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Tetra-Amelia Syndrome

[*Tetra-Amelia, Autosomal Recessive*]

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Summary

Disease characteristics. Tetra-amelia syndrome is characterized by the (complete) absence of all four limbs and anomalies involving the cranium and the face (cleft lip/cleft palate, micrognathia, microtia, single naris, choanal atresia, absence of nose); eyes (microphthalmia, microcornea, cataract, coloboma, palpebral fusion, hypoplasia/atresia lacrimal ducts and sacs); urogenital system (renal agenesis, persistence of cloaca, absence of external genitalia, atresia of vagina); anus (atresia); heart; lungs (hypoplasia/aplasia), skeleton (hypoplasia/absence of pelvic bones, absence of ribs, absence of vertebrae), and central nervous system (agenesis of olfactory nerves, agenesis of optic nerves, agenesis of corpus callosum, hydrocephalus). Affected infants are often stillborn or die shortly after birth.

Diagnosis/testing. The diagnosis of tetra-amelia syndrome can be established clinically and is usually made on routine prenatal ultrasonography. *WNT3* is the only gene known to be associated with tetra-amelia syndrome. Molecular genetic testing is available on a clinical basis. The mutation detection frequency is unknown as only a limited number of families have been studied.

Management. Affected infants are often stillborn or die shortly after birth. Management of (yet unreported) persons who survive will depend on the presence and severity of associated malformations and require the support of several medical disciplines.

Genetic counseling. Tetra-amelia syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes (carriers) are asymptomatic. Prenatal testing by molecular genetic testing is possible if the disease-causing mutations in the *WNT3* gene have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Tetra-amelia is characterized by the (complete) absence of all four limbs (Figure 1). The diagnosis of tetra-amelia can be established clinically and is usually made on routine prenatal ultrasonography (Figure 2).

In the few families described to date, tetra-amelia was associated with craniofacial, urogenital, cardiopulmonary, nervous system, and skeletal malformations, in which instance the correct terminology should be tetra-amelia syndrome.

Testing

Cytogenetic analyses, performed in some of the reported cases, showed normal karyotypes without 'premature centromere separation' (see Roberts Syndrome).

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *WNT3* has been shown to be associated with tetra-amelia syndrome in one family [Niemann et al 2004].

Other loci. Genetic heterogeneity of tetra-amelia syndrome is strongly suggested by Krahn et al (2005), who describe a new consanguineous family with tetra-amelia, agenesis of both lungs, cleft lip/cleft palate, and micrognathia. Sequence analysis of *WNT3*, (all exons and exon-intron boundaries), *FGF10* (all exons and exon-intron boundaries), *FGFR2* (exon 9), *HS6ST1* (coding region), and *HS6ST3* (coding region) did not identify a mutation in any of the genes.

Clinical testing

- **Sequence analysis.** Direct sequencing of genomic DNA of the entire *WNT3* coding region (exons 1-4). Percentage of detectable mutations is unknown, as a *WNT3* mutation has so far only been demonstrated in a single family with tetra-amelia syndrome [Niemann et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Tetra-Amelia Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*WNT3* mutation p.Gln83X (c.366C>T) [2]	Unknown	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. Only one family studied to date [Niemann et al 2004]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband, sequence analysis of *WNT3* can be performed; however, the mutation detection frequency is unknown because to date only one family with tetra-amelia syndrome has been reported to have a mutation in *WNT3*.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other disorders have been reported to be associated with mutations in *WNT3*.

Clinical Description

Natural History

In addition to complete absence of all four extremities, phenotypic manifestations of tetra-amelia syndrome in affected individuals may include craniofacial, urogenital, cardiopulmonary, nervous system, and skeletal malformations. The following list is based on the findings in affected individuals in the few families reported [Zimmer et al 1985, Gershoni-Baruch et al 1990, Rosenak et al 1991, Zlotogora et al 1993, Basaran et al 1994, Ohdo et al 1994, Niemann et al 2004, Krahn et al 2005].

While the affected individuals in these families have all had similar findings, a mutation in *WNT3* was only identified in the family reported by Niemann et al (2004). No molecular studies were undertaken in the other families with the exception of the family reported by Krahn et al (2005) in which *WNT3*, *FGF10*, *FGFR2*, *HS6ST1*, and *HS6ST3* were analyzed but no mutation identified. Therefore, in the absence of molecular genetic information to suggest subtypes of tetra-amelia syndrome, all reported cases are grouped together in this review. The findings in the family with a *WNT3* mutation are compared in Table 2 with the findings in families in which no molecular studies were undertaken or no *WNT3* mutation was identified.

