

Sirenomelia. Pathological features, antenatal ultrasonographic clues, and a review of current embryogenic theories

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We aimed to discuss the prenatal diagnosis and pathological features of sirenomelia, and to review current embryogenic theories. We observed two sirenomelic fetuses that were at the 19th and 16th gestational week respectively. In the former, transvaginal ultrasound revealed severe oligohydramnios and internal abortion, whereas bilateral renal agenesis, absence of a normally tapered lumbosacral spine, and a single, dysmorphic lower limb were detected in the latter. In both cases, X-rays and autoptic examination allowed categorization on the basis of the skeletal deformity. Subtotal sacro-coccygeal agenesis was present in both cases. Agenesis of the urinary apparatus and external genitalia and anorectal atresia were also found. Classification of sirenomelia separately from caudal regression syndrome is still debated. Recent advances in the understanding of axial mesoderm patterning during early embryonic development suggest that sirenomelia represents the most severe end of the caudal regression spectrum. Third-trimester ultrasonographic diagnosis is usually impaired by severe oligohydramnios related to bilateral renal agenesis, whereas during the early second trimester the amount of amniotic fluid may be sufficient to allow diagnosis. Early antenatal sonographic diagnosis is important in view of the dismal prognosis, and allows for earlier, less traumatic termination of pregnancy.

Key words: caudal regression/congenital malformations/prenatal diagnosis/sirenomelia/ultrasound

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Introduction

Sirenomelia is a very rare congenital malformation, with an incidence of between 1:60 000 (Nyberg *et al.*, 1989) and 1:100 000 births (Lituania and Tomà, 1996). Males are predominantly affected, with a sex ratio of 2.7:1, and the anomaly is more common in one of two monozygotic twins (Murphy *et al.*, 1992). Sirenomelia is characterized by single or fused lower limbs associated with other severe anomalies, such as bilateral renal agenesis, which are incompatible with life in

the vast majority of cases (Stocker and Heifetz, 1987; Van Zalen-Sprock *et al.*, 1995); however, exceptional cases of surviving newborns with minor renal abnormalities or even normal kidneys have been reported (Savader *et al.*, 1989; Murphy *et al.* 1992; Clarke *et al.*, 1993; McCoy *et al.*, 1994). Agenesis of the external genitalia and anorectal atresia are also invariably found.

The presence of severe oligohydramnios related to bilateral renal agenesis usually hinders a reliable ultrasonographic exploration of the caudal extremity of the fetus; therefore, the diagnosis is usually made at autopsy (Sirtori *et al.*, 1989; Van Zalen-Sprock *et al.*, 1995). To our knowledge, only two cases of early second trimester diagnosis have been reported so far (Van Zalen-Sprock *et al.*, 1995). The present study reports two cases with ultrasonographic findings at the 16th and 19th gestational week, and post-mortem radiological and pathological results. Clues for an early prenatal diagnosis and pathological features are discussed; a review of current embryogenic views is also presented, mainly focusing on the

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relationships between sirenomelia and caudal regression syndrome (CRS).

Ultrasound diagnosis and case study details

Case no. 1

A 28-year-old woman, gravida 1, para 0, was referred to our institution at 19 weeks gestational age, as determined by her last menstrual period, to undergo ultrasound examination as part of a routine screening of neural tube defects. The maternal medical and obstetric histories were uneventful, as well as the family history. Ultrasonography was performed using an Aloka SSD 680 (Japan) apparatus with a 3.5 MHz Convex probe for transabdominal scanning, and a 5 MHz probe was used for transvaginal scanning. The ultrasound revealed severe oligohydramnios with bilateral renal agenesis and absence of a bladder. The lumbosacral spine could not be adequately evaluated. Severe oligohydramnios also hindered a thorough morphological assessment of the lower limbs. Active movements and cardiac activity could not be demonstrated in the fetus, and a diagnosis of internal abortion was made. The expulsion of the fetus was induced by two intramuscular injections of prostaglandins (PGE₂) at a 500 µg dose, 6 hr apart.

External examination revealed a fetus weighing 60 g with a single, severely hypoplastic lower limb. The placenta was normal with a centrally attached two-vessel cord.

