder of the skeleton inherited in an autosomal recessive pattern and characterized by disorganization of the spine (hemivertebrae, fused vertebrae) and a crablike appearance of the rib cage.

Etiology
Autosomal recessive.

Incidence
In a recent review of the literature, 35 cases were reported. Probands of Puerto Rican descent constitute a significant number of these cases.

Pathology
Spondylocostal dysplasia has been subdivided into two types. Type I is inherited with an autosomal recessive pattern, often occurs in families of Puerto Rican descent, is characterized by severe involvement of the spine, and generally causes respiratory failure and death in affected children before they reach 15 months of age. Type II is inherited as an autosomal dominant trait, is found most often in Caucasians, is characterized by milder involvement, and is associated with nearly normal longevity. Because it is not known if type II can be diagnosed in utero, this section is confined to the description of type I.

A recent classification of spondylocostal dysplasia was proposed by Ayme and Preus. Using cluster analysis of all informative cases in the literature, they suggested that spondylocostal dysplasia be subdivided into a severe form inherited with an autosomal recessive pattern and a mild form inherited with an autosomal recessive or dominant pattern.

Figure 10-88. Lateral x-ray of a fetus with Jarcho-Levin syndrome. Note the characteristic chest deformity with posterior fusion and anterior flaring of the ribs. Disorganization of the vertebral bodies is apparent.
and anterior flaring of the ribs. The rest of the skeleton is spared.

**Associated Anomalies**

The following anomalies have been reported: prominent occiput (37 percent), microcephaly (15 percent), triangular opening of the mouth (15 percent), cleft palate (10.5 percent), spina bifida occulta (31.5 percent), lordosis (26.3 percent), abdominal wall defect (26.3 percent), anal defects (10.5 percent), long arms (37 percent), syndactyly (15 percent), and camptodactyly (31.5 percent).1,9

**Figure 10-89.** Anteroposterior radiograph of the fetus displayed in the previous figure. It is a 24-week-old fetus with Jarcho-Levin syndrome. Note the dramatic spinal shortening, chest deformity, and unaffected long bones.

**Figure 10-90.** Coronal section of the spine of a fetus with Jarcho-Levin syndrome at 23 weeks. Note the shortening of the spine and flaring of the vertebral canal (arrows).

**Diagnosis**

The condition should be suspected when spinal disorganization is associated with an abnormal chest configuration. Spinal disorganization consists of fused vertebrae or hemivertebrae (Figs. 10-90, 10-91). A more precise diagnosis can be made in a family with previous affected probands.

The prenatal diagnosis of spondylocostal dysplasia type I has been made in families at risk by radiograph.8,9 We have recently made this diagnosis using ultrasonography in a 23-week-old fetus with no positive family history.

The differential diagnosis of spinal disorganization in a fetus includes spondylocostal dysplasia, dyssegmental dysplasia, spondyloepiphyseal dysplasia congenital, the VACTERL association, and the costovertebral segmentation defect with mesomelia (COVESDEM) association. Dyssegmental dysplasia is characterized by severe micromelia (extreme shortening of all segments of the extremities) and occipital cephalocele, and it lacks the crablike appearance of the chest. The VACTERL association is characterized by vertebral anomalies, anal atresia, tracheoesophageal fistula, cardiac anomalies (generally a ventricular septal defect), and radial limb dysplasia (including preaxial polydactyly, syndactyly, radial hypoplasia, and thumb hypoplasia). A single umbilical artery can also be observed. A diagnosis of this condition requires the presence of at least 3 of the 7 cardinal anomalies of the association. Spondyloepiphyseal dysplasia congenita is characterized by ovoid vertebral bodies and severe platyspondyly (flattening of vertebral bodies). Hemivertebrae are absent. The limbs may or may not be shortened, but severe dwarfism is not seen. The thorax is bell-shaped in the anteroposterior projection, but lacks the crablike mor-
Figure 10-91. Ultrasound images in a fetus with Jarcho-Levin syndrome. 
A. The left panel of the figure represents an oblique section through the fetal chest. Note the posterior fusion of the ribs (empty arrow). H, humerus. 
B. The right panel shows a transverse section through the fetal chest. Posterior fusion of the ribs is visible (empty arrow). S, spine.

Phylogeny seen in Jarcho-Levin syndrome. Another condition to be considered is the COVESDEM association.12 This condition includes mesomelic dysplasia (particularly of the upper extremities), costovertebral segmentation defects (hemivertebrae, vertebral fusion, and butterfly vertebrae), and facial abnormalities (hypertelorism, depressed nasal bridge, large bony upper lip, constantly open mouth, and peg teeth). Mesomelia is absent in Jarcho-Levin syndrome.

Prognosis

The severe form of spondylocostal dysplasia is considered a uniformly lethal condition. Death occurs from respiratory failure generally caused by recurrent pneumonia by 15 months of age.

Obstetrical Management

If a prenatal diagnosis of type I spondylocostal dysplasia is made before viability, the option of pregnancy termination should be offered to the parents. Cases identified after viability constitute a difficult ethical dilemma and we recommend that the issue be discussed with the parents. A nonaggressive management for cases with fetal distress may be considered, as the condition seems to be uniformly lethal.

REFERENCES