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REVIEW ARTICLE

Sirenomelia: Can it be Missed in the First Trimester? A Case Series of A Rare Condition

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Abstract Sirenomelia is a very rare congenital developmental disorder of the lower extremities, and all the other derivatives from the caudal mesoderm, mainly the viscera i.e. kidneys, gonads and hindgut. In the majority of cases, it is incompatible with life in the neonatal period as it is associated with renal agenesis. The importance of detecting this anomaly in the first trimester lies in this lethality in order to offer the option of termination of pregnancy at an earlier gestation. Appropriate counselling at diagnosis is essential to give the couple a clear picture of what they might expect postnatally regarding the renal anomalies or the many surgeries which might be required for the lower limbs and viscera. We present a case series (n = 5) diagnosed by ultrasound at our center between January 2014–2020. Through this brief article, we aim to give a key to the antenatal diagnosis of this rare anomaly, an aid on how not to miss it and its subsequent management.

Keywords Sirenomelia · Mermaid syndrome · Single umbilical artery · Renal agenesis · Caudal regression syndrome

Introduction

Sirenomelia is also known as mermaid syndrome, sirenomelia syndrome, sirenomelus or sirenomelia sequence. Derived from the Greek word 'seirēn', it referred to the mythological sirens, some of them who resembled mermaids, and 'melos' for limb. The cases were thus described because the head and upper body was like that of a human and the lower body, like that of a fish. They were interestingly described to be creatures with the head of a woman and the body of a bird from the wings down. When history wrote new stories, the description of these bird women changed to being more like aquatic creatures with a mermaid like appearance (Fig. 1).

First reported in 1542, it is described to have an incidence of 1 in 100,000 live births; studies have produced rates from 1 in 68,741 to 1 in 97,807 [1]. it is 100 to 150 times more likely in identical (monozygotic) twins than in singletons or fraternal twins [1]. In 1927, Otto Kampmeier discovered the association between sirenomelia and single umbilical artery [1]. Duhamel coined the term "caudal regression syndrome" in 1961 to describe the association of sirenomelia with anorectal, genitourinary and vertebral anomalies [2]. Later a distinction was described between caudal regression syndrome (CRS) a diabetic embryopathy, and sirenomelia, a vascular 'steal' phenomenon, most commonly sporadic [3].

Case Summaries

1. A 22 year old, G3P1 + 1 had attended our centre for a routine first trimester screening at 12 weeks of gestation. The NT was raised (3.8 mm) with a grossly normal anatomy on first look examination. She had a high BMI. To be clearer about the anatomy and to rule out a structural anomaly for the increased NT, a transvaginal examination was done. A diagnosis of sirenomelia type III with bilateral renal agenesis was made (Fig. 2).
2. A 36 year old Primigravida at 14 weeks gestation, IVF conception attended for a first trimester screening.

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Fig. 1 Vase at the metropolitan museum of art, New York, depicting a mermaid

A sirenomelia type III, persistent vitelline artery and bilateral echogenic kidneys with subjective oligamnios was noted (Fig. 3).

3. A 32 year old G3P0 + 2, previous first trimester miscarriages, had come for first trimester screening at 11 weeks 3 days. It had been a single embryo transfer of a normally karyotyped embryo on PGS. Findings were of an MCDA twin with one of them having a type III sirenomelia with absent kidneys. The other fetus showed a demise.
4. A 22 year old Primigravida had come at 14 weeks 6 days for a late first trimester screening and was found to have a fetus which showed persistent vitelline artery, absent inferior vena cava, bilateral renal agenesis and sirenomelia type IV (Fig. 4).
5. A 28 year old G3P0 + 2, previous first trimester miscarriages, attended for an anomaly scan at 21 weeks of gestation. The findings were of multiple hemivertebrae, persistent vitelline artery and absent kidneys. It was a type V sirenomelia.

All of them opted for termination of pregnancy. The first case highlights the concept of resorting to a transvaginal approach if the operator is not satisfied with the transabdominal scan findings. The last case stresses the importance of covering all aspects mentioned in the guidelines systematically so that such cases do not end up being missed in the first trimester.