A radiograph of the body of the fetus confirmed the diagnosis of sirenomelia. The upper limbs were normal except for agenesis of the right thumb. The right hip was absent, whereas only a rudimentary ileum was seen on the left side. There was a single, rudimentary left lower limb with a single femur and tibia. Partial sacrococcygeal agenesis was detected, with only the ossification centres of S1 and S2 present.

Autopsy also confirmed the diagnosis of sirenomelia. The head, neck, and lungs were normal. The right cardiac ventricle was markedly hypertrophied. There was agenesis of the kidneys, ureters and bladder, and hypoplastic renal arteries bilaterally. The external genitalia were undetermined, and the male gonads lay at the internal inguinal orifice. There was anorectal atresia, and the colon ended blind with the sigma. A hypoplastic ileum, femur and tibia were the only rudiments of the hip and left lower limb, whereas the right lower limb was altogether absent.

Case no. 2

A 26-year-old woman, gravida 1, para 0, was first seen at our institution at 16 weeks gestation. Transabdominal ultrasound performed 1 week earlier by her doctor had shown indistinct abnormalities in the lower extremity of the fetus, so the patient had been referred to our institution to undergo transvaginal ultrasound. The patient had been diagnosed with systemic lupus erythematosus (SLE) at age 18 years, but she was not

under treatment for that disease. The family and maternal obstetric histories were uneventful. Ultrasound was performed employing an Aloka SSD 680 (Japan) apparatus with Convex probe (3.5 MHz) for transabdominal scanning and a 5 MHz probe for transvaginal scanning. The examination revealed a fetus with biometric parameters corresponding to 14 weeks gestational age, showing normal cardiac activity and active body movements. There was partial amniochorial disconnection, and the fetus and placenta lay within two separate sacs. The amniotic fluid was slightly reduced, and there was agenesis of the kidneys and bladder. A normally tapered lumbosacral spine could not be demonstrated. In scanning through the lower fetal extremity, only a single femur was clearly visible; the presence of a rudimentary tibia and calcaneum was questionable (Figure 1A–C). A diagnosis of sirenomelia was made, and the pregnancy was interrupted by endovaginal administration of a suppository containing 500 µg of PGE₂, according to the patient's wish and in agreement with Italy's regulations. External examination (Figure 1D) revealed a fetus weighing 40 g with a single, severely hypoplastic right lower limb. Contralaterally a small, congested mesenchymal bud was the only remnant of the left lower limb. The placenta was normal with an eccentrically attached two-vessel cord.

A radiograph of the body of the fetus (Figure 1E) confirmed the diagnosis of sirenomelia. The left hip was absent, and only a rudimentary ileum was seen on the right side. There was a single, rudimentary right lower limb with a hypoplastic femur and a rudimentary ossification centre for the calcaneum. Subtotal sacrococcygeal agenesis was detected, with only the ossification centre of S1 present.

At autopsy, the head, neck, upper limbs, heart and lungs were normal. There was agenesis of the kidneys, ureters and bladder, and both renal arteries were hypoplastic. The external genitalia were undetermined, and the male gonads lay at the internal inguinal orifice. There was anorectal atresia, and the colon ended blind with the sigma. A hypoplastic right ileum, femur and calcaneum were present, whereas a small, congested mesenchymal bud was the only remnant of the right lower limb.

Maternal history

The only maternal disease that is known to be associated with sirenomelia is diabetes mellitus (2% of cases), albeit much less frequently than with CRS (22% of cases) (Twickler *et al.*, 1993; Van Zalen-Sprock *et al.*, 1995). The only relevant finding in the maternal histories of our cases was a prior diagnosis of SLE in case no. 2. The effects of SLE on the course of pregnancy and on the fetus are well known, and include an incidence of spontaneous abortion (20–30% of cases) that is twice the normal rate, prematurity and intrauterine growth delay, increased fetal mortality, gestosis, and a neonatal lupus syndrome that characteristically includes cutaneous and hae-

