Fetal Musculoskeletal Malformations with a Poor Outcome: Ultrasonographic, Pathologic, and Radiographic Findings

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The early and accurate antenatal diagnosis of fetal musculoskeletal malfomations with a poor outcome has important implications for the management of a pregnancy. Careful ultrasonographic examination of a fetus helps detect such anomalies, and a number of characteristic features may suggest possible differential diagnoses. During the last five years, we have encountered 39 cases of such anomalies, and the typical prenatal ultrasonographic and pathologic findings of a number of those are described in this article.

Fetal musculoskeletal malformations take a number of pathologic forms, among which a variety of lethal dysplasias and several anomalies have a poor perinatal and postnatal outcome. Precise antenatal ultrasonographic diagnosis of bone dysplasia may be very difficult, but differentiation between a lethal and a nonlethal variety is very important in terms of antenatal care and the prediction of fetal outcome. Several anomalies leading to limb loss or contracture as the expression of other pathologic entities have a poor outcome, and their early detection is also very important for the management of a pregnancy. During the last five years, we have encountered 39 cases of fetal musculoskeletal malformations with a poor outcome (Table 1), and the typical prenatal ultrasonographic and pathologic findings of a number of these are described in this article.

Index terms:
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Table 1. Prenatally Diagnosed Musculoskeletal Anomalies with a Poor Outcome Encountered During Five-year Period

Lethal Musculoskeletal Dysplasia	
Thanatophoric dysplasia	6
Osteogenesis imperfecta	7
Achondrogenesis	1
Short-rib syndrome with or without polydactyly	5
Camptomelic dysplasia	1
Chondrodysplasia punctata	1
Other Anomalies with a Poor Outcome	
Amniotic band syndrome	8
Limb-body wall complex	5
Sirenomelia	1
Arthrogryposis multiplex congenita	4
Total	39

Lethal Dysplasias

Thanatophoric Dysplasias

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia, with an incidence of one per 10,000 births (1). The term 'thanatophoric' means 'death bearing' (2), and affected individuals usually die of pulmonary hypoplasia soon after birth. TD has been subdivided into two categories: type I is more common and is characterized by curved long bones (with a 'telephone receiver' appearance) and severe platyspondylia, usually without a cloverleaf skull, while in type II, long bones are relatively straight, platyspondylia is less severe, and a cloverleaf skull is usually present (3).

The sonographic diagnosis of TD during the second trimester is a straightforward matter. Severe rhizomelic micromelia with bowing is observed, the thorax is narrow and bell shaped, and the ribs are shortened. The normal abdomen is protuberant compared with the small thorax (Fig. 1), and macrocrania, frontal bossing and a depressed nasal bridge are usually present. The skin appears thick because of extreme redundancy, and polyhydramnios occurs in approximately 50% of cases. Holoprosencephaly, agen-

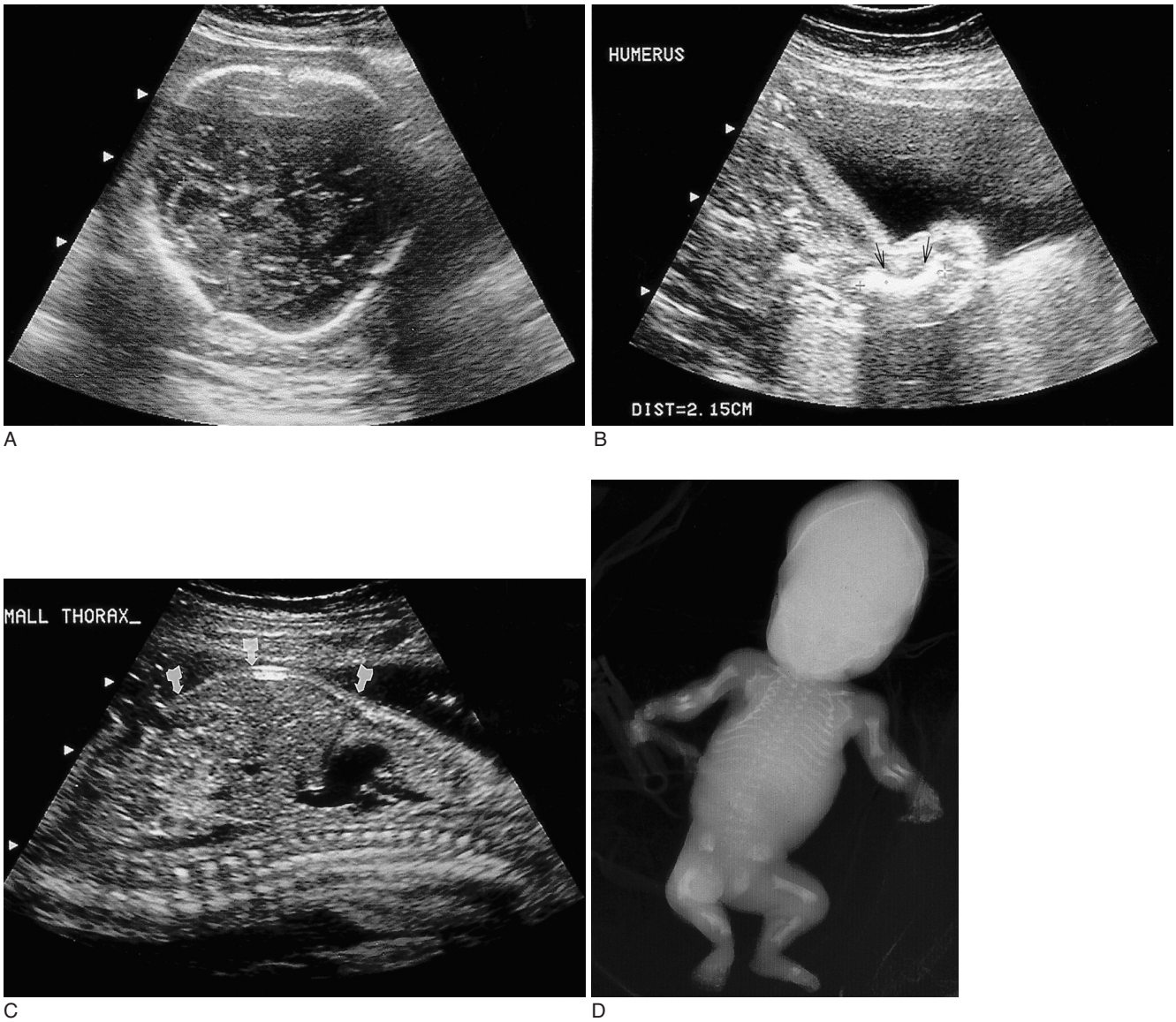

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Fig. 1. Thanatophoric dysplasia in a 21-week fetus.
A. Ultrasonogram demonstrates a cloverleaf-like skull.
B. Rhizomelic micromelia with bowing of the humerus is apparent (arrows). The skin appears thick because of extreme redundancy.
C. The normal abdomen (arrows) is protuberant compared with the small thorax.
D. Postmortem radiograph shows generalized severe micromelia and a constricted thorax. Bowing is more apparent in the lower extremities.

esis of the corpus callosum, and ventriculomegaly may be associated with cloverleaf deformity, and there may be renal and cardiovascular anomalies (4).

