Original Article

Prospective analysis of the prognostic value of prenatal MRI measurement of cystic volume ratio in fetal congenital cystic adenomatoid malformation

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Background: The cystic volume ratio (CVR) has been used to predict the prognosis of fetal lung disease, but most of them are reported on ultrasound. The purpose of this study was to investigate the prognostic value of prenatal magnetic resonance imaging (MRI) measurement of CVR in fetal congenital cystic adenomatoid malformation (CCAM).

Methods: To collect follow-up data on postnatally confirmed CCAM fetuses. According to the size of CVR, they were divided into a CVR ≥1.26 group and a CVR <1.26 group. The lesions were divided into macrocystic (diameter ≥5 mm) and microcystic (diameter <5 mm) types according to the size of cysts in the lesions. The collected contents also included the location of the lesions, prenatal symptoms, postpartum clinical prognosis, and pregnancy outcomes.

Results: In all, 51 cases were collected. Of these, 11 were placed into the CVR ≥1.26 group, and 40 were placed into the CVR <1.26 group; meanwhile 34 were classified as macrocystic lesions and 17 as microcystic lesions; 7 cases involved a terminated pregnancy. In the CVR ≥1.26 group, 81.82% (9/11) and 36.36% (4/11) had displacement of large vessels/heart and increased amniotic fluid, respectively; meanwhile, in the CVR <1.26 group, these phenomena occurred in 35.00% (14/40) and 2.50% (1/40) of cases (P=0.006, 0.010). Additionally, 83.33% (5/6) of live infants in the CVR ≥1.26 group had dyspnea, a significantly higher proportion than the 21.05% (8/38) in the CVR <1.26 group (P=0.011). Moreover, 45.45% (5/11) of the cases in the CVR ≥1.26 group were terminated pregnancies, a significantly higher proportion than the 5.26% (2/38) in the CVR <1.26 group (P=0.001). Finally, the CVR of macrocystic lesions was 0.55 (0.34–1.31), which was significantly greater than the 0.34 (0.17–0.57) of microcystic lesions (P=0.022). Logistical regression analysis identified that CVR is an independent factor associated with the postpartum prognosis of CCAM.

Conclusions: Prenatal symptoms and postpartum prognosis were worse than CVR <1.26 when fetal CVR ≥1.26 measured by prenatal MRI; and the measurement of CVR of CCAM through prenatal MRI has considerable practical value in prenatal consultation, evaluation, and postpartum treatment.

Keywords: Congenital cystic adenomatoid malformation (CCAM); cystic volume ratio (CVR); magnetic resonance imaging (MRI); fetuses

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Introduction

Fetal congenital cystic adenomatoid malformation (CCAM) is the most common lung dysplasia in fetuses (1,2), but its prognosis is difficult to determine (3). Some lesions may shrink and even disappear, while some may continue to enlarge, resulting in pulmonary dysplasia, edema, and even death (4). The cystic volume ratio (CVR) value can be used to judge the proportion of normal lung tissue in CCAM fetuses and the degree of lung development. CVR can objectively compare fetuses of different gestational ages individually and individually, CCAM is mainly screened by prenatal ultrasound examination, which may, however, cause missed diagnosis and misdiagnosis; meanwhile prenatal magnetic resonance imaging (MRI) can more clearly visualize the fetal lung structure (5). Only a few reports exist that have evaluated the prognosis of fetal CCAM through prenatal MRI examination in China, with this lack being mainly attributable to the dearth in hospitals capable of conducting prenatal MRI examinations. Our team has thus been engaging in research on prenatal MRI examination for the diagnosis of fetal lung masses for many years (6-8). In this study, the value of prenatal MRI examination in the measurement of CVR for the prognosis of CCAM was evaluated. We present the following article in accordance with the STARD reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-973/rc).

Methods

General materials

The follow-up data of fetuses with CCAM confirmed by pathological results through computed tomography (CT) examination and/or operations after birth in Huzhou Maternity & Child Health Care Hospital and Anhui Provincial Children's Hospital from June 2016 to December 2020 were collected. All fetuses underwent prenatal MRI examination within 24 to 48 h after prenatal ultrasonography. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of Huzhou Maternity & Child Health Care Hospital (No. 2016-009) and Anhui Provincial Children's Hospital (No. EYLL-2018-013), and all pregnant women voluntarily signed the informed consent prior to examination.

