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Original Article

Explore the clinical value of color Doppler assessment of S/D values of UA, MCA, and DV in the diagnosis of maternal fetal distress in the third trimester

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Abstract: Objective: To explore the value of color Doppler ultrasound in fetal distress in the third trimester, and to determine the diagnostic value of the systolic/diastolic ratios (S/D) of umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV) according to the receiver operating characteristic (ROC) curve. Methods: In this retrospective controlled study, we collected 450 pregnant women who gave full-term birth, including 168 women with fetal distress (the observation group) and 282 women without fetal distress (the control group). All study subjects were with complete clinical data and received color Doppler ultrasound. The results of color Doppler ultrasound of the two groups were compared. ROC curve was employed to analyze the value of S/D values of UA, MCA, and DV in the clinical diagnosis of obstetric fetal distress in the third trimester. Results: Pregnant women in the observation group had markedly higher S/D values of UA and DV and lower S/D values of MCA than women in the control group ($P<0.001$). ROC curve analysis indicated that the AUC of S/D value for the diagnosis of fetal distress was 0.763 in UA, 0.828 in MCA, and 0.812 in DV. The combined diagnosis of fetal distress by S/D values of UA, MCA, and DV in the third trimester was performed according to the cut-off values of the three S/D values indicated by the Youden's index. Fetal distress was diagnosed if any two of the three results turned positive. The AUC of combined diagnosis of fetal distress by S/D values of UA, MCA, and DV was 0.935 (95% CI: 0.894 to 0.956), and the accuracy of combined diagnosis was 91.78%. Kappa consistency analysis showed a Kappa value of 0.829 (95% CI: 0.162 to 0.903; $P<0.001$), suggesting a strong consistency between the combined diagnosis and the clinical diagnosis after delivery. Conclusion: The combined diagnosis of fetal distress by S/D values of UA, MCA, and DV in the third trimester assessed by color Doppler ultrasound is highly consistent with the clinical diagnosis of obstetric fetal distress, also consistent with the diagnosis by fetal heart rate after delivery and the 1 min Apgar score. This combined diagnosis is worthy of clinical application.

Keywords: Fetal distress, Doppler ultrasound, umbilical artery, middle cerebral artery, ductus venosus

Introduction

Fetal distress is a clinical syndrome characterized by hypoxia, asphyxia, and acidosis when the fetus was in the uterus due to various causes. Fetal distress in the uterus, often accompanied by various complications such as hypoxic-ischemic encephalopathy and neonatal asphyxia, has very high mortality and disability [1, 2]. Data shows that the new case number of fetal distress in China each year reaches 300,000 [3]. Prevention and treatment of fetal distress is the clinical focus. The key to reducing the incidence of fetal distress and improving the development of neonatal nervous system lies in timely diagnosis and treatment.

Current clinical diagnostic indexes for fetal distress are far from accurate due to the complex pathogenesis. Monitoring of fetal heart and fetal movement to judge the development of fetal distress is unable to quantify the fetal hypoxia and is affected by the doctor's experience, technical level, maternal obesity, malpresentation, and frequent fetal movement [4].

Rapid development and innovation in ultrasound technology facilitate the wide application of color Doppler ultrasound in the clinical diagnosis of fetal distress. In the study by Rizzo et al. which collected 7645 cases of singleton pregnancy and their perinatal outcomes, UA Doppler assessment detected changes in the fetal size and pulsatility index (PI) of the artery and venous at the time of fetal growth restriction [5]. Their study assessed fetal growth through arterial and venous blood flow, but did not evaluate it in pregnant women with fetal distress. The study by Zhao et al. found that the average systolic/diastolic ratios (S/D) and PI values of renal artery were markedly higher in the distressed fetus than in normal fetus [6]. The blood supply to the brain is important for fetal development of the fetus in distress, but the cerebrovascular S/D value was not measured in Zhao's study. The study by Sekizawa et al. suggests that umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV) have an application value in the clinical diagnosis of fetal distress, but it only analyzes their relationship with fetal distress, with no attempt to verify their value in fetal distress using statistical methods [7].

