Am J Transl Res 2023;15(3):1982-1989
www.ajtr.org /ISSN:1943-8141/AJTR0147054

Original Article

The clinical value of prenatal ultrasound in the diagnosis of caudal regression syndrome

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Received October 16, 2022; Accepted February 6, 2023; Epub March 15, 2023; Published March 30, 2023

Abstract: Objective: Caudal regression syndrome (CRS) is a rare and fatal anomaly that can easily be missed in prenatal two-dimensional (2D) ultrasonography. This retrospective analysis aimed to determine the performance of combined 2D and three-dimensional (3D) ultrasound for the prenatal diagnosis of CRS. Methods: We retrospectively analyzed 168 fetuses diagnosed with spinal lesions by combined 2D and 3D ultrasound at the First Affiliated Hospital of Anhui Medical University from January 2016 to June 2022. We analyzed the sonographic characteristics of these cases and assessed the diagnostic value of ultrasound in fetal CRS. Results: Fourteen fetuses were confirmed to have CRS after labor induction and postpartum, and 13 of these were correctly identified by prenatal ultrasound imaging. The sensitivity, specificity, accuracy, and Youden index of prenatal ultrasound were 85.7%, 93.5%, 92.9%, and 0.79, respectively. Conclusion: The typical prenatal sonographic features of CRS include different degrees of lumbar and sacrococcygeal spine loss combined with abnormal lower limb development. Prenatal ultrasound can assess the extent and location of lesions, highlighting its high diagnostic value.

Keywords: Prenatal ultrasound, tail degeneration, caudal regression syndrome

Introduction

Caudal regression syndrome (CRS) is a very rare congenital malformation caused by limited development of the caudal cell mass during the embryonic period. CRS often manifests as different degrees of sacrococcygeal vertebral dysgenesis, spinal cord development disorder, and lower limb malformation. Current evidence suggests that the incidence of CRS is approximately 1:60,000 to 1:100,000 live births [1]. Although little is known about the mechanism, the pathogenesis of CRS is suspected to be driven by the interplay between genetic predisposition and environmental factors resulting in a spectrum of phenotypic expression and originating from disorders in either primary or secondary neurulation. Maternal pregestational diabetes is a known risk factor for CRS; there is a relatively high risk of CRS in infants of diabetic mothers compared with infants of nondiabetic mothers, much higher than for any other birth defect. Insulin-dependent diabetes mellitus has been reported in 15%-25% of mothers of children with CRS, and poor metabolic control is a key risk factor in diabetic women [2]. The underlying defect is the failure of notochord formation during the gastrulation phase of embryogenesis. The severity of vertebral and spinal cord defects and the associated malformations determines long-term prognosis. Neurogenic bladder and bowel dysfunction (NBBD) is also commonly observed in CRS. Today, the majority of children with NBBD, as with spina bifida, can preserve their renal function and achieve fecal and urinary continence [3]. Good results have also been reported in sacral agenesia. Prenatal diagnosis of this disease is rarely reported; most cases are diagnosed postnatally [4, 5].

Prenatal two-dimensional (2D) ultrasound plays an important role in CRS diagnosis as a noninvasive, convenient, and real-time dynamic examination method. In addition, three-dimensional (3D) ultrasound provides objective and accurate imaging of each section of the spine, increasing the accuracy of prenatal diagnosis [6, 7]. The present study expounds on the value of prenatal ultrasound in diagnosing CRS and

analyzes the sonographic characteristics of CRS to provide an important reference for clinical prenatal consultation and perinatal care.

Participants and methods

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ-2022-0846). Written informed consent was obtained from all participants and their families before they participated in the study.