MRI examination

Using a Siemens Avanto 1.5T MR imaging system (Siemens, Munich, Germany). Gradient field strength of 45 $mT \cdot m^{-1} \cdot s^{-1}$, a 32-channel phased array heart coil, and 1–2 excitations. We employed 3 MRI sequences: (I) true fast imaging with steady-state precession (true FISP) sequences, repeat time (TR) of 3.6–4.2 ms, an echo time (TE) of 1.0–2.0 ms, a reversal angle of 90°, and a scan time of 0.5–2.0 s per layer; (II) half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences with a TR of 1,150–1,500 ms, a TE of 42–145 ms, a reversal angle of 160°; and (III) 2-dimensional FLASH T1WI (TFL) sequences with a TR of 1,680–2,000 ms, a TE of 2.9–4.5 ms, an inversion angle of 15°.

An Achieva Nova Dual MR Imager (Philips, Amsterdam, the Netherland) with a 4-channel abdominal surface coil and 1–2 excitations was used for the following: (I) single-shot fast spin-echo (SSFSE) sequences, with a TR of 12,000.0 ms, a TE of 120.0 ms, and a flip angle of 80°; (II) and a balanced fast field echo (B-FFE) sequence, with the TR and TE values equal to the minimum values set by the system, a flip angle of 90°.

First, a localization scan of the coronal plane in the lower abdomen was carried out, which was followed by routine brain, chest, and abdomen cross-sectional, sagittal, and coronal plane.

Prenatal ultrasonography

Ultrasonography was completed with a Voluson 730 Experd 4D Ultrasound Machine (GE Healthcare, Chicago, IL, USA) and an X300 Color Doppler Ultrasound Diagnostic System (Siemens), with a convex array probe at a frequency of 4.0–8.0 MHz.

CCAM classification methods

Traditionally, CCAM has been classified into 3 types according to the classification method described by Sanders (9): type I or macrocystic CCAM, consisting of a single or several cysts with a diameter of ≥20 mm; type II or minicystic CCAM, consisting of a single or several cysts with a diameter of <10 mm; and type III or microcystic CCAM, consisting of a single or several cysts with a diameter of <5 mm or noncystic solid lesions. One study research has shown that type I and type II are different in terms of cyst size but have similar appearance on imaging, with the large and small cysts often being mixed (10). In line with the classification methods of other scholars (10-12), CCAM was divided into the macrocystic type

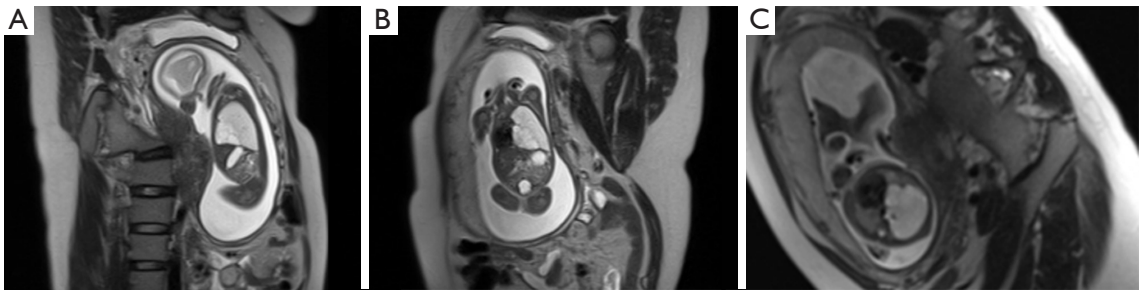

Figure 1 A left lung CCAM in which the pathology was confirmed after induced labor. (A) There are several cysts of varying sizes in the lesion; (B) the blood supply vessels produce low signals; (C) the volume of the left lung is significantly increased, the heart and large vessels have shifted to the right, and the supply of the pulmonary artery is visible. CVR =2.31. CCAM, congenital cystic adenomatoid malformation; CVR, cystic volume ratio.

(diameter ≥5 mm) and the microcystic type (diameter <5 mm) in this study.