Osteogenesis Imperfecta Type II

Osteogenesis imperfecta (OI) is the name given to a variety of heterogeneous connective tissue conditions in which defective type-I procollagen formation occurs. The main characteristic is fragile and brittle bones. On the basis of clinical presentation and typical X-ray findings, OI can be divided into four types, and type II, which is most common and is usually lethal due to pulmonary hypoplasia, into three subtypes (5).

Type II is characterized by severe rhizomelia, bone irregularity and bowing due to multiple fractures, a small thorax, and a varying degree of hypomineralization. The prenatal ultrasonographic findings of this type are a compressible thin calvaria (which at sonography is transparent), severe shortening and bowing of the long bones, with multiple fractures, and a narrow thorax associated with multiple rib fractures (6) (Fig. 2).

Achondrogenesis

Achondrogenesis, which arises due to the inadequate for-

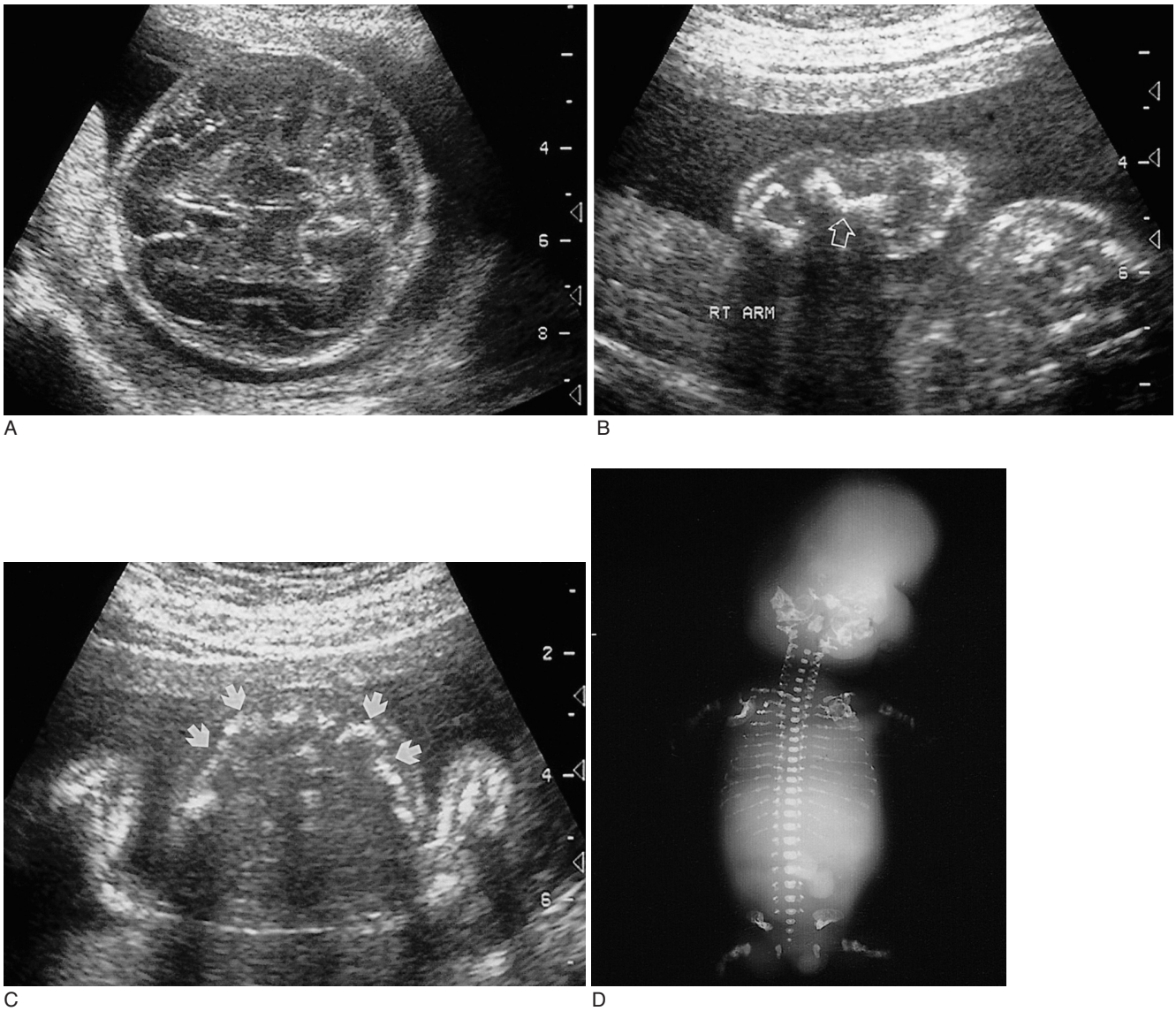

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Fig. 2. Osteogenesis imperfecta type II in a 22-week fetus.
A. Axial image of the fetal head shows decreased echogenicity of the calvaria, through which transmission of the ultrasound beam is abnormally increased.
B. Ultrasonogram depicts severe micromelia and deformity secondary to fractures (open arrow).
C. Axial image shows multiple rib fractures (arrows), with collapse of the thoracic cage.
D. Postmortem radiograph show decreased mineralization and severe micromelia, with innumerable fractures.

mation of cartilaginous matrix, is a lethal form of chondrodystrophy. Its presence may be associated with defective chondroitin sulfate or type-II collagen synthesis. Two types exist, each with distinct histological and radiological features (7, 8). Type I, the Fraccaro-Houston-Harris type, accounting for 20% of cases, is a disorder of both endochondral and membranous ossification characterized by a partial or complete lack of ossification of the calvaria and spine as well as extremely short bones and, frequently, multiple rib fractures. Type II, the Langer-Saldino type, which accounts for 80% of cases, is a disorder of endochondral ossification only. It is less severe than type I, and involves a varying degree of calcification of the calvaria and spine. Fractured ribs are not present, and skull ossification is relatively normal (9).

The prenatal ultrasonographic features include severe micromelia with bowing, decreased mineralization, and a shortened trunk and small thorax (8, 9). Vertebral body ossification is lacking in both types (Fig. 3), and this may be more pronounced in the distal spine. The head is disproportionately enlarged and severe fetal hydrops, edema, and polyhydroamnios are present. In type I, the skull is

