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Evaluation of brain microstructure changes in surviving fetus of monochorionic twin pregnancies with single intrauterine fetal death using diffusion weighted imaging: a MRI-based cohort study

Aonan Wang[1], Ran Huo[1], Yuan Wei[2], Xiaoyue Guo[2], Zheng Wang[1], Qiang Zhao[1], Ying Liu[1*] and Huishu Yuan[1*]

Abstract

Background Single intrauterine fetal death (sIUFD) will lead to an increased risk of adverse events such as fetal brain abnormalities in the survivor. However, how to detect these anomalies in the early stages remains to be explored.

Objective To compare apparent diffusion coefficient (ADC) values of fetal brain in cases of single intrauterine fetal death (sIUFD) with twins control and singleton control using diffusion weighted imaging (DWI), and to perform follow-up study to reveal the underlying cerebral microstructure changes.

Materials and methods In this prospective MRI-based cohort study, we compared 43 surviving fetuses of sIUFD (18 following selective fetal reduction, 2 following laser ablation treatment for twin-to-twin transfusion syndrome, and 23 spontaneous) with 2 control cohorts (43 healthy twin fetuses, 43 singletons). All fetuses underwent fetal brain MRI. DWI was performed and ADC map was reconstructed. ADC values of certain regions were compared among the three groups.

Results ADC values were lower in bilateral white matter of frontal, parietal, temporal lobes and cerebellum in surviving fetuses compared with twins control and singleton control, respectively. ADC values of bilateral basal ganglia, thalamus and cerebellum in surviving fetuses, that of bilateral frontal lobes, cerebellum in twins control and that of right temporal lobe, left basal ganglia, and bilateral cerebellum in singleton control, were negatively correlated with gestational age. ADC values of left cerebellum in surviving fetuses were positively correlated with interval time.

Conclusions DWI is a very useful sequence for detecting underlying changes. ADC value might be a effective indicator of subtle anomalies in surviving fetuses.

Keywords Diffusion weighted imaging, Apparent diffusion coefficient, Twin pregnancies, Single intrauterine fetal death

*Correspondence:
Ying Liu
lyyulia@163.com
Huishu Yuan
huishuy@bjmu.edu.cn
Full list of author information is available at the end of the article

Introduction

Monochorionic twin pregnancies have some complications [1–5]. As one of the main complications, single intrauterine fetal death (sIUFD), occurs approximately 6% of twin pregnancies after 20 weeks of gestation [6, 7], which usually has an effect on the surviving fetus, especially in the second and third trimesters. sIUFD causes preterm delivery and associated comorbidities such as long-term neurological complications, and neonatal death, which accounts for the increasing morbidity and mortality [8, 9]. sIUFD will lead to an increased risk of adverse events such as fetal brain abnormalities in the survivor. However, how to detect these anomalies in the early stages remains to be explored.

In recent years, fetal MRI, as a valuable complementary technique, is being increasingly used to evaluate fetal brain, provides improved anatomic detail and physiologic information than ultrasound [10–14]. For surviving fetus, severe brain damage might be detected by ultrasound and prenatal MR imaging [15–17]. In some cases, no abnormal echo or signal of brain in the surviving fetus could be found on ultrasound or conventional MRI sequences after the death of one fetus. However, brain abnormalities were found in subsequent prenatal examination or postnatal follow-up. In the circumstances, it is necessary to identify the potential anomalies of brain in surviving fetus by other methods. Diffusion weighted imaging (DWI) has been applied to fetal MRI to evaluate the microstructure and biophysical status of tissues and intracranial lesions [18, 19], which contributes to identify abnormal ischemic tissue in early stages.

Hoffmann et al. [20] reported that acute ischemic lesions were detected on DWI within one week after the death of one fetus, which were not detected on ultrasound or conventional MRI examination. Apparent diffusion coefficient (ADC) is derived from DWI sequence, which can quantitatively detect the degree of diffusion of water molecules. ADC value of fetus brain has been studied in many studies, about fetal maturity and fetal brain injury [21–24]. The decrease of ADC value may be an index of brain injuries and an early ischemic manifestation of fetal brain, which was more sensitive than measurements evaluated by conventional MRI examination [25, 26].

Our study aim to compare ADC values of different brain area and the follow-up outcomes of surviving fetuses with twins control and singleton control, and to reveal the underlying cerebral microstructure changes.