Of 35,471 pregnant women who underwent prenatal screening in the First Affiliated Hospital of Anhui Medical University from January 2016 to June 2022, 168 were diagnosed with fetal spinal lesions and retrospectively analyzed. The inclusion criteria were: (1) singleton pregnancy; (2) health care manuals and complete clinical data established and filed in community or regular hospitals before delivery; (3) spinal lesions detected by prenatal ultrasound; (4) all participants and family members willing to undergo relevant examination; and (5) complete prenatal ultrasound examination data. Patients were excluded for the following reasons: (1) presence of comorbidities, such as psychiatric or neurological diseases, or (2) loss to follow-up. All examinations were performed during middle and late pregnancy using a GE Volusion E10 Color Doppler ultrasound unit equipped with a CV1-8A volume probe and a C2-6 convex array probe.

2D ultrasound

All fetuses were routinely scanned according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines and underwent conventional biological indicator assessment. Fetuses with suspicious spinal lesions were examined in three planes (transverse plane, coronal plane, and sagittal section) for a comprehensive evaluation, which included observing the position of the conus medullaris, recording static or dynamic video images and measurement data, and noting complications of the rectum, anus, heart, kidney, limbs, and other structures.

3D ultrasound

3D ultrasound was routinely conducted for fetuses showing spinal abnormalities on 2D ultrasound. OmniView and tomographic ultrasound imaging were used to process the 3D data. The lesion locations were visually evaluated in various coronal sections and cross-sections, including orthogonal and non-orthogonal planes.

Follow-up

Clinical follow-up was performed for participants who decided to terminate their pregnancy after the first prenatal examination revealed abnormal fetal ultrasound findings. Clinical follow-up was also performed for participants who decided to continue their pregnancy to evaluate the surgical results after birth until 6 months.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. The measured data were expressed as mean ± standard deviation (SD), and the differences were compared using *t*-test. Quantitative data were expressed as percentages, and differences were assessed by the Chi-square test. *P*-values less than 0.05 were considered statistically significant.

Results

General information

Fourteen cases of CRS were confirmed by autopsy after labor induction or imaging after spontaneous delivery. The mean maternal age at the discovery of CRS by prenatal ultrasonography was 29.43±1.41 years (range 23-37 years), and the mean gestational age was 25^{+2} weeks (23^{+6} to 30^{+2} weeks). In 11 cases, pregnancy was terminated by amniotic cavity injection of ethacridine lactate after the prenatal diagnosis consultation. The remaining three cases were full-term fetuses that were spontaneously delivered and underwent anal atresia surgery. These infants were followed for 6 months and exhibited normal growth and development. Thirteen of the 14 cases were accurately diagnosed by prenatal ultrasonography, for an accuracy of 92.9%. Gestational diabetes mellitus was found in two cases. **Table 1** provides more detailed information on the characteristics of the 14 cases.

Ultrasound diagnostic characteristics: spine and conus medullaris

Thirteen of the 14 fetuses with CRS were correctly diagnosed by prenatal ultrasound, and all showed different degrees of sacrococcygeal

Table 1. General information of 14 fetuses diagnosed with CRS

NO	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (years)	23	26	33	32	25	27	34	37	30	26	29	32	30	26
Gestational diabetes mellitus			+					+						
Gestational age (weeks)	30^{+2}	24^{+6}	25^{+1}	25^{+4}	23^{+6}	24	25	23	27^{+1}	26	24	24^{+3}	23	25^{+1}
Pregnancy outcome														
Induced labor	+		+	+	+	+		+	+	+		+	+	+
Full-term normal delivery		+					+				+			

CRS: Caudal regression syndrome.

