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MATERNAL-FETAL MEDICINE

Isolated bladder exstrophy in prenatal diagnosis

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Abstract

Purpose Isolated classic bladder exstrophy (CBE) is the most common variant of the bladder-exstrophy–epispadias complex (BEEC). The BEEC represents a spectrum ranging from isolated epispadias over CBE to the most severe form, cloacal exstrophy. We report on a series of 12 cases with CBE diagnosed prenatally and illustrate the spectrum of prenatal ultrasound findings with comparison to prior published reports on this entity.

Methods This was a retrospective study involving 12 fetuses with CBE at two large tertiary referral centers in Germany over a 14-year period (2004–2018).

Results Median diagnosis was made with ultrasound in 24 + 5 ($IQR_{25,75}$: 21 + 2, 29 + 0) weeks of gestation. All fetuses presented with the pathognomonic findings non-visualization of the fetal bladder and protruding abdominal mass below the umbilical cord insertion. All fetuses showed normal kidney anatomy and normal amniotic fluid throughout pregnancy. Epispadia was visible prenatally on ultrasound in 6/8 male fetuses. 1/12 Parents opted for termination of pregnancy, 11/12 fetuses were live born and received reconstructive surgery.

Conclusions Isolated CBE is an extremely rare prenatal sonographic finding. Prenatal diagnostics should exclude additional malformations within the spectrum of cloacal malformations.

Keywords Bladder exstrophy · Fetus · Prenatal diagnosis

Introduction

Isolated classic bladder exstrophy (CBE) is the most common variant within the bladder–exstrophy–epispadias complex (BEEC) [1]. With 2–4/100,000 births the general prevalence of this entity is low [2, 3]. Abnormal partitioning of the cloacal membrane prevents mesodermal fusion and results in the congenital malformations of the BEEC spectrum. Depending on the time of disruption the BEEC represents a spectrum ranging from isolated epispadias (later embryonic failure) over CBE to the most severe form, cloacal exstrophy (earliest disruption) [1]. The latter is often been referred to as OEIS complex as it is associated with omphalocele, imperforate anus, and vertebral defects [4].

Minor malformations such as epispadias often are isolated and can easily be overseen in prenatal ultrasound diagnostics. The OEIS complex as most severe form presents with additional malformations and its clinical picture might change during pregnancy [5–7]. Several sonographic features in the prenatal setting have been proposed in either small prenatal series or single case reports that have not been validated in larger series: The pathognomonic feature of CBE in prenatal ultrasound is the inability to visualize the fetal bladder on repeated prenatal ultrasound examination in the presence of normal appearing kidneys and amniotic fluid volume given an adequate time (30–60 min) to fill [8]. Instead of the fetal bladder, the second pathognomonic feature of bladder exstrophy in prenatal ultrasound can be identified: the protrusion of a solid mass between the two

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umbilical arteries just below the third pathognomonic feature of bladder exstrophy: the extraordinary low insertion of the umbilical cord [9]. Depending on the extend of bladder exstrophy malformations of the genitalia ranging from epispadias in male, bifid scrotum in male or bifid clitoris in female patients to even undetectable genitalia have been described [10–13].

Due to the rarity of the disease only small series and single case reports have been published on prenatally diagnosed isolated CBE. This rarity results in a lack of knowledge concerning the most appropriate counseling for affected parents [8]. For the least severe form, isolated epispadias, more data regarding prenatal diagnostic and postnatal outcome exists and the mild form of malformation usually is no reason for termination of pregnancy. The opposite is true for fetuses with OEIS that often present with severe additional malformations [7]. In consequence the overall majority of parents decide for termination of pregnancy [7]. As delineated above isolated CBE represents an intermediate form within the BEEC spectrum in regards to the severity of the defect between epispadias and cloacal exstrophy. Consequently there is little knowledge on prenatal course as well as perinatal management to guide parents counseling [8].

We report here on a prenatal series of 12 cases with isolated bladder exstrophy diagnosed prenatally and illustrate prenatal course and postnatal outcome.