Materials and methods

Subjects

This prospective study enrolled 43 surviving fetuses of sIUFD diagnosed by the department of obstetrics and gynecology of Peking University Third Hospital from January 2018 to November 2022. In 18 patients, selective fetal reduction was performed; In 2 pregnancies, sIUFD occurred following laser ablation treatment for twin-to-twin transfusion syndrome (TTTS); and 23 sIUFDs were spontaneous.The inclusion criteria for the sIUFD group were as follows: 1) gestational age $\geq$ 20 weeks; 2)monochorionic twin pregnancies with one fetus died in utero confirmed by ultrasound examination; and 3) no abnormal echo of the brain in the surviving fetus detected by ultrasound examination. Control groups were uncomplicated twin pregnancies and singleton pregnancies who had fetal brain MRI with normal brain imaging findings in the same period. The inclusion criteria for control groups were uncomplicated twins and singletons with normal brain structure assessed by fetal brain MRI. The exclusion criteria were as follows: 1) gestational age < 20 weeks; 2) brain abnormalities diagnosed by ultrasound examination. The maternal age, gestational age and the interval time between one fetus demise and MR scanning were recorded. The current study was approved by the local ethical committee, and written informed consents were obtained from all the participants.

The followed-up clinical outcomes

All fetuses were followed-up for at least one year. The clinical outcomes including terminate pregnancy, died or various complication were recorded by a trained researcher who was blinded to the MRI findings.

MR imaging protocol

The fetal brain MRI was performed in a 1.5-T MR scanner (Optima MR360, GE Healthcare, Milwaukee, USA). The protocol included the following sequences: 1) Single-Shot Fast Spin Echo (SSFSE) sequence: repetition time (TR)/echo time (TE) 50.4/140 ms, slice thickness 5 mm, slice interval 1 mm, scanning time 14 ~ 20 s); 2) Fast-Imaging Employing Steady-State Acquisition (FIESTA) sequence: TR/TE 4.6/2.09 ms, flip angle 60°, slice thickness 5 mm, slice interval 1 mm, scanning time 16 ~ 20 s; and 3) DWI was performed using single-shot spin-echo planar imaging (EPI) in the axial plane: TR/ TE 2831/77 ms, slice thickness 5 mm, slice interval 1 mm, FOV 320 mm^2, b = 0 and b = 600 s/mm^2, scanning time 16 ~ 20 s, 20 ~ 24 slices.

Image processing

ADC maps were obtained automatically on post-processing software (W4.7, GE Healthcare, Waukesha, Wisconsin, USA) after DWI sequence scanning. Two radiologists with more than 3 years' experience in fetal MR imaging independently drew the regions of interests (ROIs) at each axial slice. ROIs were placed bilaterally over the

desired anatomical areas, including white matter of frontal lobes, parietal lobes, temporal lobes and occipital lobes, basal ganglia, thalamus and cerebellum. Each ROI was measured twice and the average value was chosen as final result. The areas of ROIs were 29.3 mm^2.

Statistical analysis

Statistical analyses were performed with SPSS software (version 20.0, SPSS, Inc., an IBM Company). One-way ANOVA was used to compare ADC among surviving fetuses, twins control and singleton control in the same ROIs. ADC values in left hemisphere were compared with those in right hemisphere of surviving fetuses using paired *t* test. Receiver-operating-characteristic-curve (ROC) was generated and the area-under-the-curve (AUC) of ADC values were calculated for discriminating surviving fetuses and singleton control. Correlations between ADC values of surviving fetuses and maternal age and interval time, and that between ADC values of all groups and gestational age were calculated by Pearson or Spearman correlation coefficients. $P < 0.05$ (two-tailed) was considered as statistically significant.

Results

Demographic characteristics of the study population

A total of 129 fetuses were included in this study. There were no significant differences of gestational ages and maternal ages among the three groups ($P > 0.05$) (Table 1). Of 43 surviving fetuses, 23 (53.5%) had a recorded time of when one fetus death occurred, and the interval time ranged from 1 to 74 days (mean time, 39 days). Of the 23 pregnancies in the sIUFD group, 2 (8.7%) performed MR examination within 1 week from the fetal demise, 5 (21.7%) between 1 and 2 weeks, 2 (8.7%) between 2 and 3 weeks, 13 (56.5%) between 4 and 10 weeks, and 1 (4.3%) beyond 10 weeks after the sIUFD occurred. No significant structural and signal abnormalities were found in fetal brain images (Fig. 1).

