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Congenital Cystic Adenomatoid Malformation Volume Ratio in Prenatal Assessment of Prognosis of Fetal Pulmonary Sequestrations*

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Summary: This study aimed to evaluate the prognosis of pulmonary sequestration (PS) by measuring congenital cystic adenomatoid malformation volume ratio (CVR) value in fetal congenital PS. The fetal CVR in 49 cases of fetal PS diagnosed by prenatal ultrasound in Xiangyang No. 1 People's Hospital from March 2010 to June 2017 were measured, and the clinical outcomes were observed. According to the prenatal ultrasound CVR value, 49 fetuses diagnosed with PS were divided into 2 groups: group 1 with CVR≥1.26, and group 2 with CVR<1.26. The incidence rate of fetal edema, respiratory distress symptoms and survival rate were compared between the two groups. The risk factors of the fetal PS were evaluated by single and multiple Logistic regression analysis. The correlation between CVR and fetal prognosis was analyzed. Of the 49 fetuses, there were 34 cases of PS (ILS) type (69.39%, 34/49), 10 cases of PS (ELS) type I (20.41%, 10/49) and 5 cases of PS (ELS) type II (10.20%, 5/49). Forty-six cases (93.88%, 46/49) were born alive, there was 1 case (CVR ≥1.26) (2.04%, 1/49) of induced abortion, and 2 cases (CVR ≥1.26) (4.08%, 2/49) of stillbirths. In group 1 (*n*=24), 21 cases were born alive, and the incidence rate of newborn respiratory distress and fetal edema was 100% (21/21) and 79.17% (19/24) respectively. In group 2 (*n*=25), there were 3 cases (12%,3/25) of newborn respiratory distress, 3 cases (12%, 3/25) of fetal edema, and the rate of live birth was 100%. There were statistically significant differences between the two groups in the incidence of fetal edema, postpartum respiratory symptoms and survival rate. CVR was a risk factor for PS and was associated with fetal prognosis. CVR in the midtrimester of pregnancy is an effective index to evaluate the prognosis of fetal PS. CVR ≥1.26 is associated with an increased risk of fetal edema, infant respiratory distress and intrauterine or postnatal death.
Key words: broncho-pulmonary sequestration; ultrasonography; midtrimester; CVR; prognosis

Pulmonary sequestration (PS) is a rare fetal pulmonary developmental malformation, accounting for 0.15% to 6.40% of congenital pulmonary dysplasia, and the ratio of men to women is approximately 4:1[1, 2]. Color-flow Doppler sonography and echogenic lung ultrasonic imaging were most commonly used methods for prenatal diagnosis of PS[3, 4]. PS can be divided into intralobar pulmonary sequestration (ILS) and extralobar pulmonary sequestration (ELS), and the latter lacks independent pleura covering that separates it from normal pulmonary lobes[5, 6]. According to the location of the PS, ELS type is divided into two subtypes, type I and type II[7, 8]. With the development of ultrasound imaging techniques, fetal PS can be diagnosed at 22 weeks in pregnancy and the lump growth could be monitored. Current studies have shown that most of the PS may regress prenatally or stay the same size, but in some cases, they grow and produce pulmonary hypoplasia, respiratory distress and fetal edema with complicated clinical prognosis[9, 10]. Some literatures have reported that the congenital cystic adenomatoid malformation volume ratio (CVR) was a useful ultrasonic indicator and can be used to evaluate the prognosis of fetal PS. CVR is

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calculated by PS length×width×height×0.523/head circumference[11, 12].

In the present study, prenatal ultrasound was used to measure CVR values in fetuses with congenital PS in the second trimester, then the data of CVR, clinical and anatomical data from the fetuses with PS were collected. Subsequently, the correlation between CVR and clinical prognosis was analyzed. Furthermore, we found that the critical value of CVR was 1.26 in this study rather than 1.6 in the literature. Specific reports are as follows.

1 MATERIALS AND METHODS

This study is a retrospective study on prognostic evaluation of PS assessed by CVR value.

1.1 Study Subjects

Forty-nine fetuses diagnosed as having PS between March 2010 and June 2017 were evaluated at the Xiangyang No.1 People's Hospital, Xiangyang (China). All of the patients had been enrolled in research protocols approved by Xiangyang No.1 People's Hospital Affiliated to Hubei University of Medicine. All of the pregnant women provided written informed consent for this study.