Craniofacial

- **Eyes.** Microphthalmia, cataract, microcornea, coloboma, palpebral fusion
- **Ears.** Absence of external ears (microtia), low-set ears
- **Nose.** Single naris, choanal atresia, prominent nose, absence of nose
- **Mouth.** Cleft lip/cleft palate, high and narrow palate, macrostomia, micrognathia

Urogenital

- Agenesis of kidney
- Rudimentary ovary and salpinx
- Persistence of cloaca
- Atresia of vagina
- Atresia of anus
- Atresia of urethra
- Absence of external genitalia
- Absence of scrotum
- Intra-abdominal location of testis

Cardiopulmonary

- Hypoplasia/aplasia of lungs
- Hypoplasia of pulmonary vessels
- Diaphragmatic defect
- Ventricular septal defect

- Mitral valve aplasia

Skeletal

- Hypoplasia/absence of pelvic bones
- Absence of vertebrae
- Absence of ribs

CNS

- Agenesis of olfactory nerves
- Agenesis of optic nerves
- Agenesis of corpus callosum
- Hydrocephalus

Other

- Polyhydramnios
- Absence of nipples
- Gastroschisis
- Agenesis of supra-adrenal gland
- Agenesis of spleen

Table 2. Clinical and Autopsy Findings in Families with Tetra-Amelia

Findings	Zimmer et al 1985, Gershoni-Baruch et al 1990	Rosenak et al 1991	Zlotogora et al 1993	Basaran et al 1994	Niemann et al 2004	Krahn et al 2005
Tetra-amelia	+	+	+	+	+	+
Cleft lip/cleft palate	+	+	+	+	+	+
Micrognathia	-	+	-	+	-	+
Ear malformation	Absent	+	-	-	-	-
Eye malformation	+	-	-	+	+	-
Nose malformation	Absent	-	-	-	+	-
Mouth malformation	+	-	-	-	-	-
Heart malformation	-	-	?	+	-	-
Pulmonary defects	+	Hypoplasia/ aplasia	?	Aplasia	+	+
Pulmonary arteries	-	Hypoplasia	?	?	-	?
Diaphragmatic defect	-	-	?	-	+	-
Pelvic bones	Hypoplasia/ aplasia	-	?	-	Hypoplasia	-
Other skeletal defects	Absent vertebrae and ribs	-	?	-	-	-
Renal malformation	-	-	?	-	Agenesis	-
Genital malformation	+	-	?	+	+	-
Anal atresia	+	-	-	-	+	-
Polyhydramnios	+	-	-	-	-	-

Hydrocephalus	+	+	?	-	-	-
Other CNS defects	Agenesis of olfactory and optic nerves, corpus callosum	-	?	-	-	-
Cases: Total/Autopsied	**7**	**3/2**	**5/0**	**2/1**	**4/3**	**2/2**

Data on the course of the disease or the prognosis are not available because the condition is rare. In nearly all reported cases, the pregnancy was terminated upon diagnosis of tetra-amelia syndrome, or infants died shortly after birth as a consequence of other malformations such as pulmonary hypoplasia. Limb agenesis is generally compatible with life if adequate assistance is provided. The natural history of the disease is likely to be determined by extent and degree of associated manifestations.

Note: An X-linked form of tetra-amelia (OMIM 301090), also termed 'Zimmer phocomelia', has been suggested for the family reported by Zimmer [Zimmer et al 1985, Gershoni-Baruch et al 1990] as all affected fetuses in this family were males connected only through female relatives. However, multiple consanguinity in the family and the fact that the gender may have been incorrectly assigned in some fetuses also suggested autosomal recessive inheritance [Gershoni-Baruch et al 1990]. (For more information see Differential Diagnosis: X-linked tetra-amelia.)

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been established to date.

Penetrance

Based on the few reports, penetrance appears to be complete with respect to absence of the limbs and incomplete with respect to the associated malformations. Expressivity of the associated manifestations is highly variable.

Nomenclature

In all cases reported so far, tetra-amelia has been associated with other malformations, as 'tetra-amelia syndrome'. However, there is evidence that tetra-amelia may occur as 'pure tetra-amelia' (or 'isolated tetra-amelia') without other anomalies.

