*Research Letter*

# Concordant Partial Urorectal Septum Malformation Sequence in Monozygotic Twins

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**To the Editor:**

The urorectal septum malformation (URSM) sequence is defined as the absence of the perineal and anal opening in association with ambiguous genitalia and urogenital, colonic, and lumbosacral anomalies. The URSM sequence is usually lethal in the newborn period due to pulmonary hypoplasia resulting from severe oligohydramnios. The abnormalities of this condition are though to arise early in development due to incomplete subdivision of the primitive cloaca and lack of breakdown of the cloacal membrane [Escobar et al., 1987; Wheeler et al., 1997].

A less severe form of URSM sequence is referred to by Wheeler and Weaver [2001] as the partial URSM sequence. Individuals with a partial URSM sequence typically have a single perineal/anal opening that serves as an outlet for a common cloaca and conduit for urine and feces to the outside. It is important to differentiate the partial from the full URSM sequence because the prognosis in the partial URSM sequence is generally good, with long-term survival a common feature.

In this article we report a case of monozygotic twins concordant for the milder and generally nonlethal form of the URSM sequence. Monozygotic twinning with this condition has not been previously reported.

The mother, a 19-year-old Caucasian woman, gravida 1, para 0, was presented to the ultrasound unit of the department of medical genetics and fetal medicine at 18 weeks of spontaneous pregnancy for routine screening. There was no family history of congenital malformations. The mother denied teratogenic exposure. On sonographic examination, a monochorionic, diamniotic twin pregnancy was diagnosed. Twin A had dilated distal bowel loops with enterolithiasis (an ultrasonographic examination revealed an echogenic bowel with multiple foci of calcified meconium intraluminally). Twin B had dilated distal bowel loops. A possible diagnosis of anal atresia was made. The genitalia could not be clearly determined. In view of the abnormal sonographic findings, amniocentesis was performed. Both fetuses had a normal 46,XY karyotype. The patient was referred to the high-risk clinic. Fetal biometry was appropriate for gestational age and a normal amount of amniotic fluid was observed. To further exclude anorectal malformation, magnetic resonance imaging (MRI) was performed which demonstrated dilated distal bowel loops (with enterolithiasis in twin A). The parenchyma of the kidneys and urinary bladder appeared normal. The twins were delivered by cesarean at 35 weeks of gestation after premature membrane rupture. Twin A weighed 1,950 g, twin B weighed 2,350 g. Postpartum examination revealed close placental insertions of both umbilical cords, each containing three vessels. Over a length of 25 cm the umbilical cords, separated by amniotic membranes, ran in such close proximity that they appeared to have a common course. The monochorionic, diamniotic twin pregnancy was confirmed and concordant fetal abnormalities were diagnosed. Both neonates had a single

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FIG. 1. External genitalia of twin A with cloaca single opening and bifid scrotum. [Color figure can be viewed in the online issue, which is available at www.interscience.willey.com.]

perineal opening at the base of the phallic structure that drained a common cloaca in combination with anal atresia (Figs. 1 and 2). The cloaca drained the bladder and colon separately. There was a short and hypoplastic colon, dilated distal bowel loops (in twin A with enterolithiasis), and a fistula between the colon and the bladder. There were also bifid scrotum, sacral hypoplasia, and coccygeal agenesis without tethered spinal cord. The diagnosis of partial URSM sequence was confirmed postnatally and the babies underwent corrective urogenital and intestinal surgeries. At present they are 2 years old and their health condition is generally good.

The partial and full URSM sequences are part of a spectrum of disorders caused by abnormalities in septation of the primitive urorectal septum. The partial URSM sequence is characterized by the presence of a persistent cloaca and a single perineal/anal opening. The cloaca drains the bladder, colon, and in females, the vagina. Long-term survival of affected individuals is common [Wheeler and Weaver, 2001].

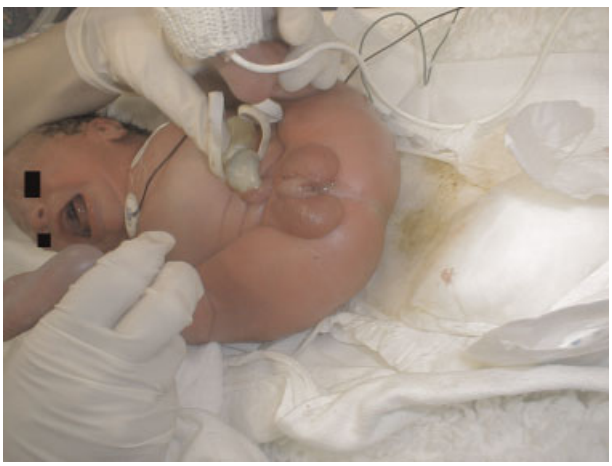

FIG. 2. External genitalia of twin B with cloaca single opening and bifid scrotum. [Color figure can be viewed in the online issue, which is available at www.interscience.willey.com.]