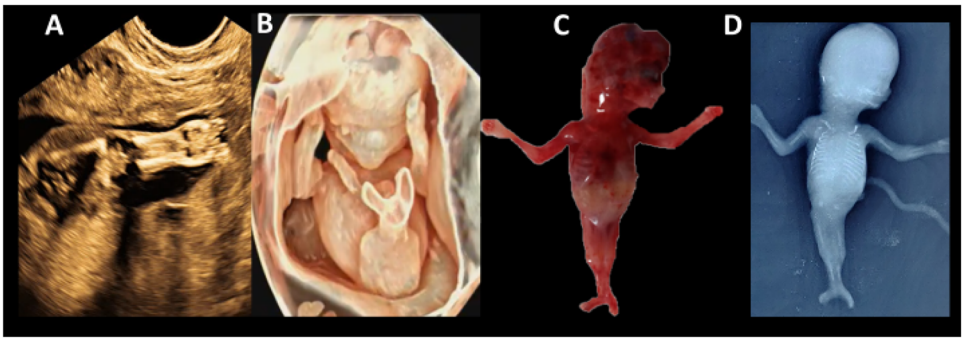


Fig. 2 Case 1 This figure shows a fetus with type 3 sirenomelia. (**a** 2D image, **b** 3D silhouette rendered mode, **c** gross specimen of the abortus, **d** post abortal X-ray)

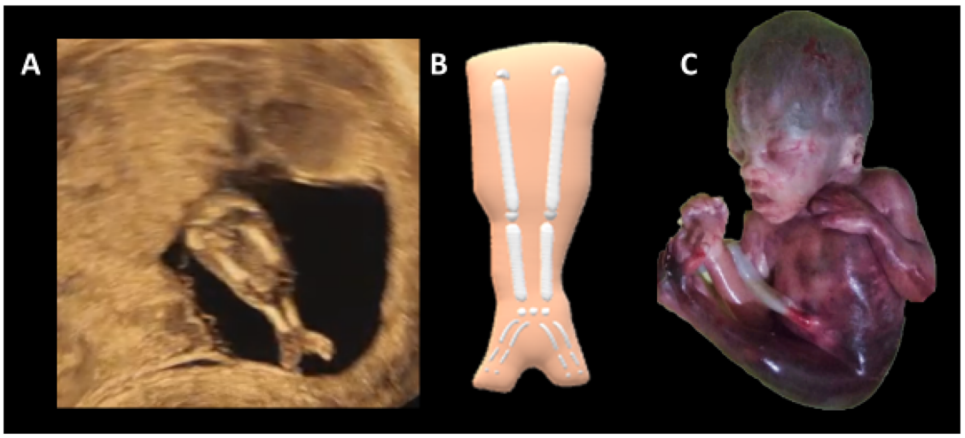


Fig. 3 Case 2 Type 3 sirenomelia. (**a** 2D image, **b** pictorial representation of the type of sirenomelia, **c** abortus)

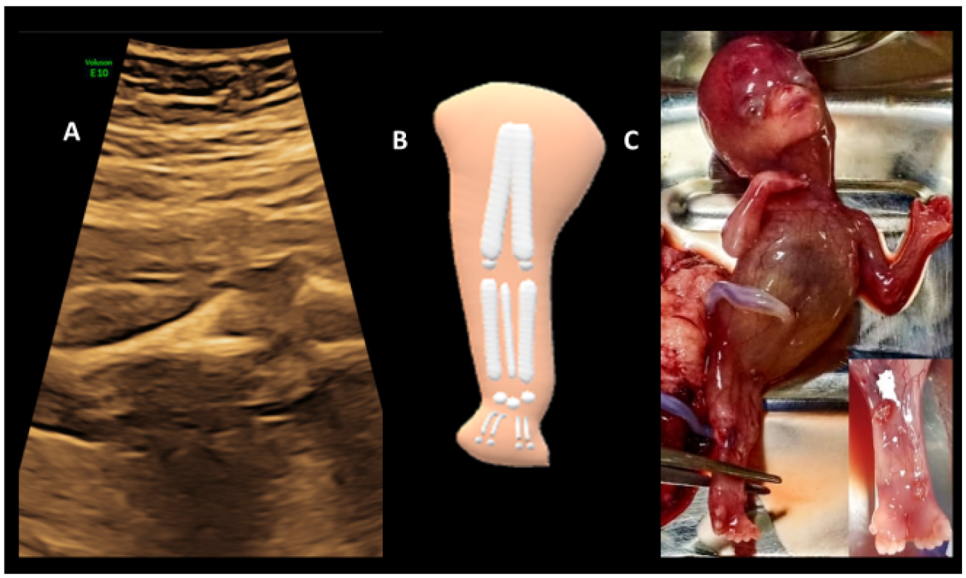


Fig. 4 Case 4 Type 4 sirenomelia (**a** 2D image, **b** pictorial representation of the type of sirenomelia, **c** abortus)

Discussion

Sirenomelia is mainly characterized by the fusion of both legs and non or malrotation of the fibula. It was previously thought to be a severe form of sacral agenesis/caudal regression syndrome whereas recent research shows that they are unrelated. It is mainly associated with [1] anomalies of the gastrointestinal tract (esophageal atresia, omphalocele, intestinal malrotation, persistent cloaca), nervous system (rachischisis, anencephaly, spina bifida, holoprosencephaly), genitourinary (renal agenesis), musculoskeletal (absence of radius), and facial, Potter's syndrome (Potter's facies, which includes large, low-set ears, prominent epicanthic fold, hypertelorism, flat nose and receding chin with oligohydramnios and pulmonary hypoplasia) as a consequence of renal agenesis) [4].