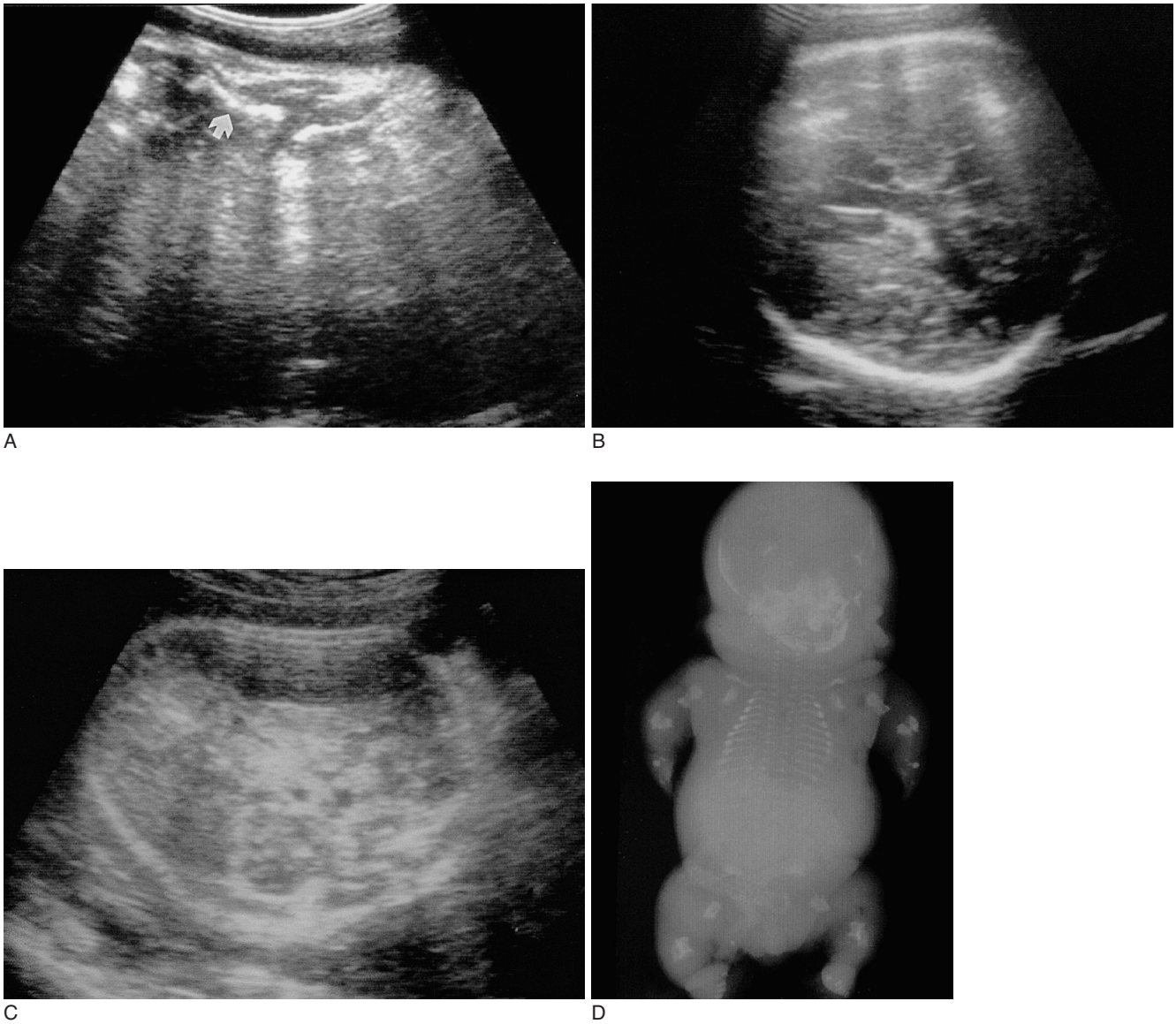

Fig. 3. Achondrogenesis in a 35-week fetus.
A. Ultrasonogram shows profound limb shortening (arrow).
B, C. Axial images of the fetal head demonstrate decreased calvarial ossification, with increased ultrasonic through-transmission. The fetal head is compressed by the transducer.
D. Postmortem radiograph shows extremely short limbs, a large head, and the absence of ossification in the ischia, pubis, vertebral body, and calvarium. The head is disproportionately enlarged and the thorax is small.

poorly ossified, allowing visualization of the intracranial contents, and is compressible by the transducer (Fig. 3). The ribs are thin in type I, but thicker in type II.

Short-Rib Syndrome with or without Polydactyly

The nosology of the short-rib syndrome is very confusing. According to the International Classification of Osteochondrodysplasias, the heading "Short-rib-dysplasia group (with/without polydactyly)" includes four short-rib polydactyly (SRP) syndromes, asphyxiating thoracic dysplasia (ATD), and Ellis-van Creveld syndrome (27). All are characterized by a narrow thorax and short ribs, and except in SRP type IV and ATD, polydactyly is a common finding. Because of the frequent overlap of these features, differential diagnosis is difficult.

In SRP type I (Saldino-Noonan), postaxial polydactyly is frequent. The limb bones are markedly shortened, and have pointed metaphyseal ends. Vertebral bodies are hypoplastic, and the ribs are extremely shortened. Anomalies of the gastrointestinal, genitourinary, and cardiovascular systems are common (11).

The characteristic features of SRP type II (Majewski) are extremely short ribs and limbs, a normal pelvis and vertebrae, disproportionately short tibiae, and polysyndactyly. Extraskeletal anomalies include hydrops, a median cleft lip, ambiguous genitalia, and hypoplasia of the epiglottis, larynx, and lung (11).

SRP type III (Verma-Naumoff) was originally separated from SRP type I. While in type I the metaphyses are pointed and narrowed, in type III they are widened and have