Prevalence

Tetra-amelia syndrome is an extremely rare disorder and has so far been described in only five families of different ethnic backgrounds (Arabic, Moroccan, Syrian-Aramaic). No estimates of prevalence and carrier frequency for tetra-amelia syndrome have been reported.

Parental consanguinity appears to account for at least some of the few cases reported to date.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Many of the associated phenotypic manifestations observed in tetra-amelia syndrome have also been observed in other syndromes. Limb deficiency as the hallmark of the disorder may occur in limb reduction syndromes different from tetra-amelia syndrome. In these syndromes, limb defects are variable, including phocomelia, amelia, and (rarely) tetra-amelia. The observation

of several individuals with (complete) absence of all four extremities in a family is highly suggestive of tetra-amelia syndrome.

Tetra-amelia with ectodermal dysplasia and lacrimal duct abnormalities (OMIM 273390) is characterized by tetra-amelia, hypotrichosis, hypoplastic lacrimal ducts and sacs opening to the exterior, lack of lacrimal openings, upward slanting palpebral fissures, and bilateral preauricular pits. One of two affected sibs in the family described by Ohdo et al (1987) had complete absence of both lower limbs and the left upper limb, and hypomelia of the right upper limb with approximately 3 cm of humerus. The other affected sib had (complete) tetra-amelia [Ohdo et al 1987].

X-linked tetra-amelia (Zimmer phocomelia) (OMIM 301090) is characterized by absence of all four limbs, absence/hypoplasia of pelvic bones, absence of vertebrae, absence of ribs, 'bilateral' left lung/hypoplasia of lungs, absence of nipples, cleft lip, microphthalmia, microcornea, cataract, coloboma, microcornea, absence of nose and external ears, nonfusion of maxillae. Other findings include hydrocephalus, agenesis of olfactory nerves, agenesis of optic nerves, agenesis of the corpus callosum, empty scrotal sacs, anal atresia, and communication of rectum and urinary bladder [Zimmer et al 1985, Gershoni-Baruch et al 1990]. X-linked inheritance in this family has later been questioned since the gender of some fetuses may have been incorrectly assigned and because of the presence of multiple consanguinity in the family indicating autosomal recessive inheritance [Kosaki et al 1996].

Management

Evaluations Following Initial Diagnosis

Tetra-amelia syndrome is usually diagnosed prenatally. Based on the few published reports, assessment of the clinical manifestations in a fetus diagnosed with tetra-amelia syndrome by ultrasonography should include careful assessment of all organs and body structures that are known to be affected in tetra-amelia syndrome.

Treatment of Manifestations

In nearly all reported cases, the pregnancy was terminated upon diagnosis of tetra-amelia syndrome, or infants died shortly after birth as a consequence of other malformations such as pulmonary hypoplasia. Data on the management of tetra-amelia syndrome therefore do not exist.

It should be noted that (complete) absence of all extremities is principally not incompatible with life. Persons without extremities depend on extensive, life-long assistance with most daily activities. They would require specifically designed wheelchairs with assistive electronic technology and input control devices operated by head, chin or tongue movements. Other individualized ambulatory devices may be indicated.

Should individuals with tetra-amelia syndrome survive, management depends on the presence and severity of associated malformations and may involve multiple interdisciplinary surgical interventions and the support of several medical disciplines.

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Tetra-amelia syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with tetra-amelia syndrome are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members and their reproductive partners is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of being carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Although such testing can determine whether a fetus is homozygous for *WNT3* disease-causing mutations, it may not be required as the accurate diagnosis of limb agenesis should be possible by ultrasonography at the time of CVS.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Ultrasound examination is recommended to assess the fetus for the presence and degree of malformations in other organs and structures affected in tetra-amelia syndrome.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Tetra-Amelia Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
WNT3	17q21	Proto-oncogene protein Wnt-3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Tetra-Amelia Syndrome

165330	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 3; WNT3
273395	TETRA-AMELIA, AUTOSOMAL RECESSIVE

Table C. Genomic Databases for Tetra-Amelia Syndrome

Gene Symbol	Entrez Gene	HGMD
WNT3	7473 (MIM No. 165330)	WNT3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: *WNT3* is composed of five exons spanning 54.2 kb of genomic sequence and encodes a transcript of 1506 nt. The 1068-nt open reading frame starts in exon 1 and terminates with a TAG stop codon in exon 4, encoding a protein of 355 amino acids.

