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Original Article

Thickness of cervical transparent layer and blood flow spectrum of venous catheter in early pregnancy of single chorionic twin pregnancy

Yanfen Chen, Qing Zhao, Huimin Pan, Guoping Xiong

Department of Gynecology and Obstetrics, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, Hubei, China

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Abstract: Twin-to-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancy (MCT), and is known to be related with nuchal translucency (NT) thickness and blood flow spectrum of ductus venosus (DV) in MCT. This study thus investigated role of NT and abnormal flow spectrum of DV (DV-RAV) in predicting TTTS. Ninety-six women with MCT (in their 11th to 14th week of pregnancy) received ultrasound examination to measure NT values, and DV blood flow spectrum. Those patients with inconsistent NT values, or DV-RAV were recorded. ROC was employed to evaluate specificity and sensitivity of ΔNT and DV-RAV in predicting TTTS. Seventy-three pregnant women with MCT were included with ΔNT values at 0.33 ± 0.11 mm. Prenatal ultrasound diagnosed 14 TTTS cases, and found 20, 53 and 17 patients with inconsistent NT, consistent NT and DV-RAV, respectively; in which 8, 6 and 12 cases developed into TTS. Both sensitivity and specificity predicting TTTS were 57.14% and 79.66% using ΔNT, 85.71% and 91.25% using DV-RAV, and 92.86% and 78.97% in combined assay, which had higher sensitivity and positive predictive value but similar specificity compared to single index. Area-under-curve of combined assay was significantly higher than the single parameter. The imbalance of hemodynamics in early MCT, as shown by fetal DV-RAV and ΔNT, provides indices for early screening. The combined assay of ΔNT and DV-RAV improves specificity and positive predictive value. It is therefore recommended to combine NT assay with DV blood flow spectrum in MCT diagnosis.

Keywords: Monochorionic twin pregnancy, early pregnancy, nuchal translucency, twin-to-twin transfusion syndrome, ductus venosus

Introduction

Twin-to-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancy (MCT), and has higher perinatal mortality rate, which is elevated as higher MCT rate [1, 2]. Clinical diagnosis of TTTS frequently adopts Quintero staging criteria [3]. Prenatal diagnosis of TTTS uses ultrasound examination at middle to late pregnancy phase, usually after 18th weeks. Early prenatal diagnosis of TTTS and treatment significantly improves birthrate of perinatal babies. Current prenatal diagnosis mainly depends on organ function failure in the fetus, where abnormal hemodynamics and cardiac structure can be revealed by screening for TTTS. Previous study has shown the random formation of body-placental blood vessel junction, when lost or having inconsistency leads to asymmetric vessel resistance [4] for TTTS. The imbalance of hemodynamics in TTTS can be seen in the early pregnant phase [5]. During middle pregnancy phases, patho-physiological alternations can be observed. Those patients with increased thickness of nuchal translucency (NT) or with intra-fetal amniotic membrane folding had higher rates of severe TTTS [6]. Elevated NT thickness can be observed by ultrasonography at 10th to 14th weeks, while intra-fetal amniotic membrane folding can be identified by ultrasonography at 15th to 17th weeks. A higher TTTS risk occurs in those MCT fetus having increased NT thickness accompanied with abnormal blood flow spectrum of ductus venosus (DV) [7]. Additional study has shown that inconsistency of NT thickness or crown-rump length in MCT fetuses can predict TTTS but with relatively higher misdiagnosis

rate [8]. Cardiac function in MCT fetuses is correlated with blood flow spectrum of fetal DV [9]. We thus performed a prospective analysis of NT inconsistency or abnormal DV flow spectrum in predicting TTTS, in an attempt to provide references for early diagnosis and treatment of TTTS.