Various causative hypothesis have been forwarded. One hypothesis is a vascular steal phenomenon due to absent aorta, aberrant abdominal and umbilical vascular pattern and a persistent vitelline artery [5]. Here, the so called association of the single umbilical artery is in fact the persistent vitelline artery. The second hypothesis is a defective blastogenesis during gastrulation—embryonic insult between 28 and 32 days affecting the caudal mesoderm. A third hypothesis is a teratogenic effect (maternal diabetes, tobacco use, retinoic acid, cocaine and heavy metal exposure) to the neural tube during neurulation [1]. A fourth hypothesis suggests a defect in the twinning process that either stops the process of caudal differentiation or generates a second primitive streak [6].

Pathogenesis: A striking characteristic of the sirenomelia phenotype is that the merged lower limbs show an abnormal position that corresponds to a 180° rotation with respect to the position of a normal leg. During normal limb development, the limb buds develop as projections on either side of the embryo, cranially and caudally. The forelimbs rotate laterally whereas the hindlimb buds rotate medially. Therefore, the ventral surface of the hindlimbs eventually faces dorsally [6]. However, because of early abnormal fusion in the midline along their posterior margins, the fused hindlimbs cannot accomplish this rotation. This abnormal fusion may be due to a defect in the caudal mesoderm and the cloacal region. This is strikingly evidenced by the soles facing anteriorly, by the abnormal flexion of the knees and by the fibulae adopting a medial position between the tibiae. It might also be a secondary phenomenon occurring as a consequence of approximation of the limb fields [7].

Genetics: Research in mouse models reveals a few genes to be the probable causes for sirenomelia. The SRN (siren) gene is observed to cause hindlimb fusion in homozygous mice [6, 8]. Also TSG1 and BMP7 gene knock out in mice have caused hindlimb fusion [6, 9, 10, 11]. The results of karyotype testing done on sirenomelia cases reported in the literature are almost all normal. A report showed a case of sirenomelia with triploid mosaic (69, XXX/46,XX) [12]. A reciprocal translocation 46X, t(X;16)(p. 11.23;p. 12.3) has also been reported in another case report, but it has been described that the disrupted genes are not the ones associated with early human development, especially blastogenesis [13].

There are case reports of a family with five affected individuals, two with sirenomelia and 3 with CRS suggesting a genetic etiology [12] A case report of discordant monozygotic twins, one with sirenomelia and the other with anal atresia makes us ponder over a genetic etiology with a variable expression [13].

In our case series of 5 cases, all had persistant vitelline artery supporting the pathogenetic difference theory. Unfortunately none of the couples agreed to be tested for the genetic make up.

Sirenomelia versus Caudal Regression Syndrome

The difference between the pathogenesis of sirenomelia and caudal regression syndrome have been debated at length. Some authors opine that caudal regression syndrome is a spectrum ranging from imperforate/ectopic anus to the extreme end, which is sirenomelia. On the other hand, some authors advocate the pathogenesis of sirenomelia to have an aberrant abdominal artery- steal phenomenon and the caudal regression syndrome to be due to a defective caudal mesoderm. Duhamel [2] described the CRS-sirenomelia spectrum that encompasses variable severities whereas Jaiyesimi [3] distinguished sirenomelia from CRS and advocated that they are unrelated in their pathogenesis.

Regarding the pathogenesis difference, abnormal umbilical arteries are not an invariable feature of sirenomelia since rare examples of normal umbilical arteries has been reported with sirenomelia [14].

Similar syndromic conditions include VACTERL, OEIS and Curririno syndromes.

VACTERL association(an acronym for V—vertebral, A—anal, C—cardiovascular anomalies, TE—tracheo esophageal fistula, R—renal anomalies, L—limb defects) is a nonrandom constellation of birth defects that affects multiple organ systems. In addition, to the above mentioned features, affected children may also exhibit less frequent abnormalities including growth deficiencies and failure to gain weight (failure to thrive). Other characteristics which occur less frequently are hemifacial microsomia, external ear malformations, lung lobation defects, intestinal malrotation and genital anomalies.

OEIS complex is a combination of defects which include O—omphalocele, E—exstrophy of the cloaca, I—imperforate anus and S—spinal defects. It is described to be the extreme end of the exstrophy—epispadiasis spectrum. It is also described to be due to a defect in early blastogenesis or a defect of mesodermal migration from the primitive streak.