Pathologic allelic variants: The p.Gln83X mutation in *WNT3* is the only mutation reported so far and was identified in a single family with tetra-amelia syndrome. The nonsense mutation at codon 83 creates a premature stop codon. The mutated transcript, unless rapidly degraded by nonsense-mediated RNA decay, is likely to result in a truncated protein of only 83 amino acids (including the signal peptide of 21 amino acids) instead of the 355 amino acids of the mature peptide.

Normal gene product: Proto-oncogene protein Wnt-3 (WNT3) is one of 19 members of the human WNT superfamily of highly conserved secreted signaling molecules that play key roles in embryonic development [Wodarz & Nusse 1998, Moon et al 2004]. Work in animal models supports the role of WNT3 signaling in the initiation of the formation of the apical ectodermal ridge, a transient structure in the embryonic limb bud critical for limb outgrowth.

WNTs act as ligands for the frizzled family of transmembrane receptors. Intracellularly, WNT signals can be transduced through aβ-catenin-dependent (i.e., canonical) and a β-catenin-independent (non-canonical) WNT signaling. In the WNT/β-catenin pathway, absence of WNT ligand leads to degradation of β-catenin by the proteasome. Conversely, upon binding of WNT ligand to frizzled, degradation of β-catenin is decreased and accumulates in the nucleus where it can activate transcription.

Abnormal gene product: The p.Gln83X mutation leads either to rapid degradation by RNA surveillance mechanisms or to truncation of WNT3 at its amino terminus and is, in either case, likely to result in a null allele for the *WNT3* gene. Loss of function of WNT3 in tetra-amelia syndrome supports the role of the *WNT3* gene as a limb-inducing gene in humans.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Compassionate Friends
PO Box 3696
Oak Brook IL 60522-3696
Phone: 877-969-0010; 630-990-0010
Fax: 630-990-0246
Email: nationaloffice@compassionatefriends.org
www.compassionatefriends.org

Helping After Neonatal Death (HAND)
A non-profit California-based group that lists support groups
www.handonline.org/resources/groups/index.html

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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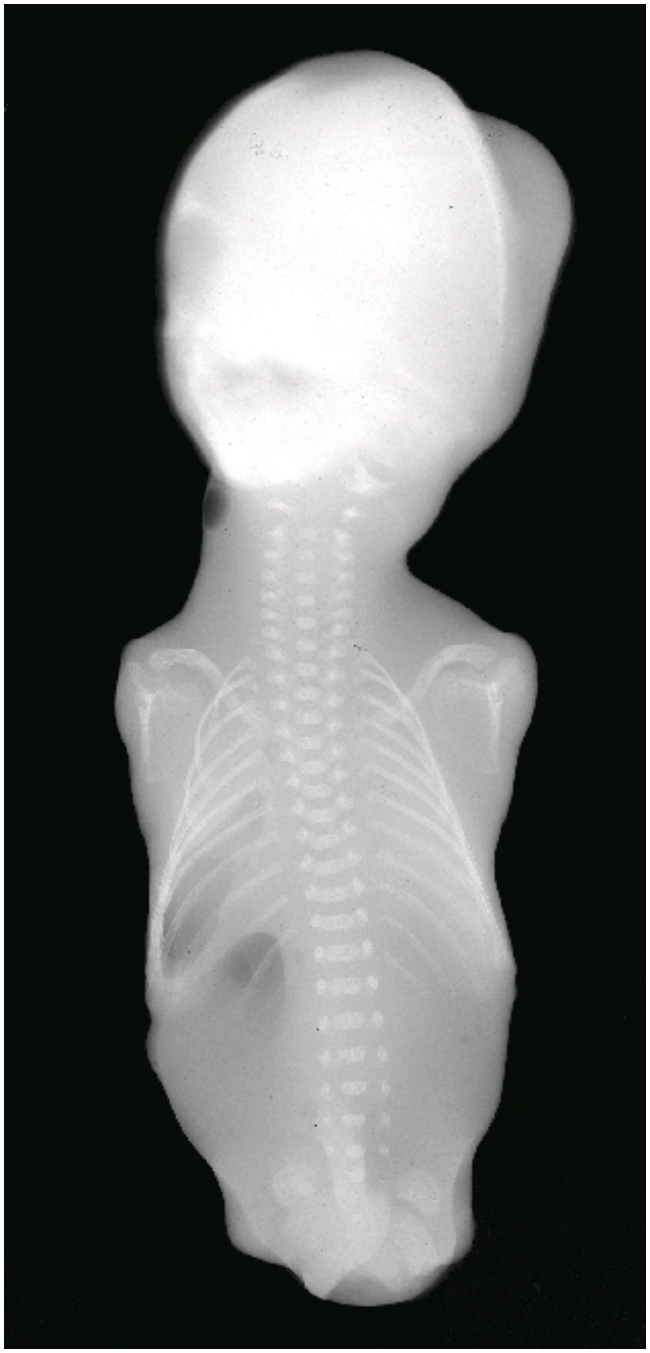