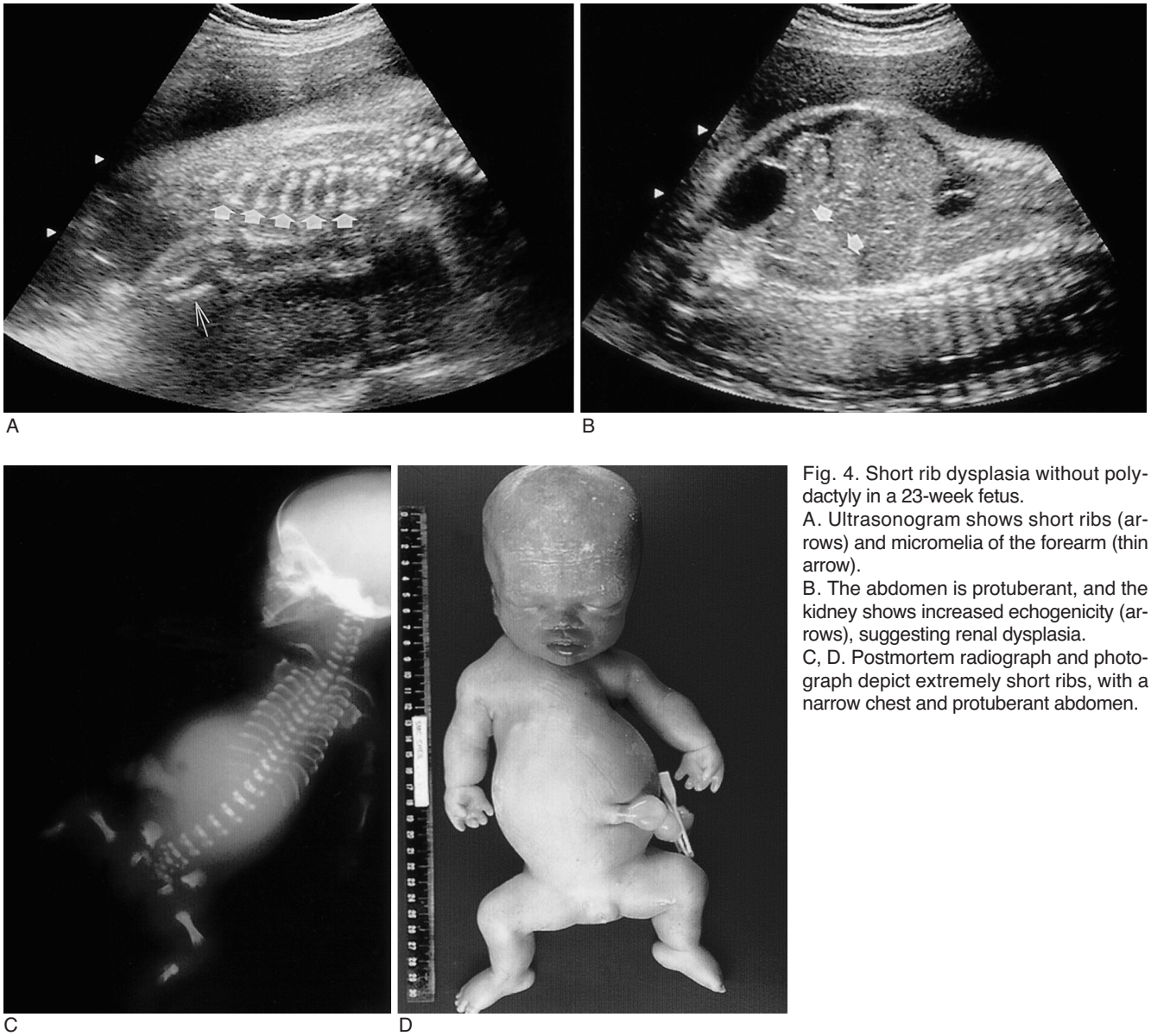

Fig. 4. Short rib dysplasia without polydactyly in a 23-week fetus.
A. Ultrasonogram shows short ribs (arrows) and micromelia of the forearm (thin arrow).
B. The abdomen is protuberant, and the kidney shows increased echogenicity (arrows), suggesting renal dysplasia.
C, D. Postmortem radiograph and photograph depict extremely short ribs, with a narrow chest and protuberant abdomen.

marginal spurs. The incidence of congenital heart disease and gastrointestinal and genitourinary anomalies is not as high as in type I (12).

SRP type IV (Beemer-Langer) shows most of the clinical features of type II, though polydactyly is absent (13) (Fig. 4).

Asphyxiating thoracic dysplasia is characterized by a long narrow thorax, rhizomelic limb shortening, hypoplastic iliac wings, horizontal acetabular roofs, cystic renal disease, hepatic fibrosis and polydactyly (14) (Fig. 5).

Ellis-van Creveld (chondroectodermal) dysplasia is characterized by the presence of short ribs, short limbs, postaxial polydactyly, and ectodermal abnormalities of the hair, nails, and teeth (15).

Camptomelic Dysplasia

Camptomelic dysplasia is a very rare form of short-limb dysplasia, characterized by prominent bowing of the long bones, especially those of the lower extremities (16). The proximal portion of the femurs and the distal portion of the tibias are usually bent, and the long bones are shortened, with ventral convex bowing (Fig. 6). The fibulas may be hypoplastic or absent, and clubfoot usually occurs (16). The scapulae are hypoplastic or absent, and the degree of narrowing of the thorax is relatively mild (Fig. 6). Facial features include a flattened nasal bridge, protuberant forehead, hypotelorism, an elongated philtrum, micrognathia, and a cleft palate (16, 17). Associated anomalies of the heart are common, as are hydrocephalus and hydronephrosis, and polyhydroamnios may also occur.

Chondrodysplasia Punctata

Rhizomelic chondrodysplasia punctata is a rare dysplasia characterized by marked shortening and disturbed ossifica-

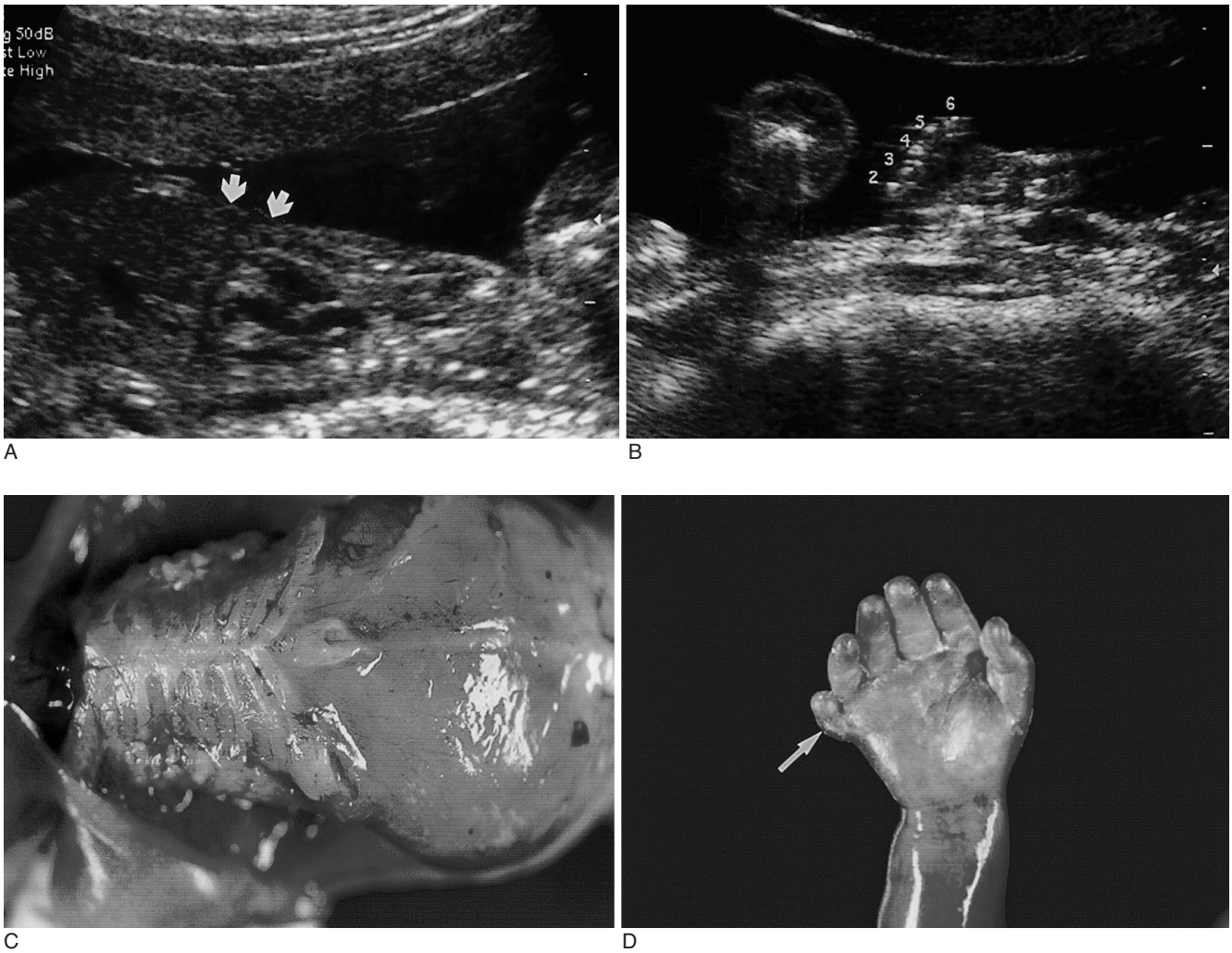

Fig. 5. Short-rib dysplasia with polydactyly in a 21-week fetus.
A. Sagittal image shows a narrow thorax and relatively protuberant abdomen (arrows).
B. There is an extra digit (6) lateral to the fifth finger.
C, D. Autopsy photographs show a narrow thorax with short ribs, a protuberant abdomen, micromelia, and postaxial polydactyly (arrow).

tion of the proximal limbs, abnormalities of the vertebral column, eye and skin defects, severe mental retardation, and recurrent infection (18). The prenatal sonographic criteria for diagnosis are pronounced humeral shortening and less marked femoral shortening, without shortening of other long bones, and expanded epiphyses containing multiple hyperechoic foci (19) (Fig. 7). Prenatal radiography may reveal stippling of the long bones and pelvis, and abnormalities of the vertebral bodies. The prognosis is poor, with death usually occurring within the first year of life, though some patients have survived longer (18).

