Discordance in Nuchal Translucency Measurements in Monochorionic Diamniotic Twins as Predictor of Twin-to-Twin Transfusion Syndrome

Ingeborg H. Linskens,[1] Yolanda M. de Mooij,[1] Jos W. Twisk,[2] Willem J. Kist,[3] Dick Oepkes,[3] and John M. van Vugt[1]

[1] *Department of Obstetrics and Gynaecology, VU University Medical Center, The Netherlands*
[2] *Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, The Netherlands*
[3] *Department of Obstetrics, Leiden University Medical Center, The Netherlands*

Objective: Discordance in nuchal translucency measurements in monochorionic diamniotic twin pregnancies was assessed as predictor of Twin-to-Twin Transfusion Syndrome. *Study Design:* A total of 61 monochorionic diamniotic twins were enrolled. Nuchal translucency (NT) and crown-rump-length (CRL) discordance was calculated as the percentage of delta NT and CRL (absolute difference NT/CRL fetus 1 and fetus 2) of the largest measurement, and correlated with subsequent development of Twin-to-Twin Transfusion Syndrome. *Results:* Twin-to-Twin Transfusion Syndrome developed in 14/61 (23%) of cases. A NT discordance of 20% or more best predicted Twin-to-Twin Transfusion Syndrome development, with a sensitivity of 64% and a specificity of 78%. We found a positive predictive value of 50% and negative predicted value of 86% for Twin-to-Twin Transfusion Syndrome development if NT discordance was 20% or more. *Conclusion:* NT discordance of more than 20% in monochorionic diamniotic twins is associated with an increased risk for subsequent development of Twin-to-Twin Transfusion Syndrome, and with earlier presentation of symptoms.

Keywords: monochorionic diamniotic twin pregnacies, nuchal translucency, Twin-to-Twin Transfusion Syndrome

Twin-to-Twin Transfusion Syndrome (TTTS) occurs in approximately 15% of all monochorionic twin pregnancies (Sebire et al., 2000; Quintero et al., 1999). The syndrome is defined sonographically by the presence of a polyhydramnios in the sac of one twin and oligohydramnios in the sac of the other twin. Without intervention, TTTS often leads to either severe morbidity mostly associated with preterm birth or demise of one or both fetuses (Berghella & Kaufmann, 2001). Timely diagnosis of TTTS is beneficial for treatment options and outcome (Huber et al., 2006; Middeldorp et al., 2007; Senat et al., 2004).

Fetal nuchal translucency (NT) measurement is an ultrasound measurement in which the thickness of a fluid collection in the neck of the fetus is measured. NT measurements are commonly used as fetal marker for aneuploidy screening between 11 and 14 weeks of gestation. An increased NT is also associated with a variety of fetal structural abnormalities, mainly cardiac defects and genetic syndromes (Hyett et al., 1997; Nicolaides et al., 1992; Souka et al., 2005).

In monochorionic diamniotic twins, an association between an increased NT in one fetus with later development of TTTS has been suggested (Kagan et al., 2007; Sebire et al., 2000; Sebire et al., 1997). The aim of the current study was to assess the value of discordance in NT measurements in monochorionic diamniotic twins to predict TTTS.

Materials and Methods

Data of all monochorionic diamniotic twin pregnancies were extracted from the fetal database of a tertiary fetal medicine referral center, the VU University Medical Center Amsterdam (VUMC), between 2004 and 2008. Data of twins that had been referred to the VUMC for prenatal Down syndrome screening in the first trimester with nuchal transluceny measurements and those who had serial follow-up ultrasonography were analyzed. All twins had an early first trimester ultrasound during which the chorionicity was determined and crown-rump-length (CRL) and NT were measured according to standards defined by the Fetal Medicine Foundation (Sepulveda et al., 1996). Risk assessment for trisomy 21 was calculated using maternal age and NT measurements of both fetuses. Parents with a screen positive test result (cut-off 1:200) were counseled concerning the risk for trisomy 21 and the risk of invasive testing and then opted for, or refrained from invasive testing.

All women had serial follow-up ultrasonography, including a detailed anomaly scan including echocardiography at 18 to 20 weeks of gestation. If TTTS was

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Address for correspondence: Ingeborg H. Linskens, VU University Medical Center, Department OBS/GYN, Suite PK 6 Z 170, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands. E-mail: I.Linskens@vumc.nl

suspected, patients were referred to the Leiden University Medical Center, the national center for invasive fetal therapy in the Netherlands. TTTS was classified according to Quintero stages (Quintero et al., 1999). Pregnancy outcome was evaluated by questionnaires and delivery room records.

Statistical Analysis

Patient characteristics of all twins are presented as median values (range) and percentages. Differences between the groups (uncomplicated vs. TTTS) were tested for significance with Chi-square tests and Mann- Whitney U test. NT and CRL discordance was calculated as the percentage of delta NT and CRL (absolute difference NT/CRL fetus 1 and fetus 2) of the largest measurement in accordance to the study of Kagan et al. (2007).

To investigate if NT discordance can predict the development of TTTS, sensitivity and specificity were calculated at different cut-off's in NT discordance to construct a receiver operating characteristics (ROC) curve. Subsequently, the area under the curve was calculated. A prediction model for TTTS was constructed using logistic regression analysis. Statistical analyses were performed using SPSS version 15.0 (Chicago, Il, USA). *P*-values < .05 were considered significant.