Materials and methods

Clinical information

Women with MCT admitted to the Central Hospital of Wuhan and the Maternal and Child Health Hospital of Wuhan from February 2012 to March 2014 were recruited and received ultrasound screening during 11th to 14th week of pregnancy. Exclusive criteria: abnormal fetal chromosomes; death of the fetus; major structural abnormality (anencephaly, lack of limb, giant bladder, encephalocele or spinal abnormality); major organ dysfunction of the mother; interrupted follow-up; or history of major congenital disease. This study has been pre-approved by the ethical committee and has obtained written consent from all participants.

Examination

Pregnant women were laid in a supine position, and received colored Doppler ultrasound (Siemens Sequoia 512 or GE Voluson 730) via abdomen or abdominal-intracavity pathway to scan and record conditions of the fetal organs. Pregnancy week was estimated by measuring the crown-rump length of the fetus while NT value was measured by the standard of UK fetal medicine foundation [10]. DV blood flow spectrum was collected from the right parasagittal section by tracing via fetal umbilical vein. A 2 mm sample frame was placed at the initial site of DV. The ultrasound beam was adjusted in parallel with blood flow direction with angle calibration. Pulsed flow rate curve of DV was collected in the fetus, and at least 5 cardiac cycles were recorded. In a normal fetus, DV blood flow spectrum presented as forward flow, whilst an abnormal spectrum was identified by inversion or absence of atrial systolic wave (A wave).

Diagnostic criteria

Fetal NT was measured, while DV blood flow spectrum was collected. NT inconsistency between the two fetuses was defined as ΔNT > 0.06 mm. DV-RAV was defined as inversion or disappearance of the A wave in either or both fetus. TTTS was diagnosed based on Quintero staging criteria as grade I (insufficient or excess amniotic fluid, as shown by < 0.2 cm or > 8 cm amniotic fluid depth), grade II (no visible bladder in blood supplying the fetus), grade III (sever abnormality in Doppler ultrasound), grade IV (fetal edema), or grade V (intrauterine fetal death) [3].

Follow-up

Those patients with inconsistent NT values received weekly ultrasound examinations. If NT was found to be increased, other clinical indexes were recruited. Confirmation of fet al. death was collected at follow-up. Confirmed diagnosis was made by postnatal body examination or aborted fetus.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. Continuous parameters were tested for normality using Kolmogorove-Smirnov method. Those that fit a normal distribution were presented as mean ± standard deviation (SD). Those that did not fit a normal distribution were presented as median and quartiles. The comparison of ratios was compared by chi-square test or corrected chi-square test. ROC analysis was used to evaluate NT values and DV-RAV in TTTS prediction. Logistic regression model was established by combined indexes. ROC was also used to analyze the diagnostic value of combined assay on TTTS. Z-test was used to compare the combined assay. A statistical significance was defined when $P < 0.05$.

Results

General information of pregnant women

A total of 96 MCT women received ultrasound screening during their 11th and 14th week of pregnancy. Eight people who did not perform follow-up were excluded, along with one triplet pregnancy, 10 fetuses had significant structural abnormalities (1 giant bladder, 3 anencephaly, 3 patients with anencephaly and acrdia, 2 spinal abnormality, and 1 holoprosencephaly), 4 individuals had chromosomal abnormality. A total of 73 pregnant women were thus eventually recruited in this study. Median age of all women was 31.4 years (19~45 years). There were 9 women older than 33 years (12.33%). The average pregnancy range was 12.3 weeks

Table 1. Distribution of TTTS in MTC (n, %)

Item	TTTS	Non-TTTS	Total
N	14 (19.17)	59 (80.83)	73
ΔNT > 0.6 mm	8 (40.00)	12 (60.00)	20
ΔNT ≤ 0.6 mm	6 (11.32)	47 (88.67)	53
DV-RAV	12 (70.59)	5 (29.41)	17
Normal DV flow spectrum	2 (3.77)	54 (96.43)	56
NT abnormality + DV-RAV	12 (100.0)	0 (0.00)	12
Normal NT or DV	2 (3.28)	59 (96.72)	61

Table 2. Sensitivity and specificity of NT difference value and DV flow spectrum abnormality in predicting TTTS