Material and methods

All cases with a prenatal diagnosis of isolated CBE in a 14-year period (2004–2018) in two large tertiary referral centers (University of Bonn and University of Cologne, Germany) were retrospectively reviewed for intrauterine course and outcome. A prenatal diagnosis of isolated CBE was made in the presence of an exstrophic fetal bladder without additional major malformations. For all ultrasound examinations, 5-MHz, 7.5-MHz or 9-MHz curved array probes were used (ATL HDI 5000 and IU22, Philips, Hamburg, Germany; Voluson 730 Expert, Voluson E8, GE Healthcare, Solingen, Germany). A postnatal examination to verify the ultrasound results was performed in all cases.

Results

We reviewed 24 pregnancies with 24 fetuses affected by bladder exstrophy. 12 fetuses with OEIS that have been described elsewhere were excluded from this analysis leaving 12 fetuses for analysis [7]. The average maternal age at diagnosis was 30 years. All couples were healthy and non-consanguineous. All pregnancies were singleton pregnancies. Median diagnosis was made with 24 + 5 ($IQR_{25,75}$: 21 + 2, 29 + 0) weeks of gestation, the earliest with 15 + 2 weeks, the latest with 33 + 6 weeks of gestation. None of the diagnoses were made in the first trimester, seven of the diagnoses were made in the second trimester and five of diagnoses were made in the third trimester. Upon diagnoses, all fetuses underwent detailed ultrasound evaluation (Table 1). Non visualization of the bladder, a lower abdominal bulge and a low set umbilical insertion was observed in all fetuses (Fig. 1). Eight fetuses were male, four fetuses were female. Of the eight male fetuses epispadias was found in six cases. One fetus (#12) presented with a small perimembraneous ventricle septal defect.

We did not observe one single case with intrauterine growth retardation (IUGR) or oligohydramnios during the course of pregnancy. Karyotyping was performed prenatally in one case and revealed a normal karyotype.

To exclude for potential missed diagnoses we searched the databases on the participating hospitals for diagnoses of any malformation within the BEEC spectrum within the study period. We could yet not observe any newborn child born in the participating delivery clinics that was postnatally diagnosed with isolated bladder exstrophy that had not been diagnosed already during pregnancy.

Following counseling 1 of 12 parents opted for termination of pregnancy (TOP), postpartale examination was performed and assured the prenatal diagnosis (Table 2). 11 Children were live born in a median of 38 + 4 ($IQR_{25,75}$: 37 + 2, 39 + 2) weeks of gestation. Of these 11 children 82% (9/11) were delivered by caesarean section, 18% (2/11) were delivered by vaginal birth. Prenatally diagnosed malformations were confirmed in all children. Postpartum reconstructive surgeries were performed in all live born children.

Discussion

Isolated CBE represents one distinct entity within the BEEC spectrum. Several sonographic features in second trimester ultrasound have been associated with CBE (Table 3) [11]: (1) Non-visualization of the bladder is the pathognomonic sign of bladder exstrophy and was observed in all fetuses in this cohort. Absent or abnormal fetal kidneys that might affect renal function should be excluded, however, in these cases amniotic fluid usually is low or absent. In addition the examiner should be aware of hypoechogenic round structures of different origin than the bladder in the fetal abdomen as both remnants of the fetal urachus and umbilical cord cysts have been described to resemble a fetal bladder in the setting of bladder exstrophy [14, 15]. Yet both can easily be distinguished from the fetal bladder as they do not show any dynamic change in size. (2) A lower abdominal bulge representing the exstrophic bladder could be seen in all patients in our cohort. (3) A smaller penis with anteriorly