CVR calculation and classification methods

Through regarding the lesion as an ellipse, prenatal MRI was used to measure the longest diameter, the widest diameter, and the highest diameter, and then the following equation was used to calculate its volume: volume = the longest diameter × the widest diameter × the highest diameter × 0.52. In order to eliminate the deviation of lesion volume of different gestational ages, CVR was used to measure the changes in lesions of different gestational ages according to the following formula: CVR = lesion volume/head circumference (13,14). With reference to the relevant literature, we divided the (15) CCAM cases into a CVR ≥1.26 group and a CVR <1.26 group.

Image analysis

MRI images were analyzed by 2 experienced associate chief radiologists using the double-blind method according to lesion signal, location, size, blood supply vessels, and heart position, amniotic fluid volume. In cases of disagreement, the radiologists arrived at a consensus through consultation.

Statistical analysis

Data were statistically analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Normally distributed measurement data are expressed as $\bar{x}\pm s$ and were compared using the *t* test. Measurement data failing to conform to a normal distribution are expressed by the median (the 25th to 75th percentile) [M (P_{25}-P_{75})] and were compared with the nonparametric test. Enumeration data are expressed as cases or percentages and were compared with the chi-squared test. Received operating characteristic curve (ROC) was drawn between CVR groups with associated symptoms and clinical prognosis, and the area under the curve (AUC) was calculated. Logistical regression analysis was used to identify the independent prognosis factors associated with CCAM. A P value <0.05 was considered to indicate a statistically significant difference.

Results

Comparison of general clinical data

In all, 51 CCAM cases were collected, with 11 of these being placed in the CVR ≥1.26 group (including 10 cases of macrocystic type and 1 case of microcystic type; *Figure 1*) and 40 in the CVR <1.26 group (including 24 cases of macrocystic type and 16 case of microcystic type; *Figure 2*). There was no statistical difference between the 2 groups of pregnant women in age, time of pregnancy, parity, or gestational weeks according to the prenatal MRI examination (P>0.05; *Table 1*).

Comparison of lesion location and prenatal symptoms between CVR and CCAM

The incidence rate of large vessel or heart displacement and increase in amniotic fluid in the CVR ≥1.26 group was greater than that in the CVR <1.26 group (P<0.05; *Table 2*). Between CVR groups, the AUC of large vessel or heart displacement was 0.734, and that of termination of pregnancy was 0.702 (*Figure 3*).

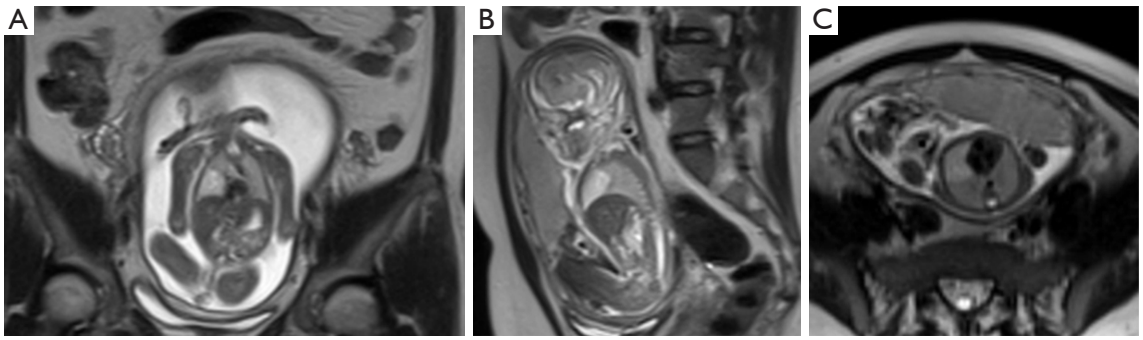

Figure 2 A right lung CCAM in which postnatal CT confirmed the disappearance of lesions. (A) The lesion is located in the lower right lung; (B) clear boundaries are visible between the normal lung tissues; (C) there is a lack of displacement of the heart and large vessels. CVR =0.17. CCAM, congenital cystic adenomatoid malformation; CT, computed tomography; CVR, cystic volume ratio.