Figure 1. Postmortem radiograph of fetus with tetra-amelia syndrome demonstrating absence of all four limbs (without defects of scapulae and clavicles)

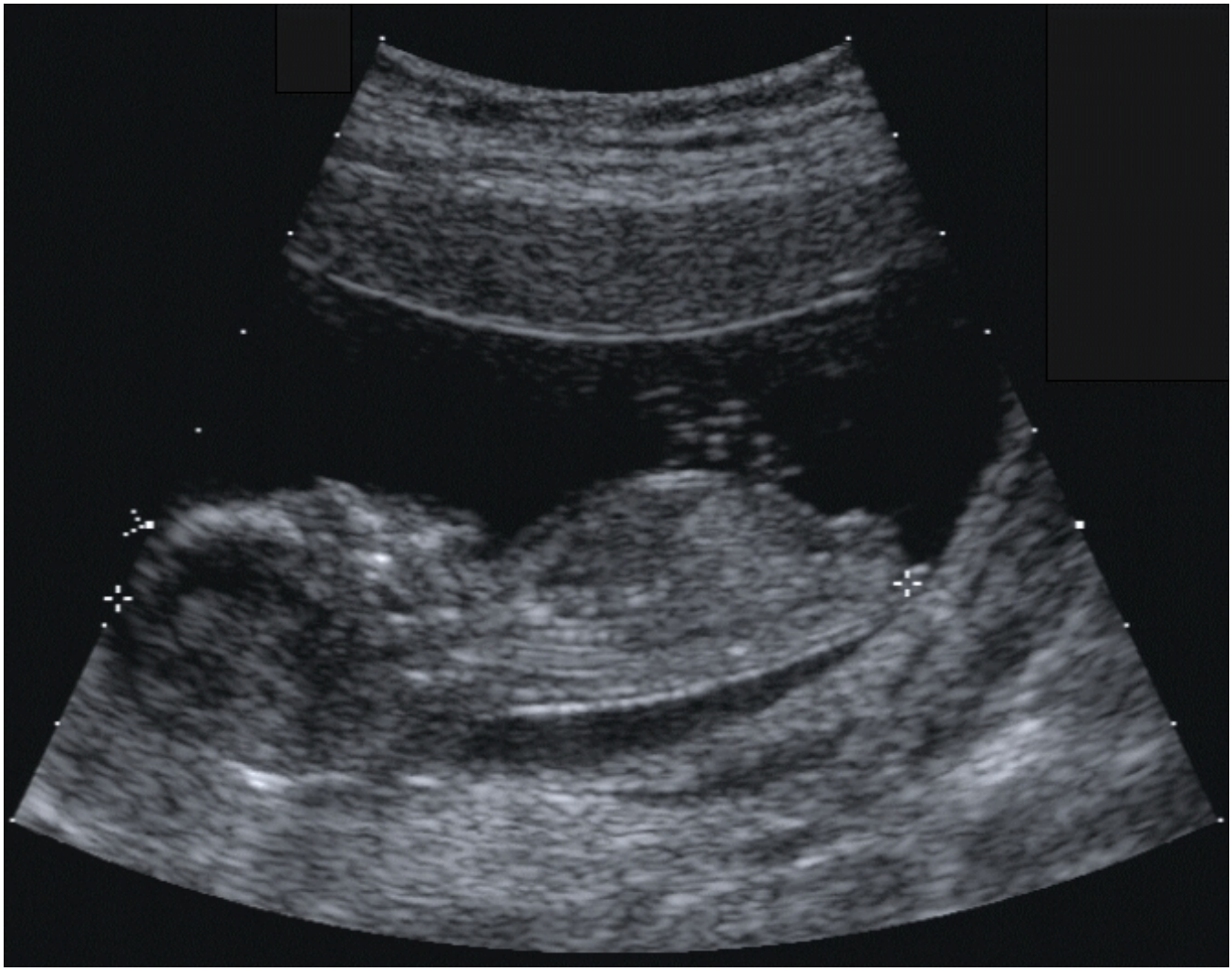

Figure 2. Prenatal ultrasonography showing fetus without limbs