The partial URSM sequence is associated with a variety of unusual external genital malformations. Males tend to have a wider range of genital abnormalities including: hypospadias, a bifid scrotum, penoscrotal transposition, and an absent penis. The most common finding in females is apparent virilization with an enlarged clitoris and/or fused labia. Renal anomalies are also common and range from unilateral agenesis to multicystic dysplasia to hydronephrosis. All surviving individuals require multiple urogenital and intestinal surgeries [Wheeler and Weaver, 2001]. The initial evaluation of these patients included chromosomal analysis, renal ultrasonography, radiographic study of the internal cloaca, and spinal radiographs or MRI if a tethered cord was suspected.

Occurrence of the syndromes in monozygotic twins concordant for the anomaly has not been previously reported. The type of twinning depends on timing of development. Monozygotic twinning, which occurs less than 4 days postconception, will result in complete duplication of the membranes, giving a dichorionic, diamniotic placenta. Twinning occurring at 4–8 days postconception results in monochorionic, diamniotic placenta. Twinning at 10–15 days postconception will result in a monochorionic, monoamniotic placenta [De Lia, 1990]. In our case, with regard to common placental insertion of umbilical cords and their 25 cm common course, twinning probably occurred before the 10th day postconception. The cloacal membrane first appears at 20–21 days postconception, while perforation of the membrane occurs at days 49–50 [Robinson and Tross, 1984].

Hence, we believe that any teratogen exposure or endogenous event preventing the formation or regression of the cloacal membrane should act before this time and concordance in monozygotic twins who share their genetic makeup can argue for a genetic factor. We suggest that the majority of urorectal septal defects are due to either new dominant mutations or possible teratogen exposure. We propose that a genetic or multifactorial etiology be considered for this rare defect.

Achiron et al. [2000] reported two cases of the URSM sequence in two sets of discordant twins (one monozygotic and one dizygotic) diagnosed prenatally by ultrasound. The first fetus was of a set of monochorionic, monoamniotic twins. The second fetus was one of dichorionic, diamniotic twins. The diagnosis of both cases was confirmed postnatally. Until then, the URSM sequence had only been reported in singleton gestations. Discordance in monozygotic twins who share their genetic makeup usually argues against a genetic factor.

Wheeler et al. [1997] presented the findings of 13 additional cases of the full URSM sequence and cases reviewed from literature. The number of affected males and females was the same. The sex ratio in the 13 new cases was 7 males to 6 females and from the literature 21 males and 28 females. They did not report recurrences of the URSM sequence within families. These data would indicate that the condition is probably not inherited in an autosomal recessive manner. Since the number of affected males and females is approximately the same, this would argue against the condition being inherited in an X-linked recessive mode. The URSM sequence could be inherited in an autosomal dominant mode, but given the condition's lethality it is not possible to prove this at this time. In 25 patients reported by Wheeler and Weaver [2001], the partial URSM sequence was more common in females, with a female to male ratio of 18 to 7. None of the reported patients with the partial or full URSM sequence has had recurrence of the condition in their siblings or in their offspring. As more is learned about this condition, multiple causes may be delineated such as new mutations leading to mesodermal abnormalities and possible teratogens causing an insult to the primitive streak mesoderm.

To date, there has been one reported case of apparent autosomal dominant inheritance of a urorectal septal defect [Mills and Pergament, 1997]. In this family, a woman who had a congenital urogenital sinus and an anteriorly placed anus had a daughter with more severe urogenital anomalies, including an absent urethra and vagina but normal anus and colon. The appearance of urorectal septal defect in a female and her offspring provides evidence that URSM sequence may be of genetic origin.

A brief review of embryology is necessary to understand the possible pathogenesis of this condition. In a human fetus, the hindgut initially forms a cloaca (common canal for urine and stool) which is bound externally by a cloacal membrane composed of ectoderm and endoderm [Sadler, 1990]. In the fourth week of development, the primitive cloaca begins to be divided into two parts by the urorectal septum which is composed of mesoderm [Stephens, 1988]. The division of the cloaca is completed by the sixth week of development when the urorectal septum fuses with the cloacal membrane. The result of this septation and fusion is the anterior primitive urogenital sinus and the posterior anorectal canal [Sadler, 1990].

Fusion of the urorectal septum with the cloacal membrane is necessary for normal development of the urogenital sinus and anorectal canal. If the urorectal septum does not merge with the cloacal membrane, then either a cloaca or a fistulous tract will result. For normal formation of the external anus, urethra, and vaginal outlets, the urogenital and anal membranes must break down appropriately in the seventh week of gestation.