Table 1 Comparison of general clinical data of two groups

Group	Cases	Age (years), mean ± SD	Times of pregnancy, mean ± SD	Parity, M [P_{25}–P_{75}]	Gestational weeks during prenatal MRI examination, mean ± SD
CVR ≥1.26	11	29.36±5.00	2.27±0.90	1 [1–1]	26.00±2.72
CVR <1.26	40	27.03±4.31	2.28±1.04	1 [1–1]	26.10±3.34
Statistics value		1.540*	–0.007*	–0.412$^{\triangle}$	–0.091*
P value		0.130	0.995	0.680	0.928

* is the *t*-test; $^{\triangle}$ is the chi-square test. MRI, magnetic resonance imaging; CVR, cystic volume ratio.

Table 2 Comparison of lesion location and prenatal symptoms between CVR and CCAM

Group	Cases	Left [cases (%)]	Large vessel or heart displacement [cases (%)]	Increase in amniotic fluid [cases (%)]
CVR ≥1.26	11	6 (54.55)	9 (81.82)	4 (36.36)
CVR <1.26	40	24 (60.00)	14 (35.00)	1 (2.50)
χ^2		0.106	7.638	7.686
P value		0.745	0.006	0.001

CVR, cystic volume ratio; CCAM, congenital cystic adenomatoid malformation.

Comparison between CVR and postpartum prognosis

In the CVR ≥1.26 group, there were 6 live births and 5 pregnancy terminations; meanwhile, in the CVR <1.26 group there were 38 live births, and 2 pregnancy terminations. For liveborn CCAM infants, the incidence rate of dyspnea in the CVR ≥1.26 group was greater than that in the CVR <1.26 group (P<0.05), and the rate of termination of pregnancy in the CVR ≥1.26 group was also greater than that in the CVR <1.26 Group (P<0.05; *Table 3*). The AUC between CVR and dyspnea after birth was 0.811 (*Figure 4*).

Comparison between macrocystic and microcystic CCAM and accompanying symptoms and postpartum prognosis

In the 51 CCAM cases, there were 34 macrocystic cases and 17 microcystic cases; The CVR in macrocystic cases was greater than that of microcystic cases (P<0.05; *Table 4*).

Risk factors associated with the postpartum prognosis of CCAM

Univariate analysis indicated that CVR, gestational weeks, and large vessel or heart displacement were factors

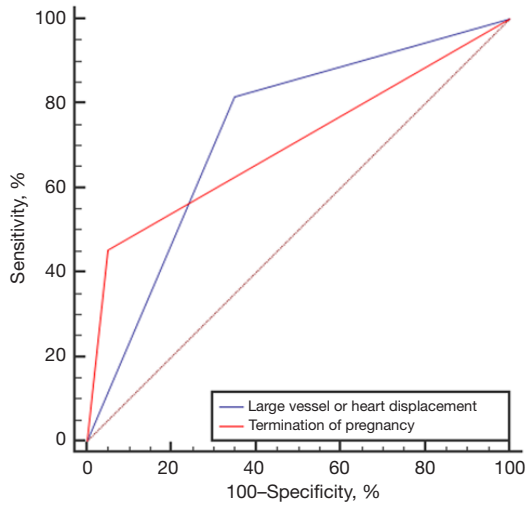

Figure 3 ROC curve of CVR with large vessel or heart displacement and termination of pregnancy. ROC, receiver operating curve; CVR, cystic volume ratio.

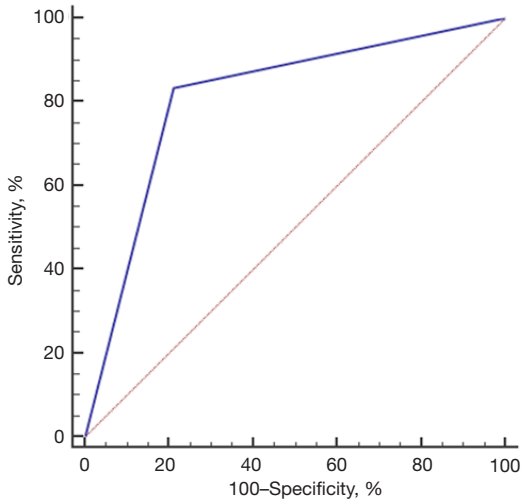

Figure 4 ROC curves of CVR and dyspnea in live-born infants. ROC, receiver operating curve; CVR, cystic volume ratio.