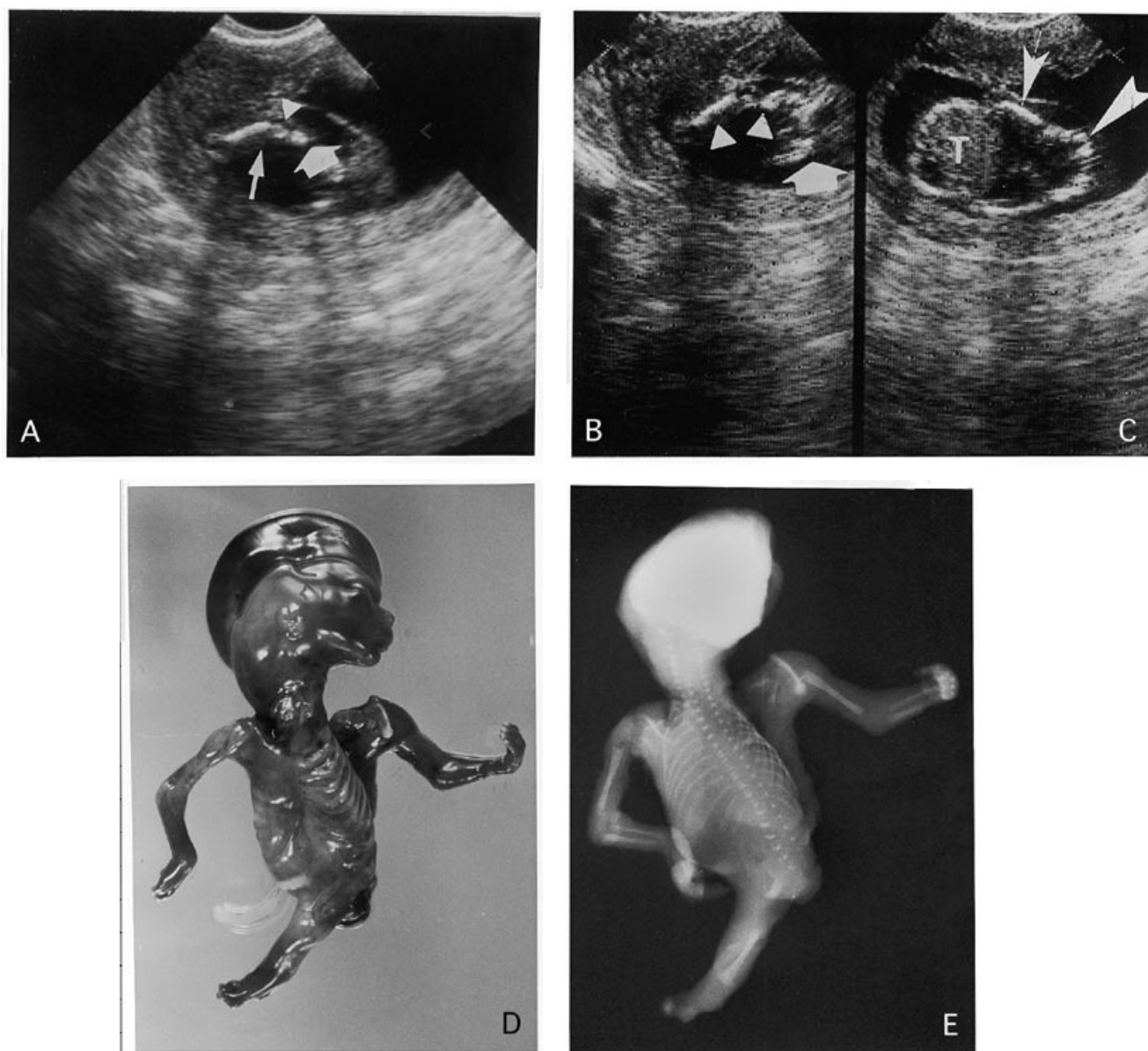


Figure 1. (Case no. 2) (A–C) Transvaginal ultrasound, 16th week. The lower limb is composed by the femur (thin arrow in **A**) and a questionable rudimentary tibia (triangle in **A**) and calcaneum (thick arrow in **A**). This was the only reliable ultrasonographic feature of sirenomelia, together with the absence of visualization of the contralateral lower limb. There is agenesis of one hip and lower limb, whereas contralaterally a dysmorphic hip (arrow in **B**) and thigh (triangles in **B**) are visible. A forearm (arrow in **C**) and hand (arrowhead in **C**) are normally visible in front of the trunk (T) in this sagittal section. (**D**) Fetus with single aberrant lower limb. (**E**) X-rays depict single femur (type VII sirenomelia) and rudimentary ossification centre of the calcaneum. There is sacrococcygeal agenesis, with only the ossification centres for S1 present.