Table 1 Clinical features of sIUFD and control groups

	sIUFD	Twins control	Singleton control	*F* value	*P* value
No	43	43	43		
Gestational ages range (wk)	25.1 ~ 36.6	24.6 ~ 33.1	23.6 ~ 38.0		
Mean gestational ages (wk)	29.2 ± 3.3	29.6 ± 2.4	30.6 ± 3.3	2.551	0.082
Maternal age range (yr)	24.0 ~ 39.0	25.0 ~ 37.0	24.0 ~ 41.0		
Mean maternal age (yr)	31.1 ± 3.8	31.6 ± 3.3	32.7 ± 4.1	1.969	0.144

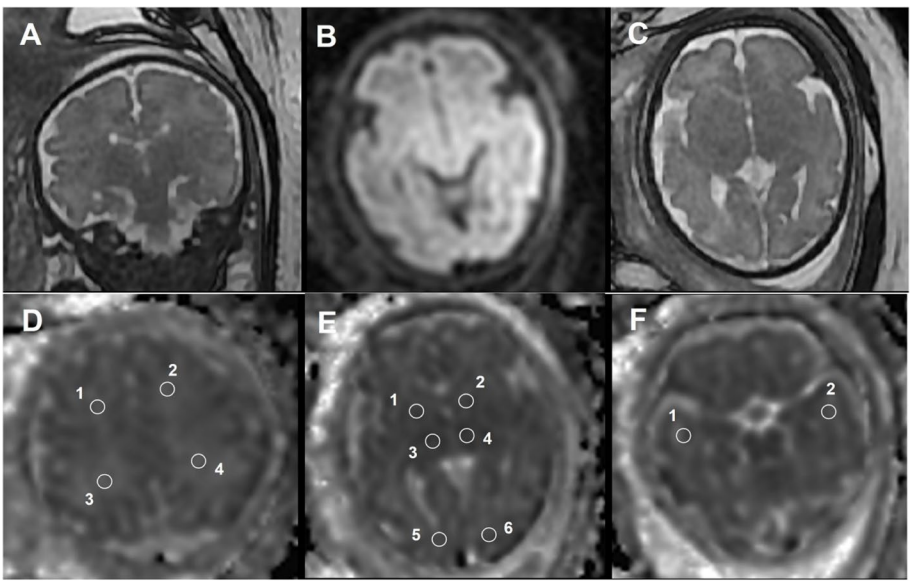

Fig. 1 The MR images of fetal brain of 31 weeks of gestation. **A** Coronal view in FIESTA sequence; (**B**) Axial view in DWI sequence; (**C**) Axial view in FIESTA sequence. **D** ROIs of frontal lobe(1,2) and parietal lobe(3,4); (E) ROIs of occipital lobe(5,6), basal ganglia(1,2) and thalamus(3,4); (F) ROIs of temporal lobe(1,2)

The differences of ADC value

The mean ADC values of surviving fetuses are shown in Table 2. ADC values were lower in bilateral frontal(L: $P<0.001$, R: $P<0.001$), parietal(L: $P<0.001$, R: $P=0.002$), temporal lobes (L: $P=0.003$, R:$P=0.005$) and cerebellum (L: $P=0.041$, R:$P=0.045$)of surviving fetuses compared with that of twins control and singleton control. Intra-group comparison showed that there were significant differences between the three groups of bilateral frontal lobes (surviving fetuses vs. twins control: L: $P=0.001$, R: $P=0.018$; surviving fetuses vs. singleton control: L: $P<0.001$, R: $P<0.001$; twins control vs. singleton control: L: $P=0.001$, R: $P=0.007$). There were differences between surviving fetuses and twins control (parietal lobes: L: $P=0.006$, R: $P=0.006$; temporal lobes: L: $P=0.001$, R: $P=0.001$), surviving fetuses and singleton control (parietal lobes: L: $P<0.001$, R: $P=0.001$; temporal lobes: L: $P=0.011$, R: $P=0.044$) of bilateral parietal lobes and temporal lobes, respectively. There were significant differences of ADC values between twins control and singleton control of bilateral cerebellum (L: $P=0.012$, R: $P=0.013$). There were no significant differences of ADC values between left and right hemisphere (all $P>0.05$) (Table 3).