Table 3 Comparison between CVR and postpartum prognosis

Group	Liveborn			Termination of pregnancy [cases (%)]
	Boy [cases (%)]	Dyspnea [cases (%)]	Lesion disappeared [cases (%)]	
CVR ≥1.26	2 (33.33)	5 (83.33)	0 (0.00)	5 (45.45)
CVR <1.26	25 (65.79)	8 (21.05)	8 (21.05)	2 (5.26)
χ^2	2.302	6.896	0.453	8.752
P value	0.129	0.009	0.501	0.003

CVR, cystic volume ratio.

associated with the postpartum prognosis of CCAM (*Table 5*). Furthermore, logistical regression analysis identified that CVR is an independent factor associated with the postpartum prognosis of CCAM (*Table 6*).

Discussion

Compared with ultrasonography, MRI has unique advantages of a large visual field, multiple parameters, and high resolution of soft tissue; it is also not restricted by fetal position or maternal figure and can better visualize the details of the normal anatomy and abnormal lesions of the fetal chest; therefore, it has been adopted as an important supplement to obstetrical ultrasonography (10,16). Fetal MRI examination is usually performed based on True FISP/B-FFE and HASTE/SSFSE sequences, which, with the fast scanning speed, can shorten the imaging time and greatly reduce the number of artifacts in fetuses and pregnant women. In addition, by virtue of the high image resolution, it can clearly obtain the images of fetal organs. For obtaining high-quality images, the pregnant women may only need to hold their breath, without the need of any sedative. Based on True FISP/B-FFE and HASTE/SSFSE sequences, the fetal lungs can show uniform high signals. The difference between the two is that the fetal heart and large vessels show high signal on the True FISP/B-FFE sequence, which can clearly show the structure of the 4 chambers of the heart and the large vessels, and can clearly show the changes in the compression of the heart and large vessels by the lesions; meanwhile, in HASTE/SSFSE, the heart may show the "black blood" signal, which can only display the position and size of the fetal heart but not the

Table 4 Comparison between macrocystic and microcystic CCAM and accompanied symptoms and postpartum prognosis

Group	Cases	Large vessel or heart displacement [cases (%)]	Increase in amniotic fluid [cases (%)]	CVR	Lesion disappeared [cases (%)]
Macrocystic	34	18 (52.94)	5 (14.71)	0.55 (0.34–1.31)	5 (14.71)
Microcystic	17	5 (29.41)	0 (0.00)	0.34 (0.17–0.57)	3 (17.65)
Statistics value		2.534$^{\diamond}$	2.772$^{\diamond}$	−2.329$^{\triangle}$	0.074$^{\diamond}$
P value		0.111	0.244	0.020	0.785

$^{\diamond}$ is the chi-square test; $^{\triangle}$ is the non-parametric test. CCAM, congenital cystic adenomatoid malformation; CVR, cystic volume ratio.

Table 5 Factors associated with postpartum prognosis of CCAM based on univariate analysis

Parameter	Variable	Postpartum prognosis		P
		Live birth	Terminations	
Age (years)	<27	19	2	0.466
	≥27	25	5	
Gestational weeks (week)	<26	17	6	0.020
	≥26	27	1	
Pregnancy time (n)	<2	10	2	0.735
	≥2	34	5	
CCAM type	Microcystic	16	1	0.250
	Macrocystic	28	6	
CVR	<1.26	6	5	0.001
	≥1.26	38	2	
Large vessel or heart displacement	No	27	1	0.020
	Yes	17	6	

CCAM, congenital cystic adenomatoid malformation; CVR, cystic volume ratio.