Previous studies have offered clinical evidence for the use of Doppler assessment of arterial and venous blood flow to analyze fetal conditions. The application of S/D values of UA, MCA, and DV in the diagnosis for fetal distress, as well as the combined diagnosis by the three parameters, is previously reported. However, such studies require support with more clinical data. The criteria for combined diagnosis in this study were met when any two of UA, MCA, and DV diagnosis turned positive. The ROC curve was also used to determine the clinical value of the combined diagnosis. Besides, the consistency between the results of combined diagnosis and the clinical delivery outcomes were tested, in an attempt to analyze the clinical diagnostic value of the combined diagnosis more comprehensively and accurately.

Materials and methods

General information

In this retrospective controlled study, 450 pregnant women who gave full-term birth in the maternity wards of Peking University International Hospital from January 2016 to January 2019 were enrolled. We assigned pregnant women with fetal distress to the observation group and those without fetal distress to the control group. Inclusion criteria: Women diagnosed with fetal distress according to the fetal heart rate and 1 min Apgar score [6]; women received Doppler ultrasound examinations in the third trimester; women with complete clinical data and records of imaging examinations; women with natural conception. Exclusion criteria: pregnant women combined with either severe heart and cerebrovascular disease, or substantial organ diseases such as in liver, kidney, and lung; women with fetal malformation or multiple births; women whose fetuses were with the umbilical cord around the neck. The inclusion and exclusion criteria were also applied to the control group, but pregnant women in the control group did not have fetal distress according to the clinical delivery outcome. Totally 450 pregnant women were collected, 168 in the observation group and 282 in the control group. This study was approved by the Medical Ethics Committee of Peking University International Hospital.

Method

Ultrasound equipment: High-end 4D color Doppler ultrasound system was employed in this study (model: EPIQ5, manufacturer: Philips). Automatic envelope and spectrum measurement were performed to calculate the S/D value. The operation was conducted using the matching Linear Probe L12-5 at a frequency of 5-12 MHz.

Examination method: Pregnant women were asked to lie in the supine position or lateral position if necessary with an empty bladder. The ultrasound probe was placed on the abdomen to measure the basic measurement indicators of the head, neck, limbs, spine, thoracic and abdomen wall and related organs, placenta, umbilical cord, and amniotic fluid. The UA parameters were collected from the free segment of the proximal placenta (**Figure 1A**), and the sampling site was knotted or tortuous [8]. The MCA parameters were collected from the middle of the MCA (**Figure 1B**) after a clear image of the Willis circle was displayed [9]. DV parameters were collected from the connection between the umbilical vein and the inferior vena cava (**Figure 1C**). The connection between the umbilical vein and the liver was identified