1.2 Apparatus and Methods

GE Voluson E8 and GE 730 fetal ultrasound diagnostic instrument with convex array probe and 3.0–5.5 MHz was employed in this study. The pregnant women were examined by routine ultrasound scanning of fetus and appendages through the abdominal wall in the supine position. The ultrasonic examination standard used for the diagnosis of PS included the presence of an intrathoracic or intraabdominal fetal echogenic mass and an abnormal arterial supply from systemic circulation. According to the location, volume, and range of motion of the mass detected by ultrasound, PS was classified into ILS type, ELS type I and ELS type II. MRI was used when ultrasonography could not completely confirm the types of PS. A sagittal and axial section for the lesion was used to measure the maximal length and width of the PS. CVR was calculated by the following equation:

CVR=(Length×Width×Height×0.523)/Head circumference.

According to the CVR values measured, the PS fetuses were divided into 2 groups: group 1 (CVR ≥1.26) and group 2 (CVR<1.26) .

All of the above cases were jointly reviewed by 4 physicians with more than 20 years of experience in ultrasound work, and the final diagnosis was obtained. The CVR value was also averaged after multiple measurements.

1.3 Clinical Follow-up

Fetal ultrasound examination was performed every 1 to 3 weeks, and MRI was performed when it was necessary to diagnose the fetal PS (fig. 1). The data of pathological results in newborns that underwent surgery after birth were collected and the specimens from induced abortions underwent routine anatomical and pathological examination (fig. 2, 3). Heart rate, amniotic fluid index, placental thickness, ratio of the peak systolic velocity to the end diastolic velocity of umbilical artery Doppler velocimetry (S/D), CVR, fetal sex, birth gestational week, 5-min Apgar score and birth weight were recorded for Logistic regression analysis.

1.4 Statistical Analysis

The statistical analysis software SPSS 19.0 was applied, and the data were expressed by rate or percentage. The incidence of newborn respiratory distress, fetal edema and survival rate were compared by χ^2 test between the two groups. P<0.05 was considered statistically significant. Single factor

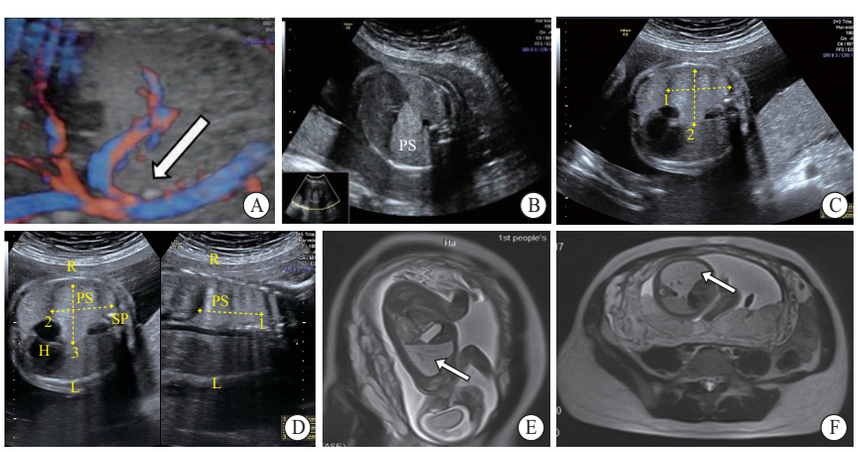

Fig. 1 Antepartum sonogram of a 22 weeks+2 days old foetus demonstrated echoic mass in left lung.
A: A systemic feeding artery was detected by Color Doppler (as indicated by the arrow). B: Ultrasonic examination showed a huge mass in the left lung of the fetus. C, D: Maximal length of the PS in sagittal view was used to measure the length. Vertical to this axis at the maximal width of the lump, the height and width of the PS were gauged. E, F: Antepartum MRI confirmed the huge mass (as shown by arrows) in the left lung.

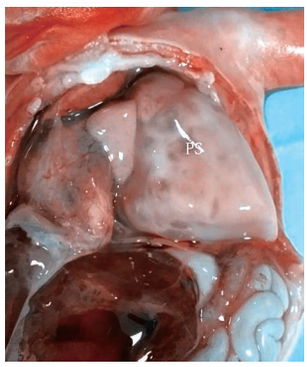

Fig. 2 Left PS in a 29 weeks and 4 days old stillbirth

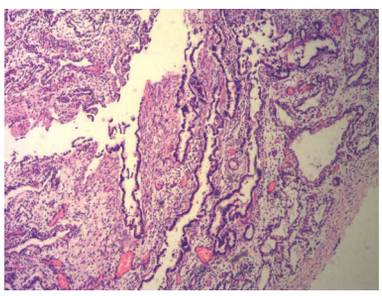

Fig. 3 Pathological analysis of PS in a stillbirth (HE, ×100)
Microscopes show fibrous tissue and poorly developed alveoli and bronchioles. It was confirmed as PS pathologically.

analysis was performed by software, and variables with statistical significance were screened for logistic regression analysis. The test level (a) was set at 0.05.