Table 6 Factors associated with postpartum prognosis of CCAM based on univariate analysis

Parameter	B	SE	P	Exp (B)	95% CI
CVR	2.558	1.125	0.023	12.908	1.424–117.028
Gestational weeks (week)	−1.506	1.089	0.167	0.222	0.026–1.874
Large vessel or heart displacement	1.151	1.271	0.365	3.162	0.262–38.196

CCAM, congenital cystic adenomatoid malformation; CVR, cystic volume ratio.

internal structure. However, due to the role of the bright "water", HASTE/SSFSE can display the shape, boundary, and internal structure of the fetal lung more clearly, while better distinguishing the fetal lung lesions from the surrounding normal lung tissues. In the case of HASTE/SSFSE, CCAM produces high signals while supplying vessels produce low signals, so it can be used to better find the source blood vessels of the lesions. In recent years, the application of prenatal MRI to screening prenatal diseases has become more widespread (17).

CVR has become an important indicator for evaluating CCAM lung development and changes in patients'

conditions (12). Studies have found that a CVR >1.6 is associated with pulmonary edema in 90% of fetuses with CCAM, and when the threshold of CVR is set to 2.0 (18,19), the specificity and positive predictive value are higher than 1.6 (20). However, in real-world clinical practice, when CVR is >1.6, the incidence of CCAM is low while the induction rate is high, making it difficult to perform follow-up on the clinical prognosis. Therefore, some scholars reduced the threshold of CVR before conducting their grouping studies. Ehrenberg-Buchner *et al.* (21) performed a grouping study based on 64 fetuses and found that when the CVR was >1.0, the risk of postpartum respiratory insufficiency increased. Ruchonnet-Metrailler *et al.* (22) performed a grouping study based on 89 fetuses and found that when the CVR was >0.84 and the amniotic fluid was increased or accompanying peritoneal dropsy was present, the possibility of severe postpartum dyspnea was greater. Currently, the measurement of CVR by prenatal MRI is rarely reported either in China or internationally. In this study, CCAM cases were divided into the CVR ≥1.26 group and the CVR <1.26 group according to the method of An *et al.* (15). It was found that the incidence of displacement of large vessels/heart and increase of amniotic fluid in the CVR ≥1.26 group was greater than that in the CVR <1.26 group ($P<0.05$). This was mainly because the larger mass could more easily compress and push the large vessels and heart, making the mediastinum move to the opposite side; when the mass oppressed the esophagus and veins, this would more likely cause an increase of amniotic fluid and fetal edema (23). One study found that a higher CVR could increase the incidence rate of postpartum respiratory symptoms (3). In our study, the incidence of dyspnea among CCAM liveborn infants in the CVR ≥1.26 group was greater than that in the CVR <1.26 group ($P<0.05$) mainly because the larger lesions compressed the normal lung tissues and aggravated the disease.

In about 15% of CCAM cases, the disease disappears before delivery (24), but postnatal CT sometimes indicates that the supposedly "vanished" lesion on prenatal ultrasonography did not actually disappear after birth. Rather, due the normal lung tissue squeezing the lesion and reducing its echo intensity, the boundary with the normal lung tissue becomes unclear, especially microcystic CCAM; therefore, CCAM found by ultrasonography should be examined by prenatal MRI to further confirm or correct the diagnosis of prenatal ultrasonography. Previous studies on the disappearance of CCAM lesions have only included a small number of cases (25,26), and the reports on the disappearance in macrocystic or microcystic cases demonstrated low precision. In this study, CCAM lesions disappeared in 8 cases, including in 5 macrocystic cases and 3 microcystic cases, all in the CVR <1.26 group. Due to the small number of cases, no further analysis was performed in this study. It was found that the CVR of the macrocystic case was significantly larger than that in microcystic the cases because macrocystic CCAM had some solid lesions, and the volume was larger due to the varying sizes of the cysts.

In conclusion, Prenatal symptoms and postpartum prognosis were worse than CVR <1.26 when fetal CVR ≥1.26 measured by prenatal MRI; the CVR of macrocystic CCAM was significantly greater than that of microcystic CCAM. The measurement of the CVR of CCAM through prenatal MRI examination can help clinicians make more accurate prognoses and configure more appropriate treatment plans. Prenatal MRI thus has high practical value in prenatal consultation, evaluation, and postpartum treatment.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-973/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-973/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-973/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of Huzhou Maternity & Child Health Care Hospital (No. 2016-009) and Anhui Provincial Children's Hospital (No. EYLL-2018-013), and all pregnant

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