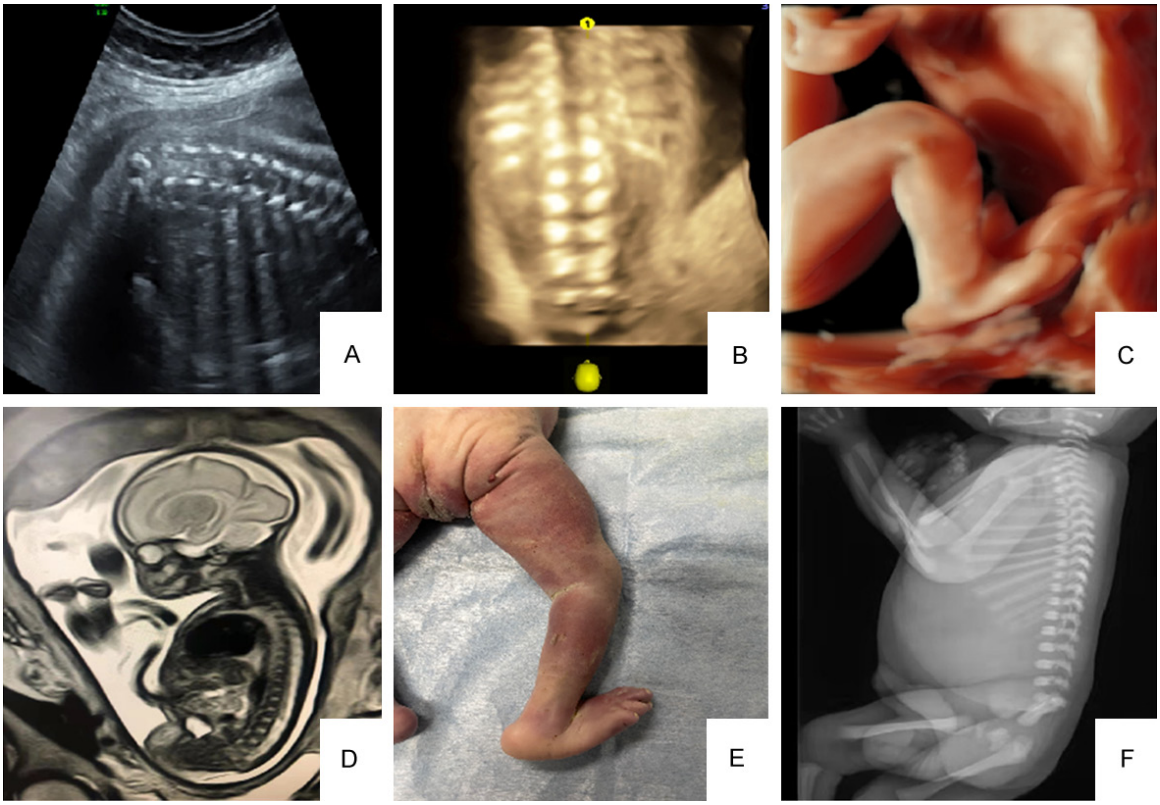

Figure 1. CRS, 27 weeks pregnant. A. Sagittal 2D ultrasound view of the fetal lower spine showing a defect in the lumbosacral vertebral body and hypoplasia of the L5 vertebral body. B. Coronal section 3D ultrasound view of the fetal lower spine showing a defect in the lumbosacral vertebral body and hypoplasia of the L5 vertebral body. C. 3D ultrasound showing rocker bottom feet with a prominent calcaneus and rigid forefoot. D. Sagittal prenatal MRI view SSFSE-T2W1 of the fetal lower spine showing a defect in the lumbosacral vertebral body and hypoplasia of the L5 vertebral body. E. The specimen after induced labor with a left-side rocker bottom foot. F. Lateral X-ray of the spine after labor induction showing a defect in the lumbosacral vertebral body and hypoplasia of the L5 vertebral body. Abbreviations: CRS, caudal regression syndrome; 2D, two-dimensional; MRI, magnetic resonance imaging.

deletion (**Figures 1A**, **1B**, **2A**, **3A**). Three of the 14 fetuses exhibited partial agenesis of the lumbar vertebral spine. Other cases of CRS exhibited abnormal conus medullaris (n=9), low conus medullaris (n=7), absent conus medullaris (n=1), and split spinal cord and lipoma (n=1) (**Figure 2A**, **2B**).

