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Nuchal translucency thickness and crown rump length discordance for the prediction of outcome in monochorionic diamniotic pregnancies

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ABSTRACT

Background: Ultrasonographic features of the underlying hemodynamic changes in twin–twin transfusion syndrome (TTTS) may be present at the first trimester scan.
Aims: To investigate the value of intertwin discordance in nuchal translucency (NT) thickness and crown rump length (CRL) to predict TTTS and other adverse outcomes.
Study design: Cohort study.
Subjects: One hundred and thirty-five unselected consecutive monochorionic diamniotic twin pregnancies.
Outcome measures: NT and CRL discordance were assessed at 11 to 13^{+6} weeks' gestation. Receiver–operating characteristics (ROC) curves were used to determine their predictive ability for the subsequent development of TTTS.
Results: TTTS complicated 16/135 (12%) pregnancies. Four other pregnancies were complicated by selective intrauterine growth restriction (sIUGR) and 3 by miscarriage <24 weeks gestation. The median NT discordance was 15% (range 0–37%) in TTTS pregnancies, 13% (12–19%) in those with miscarriage <24 weeks' gestation, 47% (30–50%) in those with sIUGR, and 14% (0–86%) in those without complications. Prediction for subsequent development of TTTS provided by the discordance in CRL, expressed as the area under ROC curve, was 0.52 (95% confidence interval 0.38–0.67), while it was 0.50 for NT discordance (95% confidence interval 0.35–0.64). NT discordance was significantly higher in sIUGR compared to both uncomplicated and TTTS pregnancies ($p = 0.004$ and $p = 0.003$, respectively).
Conclusion: In an unselected population of monochorionic twin pregnancies, discordance in CRL and NT measured during first trimester scan is not a clinically useful predictor of the subsequent development of TTTS. Therefore, strict ultrasound follow up is recommended for the timely diagnosis of TTTS.
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1. Introduction

The high mortality before 24 weeks' gestation in monochorionic twins is due to unbalanced intertwin transfusion mediated by unidirectional arteriovenous anastomoses, with inadequate or absent compensation along bidirectional superficial anastomoses resulting in severe early onset twin-to-twin transfusion syndrome (TTTS), miscarriage or spontaneous death of at least one fetus in 12% of cases [1]. TTTS has a poor prognosis if left untreated, with perinatal mortality rates of 80–100% and a substantial risk of neurological sequelae in survivors [2,3]. Close ultrasound surveillance during the second trimester of pregnancy is aimed at detecting TTTS at a stage at which effective treatment can be performed by endoscopic laser coagulation of the communicating placental vessels [4]. Such surveillance is time consuming and cost demanding, as it requires frequent ultrasound examinations at least every 2–3 weeks according to the few available guidelines [5,6]. Ultrasonographic features of the underlying hemodynamic changes in TTTS may be present at the 11 to 13^{+6} weeks' scan and manifest as increased nuchal translucency (NT) thickness in the recipient fetus [7,8], or as a high intertwin difference in NT or crown rump length (CRL) in pregnancies that subsequently develop TTTS compared with those without TTTS [9,10]. However the relationship between first trimester ultrasound measurements and the subsequent outcome of monochorionic diamniotic twin pregnancies is controversial and is mainly derived from relatively small series or from heterogeneous populations [7–10].

The aim of our study was to investigate the value of intertwin discordance in NT and CRL for the prediction of the subsequent development of twin–twin transfusion syndrome and other adverse outcomes in an unselected population of monochorionic diamniotic twin pregnancies.

2. Methods

In our centre a transabdominal ultrasound examination is routinely performed at 11–13^{+6} weeks' gestation in all multiple pregnancies to

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Table 1
Characteristics of pregnancies who developed TTTS.

Patient	Gestational age (weeks)	CRL 1 (mm)	NT 1 (mm)	CRL 2 (mm)	NT 2 (mm)	NT discordance %	CRL discordance %	Gestational age at diagnosis (weeks)
1	12 + 3	53	0.7	54	1.1	36%	2%	18 + 0
2	12 + 0	60	0.9	55	0.9	0%	8%	21 + 1
3	13 + 1	76	1.1	77	1.3	15%	1%	23 + 0
4	13 + 6	84	1.8	83	2.1	14%	1%	17 + 6
5	11 + 5	44	0.9	50	1.0	10%	12%	19 + 0
6	12 + 0	47	0.9	48	1.2	25%	2%	19 + 0
7	13 + 4	76	2.2	82	3.5	37%	7%	25 + 2
8	12 + 0	59	1.8	61	1.9	5%	3%	17 + 6
9	12 + 5	58	1.3	67	1.6	19%	24%	18 + 0
10	12 + 3	61	1.1	56	1.1	0%	8%	17 + 2
11	12 + 4	59	1.0	58	1.4	29%	2%	17 + 4
12	13 + 1	76	1.2	74	1.4	14%	3%	16 + 4
13	12 + 6	80	1.4	73	1.5	7%	9%	29 + 6
14	12 + 5	71	1.4	74	1.5	7%	4%	24 + 6
15	11 + 6	49	0.7	50	0.9	22%	2%	27 + 4
16	12 + 4	65	1.2	68	1.8	33%	4%	19 + 1