Table 1 Prenatal presentation of fetuses with bladder exstrophy

Fetus	Gestational age at diagnosis	Sex	Presentation of bladder exstrophy								
			Solid mass in the lower anterior fetal abdomen	Nonvisible fetal bladder	Low-set insertion of the umbilical cord	Normal kidney anatomy	Normal amniotic fluid volume	Pubic diastasis (mm) at diagnosis	Umbilical cord insertion-to-genital tubercle length (mm) at diagnosis	Urine jet into the abdomen	External genitalia malformation
#1	25+4	Male	+	+	+	+	+	16.2	n.d	n.d	Epispadia
#2	25+5	Male	+	+	+	+	+	15.9	5.2	n.d	Epispadia
#3	28+2	Male	+	+	+	+	+	n.d	n.d	+	
#4	23+5	Male	+	+	+	+	+	12.6	7.2	+	Epispadia
#5	15+2	Male	+	+	+	+	+	11.6	5.1	n.d	
#6	33+6	Male	+	+	+	+	+	16.3	9.1	n.d	Epispadia
#7	33+1	Male	+	+	+	+	+	18.6	7.2	n.d	Epispadia
#8	23+3	Male	+	+	+	+	+	13.1	6.0	n.d	Epispadia
#9	31+2	Female	+	+	+	+	+	21.1	9.6	n.d	
#10	21+5	Female	+	+	+	+	+	13.1	4.3	n.d	
#11	19+5	Female	+	+	+	+	+	11.7	4.6	n.d	
#12	19+4	Female	+	+	+	+	+	12.3	6.3	n.d	

Prenatal findings in 9 fetuses with isolated bladder exstrophy

n.d., not determined

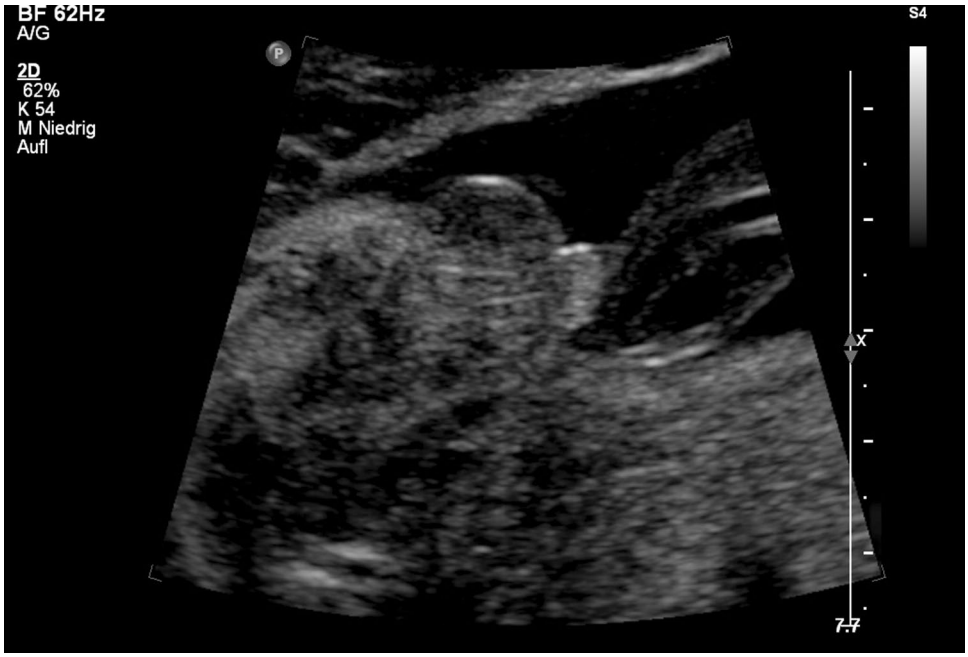

Fig. 1 Fetal bladder exstrophy. Mid-sagittal image of the fetal abdomen and pelvis showing a low-set umbilical cord insertion and an anterior abdominal wall mass in fetus #8 in 23 + 3 weeks of gestation