Ultrasound diagnostic characteristics: complications

Seven of the 14 fetuses presented with abnormal posture of both lower limbs (50%), and five cases had reduced muscle mass in the lower limbs (35.7%). Eleven of the 14 fetuses exhibit-

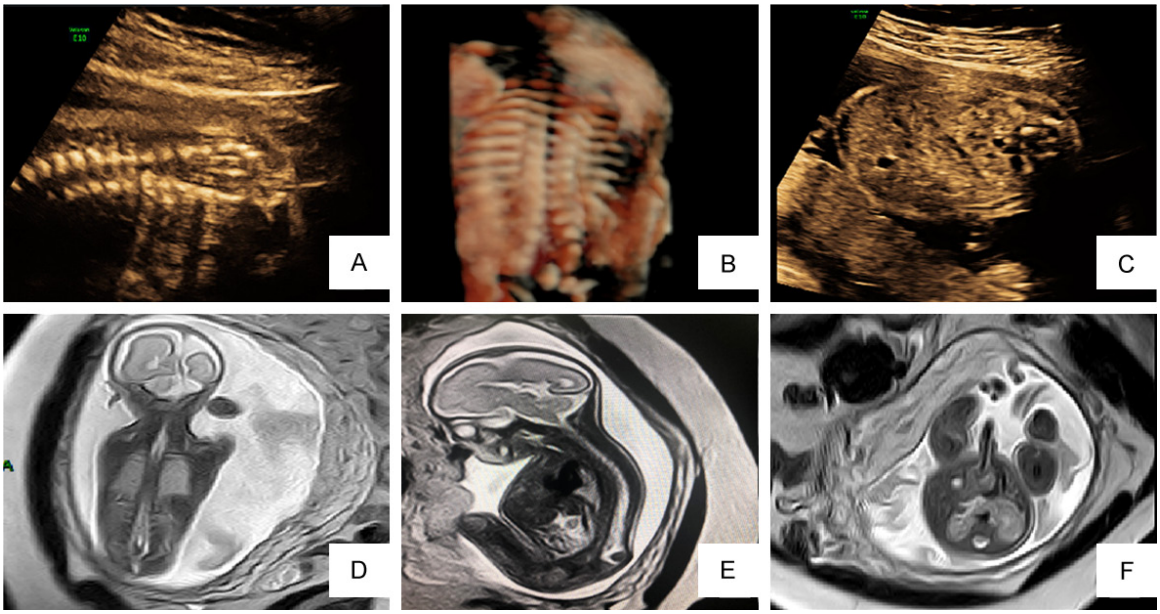

Figure 2. CRS, 30 weeks pregnant. A. Sagittal 2D ultrasound view of the fetal lower spine showing a defect in the lumbosacral vertebral body and intraspinal lipomas. B. Coronal section 3D ultrasound view of the fetal lower spine showing a defect in the lumbosacral vertebral body and intraspinal lipomas. C. Transverse view showing the fusion of the lower poles of both kidneys in front of the spine, presenting as "horseshoe kidneys". D. Coronal SSFSE-T2W1 intraspinal lipoma with longitudinal spinal cord fissure. E. Sagittal SSFSE-T2W1 of the fetal lower spine showing a defect in the lumbosacral vertebral body and intraspinal lipomas. Abbreviations: CRS, caudal regression syndrome; 3D, three-dimensional. F. Axial SSFSE-T2WI showed that the lower poles of both kidneys were connected.