Other Musculoskeletal Anomalies with a Poor Outcome

Amniotic Band Syndrome

Amniotic band syndrome (ABS) is a common cause of fetal malformation. This ranges from mild limb deformities to severe complex anomalies that are incompatible with postnatal life. The pathogenesis of ABS is unknown, but is thought to be due to disruption of the amnion. The constrictive bands, which subsequently arise, can encircle developing limbs, resulting in annular constriction, secondary syndactyly, and intrauterine amputations (20). If early amnionic disruption occurs during the period of embryogenesis, embryologic development may be interrupted, leading to exencephaly, facial cleft, or abdominal wall defects (21). In addition, spinal scoliosis and deformity may occur. ABS can be diagnosed at ultrasonography by the presence of asymmetrical lymphedema or an amputated extremity (Fig. 8). In a severe case, exencephaly, a bizarre facial cleft, and a large abdominal wall defect can be detected during early gestation (Fig. 9). Amniotic bands are not always vi-

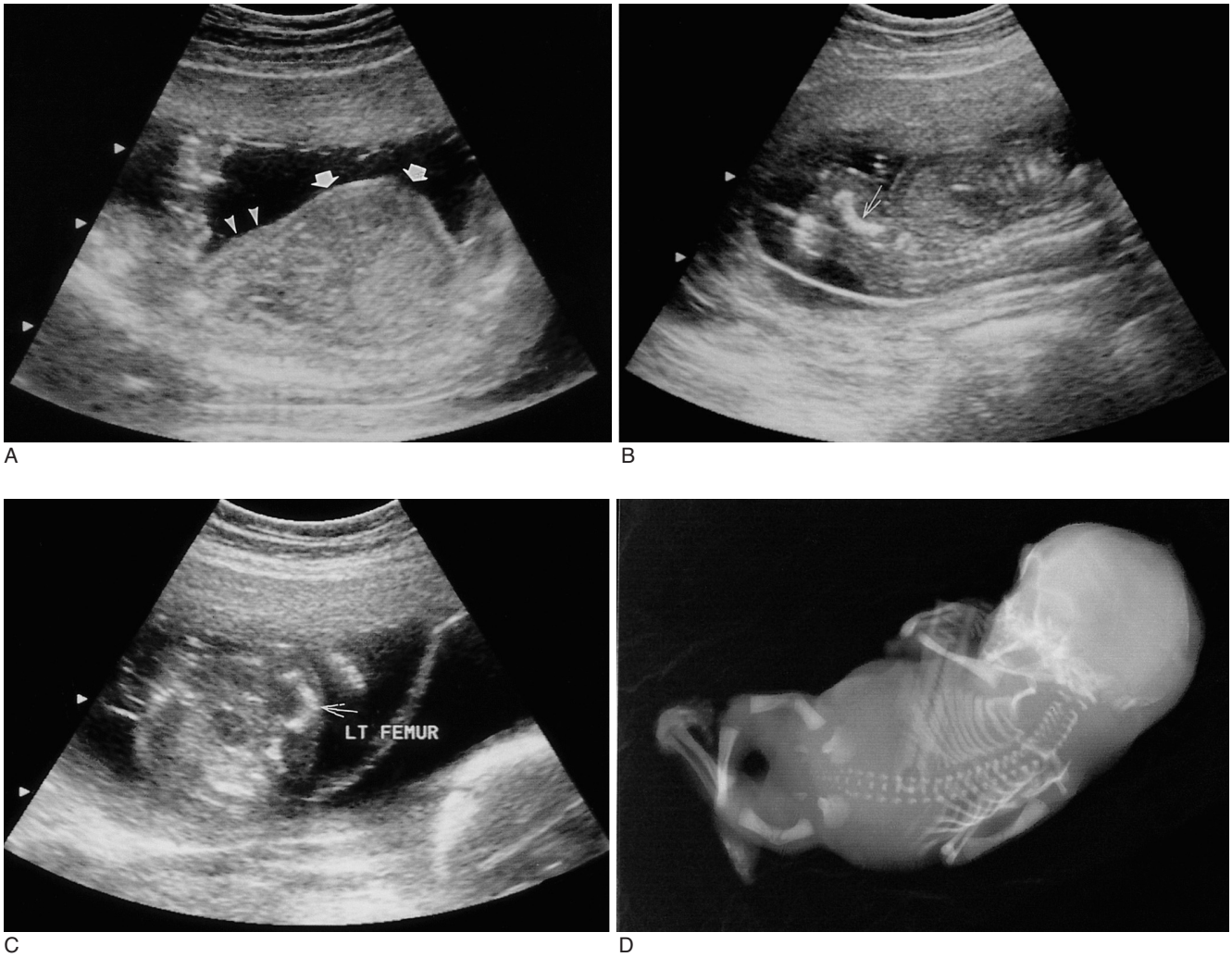

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Fig. 6. Camptomelic dysplasia in a 20-week fetus.
A. Prenatal ultrasonogram depicts a moderately small thorax (arrowheads) with a protuberant abdomen (arrows).
B, C. The femurs (arrow) are short and bowed, and anterolaterally convex.
D. Postmortem radiograph demonstrates bowing of the femur and severe clubfoot deformity. The scapula is hypoplastic, but the humerus is relatively preserved.

sualized (22).

Limb-Body Wall Complex

Limb-body wall complex (LBWC) is an entity characterized by the presence of an abdominal wall defect, a short umbilical cord, distinctive spinal scoliosis, limb anomaly, and craniofacial defect. Its pathogenesis is still unknown, though the most popular theory is that its cause is disrupted blood flow, resulting in hemorrhagic necrosis and anoxia during early embryonic development (23). Another theory is that early amnionic rupture leads to abdominal wall and spinal defects, and a short umbilical cord. This theory suggests that LBWC may be at the other end of the spectrum from ABS (24).

At prenatal ultrasonography, the presence of a large body wall defect and scoliosis suggests LBWC. The body wall defect is readily identifiable as a large complex mass anterior to the fetal chest or abdomen, and in the majority of cases, scoliosis is severe (Fig. 10). The umbilical cord is usually short or invisible, and facial clefts, cephalocele or exencephaly are detected in 40% of cases. The presence of a fetal membrane or bands continuous with the body wall, or neural tube defect, is also a characteristic feature, but not always visualized (25).