ROC analysis

The ROC analyses are shown in Fig. 2. In discriminating surviving fetuses and singleton control, the AUCs of ADC values in frontal lobe (left: 0.878, 95% CI 0.810–0.947; right: 0.795, 95% CI 0.704–0.886), parietal lobe (left: 0.731, 95% CI 0.624–0.838; right: 0.698, 95% CI 0.588–0.807) ranged from 0.698 to 0.878.

Table 3 ADC values of left and right hemisphere in the surviving fetuses

		ADC values (μm^2/ms, $n=43$)	*t* value	*P* value
Frontal lobe	Left	1.71 ± 0.10	−0.623	0.537
	Right	1.72 ± 0.12		
Parietal lobe	Left	1.81 ± 0.15	−0.881	0.383
	Right	1.82 ± 0.12		
Temporal lobe	Left	1.63 ± 0.14	−0.255	0.800
	Right	1.63 ± 0.13		
Occipital lobe	Left	1.73 ± 0.14	0.296	0.769
	Right	1.73 ± 0.15		
Basal ganglia	Left	1.46 ± 0.12	1.767	0.085
	Right	1.43 ± 0.11		
Thalamus	Left	1.34 ± 0.12	1.001	0.322
	Right	1.33 ± 0.13		
Cerebellum	Left	1.47 ± 0.15	0.177	0.861
	Right	1.47 ± 0.15		

Correlation analysis

Maternal ages were not correlated with ADC values in all selected cerebral regions of the surviving fetuses (all $P>0.05$). ADC values of bilateral basal ganglia (L: $P=0.001$, R: $P=0.007$), thalamus (L: $P=0.001$, R: $P=0.001$) and cerebellum (L: $P<0.001$, R: $P=0.003$) in surviving fetuses, that of bilateral frontal lobes (L: $P=0.014$, R: $P=0.044$) and cerebellum (L: $P=0.003$, R: $P=0.003$) in twins control and that of right temporal lobe ($P=0.046$), left basal ganglia ($P=0.030$) and bilateral cerebellum (L: $P=0.037$,

Table 2 ADC values of different regions in the surviving fetuses of sIUFD, twins control and singleton control

		ADC values (μm^2/ms)			*F* value	*P* value
		sIUFD ($n=43$)	Twins control ($n=43$)	Singleton control ($n=43$)		
Frontal lobe	Left	1.71 ± 0.10	1.79 ± 0.14	1.88 ± 0.10	22.062	< 0.001
	Right	1.72 ± 0.12	1.78 ± 0.15	1.86 ± 0.12	13.389	< 0.001
Parietal lobe	Left	1.81 ± 0.15	1.89 ± 0.13	1.92 ± 0.13	8.206	< 0.001
	Right	1.82 ± 0.12	1.90 ± 0.17	1.92 ± 0.13	6.589	0.002
Temporal lobe	Left	1.63 ± 0.14	1.73 ± 0.16	1.71 ± 0.12	6.138	0.003
	Right	1.63 ± 0.13	1.73 ± 0.16	1.69 ± 0.11	5.461	0.005
Occipital lobe	Left	1.73 ± 0.14	1.76 ± 0.17	1.74 ± 0.13	0.426	0.654
	Right	1.73 ± 0.15	1.79 ± 0.17	1.74 ± 0.13	2.237	0.111
Basal ganglia	Left	1.46 ± 0.12	1.44 ± 0.14	1.43 ± 0.09	0.617	0.541
	Right	1.43 ± 0.11	1.45 ± 0.12	1.42 ± 0.08	1.103	0.335
Thalamus	Left	1.34 ± 0.12	1.34 ± 0.17	1.32 ± 0.08	0.263	0.769
	Right	1.33 ± 0.13	1.35 ± 0.15	1.33 ± 0.09	0.290	0.748
Cerebellum	Left	1.47 ± 0.15	1.51 ± 0.19	1.42 ± 0.13	3.280	0.041
	Right	1.47 ± 0.15	1.51 ± 0.18	1.42 ± 0.12	3.170	0.045