Table 2 Outcome, postnatal reconstructive surgeries and follow-up

Fetus	Outcome	Gestational age at birth	Postnatal reconstructive surgeries	Continence	Postnatal follow-up
#1	Live birth	35 + 5	Day 1: primary closure of the bladder exstrophy Year 2: Rekonstructive surgery epispadias Year 7: Bladder neck plastic + Cologne Pouch	Yes	120 months
#2	Live birth	38 + 6	Day 3: primary closure of the bladder exstrophy	n.a	15 months
#3	Live birth	38 + 4	Day 10: primary closure of the bladder exstrophy Year 1: Bladder neck plastic + Mitrofanoff stoma + bilateral ureterokutaneostomy Year 5: Cologne Pouch variant (vesicosigmoideostomy)	Yes	161 months
#4	Live birth	39 + 2	Month 2: primary closure of the bladder exstrophy + Rekonstructive surgery epispadias Year 4: Rekonstructive surgery epispadias	No	67 months
#5	Live birth	39 + 1	Day 3: primary closure of the bladder exstrophy	–	–
#6	Live birth	38 + 0	Day 1: primary closure of the bladder exstrophy Year 2: Rekonstructive surgery epispadias	Yes	46 months
#7	Live birth	39 + 2	Day 1: primary closure of the bladder exstrophy Year 2: Rekonstructive surgery epispadias Year 8: Bladder neck plastic	Partial	156 months
#8	TOP				
#9	Live birth	40 + 3	Month 1: primary closure of the bladder exstrophy	n.a	14 months
#10	Live birth	36 + 4	Day 3: primary closure of the bladder exstrophy	Yes	38 months
#11	Live birth	36 + 3	Day 1: primary closure of the bladder exstrophy Year 1: Vesicostoma Year 3: Bladder augmentation + Mitrofanoff stoma Year 5: Closure of the vesicostoma	Yes	84 months
#12	Live birth	38 + 4	Month 1: Cologne pouch with ureterosigmoideostomy	Yes*	119

Outcome and gestational age at birth were obtained. All postnatal reconstructive surgeries as well as postnatal follow-up were obtained from the respective pediatric surgeons

n.a., not assesible due to age

*Continence via the cologne bladder pouch

Table 3 Prenatal ultrasound findings in isolated fetal bladder exstrophy in the literature

Fetus	References	Gestational age at diagnosis	Sex	Prenatal ultrasound findings								Outcome
				Solid mass in the lower anterior fetal abdomen	Nonvisible fetal bladder	Low-set insertion of the umbilical cord	Normal kidney anatomy	Normal amniotic fluid volume	External genitalia malformation	Pubic diastasis diameter (mm)	Urine jet into amniotic cavity	
#1	Mirk et al. [26]	36	M	Yes	Yes			Yes				Live born at 39 weeks
#2	Barth et al. [27]	24	F	No	Yes			Yes				Live born at 41 weeks
#3	Jaffe et al. [10]	30	M	Yes	Yes	Yes	Yes	Yes	Normal scrotum, penis not visible			Live born at 40 weeks
#4	Erb and Jeanty [28]	18										TOP
#5	Bronshtein et al. [29]	14		Yes	Yes	Not clearly visible	Yes	Yes				TOP
#6	Messelink et al. [30]	18	M	No	Yes	Yes		Yes				Live born
#7–#9	Gearheart et al. [11]			8/12	12/17	5/17			8/17			
#10	Khandelwal et al. [31]	21			Yes			Yes				
#11	Pinette et al. [12]	27	M	Yes	Yes	Yes	Yes	Yes	Microphallus			Live born at 40 weeks
#12	Pinette et al.	19	M	Yes	Yes	n.a	Yes	Yes	Not clearly identifiable			TOP
#13	Chreston et al.	24	F									Live born at 39 weeks
#14	Cacciari et al. [8]	22	M	Yes	Yes							TOP
#15	Goldstein et al. [14]	22	M	Yes	Yes	Yes	Yes	Yes				TOP
#16	Evangelidis et al. [19]	33	F	Yes	Yes	Yes	Yes	Yes				Live born at 39 weeks
#17	Tong et al. [15]	16	F	Yes	No		Yes	Yes				Live born at 41 weeks
#18	Mabille et al. [32]	23			Yes	Yes			Normal			Live born at 38 weeks
#19	Goldman et al. [21]				Yes		Yes					Live born
#20	Goldman et al.				Yes		Yes					Live born

Table 3 (continued)