Sirenomelia Sequence

Sirenomelia is a rare and invariably lethal congenital anomaly characterized by fusion of the lower extremities and the presence of other severe anomalies such as bilateral renal agenesis. It has been described as the most severe form of caudal regression syndrome, but recent studies regard this syndrome as a separate entity. Stevenson et al. (26) proposed a "vascular steal" theory as the etiologic factor in sirenomelia. According to this theory, diversion of

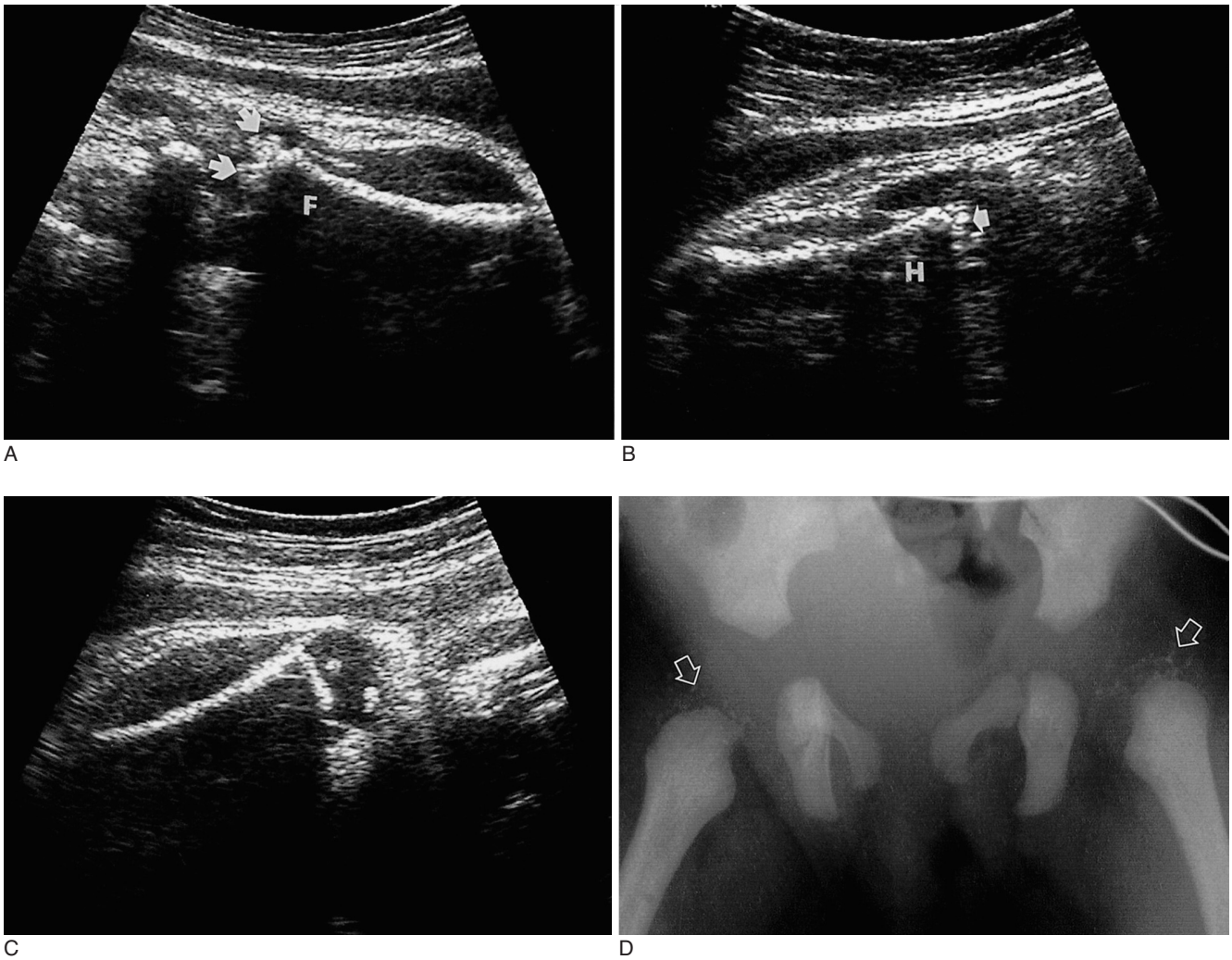


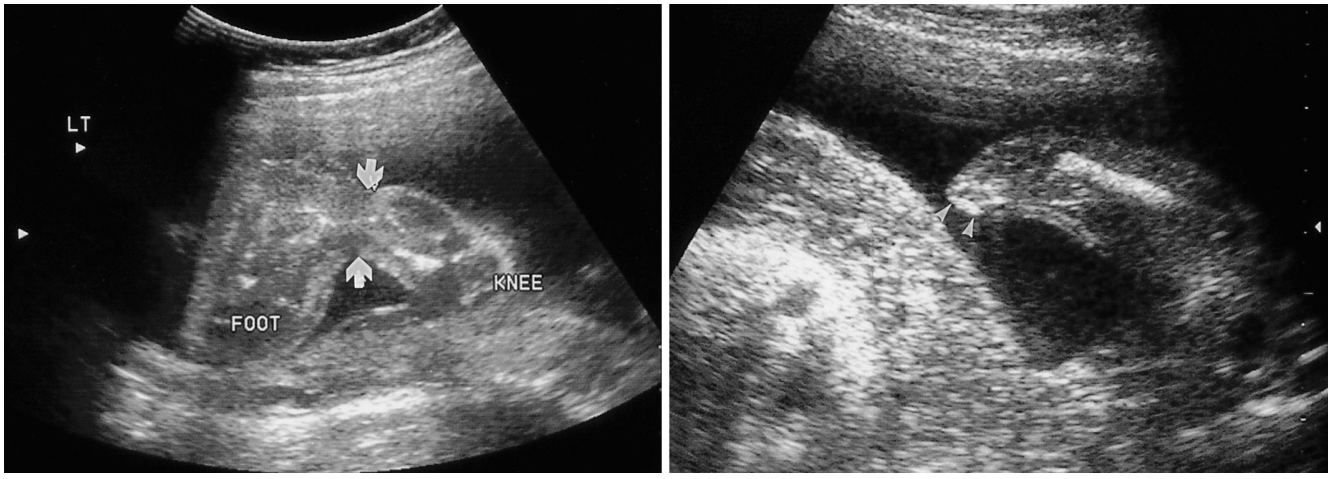
Fig. 7. Chondrodysplasia punctata in a 35-week fetus.
A, B. Prenatal ultrasonograms depict stippled ossification at the proximal epiphyses (arrows) of the femur and humerus.
C. There is no abnormal ossification of the distal epiphysis.
D. Postnatal radiograph shows stippled ossifications (open arrows) of the proximal femoral epiphyses.

blood flow through an aberrant vessel to the placenta produces poor perfusion to the caudal portion of the embryo, resulting in severe malformation of the spine and the genitourinary and lower gastrointestinal systems.