2 RESULTS

Of the 49 fetuses, 18 were females (36.73%, 18/49), and 31 were males (63.27%, 31/49). There were 28 fetuses with PS in the right lung (57.14%, 28/49), and 21 fetuses with PS in the left lung (42.86%, 21/49). Twenty-four fetuses with PS were categorized into group 1 (CVR≥1.26) and 25 fetuses into group 2 (CVR<1.26). In group 1, 1 case of PS had severe edema, hydrothorax, peritoneal effusion and cardiac malformation at gestational week 26 to 32, and the fetus was subjected to induced labor, and 2 cases died in uteri due to severe intrauterine complications and intrauterine distress. Forty-six of 49 fetuses (93.88%) were born alive, including 21 fetuses in group 1 (CVR≥1.26) and 25 fetuses in group 2 (CVR<1.26). There were 27 term infants (2 in group 1, and 25 in group 2) and 19 premature infants (all in group 1).

Fetal edema occurred in 22 cases (44.90%, 22/49), and newborn respiratory distress was found in 24 of 46 live births (52.17%). Thirty-four fetuses (13 in group 1, and 21 in group 2) were subjected to surgery after birth. The postoperative pathological results showed that 33 fetuses were diagnosed as having PS, one fetus (CVR≥1.26) was diagnosed as having PS and pulmonary cystadenoma, and 34 newborns recovered well after resection. Among the 12 newborns given conservative treatment, 8 patients whose PS was too big to resect (CVR≥1.26) died of severe pneumonia, respiratory distress, multiple organ failure and premature dystrophy within 1 to 6 months after birth; 4 newborns (CVR<1.26, PS mass was reduced in 3 cases, and PS mass disappeared in one case) recovered well with conservative treatment in local hospitals.

In group 1 (CVR≥1.26), the newborn respiratory distress occurred in 21 fetuses (100%), fetal edema occurred in 19 fetuses (79.17%), and there were 21 live-born infants (87.5%). In group 2 (CVR<1.26), respiratory distress occurred in 3 fetuses (12%), fetal edema occurred in 3 fetuses (12%), and there were 25 live-born infants (100%). There were significant differences in the postpartum respiratory distress, fetal edema rate and survival rate between the two groups (P<0.05, table 1). Amniotic fluid index, placental thickness, S/D, CVR, birth gestational week, 5-min Apgar score, and birth weight were risk factors of the fetal PS (P<0.05, table 2). Multiple factor Logistic regression analysis showed that CVR was the risk factor for an adverse outcome of the fetal PS (P<0.05, table 3). CVR was closely associated with the postnatal respiratory distress, fetal edema, intrauterine or postnatal death (table 4).

3 DISCUSSION

This study suggested that PS fetuses without fetal edema and infant respiratory distress had an ideal prognosis. CVR ≥1.26 was associated with fetal edema, postpartum respiratory symptoms and survival rate (table 1).

Oversize fetal PS mass led to fetal edema and dysplasia of lung[13–15]. Our research confirmed that the incidence of fetal edema, postpartum respiratory

Table 1 CVR in fetal PS and prognosis (*n*)

Groups	Infant respiratory distress		Fetal edema		Intrauterine or postnatal death	
	No	Yes	No	Yes	No	Yes
CVR≥1.26	0	21	2	19	13	11
CVR<1.26	22	3	22	3	25	0
χ^2 value	–(Fisher's Exact Test)		25.111		–(Fisher's Exact Test)	
P value	<0.000		<0.000		<0.000	

Table 2 Single factor Logistic regression analysis of prognostic factors for fetal PS

Influencing factor	*B*	S.E.	Wald	*P*	OR	95%CI
Heart rate	0.032	0.020	2.554	0.110	1.033	0.993–1.074
Amniotic fluid index	0.246	0.106	5.404	0.020	1.279	1.039–1.573
Placental thickness	1.491	0.543	7.544	0.006	4.441	1.533–12.866
S/D	1.322	0.588	5.054	0.025	3.749	1.184–11.870
CVR	2.247	0.713	9.938	0.002	9.456	2.339–38.224
Fetal Sex	–0.021	0.711	0.001	0.977	0.980	0.234–3.949
Birth gestational week	–0.490	0.183	7.149	0.008	0.612	0.428–0.877
5-min Apgar score	–1.060	0.487	4.727	0.030	0.347	0.133–0.901
Birth weight	–0.003	0.001	9.210	0.002	0.997	0.995–0.999

Amniotic fluid index, placental thickness, S/D, CVR, birth gestational week, 5-min Apgar score, and birth weight are risk factors for an adverse outcome of the fetal PS.