Fetus	References	Gestational age at diagnosis	Sex	Prenatal ultrasound findings							Outcome
				Solid mass in the lower anterior fetal abdomen	Nonvisible fetal bladder	Low-set insertion of the umbilical cord	Normal kidney anatomy	Normal amniotic fluid volume	External genitalia malformation	Pubic diastasis diameter (mm)	Urine jet into amniotic cavity	
#21	Wolniakowski et al. [13]	20		Yes	Yes	Yes	Yes	Yes	Small penis, widened scrotum			Live born at 41 weeks
#22–#27	Fishel-Bartal et al. [17]	15.7			6/6	6/6						TOP
#28–#31	Bronshtein et al. [18]	3 × 15, 1 × 23									4/4	TOP
#32–#47	Antomarchi et al. [16]									15.4 ± 3.3		

All articles of case reports or case series on fetuses with isolated CBE were screened for published prenatal ultrasound signs of isolated CBE

displaced scrotum was documented in the majority of male fetuses. Consistent with newer reports on this entity we could observe (4) a widened pubic diastasis and (5) a shortened fetal umbilical cord insertion-to-genital tubercle length in our cohort of fetuses with isolated CBE [16, 17]. The sonographic feature of (6) direct urine excretion from the ureters into the amniotic fluid yet is a sign that is difficult to assess in retrospective studies and should be validated in further prospective studies [18].

Despite the relatively small patient cohort and the retrospective nature as limitations of this study, recommendations for parents counseling when fetal isolated CBE is detected can be made.

First, prenatal assessment should include a systemic evaluation of the fetal anatomy to identify potential malformations that may guide the diagnosis. Special emphasis should be laid on the distinction of isolated CBE from other malformations of the BEEC. Most importantly accompanying bowel malformations should be identified as these indicate cloacal exstrophy. The fetal anus might be identified as a hypoechoic ring with an echogenic center ("target sign" by the perianal muscular complex, Fig. 2). Absence of this sign is associated with the presence of anal atresia respectively rectal agenesis with imperforate anus as part of cloacal exstrophy. A normal recto-anal anatomy and the absence of spinal defects or omphalocele exclude cloacal exstrophy. Malformations of the external genitalia should thoroughly be described and, if 2D-ultrasound fails to assure the exact genital malformation in complex cases, 3D-ultrasound and MRI may aid in the counseling of affected parents [13, 19]. In addition to the visualization of the ureters ending in the protruding mass, especially MRI allows for the identification of the gender, the exact genital malformation and may also help in the exclusion of cloacal exstrophy [20, 21]. In fetuses with isolated epispadias, the mild form of malformation eases prenatal parents counseling and results generally not in a termination of pregnancy. The opposite is true for fetuses with OEIS complex that often present with severe additional malformations and termination of pregnancy is performed in the overall majority of cases [7]. Isolated CBE represents a somewhat intermediate form between epispadias and cloacal exstrophy and has nowadays a most favorable postnatal outcome.

Second, genetic counseling should be performed. With respect to our cohort and to other reports on this malformation no abnormal karyotyping could be identified. Prenatal karyotyping is consequently unlikely to add relevant information for the parents. While recent genetic studies have identified duplications of chromosomal region 22q11.2 as a rare cause for isolated CBE, none of the duplication carriers had signs of intellectual disability or other congenital anomalies suggesting that the pregnancy outcome with or without duplication will be favorable [22].