Fusion of the lower extremities in sirenomelia ranges from membranous fusion of the soft tissue to total fusion of the lower legs, with one midline femur (Fig. 11). Severe oligohydramnios, a sonographic marker of an absent or non-functioning kidney, may obscure prenatal sonographic evaluation of the condition (27). The aberrant vessel can be identified at color Doppler ultrasonography, and is a feature which may distinguish sirenomelia from other causes of oligohydramnios (28).

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita (AMC) is the term used to describe a condition in which multiple joint contractures are caused by decreased fetal movement. This decrease may be due to factors that include neuropathic, muscular, or connective tissue abnormalities, space limitations within the uterus, intrauterine vascular compromise, and maternal diseases (29). A variety of other congenital abnormalities such as bilateral renal agenesis, spina bifida, sacral agenesis, and metatrophic or diastrophic dwarfism, may be associated with AMC (30), and its outcome depends on the underlying etiology and concomitant anomalies. The ultrasonographic findings of AMC are absent



A B

Fig. 8. Amniotic band syndrome in 23-week (A) and 22-week (B) fetuses.
A. There is focal constriction (arrows) at the left ankle, with severe lymphedema of the foot.
B. The upper extremity is amputated at the proximal forearm (arrowheads).

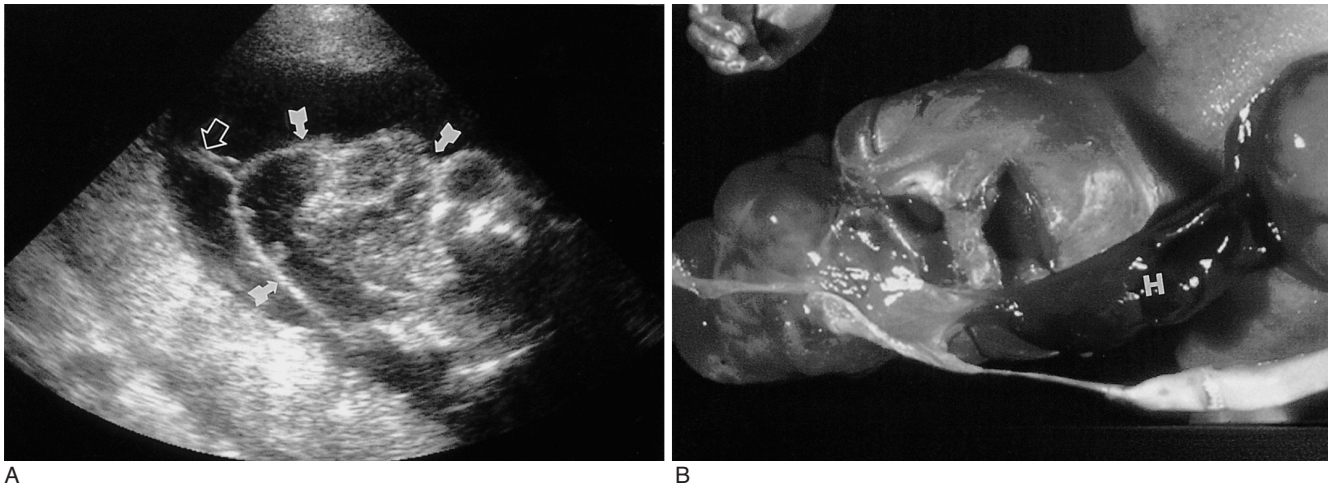


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Fig. 9. Amniotic band syndrome with exencephaly and extensive body wall defect.
A. Ultrasonogram shows that the calvaria is absent, giving rise to exencephaly (arrows). Note the presence of an adherent amniotic band (open arrow) on the fetal head.
B. Postmortem photograph shows exencephaly and asymmetrical body-wall defect, with a herniated heart (H) and abdominal contents.