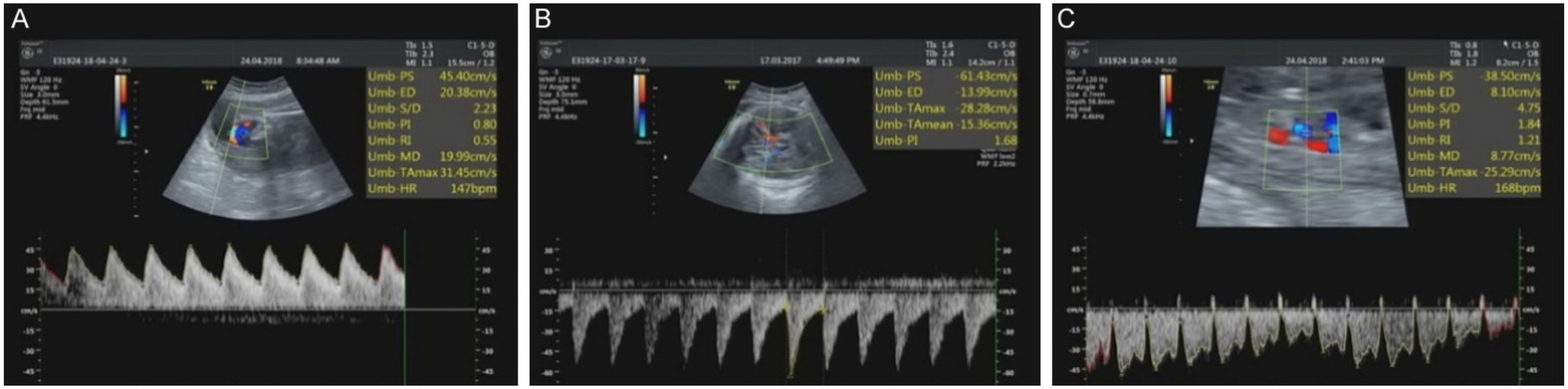

Figure 1. The basic measurement indicators detected by high-end 4D color Doppler ultrasound system. A: The UA parameters collected from the free segment of the proximal placenta; B: The MCA parameters collected from the middle of the MCA; C: DV parameters collected from the connection between the umbilical vein and the inferior vena cava. UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus.

Table 1. Comparison of baseline data ($\overline{x}$±sd, n (%))

Group	Observation group (n=168)	Control group (n=282)	χ^2	P
Age (year)	28.8±6.2	27.7±5.7	1.864	0.063
Gestational weeks (week)	35.9±5.3	36.1±4.9	0.280	0.779
Pregnancy history			0.593	0.441
First time	106 (63.095)	188 (66.667)		
≥2 times	62 (36.905)	94 (33.333)		

Table 2. Comparison of S/D values of UA, MCA, and DV ($\overline{x}$±sd)

Group	Observation group (n=168)	Control group (n=282)	t	P
UA	7.02±0.42	4.72±0.37	58.969	<0.001
MCA	3.81±0.34	6.14±0.43	63.561	<0.001
DV	5.88±0.50	2.35±0.34	81.026	<0.001

Note: S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus.

and the fine vessels were detected for accurate exploration [10]. The line of UA, MCA, and DV parameters assessment was parallel to the blood flow direction of the blood vessel to be tested. The assessment angle was <20° for UA and MCA, and <45° for DV. Blood flow indices were measured by the Auto Trace function of the ultrasound device to collect at least 5 clear and complete continuous spectra (3 of the 5 results were selected to give a mean value). Indices to be measured included S/D, PI, and resistance index (RI). All measurements were performed by a senior doctor with an experience of ultrasound examination for more than 5 years.

Diagnostic criteria for fetal distress: The observation group: Meconium-staining amniotic fluid; fetal heart rate >160 beats/min or more than 180 beats/min continuously; fetal heart rate <120 times/min or <100 times/min at the time of severe acidosis [11].

Outcome measures: The measurements including: S/D values of UA, MCA, and DV in the two groups; the efficiency of single diagnosis by the S/D value of UA, MCA and DV for fetal distress and the combined diagnosis according to the ROC curve analysis; the consistency test between the results of combined diagnosis and the clinical delivery outcomes.

Statistical analysis

Statistical analysis was performed using SPSS 24.0. The count data were indicated by the rate (percentage) (n (%)) and analyzed by χ^2 test (bilateral α=0.05). The measurement data were indicated by the mean ± standard deviation ($\overline{x}$±sd) and were compared between the two groups by the independent sample t-test (bilateral α=0.05). A statistical difference was recognized when P<0.05. The ROC curve of S/D values of UA, MCA, and DV was drawn to analyze the diagnostic efficacy. The clinical diagnostic value was confirmed when the area under the curve (AUC) was >0.5. A larger AUC indicated a higher clinical diagnostic value. Youden index = Sensitivity + Specificity-1, the maximum test result value of Youden index was the optimal critical value. The Kappa consistency test was performed between the results of combined diagnosis and the clinical delivery outcomes. Kappa ≥0.75 suggested good consistency, while Kappa <0.40 suggested poor consistency.

Results

Baseline data

The two groups of pregnant women were not statistically different in baseline data such as age, gestation age and pregnancy history (P>0.05). See **Table 1**.