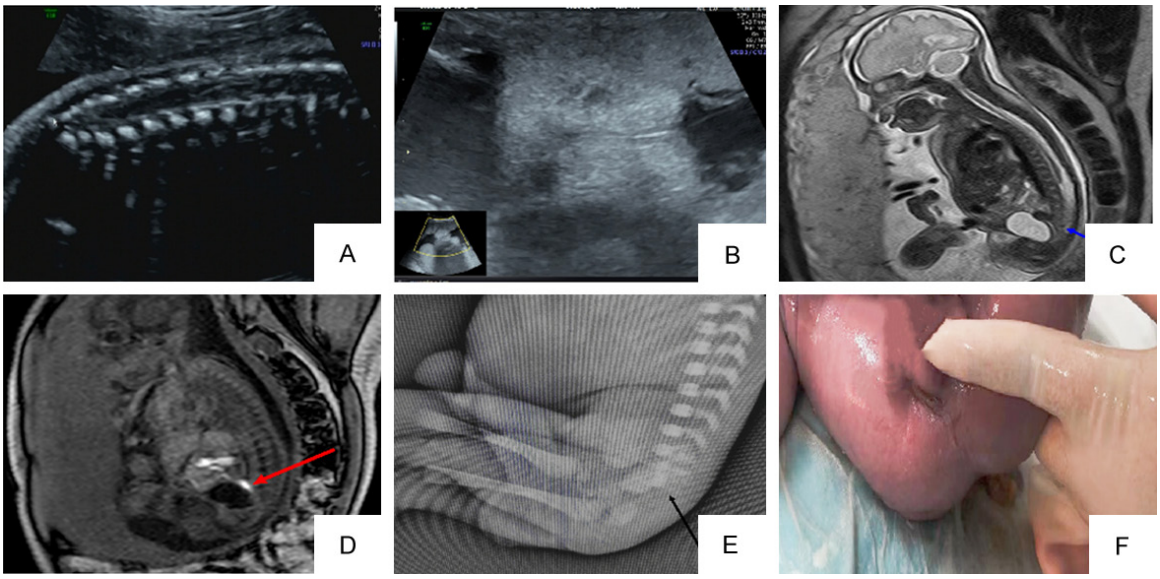

Figure 3. CRS, 25 weeks pregnant. A. Sagittal 2D ultrasound view of the fetal lower spine showing a defect in the lumbosacral vertebral body. B. 2D ultrasound showing only a linear hyperechoic structure with no target sign in the fetal anus. C. Sagittal prenatal MRI view SSFSE-T2W1 of the fetal lower spine showing a defect in the lumbosacral vertebral body. D. Sagittal SSFSE-T1W1 showing the proximal end of the rectum. Its distal end is not shown. E. Lateral X-ray of the spine after labor induction showing a defect in the lumbosacral vertebral body. F. After labor induction, no anal recess or anal atresia were found. Abbreviations: CRS, caudal regression syndrome; 2D, two-dimensional; MRI, magnetic resonance imaging.

ed abnormal foot posture, including varus feet (n=7) and rocker bottom feet (n=2) (**Figure 1C**). Moreover, two cases exhibited feet syndactyly and polydactyly, and one presented with com-

Table 2. Prenatal ultrasound features of 14 fetuses with CRS

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Spinal lesions														
Sacrococcygeal defect	+	+	+	+	+	+	+	+	+	+	-	+	+	+
Combined with other spinal abnormalities	-	+	-	+	+	+	-	-	+	+	+	-	-	-
End of the conus medullaris														
Low	+	+	-	+	-	+	-	+	-		-	-	+	+
Defect	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Triton	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spina bifida and lipoma	-	-	-	-	-	-	-	-	-	+	-	-	-	-
Abnormal posture of both lower limbs														
Crosswise or straight	+	+	+	-	-	+	-	+	+	-	-	-	+	-
Atrophy of both calf muscles	+	-	+	-	-	+	-	+	-	-	-	-	+	-
Sirenomelia	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Abnormal posture of both feet														
Clubfoot	+	-	+	-	+	+	-	+	+	-	-	-	+	-
Rocker bottom feet	-	+	-	+	-	-	-	-	-	-	-	-	-	-
Syndactyly and polydactyly	-	-	-	-	+	+	-	-	-	-	-	-	-	-
Monopodia	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Renal dysplasia														
Absence	+	-	-	-	-	-	-	-	-	-	-	-	-	+
Ectopic kidney	-	+	-	-	+	-	-	-	+	-	-	-	-	-
Polycystic kidney	-	-	+	-	-	+	-	-	-	-	-	-	-	-
Horseshoe kidneys	-	-	-	-	-	-	-	+	-	+	-	-	-	-
Hydronephrosis	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Cardiac anomalies														
Tetralogy of Fallot	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Ventricular septal defect	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Endocardial cushion defect	-	-	-		-	+	-	-	-	-	-	-	-	-
Anal atresia	+	+	-	-	+	-	-	+	+	+	-	-	+	+
Hypospadia	-	-	-	+	-	-	+	-	-	-	-	-	-	-
acromphalus	-	+	-	-	-	-	-	-	-	-	-	-	+	-
Exstrophy of the bladder	-	+	-	-	-	-	-	-	-	-	-	-	+	-