CRL, crown rump length; NT, nuchal translucency.

define chorionicity, diagnose major fetal defects and for measurement of the CRL and NT thickness of each fetus. We searched our twin database to identify women with first trimester viable monochorionic twin pregnancies who were prospectively followed up at our centre with a first trimester scan performed between 11 and 13^{+6} weeks' gestation. Pregnancies referred at a later gestation were excluded from the study, even if first trimester NT and CRL data were available. As this was a retrospective audit of clinical data presented in anonymised form, no Institutional Review Board approval was necessary according to Italian national regulations.

The pregnancies were diagnosed as being monochorionic because there was a single placental mass with absent lambda sign [11]. CRL and NT were measured in a sagittal section of the fetus with the head in a neutral position [7]. Reference values for NT measurement percentiles were those provided by the Fetal Medicine Foundation [12]. The ultrasonographic examinations were performed by sonographers who had received the Fetal Medicine Foundation certificate of competence in the theory and practice of the first trimester scan. In each pregnancy the intertwin discordance in NT and CRL was calculated as the difference in each measurement between the two fetuses expressed as a percentage of the larger measurement. Follow-up of monochorionic twins included ultrasound examinations at 16 weeks and 2-weekly thereafter, unless there was evidence of TTTS, in which case the frequency of examinations was increased as necessary. Twin-to-twin transfusion syndrome was defined by the association of polyhydramnios in one sac with a deepest vertical pool of amniotic fluid of at least 8 or 10 cm before and after 20 weeks respectively, together with oligo-hydramnios in the other sac with a deepest vertical pool of less than 2 cm. Selective intrauterine growth restriction (sIUGR) was defined as an estimated fetal weight below the 10th percentile in one twin together with abnormal umbilical artery Doppler [13].

The primary outcome was to determine the predictive ability of intertwin discordance in NT and CRL, expressed as percentage of the larger measurement, for subsequent development of TTTS. The development of TTTS, miscarriage at less than 24 weeks' gestation, spontaneous death of at least one fetus, and sIUGR were defined as adverse pregnancy outcomes. Receiver-operating characteristics (ROC) curves were used to determine the predictive ability of intertwin discordance in NT and CRL, expressed as a percentage of the larger measurement, for subsequent adverse pregnancy outcome. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for different thresholds of CRL and NT discordance. The Kruskal–Wallis and Kolmogorov–Smirnov tests were applied for intergroup comparisons. Correlations were assessed with Spearman's correlation coefficient (ρ>). All statistical calculations were performed with the SPSS statistical software (release 16, SPSS Inc., Chicago, IL, USA). P values <0.05 were considered statistically significant.

3. Results

From February 2001 to April 2009 we examined 136 monochorionic diamniotic twin pregnancies in the first trimester. Karyotype was normal in 135 cases, one pregnancy was complicated by trisomy 21 in both fetuses and excluded from further analysis.

TTTS complicated 16/135 (12%) pregnancies, details of which are listed in Table 1. Four other pregnancies were complicated by sIUGR (Table 2). Miscarriage <24 weeks' gestation occurred in three cases (Table 3). The median NT discordance was 15% (range 0–37%) in TTTS pregnancies, 13% (12–19%) in those with miscarriage <24 weeks' gestation, 47% (30–50%) in those with sIUGR, and 14% (0–86%) in those without complications. The median CRL discordance was 4% (1–24%) in TTTS pregnancies, 1% (0–8%) in those with miscarriage

Table 2
Characteristics of pregnancies who developed selective intrauterine growth restriction (sIUGR).

Patient	Gestational age (weeks)	CRL 1 (mm)	NT 1 (mm)	CRL 2 (mm)	NT 2 (mm)	NT discordance %	CRL discordance %	Gestational age at delivery (weeks)
17	11 + 1	46	1.4	47	2	30%	2%	sIUGR requiring laser treatment at 22 weeks gestation, subsequent IUD
18	12 + 5	58	0.6	48	1.2	50%	17%	31 + 0
19	11 + 6	48	1.5	55	2.8	46%	13%	33 + 0
20	11 + 6	49	1.5	54	2.9	48%	9%	32 + 0

CRL, crown rump length; NT, nuchal translucency; IUD, intrauterine death.