Wheeler and Weaver [2001] postulated a spectrum of URSM disorders that occur secondary to caudal mesodermal and endodermal deficiencies, abnormal development of the urorectal septum, and/or lack of cloacal membrane breakdown. The most severe of these conditions is the full URSM sequence. It results from a lack of breakdown of the cloacal membrane with a deficiency in urorectal septal development. Because normal cloacal membrane breakdown does not occur, no perineal or anal openings develop. Most of the other associated defects are related to a deficiency in mesoderm migrating into the caudal region of the embryo [Alles and Sulik, 1993; Nievelstein et al., 1998]. In the partial URSM sequence, there is a partial breakdown of the cloacal membrane. Due to a lack of mesodermal cells in the caudal region of the embryo, there is an incomplete descent of the urorectal septum and deficient development of the hindgut and surrounding tissues. The result is a single perineal/anal opening and other malformations associated with this condition. The abnormalities of the external genitalia probably develop as a result of either abnormal induction of the early external genital structures and/or lack of mesoderm to form these structures. The internal genital anomalies seen in females (i.e., septate/bifid vagina and uterus) may result from mechanical interference by the persistent cloaca, preventing the normal fusion of the Müllerian ducts, or alternatively, deficiency of the mesoderm required to form these organs. The partial and full URSM sequences are specific subsets of lower mesodermal defects [Pauli, 1994; Wheeler and Weaver, 2001].

The underlying cause and pathogenesis of urorectal septal defects are unknown. One current hypothesis is that mesodermal deficiencies are responsible for these defects. Sulik and associates have shown that several different teratogens, ochratoxin A (a fungal toxin) in chick embryos and etretinate (a retinoic acid derivate) in mouse embryos, selectively damage mesoderm and lead to conditions similar to the full and partial URSM sequences [Alles and Sulik, 1993; Mesrobian et al., 1994; Wei and Sulik, 1996; Jo Mauch and Albertine, 2002]. The spectrum of abnormalities in the affected mouse embryo seems to be related to the timing of exposure, with earlier exposures resulting in more severe effects. Mouse embryos exposed to etretinate at day 8 of gestation had abnormalities closer to the full URSM sequence, while those exposed at day 9 of gestation had less severe abnormalities, similar to the partial URSM sequence [Alles and Sulik, 1993; Mesrobian et al., 1994].

Additional evidence supporting mesodermal defects in the pathogenesis of the URSM sequence comes from studies of fetal lamb twins. Discordance

among dizygous twins suggested that teratogens were less likely to be implicated in the etiology. Rather, alterations in homeobox (*Hox*) codes that control local rates of cell proliferation, and alterations in *sonic hedgehog* were implicated in caudal mesodermal deficiency during blastogenesis [Jo Mauch and Albertine, 2002]. Mouse knockout models support the role of these genes in the disruption in signaling between endoderm and mesoderm. *Hox* mouse mutants show features of the URSM sequence [Warot et al., 1997]. *Hox* expression is amplified in *Gli* mutant mice [Moribe et al., 2000]. *Gli* proteins are *sonic hedgehog*-responsive transcription factors, and *Gli* knockout mice have hindgut and persistent cloacal abnormalities [Mo et al., 2001]. Defects in these genes result in deficiencies in the caudal mesoderm by way of interaction with *sonic hedgehog*. Retinoic acid, a well-documented teratogen, also regulates *sonic hedgehog* gene expression [Chang et al., 1997].

An anorectal malformation may be suspected when a dilated bowel in the lower abdomen of the fetus is seen [Petrikovski et al., 1988]. However, the combination of ambiguous genitalia with normal male karyotype should arouse suspicion of a URSM disorder. Absence of perineal orifices and fistulas are far more difficult to identify when using in utero ultrasound. The appearance of echogenic foci within a low pelvic cystic mass indicates the presence of enterolithiasis which can result from urine mixed with luminal meconium [Achiron et al., 2000]. Vesicoenteric fistulas were previously reported as having the same sonographic appearance as dilated bowel containing echogenic foci [Sepuvelda et al., 1994].

We have shown, for the fist time, the partial URSM sequence in monozygotic twins concordant for this anomaly. Monozygotic twinning with this condition has not been previously reported. The management of fetuses with a prenatally detected lower abdominal cystic mass, without oligohydramnios, is difficult because the underlying cause is often uncertain, as in the present case. Expectant management should be adopted unless there are other findings that indicate a poor prognosis. The prenatal sonographic diagnosis of more severe forms of urorectal septal defects (URSM disorders) is important for planning a rational intervention program and counseling the parents.

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