Note: -, absent on prenatal ultrasound; +, present on prenatal ultrasound. CRS: Caudal regression syndrome.

plete fusion of the legs with only one abnormal foot found in a single posture (sirenomelia, or "mermaid syndrome"). Eight of the 14 fetuses had anal atresia (57.1%) (**Figure 3B**), 2 had hypospadias (14.2%), and 2 had omphalocele and bladder exstrophy (14.2%). Ten of the 14 fetuses had renal abnormalities (71.4%), including renal agenesis (n=2), ectopic kidney (n=3), polycystic kidney (n=2), obstructive hydronephrosis (n=1), and horseshoe kidney (n=2) (**Figure 2C**). Three of the 14 fetuses presented with cardiac malformations (21.4%), including tetralogy of Fallot (n=1), absence of endocardial cushion (n=1), and ventricular septal defect (n=1) (**Table 2**).

Follow-up

CRS diagnosis was confirmed by pathological anatomy analysis after labor induction, and imaging examinations were performed for the fetuses that were spontaneously delivered (**Figures 1D-F**, **2D-F**, **3C-F**), revealing that 13 cases were correctly diagnosed by prenatal ultrasonography. In the diagnosis of complications, anal atresia (n=6) and abnormal conus medullaris (n=2) were missed by prenatal ultrasound. The sensitivity, specificity, accuracy, and Youden index of prenatal ultrasound diagnosis of CRS were 85.7%, 93.5%, 92.9%, and 0.79, respectively (**Table 3**).

Table 3. Evaluation of prenatal ultrasound for CRS diagnosis

Indicators	Nature	CRS (n=14)	Non-CRS (n=154)	Sensitivity	Specificity	Accuracy	Youden index
2D+3D US	Positive	12	10	85.7%	93.5%	92.9%	0.79
	Negative	2	144				

CRS: Caudal regression syndrome.

Discussion

CRS is a rare condition with an incidence of 0.1-0.25 per 10,000, and its pathogenesis remains largely unclear. The prevalence of CRS in infants of diabetic mothers has been reported to be up to 1 in 350 live births, and 20%-25% of mothers of infants with CRS have insulin-dependent diabetes mellitus [8, 9]. Genetic and environmental factors may also contribute to the occurrence of CRS [10, 11]. In addition to spinal abnormalities, fetuses with CRS may present with other abnormalities involving the lower limbs and skeleton, anal atresia, renal agenesis, ectopic kidneys, neurogenic bladder, and abnormal or undeveloped genitals. The prognosis of CRS is mainly related to the degree of sacrococcygeal absence and the severity of its complications, for which surgery and supportive treatment remain the mainstay of treatment [12, 13]. In the present study, gestational diabetes mellitus was only present in two of the 14 pregnancies (14.3%). Draaken et al. [14] reported that gene mutations-e.g. heavy polypeptide-like 1 (*CLTCL1*) and PDZ domain containing 2 (*PDZD2*) mutations-in diabetic patients could lead to genetic variation of CSR, which somewhat elucidates the relationship between CRS and gestational diabetes mellitus. However, Assimakopoulos et al. [15] and Zaw et al. [16] reported that environmental factors more importantly influenced CRS cases in monozygotic and dizygotic twins carried by diabetic individuals. These results suggest that CRS is caused by the interplay of pathogenic factors.