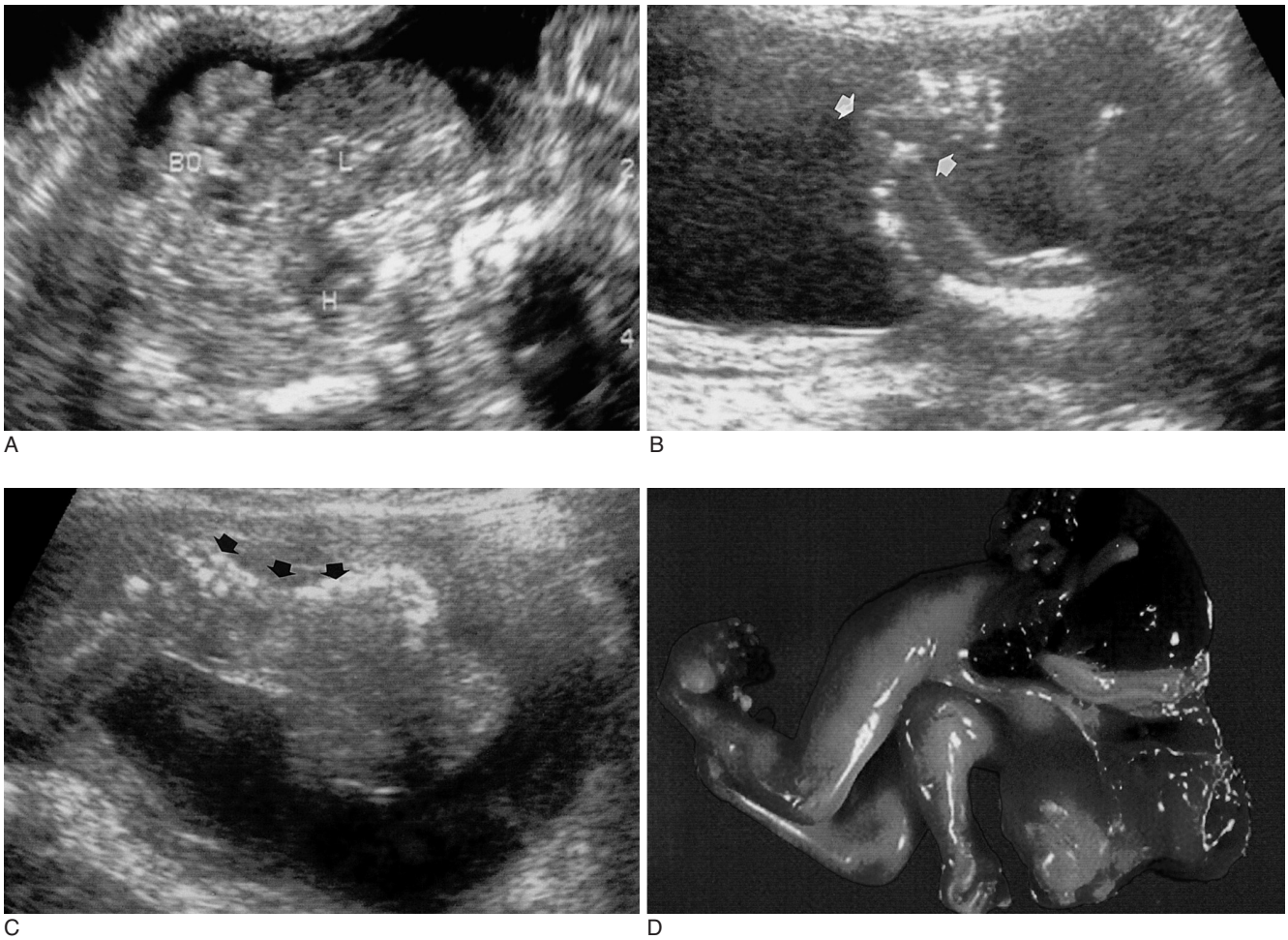

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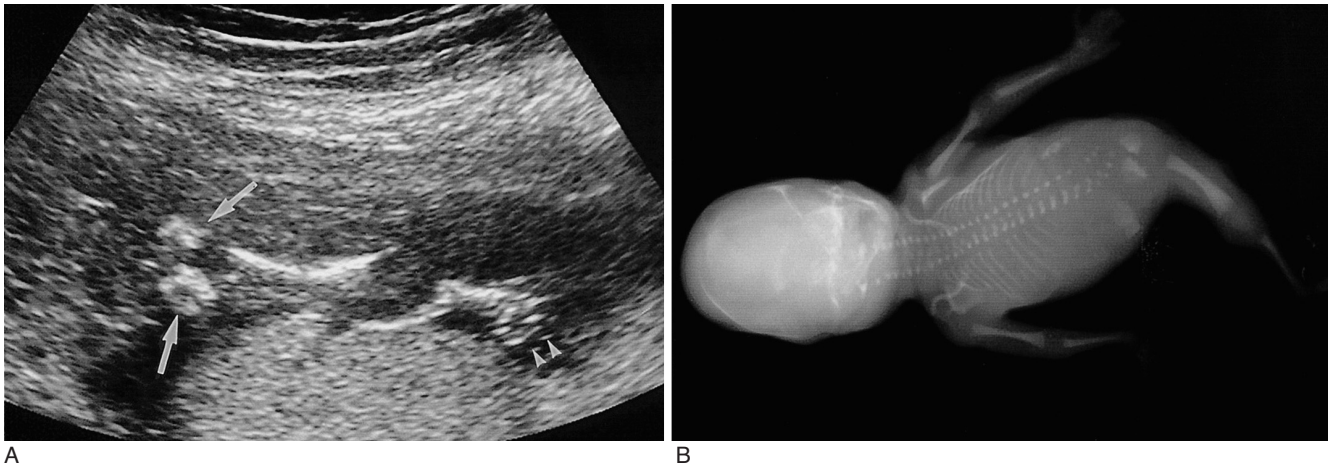
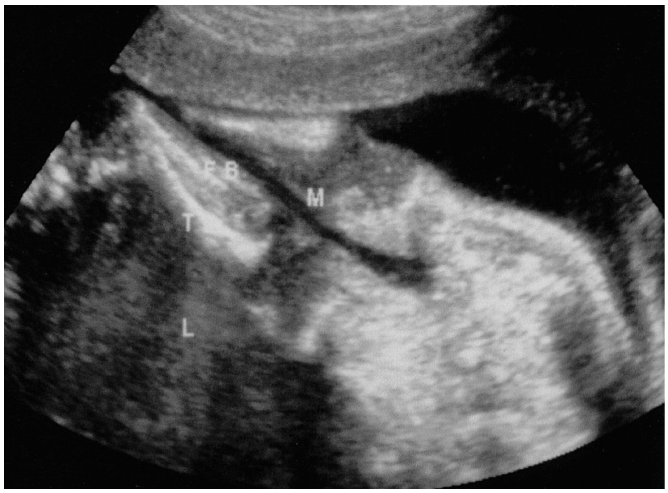
Fig. 10. Limb-body wall complex in a 14-week fetus.
A. A complex mass consisting of the liver (L), bowel (BO), and heart (H) is identifiable lateral to the fetal abdomen and thorax at transvaginal ultrasonography.
B. The ankle (arrows) is abnormally angulated.
C. Kyphoscoliotic spinal curvature is apparent (arrows).
D. Postmortem photograph demonstrates the presence of limb-body wall complex. Thoraco-abdominoschisis, limb anomalies, and exencephaly are present.



A B

Fig. 11. Sirenomelia in a 16-week fetus.
A. Prenatal ultrasonogram shows a single femur and tibia at the midline, and a deformed foot (arrowheads). The iliac bones (arrows) are abnormally located.
B. Postmortem radiograph shows a single lower extremity and hypoplastic pelvic bone.



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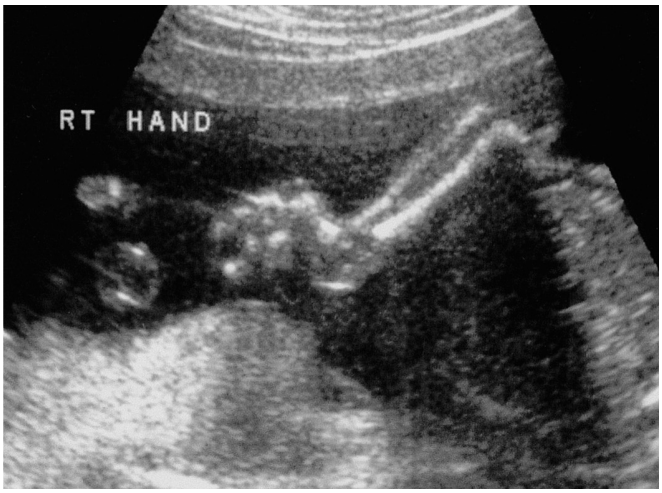

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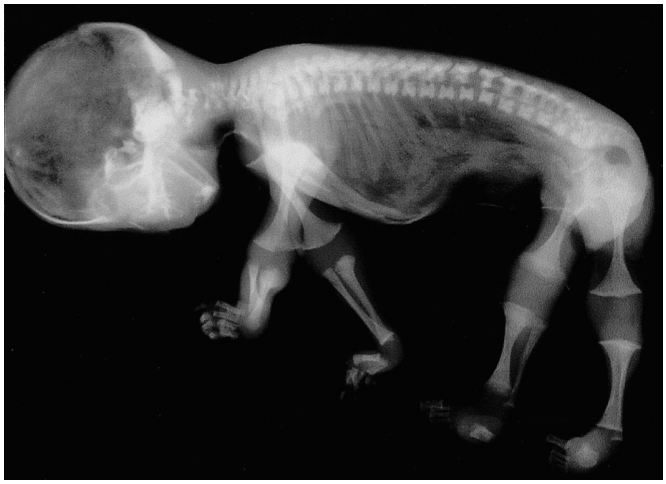

C

Fig. 12. Arthrogryposis multiplex congenita in a 19-week fetus.
A. Ultrasonogram demonstrates unusual extension of both knees, without postural change.
B. Both hands and fingers show contracture and abnormal angulation deformities.
C. Postmortem radiograph shows extension deformity of the knee joints, clubfoot, and abnormal angulation deformity of both hands.

joint movement and severe flexion deformities of the fetal extremities (31) (Fig. 12).

SUMMARY

The early and accurate antenatal diagnosis of lethal skeletal dysplasia and other skeletal anomalies with a poor outcome has important implications for the management of a pregnancy. Careful ultrasonographic examination of a fetus helps detect such anomalies, and a number of characteristic features may suggest possible differential diagnoses. Antenatal consultation with a clinical geneticist familiar with these disorders is mandatory for differential diagnosis and for the planning of further management.

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