Table 3
Characteristics of pregnancies complicated by miscarriage before 24 weeks gestation.

Patient	Gestational age (weeks)	CRL 1 (mm)	NT 1 (mm)	CRL 2 (mm)	NT 2 (mm)	NT Discordance %	CRL Discordance %	Gestational age at diagnosis (weeks)
21	13+1	71	1.5	71	1.7	12%	0%	16+0
22	12+4	71	1.3	72	1.5	13%	1%	18+1
23	12+0	60	1.3	65	1.6	19%	8%	17+5

CRL, crown rump length; NT, nuchal translucency.

<24 weeks' gestation, 11% (2–17%) in those with sIUGR, and 4% (0–20%) in those without complications.

Fig. 1 shows the individual data points of NT and CRL discordance in the four groups. Discordance in CRL was not significantly different among the four groups ($p=0.22$). However, NT discordance was significantly higher in the sIUGR group compared to both uncomplicated and TTTS pregnancies ($p=0.009$ and $p=0.003$, respectively). The prediction of the subsequent development of TTTS provided by the discordance in CRL, expressed as the area under the ROC curve was 0.52 (95% confidence interval 0.38–0.67), while it was 0.50 for NT discordance (95% confidence interval 0.35–0.64). The area under the ROC curve for sIUGR prediction was 0.77 (95% confidence interval 0.37–1.00) for the discordance in CRL, and 0.93 (95% confidence interval 0.87–1.00) for NT discordance. Sensitivity, specificity, positive predictive value and negative predictive value of different discordance cut offs of CRL and NT for TTTS are shown in Tables 4 and 5.

NT was above the 95th percentile in one of the twins in 8/135 pregnancies: one of these pregnancies (patient 7, Table 1) subsequently developed TTTS and 2 (patients 20 and 21, Table 2) developed sIUGR. Both twins had a NT above the 95th percentile in 5/135 pregnancies, none of which developed TTTS. There was no significant correlation between NT discordance and CRL discordance ($\rho=0.08$, $p=0.35$), nor between NT discordance and gestational age at the onset of TTTS ($\rho=0.10$, $p=0.71$).

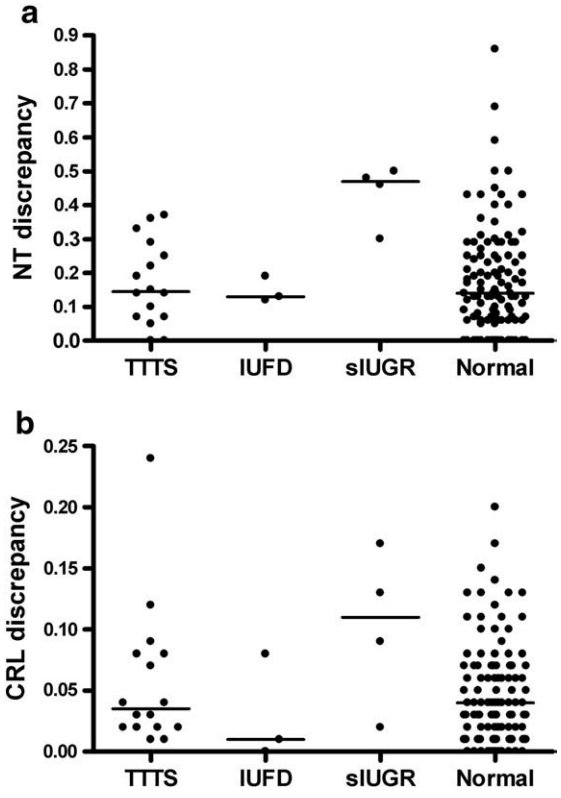

Fig. 1. Individual data points of NT (a) and CRL (b) discordance in the four groups. Horizontal bars represent medians. CRL, crown rump length; NT, nuchal translucency; TTTS, twin-to-twin transfusion syndrome; IUD, intrauterine death; sIUGR, selective intrauterine growth restriction.

4. Discussion

Our results suggest that in a population of unselected monochorionic diamniotic pregnancies followed up longitudinally, intertwin NT discordance is not an effective early marker for TTTS. We had 16 cases of TTTS and 10 of these (63%) had intertwin discordance below 20%. This means that such a finding in the first trimester cannot be considered fully reassuring, and close ultrasound surveillance is needed to detect the subsequent development of twin-to-twin transfusion syndrome at a stage at which effective treatment can be offered by either endoscopic laser coagulation of the communicating placental vessels, or timely delivery if gestational age allows.