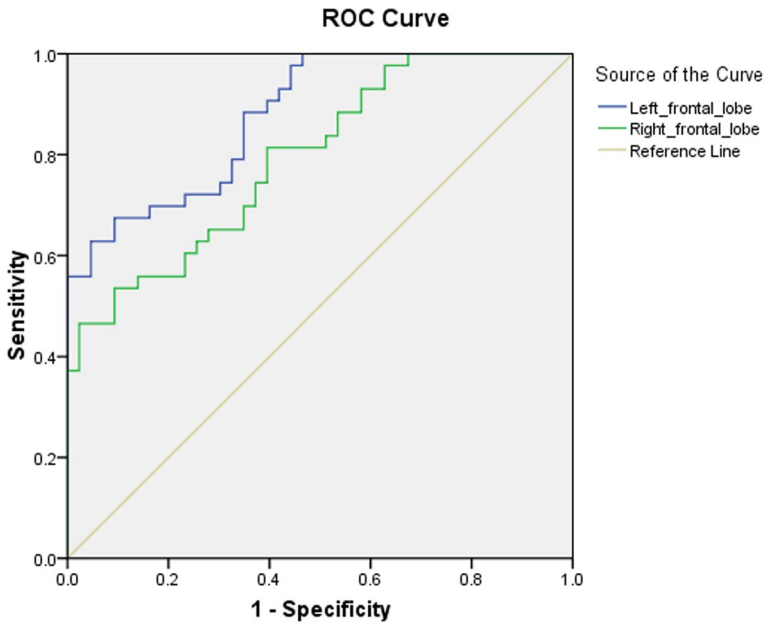

Fig. 2 ROC curves for ADC values of frontal lobes in surviving fetuses and singleton control

R: $P=0.010$) in singleton control, were negatively correlated with gestational age (Table 4). ADC values of left cerebellum in surviving fetuses were positively correlated with interval time ($r=0.435$, $P=0.038$), while ADC values of the other brain regions showed no significant correlation with interval time.

Follow-up results

Among the 43 surviving fetuses, 2 fetuses were terminated and 2 fetuses died after birth. Of the remaining 39 fetuses, 11 (28.2%) were born prematurely (30 ~ 36 weeks, 1 was complicated with congenital pneumonia and cryptorchidism), 8 (20.5%) were followed up by ultrasound and MRI examination (3 of which had brain abnormalities, including 1 with enhanced echoes of white matter in the right paraventricular with effusion

Table 4 Correlations between ADC values and gestational age

Cerebral regions		Surviving fetuses ($n=43$)		Twins control ($n=43$)		Singleton control ($n=43$)	
		r	*P* value	*r*	*P* value	*r*	*P* value
Frontal lobe	Left	−0.262	0.089	0.371	0.014	0.301	0.050
	Right	−0.161	0.304	0.309	0.044	0.206	0.184
Parietal lobe	Left	−0.105	0.502	0.219	0.157	−0.112	0.473
	Right	−0.175	0.263	0.093	0.551	−0.144	0.359
Temporal lobe	Left	−0.010	0.952	0.288	0.061	0.141	0.366
	Right	0.040	0.801	0.202	0.195	0.306	0.046
Occipital lobe	Left	−0.061	0.698	0.167	0.283	−0.206	0.185
	Right	−0.074	0.639	0.128	0.412	−0.284	0.065
Basal ganglia	Left	−0.502	0.001	−0.268	0.083	−0.331	0.030
	Right	−0.408	0.007	−0.262	0.090	−0.220	0.157
Thalamus	Left	−0.504	0.001	−0.139	0.374	−0.105	0.503
	Right	−0.480	0.001	−0.163	0.298	−0.147	0.345
Cerebellum	Left	−0.568	< 0.001	−0.449	0.003	−0.319	0.037
	Right	−0.441	0.003	−0.438	0.003	−0.391	0.010

in the posterior fossa, and 2 with enlarged supratentorial ventricles after birth). Follow-up data showed that 2 infants had obvious growth retardation, and 1 infant had hearing loss.

Discussion

The present study investigated the differences of ADC values of brain regions among the surviving fetuses, twins control and singleton control. Our study showed lower ADC values of frontal, parietal and temporal lobe and cerebellum in the surviving fetuses compared with twins control and singleton control. Furthermore, our findings showed a negative correlation between ADC values and gestational age in several brain regions.