matological abnormalities, splenomegaly, hepatomegaly, and cardiac malformations (Hayslett, 1991). However, we were unable to find any report on an association between sirenomelia and SLE, and we were unable to determine whether the association was casual or not in our case.

Clues for an antenatal ultrasonographic diagnosis

In sirenomelic fetuses, bilateral renal agenesis causes severe oligohydramnios, hindering a reliable sonographic evaluation

of the lower extremity in the second and third trimesters (Chenoweth *et al.*, 1991; Van Zalen-Sprock *et al.*, 1995). In some cases, bilateral renal agenesis is the only antenatal sonographic finding, and the diagnosis is made after termination of pregnancy. Sirtori *et al.* (1989) were able to identify sirenomelia sonographically in five out of 11 cases (none before 22 weeks gestational age), whereas a diagnosis of renal agenesis was advanced in the remainder. In cases where ultrasound reveals an absence of cardiac activity and active fetal movements, as occurred in case no. 1, there is obviously no need for further investigations and the pregnancy should be rapidly terminated. However, if the fetus is vital, additional diagnostic tools may be used to visualize the lower fetal extremity better, such as infusion of normal saline solution into the uterine cavity (Gembruch and Hansmann, 1988; Sirtori *et al.*, 1989; Chenoweth *et al.*, 1991) and high-frequency transvaginal ultrasonographic probes (Van Zalen-Sprock *et al.*, 1995).

Whereas oligohydramnios is a sonographic marker of absent or non-functioning kidneys from the second half of pregnancy onwards (Van Zalen-Sprock *et al.*, 1995), in earlier gestational stages other contributors to the production of amniotic fluid are present (Bronshtein *et al.*, 1993); therefore, early in the second trimester the amount of amniotic fluid may be sufficient to allow detection of abnormal lower limbs, as we noticed by ultrasound at the 16th week in case no. 2. Other than bilateral renal agenesis and the absence of a bladder, ultrasonographic features which may become apparent in the presence of a sufficient amount of amniotic fluid include undetermined external genitalia, anorectal atresia and lumbosacral agenesis. Other frequent abnormalities involve the abdominal wall and cardiovascular system. Hypertrophy of the right ventricle may ensue in later stages as a consequence of renal agenesis and oligohydramnios (Reed *et al.*, 1988). Doppler flow imaging invariably reveals a two-vessel umbilical cord (Van Zalen-Sprock, 1995).

An early antenatal diagnosis of sirenomelia may be suspected in the presence of bilateral renal agenesis, malformed lower limbs and a single umbilical artery. Such sonographic signs were readily apparent in our 16th week fetus (case no. 2), whereas severe oligohydramnios hindered a precise evaluation as early as in the 19th week in case no. 1. Therefore, we encourage an active search for sonographic signs of sirenomelia in the early second trimester in all fetuses with bilateral renal agenesis, as the diagnosis may be more readily made in this period than later, when oligohydramnios develops. Early diagnosis will allow termination of the pregnancy at an early stage, with minor risks and discomfort for the patient.

Pathological features and correlation with embryogenic theories

As previously stated, dysmorphic lower limbs are a principal feature of sirenomelia. The spectrum of lower limb anomalies ranges from simple fusion of the soft tissues to the presence of

a single, rudimentary limb; according to current classification schemes (Stocker and Heifetz, 1987), seven variants may be identified (Table I).