Previous studies demonstrated a higher prevalence of increased NT among monochorionic twins [7,8]. In a series of 74 monochorionic diamniotic twins, 43% of pregnancies later complicated by TTTS had a discordance in the NT measurement of more than 0.5 mm compared with 45% among twins without signs of TTTS [14]. Kagan et al., based on a series of 512 pregnancies, suggest that when discordance in NT is 20% or more the detection rate of severe TTTS is about 50% with 20% false positive rate [9]. For the same NT discordance we observed 38% sensitivity and 39% false positive rate (Table 5) which are comparable to these previous studies. Casabuenas et al. and Matias et al. also reported a suboptimal predictive ability of TTTS using either NT discordance or NT measurements above a defined cut off [15,16]. Our sample size of 135 pregnancies, with a TTTS incidence of 13%, allowed to estimated the sensitivity of NT discordance with a precision of 24%, and specificity with a precision of 9% [17].

We found an NT measurement above the 95th percentile in one or both twins in 13/135 (10%) patients, but only 1/13 pregnancies developed TTTS later on in pregnancy. Sperling et al. reported a series of 74 monochorionic diamniotic twin pregnancies: 15 of these were subsequently complicated by TTTS but none of the NT measurements in these fetuses was above the 95th percentile [13]. Another recent study showed that increased nuchal translucency is more common among monochorionic compared with dichorionic twins, and that this may be due to the increased risk of structural defects in monozygotic twins rather than being an early sign of TTTS [18]. In our series the outcome was normal in 10/13 cases with NT above the 95th percentile, while 2/13 cases were complicated by sIUGR. These findings are in agreement with previous studies in singleton pregnancies reporting that increased NT in fetuses with normal

Table 4
Sensitivity, specificity, positive predictive value and negative predictive value of different CRL discordance cut offs for TTTS.

CRL discordance cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
5%	0.40	0.58	0.11	0.89
10%	0.13	0.86	0.11	0.88
15%	0.06	0.97	0.20	0.89
20%	0.07	0.99	0.50	0.89

Table 5
Sensitivity, specificity, positive predictive value and negative predictive value of different NT discordance cut offs for TTTS.

NT discordance cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
10%	0.68	0.33	0.12	0.88
15%	0.50	0.50	0.12	0.88
20%	0.38	0.61	0.12	0.87
25%	0.31	0.70	0.13	0.88
30%	0.19	0.81	0.12	0.88
35%	0.06	0.85	0.05	0.87

karyotype is associated with a poor pregnancy outcome, the chances of which increased exponentially with increasing NT thickness, from 8% when NT ranges between the 95th and 99th percentiles, to 80–85% when the NT is above 6.5 mm [19,20].

In our series, discordance in CRL between fetuses did not add significantly to the prediction of the subsequent development of TTTS. Lewi et al. reported a CRL discordance ≥10 mm to be indicative of a high risk of developing TTTS [21]. However, CRL discrepancies of this magnitude were found in only 3/135 (2%) patients in our study population: one developed selective IUGR (patient 19, Table 2) and the other 2 had normal outcome. Bhide et al. reported that a discordance in CRL above 19% is significantly associated with fetal loss [22]; however in their population fetal loss rate was 24/125, which seems to be higher than the one we observed. In part this may be due to the fact that they pooled together fetal losses at any gestational age after 14 weeks. In our series the only fetal deaths after 24 weeks were associated with the development of TTTS diagnosed at biweekly ultrasound follow up. Moreover, it is our institution's policy to deliver uncomplicated monochorionic twin pregnancies at 36–37 weeks' gestation, which might prevent some of the rare cases of late intrauterine death in these pregnancies [23].

In the present study population, sIUGR seems to be associated with increased NT discordance in first trimester and, at a minor extent, also with CRL discordance. However, given the small numbers involved, the potential usefulness of this observation for the prediction of sIUGR must be confirmed in larger series.

In conclusion we demonstrated that, in an unselected population of monochorionic twin pregnancies, discordance in CRL and NT measured at the first trimester scan is not a clinically useful predictor of the subsequent development of TTTS. Therefore, strict ultrasound follow up, which is performed biweekly at our and in other institutions [24], is recommended for the timely diagnosis of TTTS. The role of additional early markers of TTTS, such as ductus venosus blood flow assessment, is currently under investigation [16].

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