Meta-analysis showed that the risk of neuro developmental morbidity in monochorionic twins was about 5 times higher compared with that in dichorionic twins after a single fetal death [3]. Cerebral hypoxic-ischemic injury might occur in the surviving fetus after sIUFD. Placental sharing and vascular communications in monochorionic twins might result in clinical symptom. The surviving fetus might present with hypotension and hypoperfusion due to the loss of circulatory equilibrium and the shunting of blood flow. The reduced cerebral blood flow might be accepted as causative factors for cerebral damage in surviving fetus. A clinical study including 49 monoamniotic pregnancies with single fetal demise has suggested that severe cerebral injury occurred in 26% of the survivors [27]. These injury and abnormal findings of brain in surviving fetus were usually detected by ultrasound or MRI. Kocaoglu et al. [28] found that DWI was superior to conventional MRI with respect to the speed of detection and sensitivity to diagnose brain lesions.

In this study, no abnormal signs were found in ultrasound or MRI of all the surviving fetuses. Our findings further provided evidence of the possibility of detecting potential brain damage by measuring ADC values in surviving fetuses following sIUFD, and ADC value might be more sensitive to detect the subtle anomalies, even changes of signal were not shown on DWI images. The reduction of ADC values in surviving fetuses might be indicative of parenchymal damage and metabolic compromise, and reflect the intracellular/extracellular water compartmentalization [29], especially the decrease in the extracellular water content. The decrease in ADC value may be due to cellular edema caused by cerebral ischemic hypoperfusion. During fetal development, the water content of white matter in the brain is relatively higher, so it may be more sensitive to ischemia and hypoxia than gray matter. When a fetus dies in utero, the vascular resistance of placental circulation decreases relatively, and blood volume flows from the surviving fetus to the death fetus through vascular anastomosis in the placenta. Subsequently, the surviving fetus experiences hypoperfusion, leading to central nervous system ischemia and hypoxia. This mechanism of fetal brain injury is consistent with the overall cerebral hypoperfusion suggested by the symmetrical ADC reduction in the left and right hemispheres of the surviving fetus in this study. Therefore, a decrease in ADC value may reveal subtle brain abnormalities, indicating brain parenchymal damage and metabolic abnormalities.

It was controversial how long after fetus death to have fetal MR examination, and in fact the interval time between sIUFD and MR imaging was not standardized. Conte et al. [30] thought the timing of MR imaging was likely to have an important effect on the ability to detect and accurately classify brain lesions, and should be performed within one week from the fetal demise. Others considered that it should be performed at 2 or 3 weeks after the sIUFD in order to allow the identification of cavitation and atrophic cerebral lesions. MRI performed too soon after one fetus demise might lead to underdiagnosis of evolving ischemic injury or malformations of cortical development. In fact, sIUFD was often an emergency and might not be found immediately. As it was detected accidentally by ultrasound, most of MR examinations of surviving fetus were performed a few weeks after sIUFD. This might make lesion characterization more robust, as early assessment may overlook or misclassify developing pathologic structure.

Our present study showed the negative correlations between ADC values of basal ganglia, thalamus and cerebellum and gestational age in surviving fetuses, which were consistent with previous study. Decreases of ADC values in the majority of brain during fetal development were reported in previous publication [31]. Significant decreases of ADC values were detected in thalamus, basal ganglia, pons and cerebellum with gestational age, but the decrease was not detected in frontal white matter [32, 33]. However, the conclusions were controversial. Hoffmann et al. [20] found that a weak trend for regional ADC decline was shown in all regions which didn't reach statistical significance with brain development. In the present study, the regions negatively related to gestational age in surviving fetuses was not completely consistent with those in twins control and singleton control, which might indicate the existed potential damage. In addition, our findings suggested the possibility of ADC values in frontal lobes in distinguishing surviving fetuses with singletons, and since the ADC values in bilateral frontal lobes were not correlated with gestational age, which implied that ADC values in frontal lobes were relatively stable and might be served as developmental indicator [34].