Comparison of S/D values of UA, MCA, and DV

Pregnant women in the observation group had markedly higher S/D values of UA and DV and lower S/D values of MCA than women in the control group (P<0.001). See **Table 2** and **Figure 2**.

The diagnostic efficacy of S/D values of UA, MCA, and DV single or combined diagnosis for fetal distress according to the ROC curve

ROC curve indicated that the AUC of S/D value for the diagnosis of fetal distress was 0.763 in UA, 0.828 in MCA, and 0.812 in DV, respectively. The combined diagnosis of fetal distress by S/D values of UA, MCA, and DV in the third trimester was performed according to the cut-off

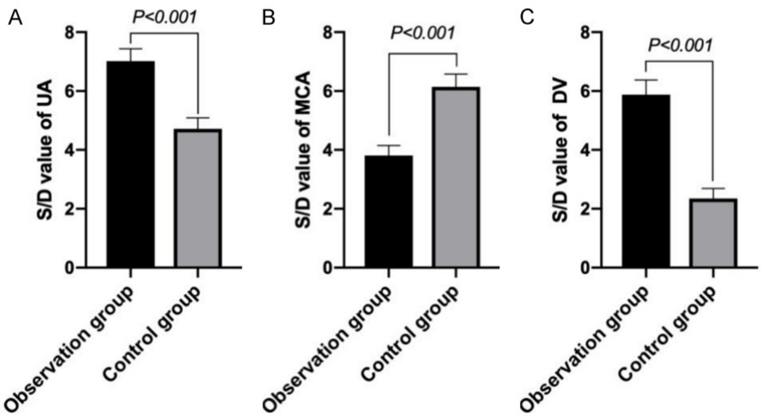

Figure 2. Comparison of S/D values of UA, MCA, and DV. A: S/D values of UA; B: S/D values of MCA; C: S/D values of DV. S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus.

values of the three S/D values indicated by the Youden's index. Fetal distress was diagnosed if any two of the three results turned positive. The AUC of combined diagnosis of fetal distress by S/D values of UA, MCA, and DV was 0.935 (95% CI: 0.894 to 0.956), higher than any of the single diagnosis (Z=5.98, P<0.01). See **Table 3**; **Figures 3** and **4**.

The diagnostic accuracy of S/D values of UA, MCA, and DV combined diagnosis for fetal distress

The combined diagnosis by S/D values of UA, MCA, and DV in the third trimester identified 189 cases of fetal distress and 261 cases of normal pregnancy, with an accuracy rate of 91.78%. According to the Kappa consistency between the results of combined diagnosis and the clinical delivery outcomes, the Kappa value was 0.829 (95% CI: 0.162 to 0.903; P<0.001). See **Table 4**.

Discussion

Fetal distress has complex pathogenesis because its occurrence and development are related to hemodynamic changes, reperfusion injury, failure of cellular energy metabolism, oxygen-free radicals, calcium influx, excitatory amino acid neurotoxicity, and delayed neuronal death [12]. In recent years, the changes in blood flow indices like UA, MCA, and DV in the process of fetal distress have been explored.

The umbilical artery (UA) connects the fetus with the mother. The early placenta has only a few chorionic villi arteries with a small diameter, resulting in large blood flow resistance, and is highly susceptible to myocardial contractility and peripheral vascular resistance. Wang et al. found that the placenta turns mature in the third trimester compared to in the early pregnancy, with reduced vascular resistance and increased local blood flow [13]. A marked feature of the mature placenta is the increased number of villus arteries with a larger diameter in UA. Ultrasound assessment of S/D value can reflect the local blood flow changes in the placenta by the blood flow velocity. The S/D value of UA in late pregnancy is significantly lower than that in the early pregnancy, indicating the maturity of the fetal circulatory system. The study by Morris et al. stated that increased peripheral vascular resistance of the placenta led to a higher S/D value of UA when the fetus is in distress [14]. In this study, the S/D value of UA was significantly higher in the observation group (fetal distress) than in the control group (normal pregnancy), which is consistent with previous studies. However, the studies by Wang and Morris did not illustrate the specific significance of S/D value of UA in the clinical diagnosis of fetal distress, which only served as an important reference for fetal distress [13, 14].