Currarino syndrome is an inherited congenital disorder with an autosomal dominant inheritance, affecting the sacrum and the surrounding abdominal viscera. Here, either the sacrum is not formed properly (fused vertebrae) or there is a presacral mass (anterior meningocele being the commonest, others include enteric cysts and teratomas) with malformations of the anus and/or rectum [15]

Diagnosis of Sirenomelia

In the antenatal period, sirenomelia can be diagnosed as early as 13 weeks by using high resolution and color doppler sonography [16, 17] The most commonly followed classification of sirenomelia is by Stocker and Heifetz [18]. They had classified sirenomelia into seven types mainly depending on the presence of skeletal elements in the thigh and leg. Type 1 is the mildest form where all bones in the limbs are present and the fusion affects only superficial tissues. The most severe type is type VII, where only a single bone is present with no differentiation of any long bones (Table 1).

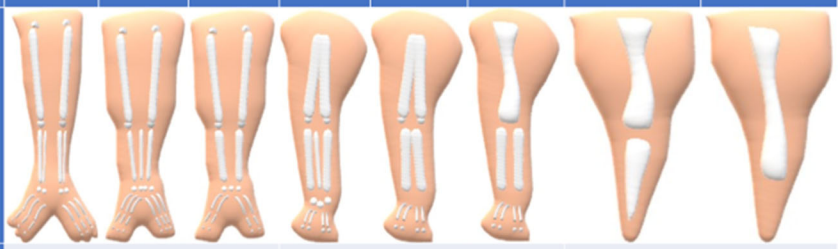
The diagnosis of sirenomelia cannot be missed if the guidelines put across by the international fetal medicine bodies regarding fetal anatomy are adhered to. The anatomy checklist from the international society of ultrasound in obstetrics and gynaecology (ISUOG) 2013 [19] includes some basic anatomy that needs to be checked. Some of the anatomy listed like visualization of kidneys, bladder and a few others have been described as optional. But the extremities come under the must-screen category and therefore a diagnosis of sirenomelia in the first trimester should rarely be missed. Counseling at such an early gestation would give the couple time to ponder over the options because of its lethality in the neonatal period in majority of the cases.

Prognosis and Genetic Counselling

Majority of the pregnancies with a sirenomelic fetus miscarry spontaneously. The main determinant for survival in the neonatal period is functioning kidney tissue [1]. About one-third to one-half of the rest are stillborn, with all but a few dying in the neonatal period as they are usually associated with renal agenesis and associated pulmonary hypoplasia.There have been only a handful of sirenomelia survivors. The longest survivor was Tiffany Yorks of Clearwater, Florida, who lived till the age of 27. A few who had minor renal abnormalities or near normal kidneys have survived as reported by McCoy et al. and Clarke et al. [20, 21] The option of termination needs to be explored sensitively. No cases of familial recurrence have been reported. However, under the pathogenetic concept of caudal regression syndrome, few familial cases are known. For those who wish to continue the pregnancy, risks of intrauterine death and the standard therapies available after delivery must be explained.

Majority of the fetuses have shown to have a normal karyotype with isolated case reports with genetic abnormalities and few with familial occurrences. An invasive

Table 1 Stocker sand Heifetz classification of sirenomelia, 1987

TYPES	TYPE I	TYPE II	TYPE III	TYPE IV	TYPE V	TYPE VI	TYPE VII	TYPE VIII
DIAGRAMS								
CLASSIFICATION	SYMPUS DIPUS OR SYMELIA			SYMPUS MONOPUS OR UROMELIA			SYMPUS APUS OR SIRENOMELIA	
FEMUR	PRESENT	PRESENT	PRESENT	PARTIAL FUSION	PARTIAL FUSION	SINGLE	SINGLE	SINGLE
TIBIA	PRESENT	PRESENT	PRESENT	PRESENT	PRESENT	PRESENT	SINGLE	ABSENT
FIBULA	PRESENT	SINGLE	ABSENT	FUSED	ABSENT	ABSENT	ABSENT	ABSENT

testing may be offered. None of our cases opted for genetic evaluation because of financial constraints.

Postnatal Management

Co-ordinated efforts of a multidisciplinary team is absolutely necessary if the baby survives. A systematic and comprehensive plan of management by pediatricians, surgeons, cardiologists, orthopedicians, nephrologists, urologists and other health care professionals will be needed.

Surgery has been successful in separating joined legs. In a brief description, balloon-like tissue expanders are inserted under the skin and the excess skin is then used to cover the legs once they are separated [22]

Conclusion

Sirenomelia is usually fatal in the newborn period despite treatment. As interesting is the history of the etymology of the word sirenomelia, so is its pathogenesis and the battle of the survivors with this condition. Prevention of embryonic insult by environmental factors can prove preventive. Optimum glycemic control in the preconceptional period and in first trimester should be maintained to prevent this anomaly. When diagnosed antenatally, termination should be offered.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed Consent Consent from the patients in the series have been taken to publish the respective case details and photographs. (Two couples refused to share the photographs and their wish was duly respected).

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