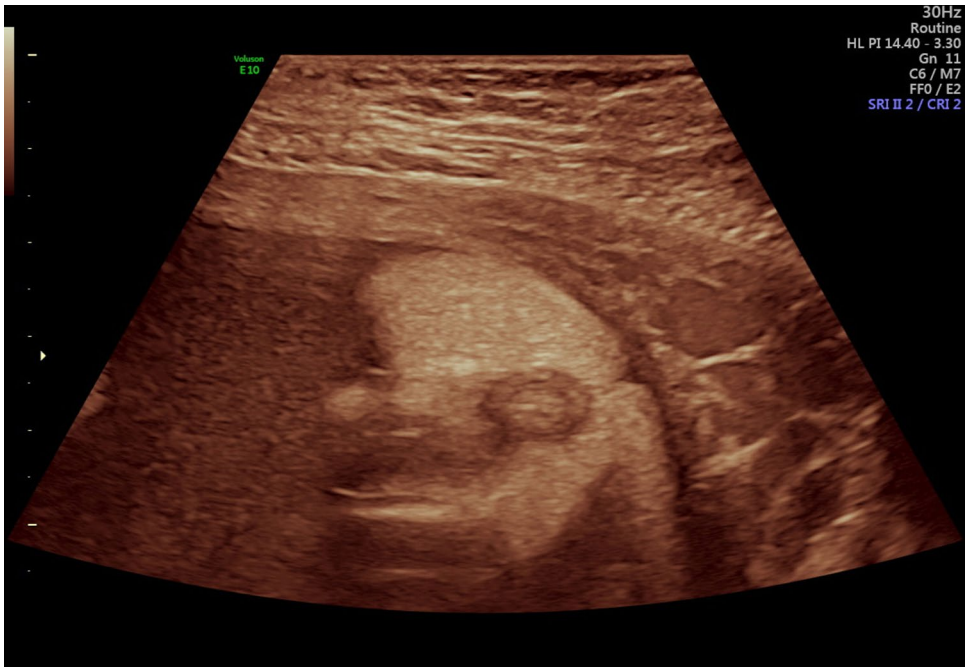

Fig. 2 Fetal target sign. The intact fetal anus can be identified as a hypoechoic ring with an echogenic center ("target sign") by the perianal muscular complex in 28 + 6 weeks of gestation

Third, counseling by a pediatric urologist and a pediatric surgeon should be performed. Quality of life of children affected by CBE has been evaluated as generally good yet impaired in comparison to the general population. The individual functional results seems to be the most likely predictive factor for the individual quality of live score and Parents should be informed on the long therapeutic follow up of their children [1, 23]. In these children, the following surgeries can be anticipated: (1) at birth: reconstruction of the bladder and primary closure of the abdominal wall with/without iliac osteotomy; (2) at age 12–18 months: corporeal lengthening and dorsal chordee release with urethroplasty in male, vulvoplasty and clitoroplasty in female patients; (3) at age 4–8 years: bladder neck reconstruction and additional operations for urinary continence; (4) antireflux procedures and additional complementary operations as necessary (5) after puberty: cosmetic surgery of the female mons area and abdominal wall [8]. With regard to long term sequelae, urinary continence following bladder reconstruction can be achieved in up to 90% depending on the type of surgical repair [24]. Most of the female patients will have normal fertility while male patients have significantly lower fertility but can achieve fatherhood on a regular basis by the use of assisted reproductive techniques [25].

Fourth, prenatal management should include regular sonographic controls to exclude deterioration of the fetal status. In our cohort we did not observe development of oligohydramnios or hydroureteronephrosis.

Fifth, an appropriate plan must be made for perinatal management. Pregnancy should be continued as usual. Spontaneous delivery can be envisaged for isolated CBE and the perinatal period should be handled as normal as possible. The hospital of delivery should be informed prenatally about the condition and the parents should be brought in touch with a surgeon who is experienced in the treatment of CBE [8]. Furthermore, the parents should be brought in touch with patients support groups, who will give the pregnant parents an inside view on the condition from their point of view. Reconstruction after 6 to 8 weeks with an appropriate dressing on the bladder is adequate and allows the parents and the child for bonding and a normal perinatal period.

Conclusion

Isolated bladder exstrophy is an extremely rare prenatal sonographic feature. Because of different approach in cloacal exstrophy, thorough prenatal ultrasound to exclude anal, spinal and other malformations should be performed. Prenatal counseling should include the usually benign prenatal course of this malformation as well as the expected postnatal reconstructive surgeries.

Author contributions MRM: project development, data collection, data analysis, manuscript writing. BM-D: data collection, data analysis. HR: data analysis, data analysis, manuscript writing. RP: data collection, manuscript editing. IG: data collection, data analysis, manuscript editing. AG: data collection, data analysis, manuscript editing. CB: data collection, data analysis, manuscript editing. TMB: project development, data collection, manuscript writing. UG: project development, data collection, data analysis, manuscript writing. All authors finally approved the manuscript.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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