The MCA change in the third trimester is also a clinical focus. MCA is the most crucial artery for the development of the fetal brain due to its abundant blood supply to the cerebral hemisphere. The brain's oxygen consumption increases as the fetus grows mature in the third trimester. In the case of fetal distress, by the maternal and fetal compensatory mechanisms, vital organs, such as the brain, will be preferentially supplied for blood. This compensatory mechanism results in decreased MCA resistance, increased perfusion, and decreased S/D value. The study by Wei et al. confirmed the value of MCA resistance in fetal monitoring in the third trimester, providing a clinical proof for the diagnosis of fetal distress by the S/D value of MCA [15, 16]. Similarly, in this study, the S/D value of MCA was significantly lower in the

Table 3. The diagnostic efficacy of S/D values of UA, MCA, and DV single or combined diagnosis for fetal distress according to the ROC curve (n, %)

	UA	MCA	DV	Combined diagnosis	χ^2/Z	P
Sensitivity (%)	62.87	71.56	70.43	95.14	7.32	<0.05
Specificity (%)	65.08	76.94	72.68	82.20	4.89	<0.05
PPV (%)	81.53	88.56	84.85	78.46	2.53	<0.05
NPV (%)	59.68	76.93	72.21	85.93	1.94	<0.05
AUC (95% CI)	0.763 (0.721, 0.820)	0.828 (0.799, 0.879)	0.812 (0.759, 0.848)	0.935 (0.894, 0.956)	5.98*	<0.01

Note: *, by Z test. S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus; ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence curve; PPV, positive predictive value; NPV, negative predictive value.

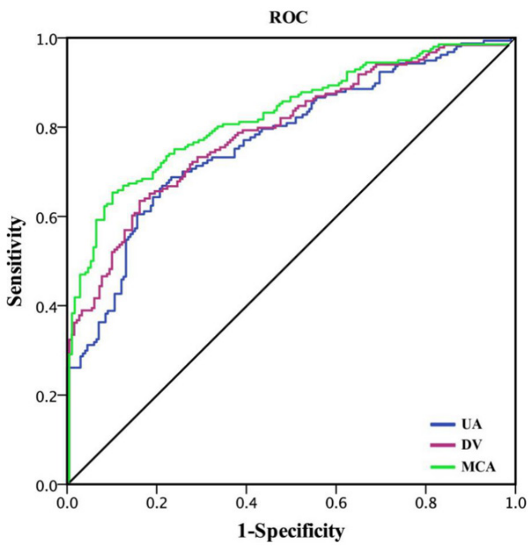

Figure 3. The S/D values of UA, MCA, and DV single diagnosis for fetal distress according to the ROC curve. S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus; ROC, receiver operating characteristic curve.

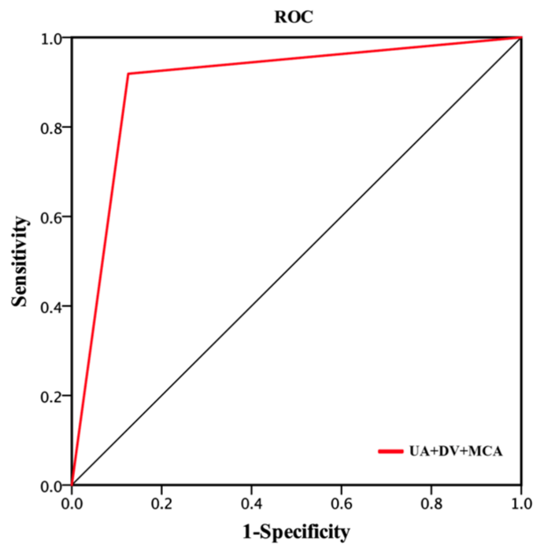

Figure 4. The S/D values of UA, MCA, and DV combined diagnosis for fetal distress according to the ROC curve. S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus; ROC, receiver operating characteristic curve.

observation group than that in the control group.