However, whether the change of ADC value represented a real anomaly was still unclear. Postnatal follow-up might be validation. A study reported 11 twin pregnancies complicated by single fetal demise, surviving fetuses with normal MRI examinations had normal neonatal neurologic outcome, only one of three fetuses diagnosed with cerebral lesions by MRI proved a normal neurologic development at follow-up [35]. Lanna et al. [36] found that 78 pregnancies complicated by single fetal death, 14 of which had cerebral lesions. Two of them identified by ultrasound and confirmed by conventional MRI had mild and respectively severe neurological sequalae. One identified by MRI and terminated two cases without MRI examination, the neonates had mild and respectively severe neurological sequalae. Segev et al. [37] compared 29 monochorionic twins complicated with sIUFD with 49 singleton fetuses and 28 uncomplicated twin fetuses, finding no significant differences in ADC values of the cerebral hemispheres, basal ganglia, and pons between the sIUFD group and either control group.

In this study, follow-up results showed that three fetuses subsequently developed brain abnormality by ultrasound or MRI. It indicated the underlying changes of brain might exist even through no abnormal signals on conventional and DWI sequence. The measurement of ADC values in surviving fetuses might help to detect the potential subtle anomalies earlier. Although changes of ADC values were shown in surviving fetuses, making crucial decisions (such as pregnancy termination) on the basis of DWI alone also could be very difficult. It might be more reasonable to discuss the possibility of termination of pregnancy in cases with large cerebral lesion on MR and DWI. For surviving fetuses with ADC values changes alone, the follow-up was necessary. However, in clinical work, some fetuses (especially fetuses with normal conventional sequence and DWI sequence images) did not receive brain MR examination follow-up after birth. In this study, only about 1/5 of the people received the follow-up brain MR imaging. The follow-up data showed that not all fetuses with decreased ADC values had a poor prognosis. Therefore, the effect of ADC value reduction warrant to be further explored and verified. The diagnosis only relying on DWI was subtle and should be carefully evaluated.

There were several limitations in the current study. Firstly, a larger sample group may contribute to more accurate conclusion. Secondly, although correlation analysis showed no significant correlation between ADC values and interval time in brain regions other than the left cerebellar hemisphere, we still cannot draw a clear conclusion on the best timing for performing MR scan regarding the wide range of the interval time and gestational age at MRI scan. Since ADC values changes over time and the degree of brain damage of surviving fetuses may vary depending on the gestational age at which sIUFD occurs. Some studies have chosen to perform MRI examination 2 weeks after the occurrence of sIUFD [15, 37], and more research is needed to verify the appropriateness of this interval time. And thirdly, a long-term studies and follow-up MR are needed to reveal the relationship between reduction of the ADC values and postnatal outcome.

Conclusion

In conclusion, the current study demonstrates that decreases of ADC values were detected in surviving fetus of sIUFD while no visible abnormalities were detected on conventional MRI. DWI, especially ADC value, is a very useful sequence for detecting underlying changes. ADC value should also be evaluated in larger clinical studies with ongoing pregnancies before adopting it as a formal work-up in cases of one fetus demise.

Abbreviations

sIUFD	Single intrauterine fetal death
DWI	Diffusion weighted imaging
ADC	Apparent diffusion coefficient
TTTS	Twin-to-twin transfusion syndrome
SSFSE	Single-shot fast spin echo
TR	Repetition time
TE	Echo time
FIESTA	Fast-imaging employing steady-state acquisition
EPI	Echo planar imaging
ROIs	Regions of interests
ROC	Receiver-operating-characteristic-curve
AUC	Area-under-the-curve
CI	Confidence interval

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Authors' contributions

Y.L. and H.Y. conceived and supported the study, and Y.L. and Y.W. supervised the study. Y.L., A.W., R.H. and Q.Z. collected the data. Y.L., A.W. and Z.W. performed statistical analysis. A.W. drafted the initial manuscript. Y.L., H.Y., X.G. and Y.W. edited the manuscript and revised it critically for important intellectual content. All authors reviewed and approved the final manuscript to be published.

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Data availability

The author confirms that all data generated or analyzed during this study are included in this published article.Furthermore, primary and secondary sources and data supporting the findings of this study were all publicly available at the time of submission.

Declarations

Ethics approval and consent to participate
This trial was approved by the institutional Ethics Committees of Peking University Third Hospital (registration number: IRB00006761-M2017316). Written informed consent was obtained from all subjects in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiology, Peking University Third Hospital, Beijing 100191, China. [2]Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China.

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