Parameter	Sensitivity/%	Specificity/%	Positive predictive value/%	Negative predictive value/%
ΔNT	57.14 (8/14)	79.66 (47/59)	40.00 (8/20)	88.68 (47/53)
DV-RAV	85.71 (12/14)	91.51 (54/59)	70.59 (12/17)	96.43 (54/56)
ΔNT + DV-RAV	92.86 (13/14)	78.97 (46/59)	92.00 (23/25)	97.92 (47/48)
χ^2	5.939	4.575	14.153	4.730
P	0.04	0.10	0.00	0.09

(11~14 weeks). The average crown-rump length was 67.88 ± 8.4 mm. The difference of crown-rump length between the two fetuses was 2.86 ± 0.94 mm. The difference of NT (ΔNT) was 0.33 ± 0.11 mm. Fourteen patients were diagnosed with TTTS by prenatal ultrasound (19.7%) and all developed into stage III or stage IV. These women showed severe abnormalities by colored Doppler ultrasound at 16th~28th weeks. Among them, 4 fetuses died prematurely, and were diagnosed after abortion.

Sensitivity and specificity of ΔNT values and DV blood spectrum abnormality in TTTS prediction

In a total of 73 MCT cases, there were 20 individuals with inconsistent NT across the two fetuses. Among them, 8 patients developed into TTTS. The other 53 patients had consistent NT values and 6 of them developed into TTTS. Among all 17 individuals with abnormal DV blood flow spectrum, 12 of them developed into TTTS (including 8 cases with normal DV blood flow spectrum in one fetus and abnormality in the other one, and 4 cases having abnormality in both fetuses). All those 12 patients were complicated with inconsistent NT. The other 5 patients all had abnormal blood flow spectrum in one fetus and did not develop into TTTS. Around the 17th~20th pregnant week, blood flow spectrum recovered. The pregnancy was terminated at 36~37 week with survival of the fetus (**Table 1**). The sensitivity and specificity in predicting TTTS were 57.14% and 79.66% when using ΔNT, and were 5.71% and 91.25% when using DV-RAV. In combined assay scenario including both NT value and DV blood flow spectrum abnormality, sensitivity and specificity in predicting TTTS were 92.86% and 78.97%. Compared to single parameter prediction, both sensitivity and positive predictive value were significantly increased ($P < 0.05$) without decrease of specificity (**Table 2** and **Figure 1**).

Predicting TTTS using ΔNT values and abnormality of DV blood flow spectrum

For each patient, X1 represented for ΔNT values (in mm) while DV blood flow spectrum was shown in X^2 (normal = -1, abnormal = 1). ROC analysis was used to evaluate the value of ΔNT in conjunction with DV-RAV in predicting TTTS. Combined indexes were used to generate a logistic regression model. Z-test results showed using combined assay, that the area under the curve was 0.856 (95% CI, 0.741~0.971), which was significantly higher than using ΔNT only (0.731, 95% CI, 0.541~0.922) or DV-RAV only (0.792, 95% CI, 0.634~0.949, $P < 0.05$ in both cases). Therefore the combined assay had better test efficiency as shown in **Figure 2** and **Table 3**.

Discussion

Colored Doppler ultrasound was used to diagnosis the connection of placental blood vessels