Table I. Classification of sirenomelia by Stocker and Heifetz (1987)

Type	Characteristics
I	All thigh and leg bones are present
II	Single fibula
III	Absent fibula
IV	Partially fused femurs, fused fibulae
V	Partially fused femurs
VI	Single femur, single tibia
VII	Single femur, absent tibia

The aetiology of sirenomelia is still widely debated (Chenoweth *et al.*, 1991; Twickler *et al.*, 1993; Van Zalen-Sprock *et al.*, 1995), and there is no widespread consensus as to the autonomous status of sirenomelia versus CRS, in which dysmorphic and maldeveloped lower limbs are found in association with both genito-urinary and anorectal anomalies and a variable degree of lumbosacral agenesis (Twickler *et al.*, 1993). The presence in sirenomelic fetuses of a large, aberrant single umbilical artery originating from the abdominal aorta could support the separation of the two entities, as such feature is not typical of CRS. Such an artery, which should actually be regarded as an abnormal persistence of the vitelline artery (Gilbert-Barness and Van Allen, 1997), is associated with hypoplasia of the aortic collaterals downwards. Therefore, vascular steal would divert nutrients from the caudal end of the embryo, with resulting underdevelopment, malformation, or arrest of caudal organs and tissues at an incomplete stage (Chenoweth *et al.* 1991). Our observation of a pelvic mesenchymal bud as the only remnant of an aplastic lower limb (case no. 2) might support this theory. Bilateral renal agenesis would be nicely explained as a result of hypoplasia of the renal arteries. However, the 'vascular steal' theory fails to explain the frequent association with other abnormalities such as cranial, cardiac and oesophageal defects, and the relationship with the VACTERL syndromic complex, which is frequently reported in the literature (Murphy *et al.*, 1992; McCoy *et al.*, 1994; Schöler and Salzano, 1994).

An alternative theory suggests that caudal deficiency represents a single anomaly of varying degrees (Chenoweth *et al.*, 1991), caused by early developmental disruption of the caudal mesoderm (Murphy *et al.*, 1992; Van Zalen-Sprock *et al.*, 1995). A teratogenic event during the gastrulation stage, i.e. during the 3rd gestational week, may interfere with the formation of the notochord, resulting in abnormal development of caudal structures (Dias and Walker, 1992). Because the notochord acts as neural inducer, neural tube defects are frequently associated (Chenoweth *et al.*, 1991; Chen *et al.*, 1997). According to such a theory, sirenomelia and CRS are nothing but

two ends of a single malformative spectrum (Böhm, 1988; Murphy *et al.*, 1992), varying in severity from minor forms with isolated coccygeal agenesis to the full-blown sirenomelic sequence; sirenomelia would result from a failure of lateralization secondary to mesenchymal deficiency of the caudal eminence (O'Rahilly and Muller, 1989). Moreover, prior authors have reported on sirenomelia associated with anencephaly (Rodriguez *et al.*, 1991) and alobar holoprosencephaly (Chen *et al.*, 1997). A vascular developmental anomaly would fail to explain such associations; rather, they strongly suggest a multisegmental failure in axial mesodermal patterning as their common cause.

The difficulties in identifying pathogenic mechanisms for sirenomelia and CRS has stimulated the search for prenatal ultrasonographic features which may prove sufficiently reliable for a differentiation of the two entities. Caudal spinal dysgenesis, consistently present in both sirenomelia and CRS, could add value to the hypothesis that sirenomelia represents an extreme form of CRS. Twickler *et al.* (1993) questioned whether sirenomelia should be included in the CRS spectrum, and stressed the fact that renal agenesis is nearly always present in sirenomelia and very rare in CRS; however, a variable degree of renal dysplasia is a well-known feature of CRS (Duhamel, 1961; Kallen and Winberg, 1974; Rubinstein and Bucy, 1975). The presence in our cases of some features typical of sirenomelia and distinctly uncommon in CRS, such as a single umbilical artery and bilateral renal agenesis, could be explained by a different degree of severity of early embryonic damage.

In conclusion, we believe that the identification of differences in sonographic signs between sirenomelia and CRS adds little, if any, support to the hypothesis of a separation between these entities. Even though we tend to believe that sirenomelia is the most severe end of the CRS spectrum, an antenatal sonographic differentiation between the two entities is nonetheless important in view of the different prognosis associated with these abnormalities.

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