Table 3 Multiple factor Logistic regression analysis of prognostic factors of fetal PS

Influencing factor	*B*	S.E.	Wald	*P*	OR	95%CI
Amniotic fluid index	0.047	0.249	0.035	0.851	1.048	0.643–1.707
Placental thickness	1.286	1.395	0.850	0.357	3.619	0.235–55.750
S/D	–0.439	1.499	0.086	0.770	0.645	0.033–12.180
CVR	2.535	1.193	4.512	0.034#	12.616	1.217–130.828
Birth gestational week	1.042	0.732	2.026	0.155	2.835	0.675–11.903
5-min Apgar score	–1.776	1.065	2.781	0.095	0.169	0.210–1.365
Birth weight	–0.001	0.003	0.134	0.715	0.999	0.994–1.004
Birth weight	–0.003	0.001	9.210	0.002	0.997	0.995–0.999

CVR is the risk factor for an adverse outcome of the fetal PS. #$P<0.05$

Table 4 Correlation between CVR and postnatal respiratory distress, fetal edema, intrauterine or postnatal death

	CVR	
	r	*P*
Postnatal respiratory distress	0.490	0.000
Fetal edema	0.485	0.000
Intrauterine or postnatal death	0.575	0.000

CVR was significantly correlated with the postnatal respiratory distress, fetal edema, intrauterine or postnatal death.

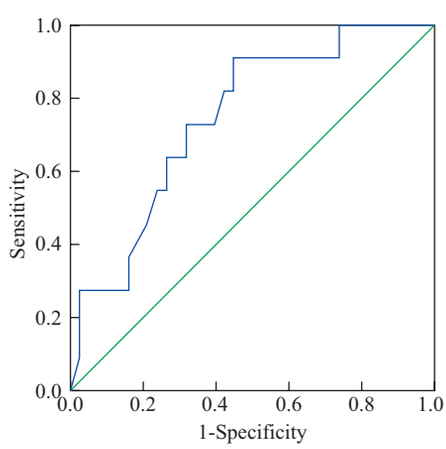

Fig. 4 ROC curve
CVR and the intrauterine or postnatal death shows a significant correlation

symptoms and intrauterine or postnatal death was higher in PS with CVR≥1.26 than in that with CVR<1.26. But CVR ≥1.26 did not necessarily lead to fetal edema, which occurred in 79.1 % of the fetuses in our study. It means that an absolute CVR value could not be chosen to guide the clinical treatment before the development of fetal edema. However, in our results the CVR is indeed a quite helpful index in classifying fetuses into groups of high or low risk of fetal edema. Such message was inestimable in advising parents and distinguishing fetuses who need continuous ultrasonic monitoring for early signs of fetal edema[16–18].

Single factor Logistic regression analysis showed that amniotic fluid index, placental thickness, S/D, CVR, birth gestational week, 5-min Apgar score, and birth weight are risk factors for an adverse outcome of the fetal PS (table 2). Multiple factor Logistic regression analysis also confirms that CVR is the risk factor for fetal PS ($P<0.05$, table 3). CVR was significantly associated with the postnatal respiratory distress, fetal edema, intrauterine or postnatal death (table 4). In ROC curve, CVR and the intrauterine or postnatal death shows a significant correlation (fig. 4). From our results, CVR is a useful sonographic indicator that can be used to evaluate the prognosis of fetal PS .

Some literatures showed that the lumps substantially or entirely regressed through ultrasonic scanning[18–20]. However, postpartum CT imaging demonstrates the existence of the PS. In our research, we have also found that lumps were decrescent in 3 cases and “disappeared” in one case. In these cases, the lumps were presented by postpartum CT scanning, indicating that the lumps did not “disappear”. A credible explanation of the phenomenon is that, with

the growth of normal lung tissue, the blood supply to the PS mass is decreased, resulting in necrosis, absorption, and apoptosis of mass tissue, or even being covered by normal lung tissue[21–23]. Therefore, it is necessary to closely observe the fetus with "disappeared" or decreased PS mass. Our studies showed the "disappeared" PS mass by postpartum CT, which effectively confirmed the explanation.

In view of treatment of the PS, postpartum surgical treatment is considered to be the most effective means[23]. In our research, 34 cases of early surgery have recovered well. Eight patients could not have surgeries because their lumps were too big, and all of them died within 6 months. It demonstrated that early operation for newborns or infants could be vital and had good outcome. Therefore, the research suggested that surgical operation or regular reexamination should be taken even in patients with asymptomatic PS. However, clinical data and long-term follow-up studies still should be obtained to support our argument.

In conclusion, our study presents that the CVR is an effective index to evaluate the prognosis of PS fetuses. The research would contribute to antepartum counseling, monitoring and determination of treatment plan of PS. The limitations of this study are that our sample size are not large enough and the possibility of bias cannot be ruled out. Hence, in the future, data of more samples should be collected, and further related researches need to be carried out.

Conflict of Interest Statement

The authors report that they have no conflict of interest.

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