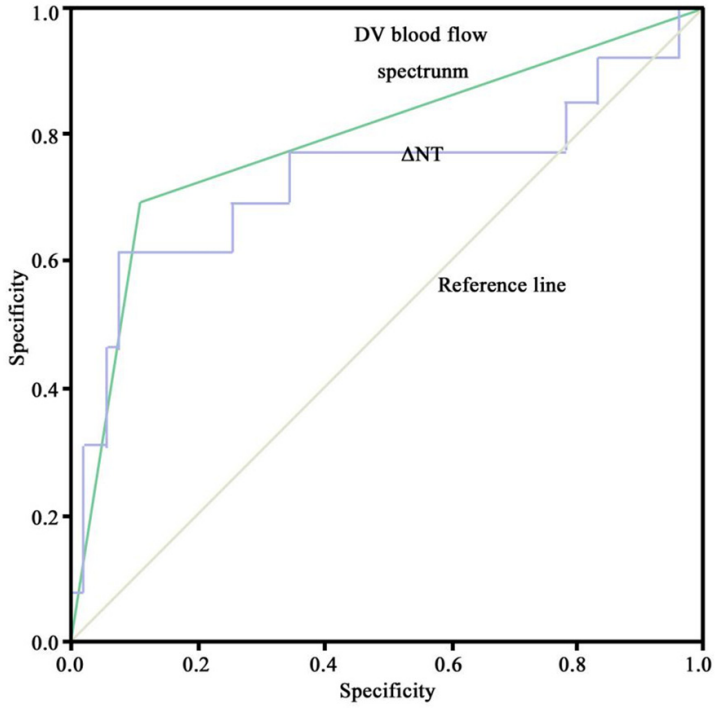

Figure 1. ROC analysis using ΔNT values and abnormality of DV blood flow spectrum.

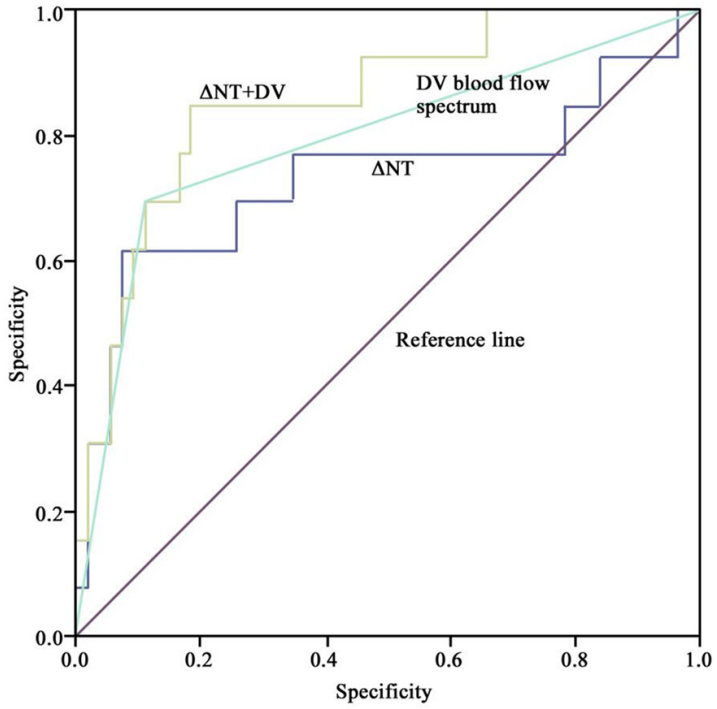

Figure 2. ROC analysis using ΔNT values and abnormality of DV blood flow spectrum in predicting TTTS.

in a non-invasive manner, as its can judge the blood flow direction and confirm the site of placental blood vessel connection [11, 12]. Classical ultrasound diagnostic standards of TTTS include MCT, unequal size of dual amniotic sac and imbalance of fetal development, but with a higher false positive rate. Another study recruited 9 patients who fitted those ultrasound features by umbilical puncture and found 4 real TTTS patients [13, 14]. The confirmed diagnosis of TTTS requires the co-existence of blood vessel connection branch, accompanied with hemodynamic changes between the two fetuses [15, 16]. The early change in an early phase TTTS fetus is neglected in the current Quintero stage. Most researchers believe that the pathological basis of TTTS was correlated with increased number of common branch of unidirectional artery-vein connections in the common placenta [17, 18]. The imbalance of blood volume in twin circulatory systems causes dysfunction of fetal organs. NT was first suggested as one index for ultrasound examination in early pregnancy as early as 1992. Some studies showed dysfunction of the fetal circulatory system by thickening of NT values, which can be used for early prediction of TTTS [19]. Other study has shown that the inconsistency between fetal crown-rump ratio (CRL) and NT value could work as an early predictive index for TTTS, but with instable sensitivity [20]. Some scholars tested NT values in 412 MCT cases and found significantly elevated TTTS risk with higher ΔNT values [21]. The follow-up of fetal deaths in 99 MCT cases showed that the specificity and sensitivity of ΔNT > 0.6 mm in predicting TTTS were 92.0% and 50.0%, respectively [22]. Abnormality in the DV blood flow spectrum might be one risk factor for TTTS [23]. As one important pathway for fetal blood circulation, DV flow spectrum during the 8th to 14th week of pregnancy is closely corre-