Ductus venosus (DV) is one of the important parts of the fetal circulatory system. It can transport hyperoxic blood directly to the heart so as to protect the blood and oxygen transport to important organs of the fetus, which is consistent with the brain-protection effect [17]. Therefore, DV blood flow changes may be used to observe the abnormalities in the fetal circulatory system. The meta-analysis by Caradeux et al. demonstrated the mechanism of DV blood flow changes during fetal distress [18]. According to this meta-analysis, increased right heart load, blocked venous return and even venous reflux during intrauterine hypoxia are the main physiological mechanisms of abnormal DV spectrum in fetal distress. In this study, the S/D value of DV was significantly higher in the observation group than in the control group, which is consistent with the results of Wei [15, 16].

Ultrasound has a unique advantage of a lower cost of mastery for the doctor and a lower examination expense for the patients. It is important to explore a more optimal way by ultrasound to diagnose fetal distress. Many experiments have studied related blood flow parameters of UA, MCA, and RA, including S/D, PI, and RI [19]. The study by Hashimoto et al. detected great differences in the blood flow parameters of UA and MCA between fetus with intrauterine hypoxia and normal fetus which is similar to the results of this study [20]. In the study by Hashimoto et al., the AUC of S/D value

Table 4. Comparison of S/D values of UA, MCA, and DV ($\bar{x}$±sd)

Combined diagnosis	Clinical outcome		Kappa value	P
	Fetal distress (n=168)	Normal pregnancy (n=282)		
Fetal distress (n=87)	80	10	0.829	<0.001
Normal pregnancy (n=37)	7	27		

Note: S/D, systolic/diastolic ratios; UA, umbilical artery; MCA, middle cerebral artery; DV, ductus venosus.

for predicting fetal hypoxia was 0.859 in UA and 0.758 in MCA, and the sensitivity was 77.1% in UA and 74.3% in MCA. However, in the present study, the AUC of MCA-S/D was higher than that of UA-S/D, which is similar to the results of Ma et al. [21]. Recent studies have praised the diagnostic value of ultrasound assessment of the blood flow parameters of UA, MCA, and DV for fetal distress. But most studies only studied the diagnosis by a single indicator [5, 22, 23]. And these indicators in some studies were not sensitive and specific enough [7, 24-27].

Considering those defects in previous studies, this study made an innovative combined assessment of S/D values of MCA, UA, and DV to explore its diagnostic efficacy for fetal distress, aiming to provide more effective indicators for the clinical diagnosis. In this study, the S/D values of MCA, UA, and DV of women with fetal distress were remarkably different from those with normal pregnancy, which is consistent with previous studies. ROC analysis showed that the combined diagnosis for fetal distress by S/D values of MCA, UA, and DV had markedly higher AUC, sensitivity, and specificity than any single diagnosis. To further assess the efficacy of the combined diagnosis, this study performed a Kappa consistency test on the results of the combined diagnosis and the pathological diagnosis, which showed a strong consistency between the results of two methods. Such results suggest that the combined diagnosis for fetal distress by S/D values of UA, MCA, and DV in the third trimester is worthy of promotion. But the value of this combined diagnosis for fetal distress needs to be verified by a larger sample size. Once the diagnostic value is confirmed, the diagnosis can be directly made by S/D values of UA, MCA, and DV using specific programs, diversifying the diagnostic methods for fetal distress.

In summary, the combined diagnosis for fetal distress by S/D values of MCA, UA, and DV is practical and has higher diagnostic value than the single diagnosis by those factors. ROC analysis displayed preferred diagnostic efficacy, higher sensitivity and specificity in the combined diagnosis than in the single diagnosis. This study design is defective due to the small number of subjects. A larger sample size is needed to verify the value of the combined diagnosis, even if the results of this study were accurate.

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Disclosure of conflict of interest

None.

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