CRS can be divided into five types according to the location and extent of the spinal lesions. Type V is the most serious, complicated by sacrococcygeal lesions and partial or complete fusion of the legs, also known as mermaid syndrome. Only one Type V case was observed in the present study.

Prenatal ultrasound plays an important role in diagnosing CRS given its non-invasiveness and accuracy. Real-time 3D ultrasound allows the fetal spine to be observed in the parasagittal, transverse, and coronal planes. However, prenatal ultrasound is influenced by many factors, including fetal position, amniotic fluid volume, and abdominal wall fat present during pregnancy, which lead to missed and misdiagnosed cases. In the present study, the sensitivity, specificity, accuracy, and Youden index of prenatal ultrasound diagnosis of CRS were 92.8%, 93.5%, 93.4%, and 0.86, respectively; however, the ultrasound examination missed conus medullaris lesions in two cases and anal atresia in six. The diagnostic accuracy of prenatal magnetic resonance imaging (MRI) for spinal and spinal cord lesions is reportedly higher than that of prenatal ultrasound [17, 18], highlighting its adjunctive value to prenatal ultrasound. In terms of complications, the incidence rates of hypospadias, toe abnormalities, and heart abnormalities during prenatal ultrasound were 2/14, 7/14, and 3/14, respectively. Compared with the previously reported incidence rates of anal atresia as a complication of CRS, the incidence rate in this study was relatively low (6/14). Anal atresia is a well-established complication of CRS and can be divided into high and low types based on the relationship between the distal rectal pouch and the puborectalis muscle. Direct signs of anal atresia include the absence of the perianal muscular complex and target sign (hypoechoic anal sphincter and echogenic anal mucosa); however, a target sign can be found in low atresia for some fetuses, making prenatal diagnosis via ultrasound especially difficult. It is widely believed that anal atresia can be indirectly diagnosed by dilated distal bowel segments and calcified intraluminal meconium in the second and third trimesters, but it is difficult to distinguish between normal and abnormally dilated bowels in the third trimester when the rectum and colon are obvious of stool. The atypicality of the direct and indirect signs of anal atresia accounts for the low accuracy of prenatal ultrasound diagnosis [19-21]. To some extent, anal

atresia is more accurately diagnosed by MRI than by ultrasound [22].

CRS is often associated with urinary system malformations. In our study, 10 of the 14 cases were complicated by renal abnormalities (71.4%), including renal agenesis (n=2), ectopic kidney (n=3), polycystic kidney (n=2), obstructive hydronephrosis (n=1), and horseshoe kidney (n=2). The accuracy of prenatal ultrasound diagnosis of these complications was 100%. Prenatal ultrasound is the most convenient and cost-effective screening method for fetal renal dysplasia, and different renal abnormalities have typical ultrasonic manifestations. In addition to urinary system abnormalities, abnormal lower limbs and feet posture were common in this study: seven of the 14 fetuses exhibited abnormal posture of lower limbs, and five showed calf muscle atrophy. Furthermore, omphalocele and bladder exstrophy were found in two fetuses.

This study has some limitations. First, the sample size analyzed in this study was small due to the low incidence of CRS. A multi-center study with a larger sample size is required to improve the robustness of our findings. However, it should be noted that our hospital is an important prenatal diagnosis center in the province. In some cases, abnormalities detected in other hospitals are referred to our center, which may lead to selection bias. In addition, whole exome sequencing was not performed for all studied cases [4, 23] despite the importance of gene mutations in CRS [14, 24, 25]. Accordingly, whole exome sequencing results will be included in our future research.

In conclusion, prenatal ultrasound is inexpensive and free of radiation and can be used for real-time dynamic observation and follow-up, thus playing an important role in CRS diagnosis. Overall, our findings provide a foothold for clinical diagnosis and prenatal consultation in this patient population.

Disclosure of conflict of interest

None.

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