Table 3. Area under the curve in ROC analysis

Test parameter	Area	Standard error[a]	Regression Sig.[b]	Regression 95% CI	
				Lower limit	Upper limit
ΔNT	0.731	0.097	0.010	0.541	0.922
DV blood flow spectrum	0.792	0.080	0.001	0.634	0.949
NT + DV	0.856	0.058	0.000	0.741	0.971

Note: a, under non-parametric hypothesis; b, null hypothesis: area = 0.5.

lated with fetal cardiac function [22, 23]. For those fetuses with limited growth or abnormal chromosomes, DV flow spectrum abnormality was frequently observed, accompanied with thickening NT. A study measured NT values and DV blood flow spectrum in MCT patients, and found that those people with inconsistency between DV flow spectrum abnormality and NT values all developed into TTTS [21, 22]. This study tested NT values and DV blood flow spectrum in 73 MCT cases. Results showed that using ΔNT > 0.6 mm as the cut-off value, and using inversion or absence of an A wave as the abnormality of DV blood flow spectrum, and found that the sensitivity and specificity in predicting TTTS were 57.14% and 79.66% when using ΔNT, and were 5.71% and 91.25% when using DV-RAV. In this study, the specificity of using ΔNT in predicting TTTS was lower than similar studies, probably due to larger bias in patient sources or operational errors.

In TTTS fetuses, there was an abnormality of the circulatory system, causing an imbalance of fetal blood circulation, cardiac damage and insufficient atrial flow in the diabolic phase, accompanied with an abnormal DV wave, in addition to thickening NT and fetal edema. Abnormality of DV blood flow spectrum and increased NT values are thus sequential parameters during TTTS progression. This study performed a combined assay of ΔNT values and DV-RAV, and performed ROC analysis to reveal that sensitivity and specificity of using a combined assay in predicting TTTS were 92.86% and 78.97%, respectively. Compared to single parameter prediction, both sensitivity and positive predictive value were significantly increased but without decrease of specificity. The area under the curve of combined assay was 0.856 (95% CI, 0.741~0.971), which was significantly higher than using ΔNT only (0.731, 95% CI, 0.541~0.922) or DV-RAV only (0.792, 95% CI, 0.634~0.949), suggesting better test efficiency of combined assay using both ΔNT values and DV-RAV. In this study, 12 out of 17 patients with abnormal DV blood flow spectrum developed into TTTS, accompanied with inconsistent NT values. Those 5 cases who did not develop into TTTS were not accompanied with NT inconsistency. During the 17th~20th pregnant week, DV blood flow spectrum recovered, suggesting the gradual recovery of a single abnormal DV blood flow spectrum during fetal development by self-regulation. Therefore it should be observed in conjunction with other clinical indexes.

Conclusion

The imbalance of hemodynamics in early pregnancy around the 11th~14th week of MCT pregnancy, plus abnormal DV blood flow spectrum and ΔNT values are probably indexes for early screening of MCT. The combined assay can increase both sensitivity and positive predictive value. Therefore, the examination of NT in MCT patients should be performed in conjunction with status of DV blood flow spectrum.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guoping Xiong, Department of Gynecology and Obstetrics, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26, Shengli Street, Jiang'an District, Wuhan 430000, Hubei, China. Tel: +86-027-65692973; Fax: +86-027-65692973; E-mail: zhongcituon@yeah.net

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