Results

A total of 61 monochorionic diamniotic twin pregnancies were included. Data on first trimester nuchal translucency measurements, serial follow-up ultrasonography and fetal outcome were known. Apart from two cases in which, a single umbilical artery was found none of the fetuses showed structural abnormalities. Either invasive diagnostics demonstrated a normal karyotype or in case a karyotyping was not done healthy neonates were born without dysmorphic features and thus considered to have normal karyotype. TTTS developed in 14/61 (23%) of the pregnancies. In three cases fetal demise of one or both fetuses occurred, and three twins were born immaturely. However in these six cases no ultrasound signs of TTTS were present and were therefore excluded from further analysis. Outcome was uncomplicated (defined as birth after 26 weeks of gestation, no TTTS or fetal demise) in 41 pregnancies (41/61 = 67%). Table 1 summarizes the characteristics of the uncomplicated and TTTS pregnancies for maternal age, ethnicity, smoking, parity, conception, median CRL/NT discordance and gestational age at birth. Detailed TTTS case descriptions are present in Table 2. CRL at the time of NT measurement ranged from 48–79 mm, median 62 mm and NT ranged from 0.7–9.6 mm, median 1.3 mm. An increased NT (> 3.5 mm) was seen in three fetuses of the TTTS group and none in the uncomplicated group.

To evaluate the best cut-off level for NT discordance, sensitivity and specificity were calculated at different cut-off levels, and a receiver operating characteristics (ROC) curve was constructed (Table 3 and Figure 1). The area under the ROC curve was 0.71. NT discordance of 20% or more demonstrated a sensitivity of 64% (9/14) and specificity of 78% (32/41) for the subsequent development of TTTS, with a positive predictive value of 50% (9/18) and negative predictive value of 86% (32/37). NT discordance of 20% or more was more frequently observed in the TTTS cases (9/14 = 64%) compared to the uncomplicated group (9/41 = 22%) (Chi-Square, p = .004).

Table 1

Characteristics of the 41 Uncomplicated Monochorionic Twin Pregnancies and 14 Pregnancies with Twin-to-Twin Transfusion Syndrome

	Uncomplicated *N* = 41	TTTS *N* = 14	*p* value
Median maternal age in years (range)	34.4 (21–41)	31.8 (20–41)	0.34
Ethnicity			
Caucasian	39 (95%)	13(93%)	0.75
Non-Caucasian	2 (5%)	1 (7%)	
Smoking			
no	37 (90%)	13(93%)	0.77
yes	4 (10%)	1 (7%)	
Parity			
nullipara	20 (49%)	7 (50%)	0.94
multipara	21 (51%)	7 (50%)	
Conception			
naturally conceived	39 (95%)	12 (86%)	0.24
assisted reproduction	2 (5%)	2 (14%)	
Median CRL discordance	3% (0–19%)	6% (0–23%)	0.22
Median NT discordance	9%(0–36%)	28% (0–91%)	0.019
Median gestational age at delivery	36+1 (28+1- 39+1)	30+6 (17+3- 40+2)	0.013

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Table 2

Twin-to-Twin Transfusion Syndrome Case Descriptions

	CRL 1 (mm)	NT 1 (mm)	CRL 2 (mm)	NT 2 (mm)	NT discordance ≥20%	Quintero stage	Therapy	Survival (n) and GA at birth
I	63	9.3	74	2.1	Yes	III	UCC 15+6 D	1, 41 wks
II	62	0.9	48	9.6	Yes	III	UCC 17+0 D	0, 18 wks
III	65	1.2	68	4.0	Yes	III	NO 16+2	TOP, 18 wks
IV	57	1.2	70	2.1	Yes	III	Laser 14+3	1, 40 wks
V	75	1.1	76	1.8	Yes	III	Laser 17+5	2, 30 wks
VI	69	1.6	71	1. 2	Yes	II	Laser 20+1	2, 34 wks
VII	53	1.6	59	1.1	Yes	III	Laser 19+3	0, 23 wks
VIII	59	1.6	59	1.1	Yes	III	Laser 19+2	2, 30 wks
IX	62	1.0	57	1.3	Yes	III	Laser 23+5	2, 37 wks
X	61	1.5	57	1.4	No	II	Laser 22+5	1, 32 wks
XI	58	2.0	63	2.0	No	III	AR 22+1	1, 38 wks
XII	55	1.1	54	1.1	No	III	Laser 20+3	0, 26 wks
XIII	67	1.3	68	1.2	No	III	Laser 20+0	1, 33 wks
XIV	62	1.5	59	1.7	No	III	Laser 24+2	2, 30 wks

Note: Nine of the 14 TTTS cases had more than 20% NT discordance. Survival of both fetuses was 5/14 (36%) and of at least one fetus 10/14 (71%).
UCC = umbilical cord coagulation; NO = no therapy, AR = amnioreduction; D = donor fetus; GA = gestational age, TOP = termination of pregnancy

Table 3

Sensitivity and Specificity Calculated From Different Cut-Off Levels of Percentage in Nuchal Translucency Discordance

NT discordance % cut-off level	Sensitivity	Specificity
5%	86%	22%
10%	71%	51%
15%	64%	63%
20%	64%	78%
25%	50%	88%
30%	50%	93%
40%	29%	100%
50%	21%	100%
60%	21%	100%
70%	14%	100%
80%	7%	100%
90%	7%	100%
100%	0%	100%

Logistic regression analysis demonstrated that NT discordance (%) was independently associated with subsequent development of TTTS (p = .008), no quadratic relation was found. For CRL discordance (%) and subsequent development of TTTS the association was not significant (p = .09). As a result of the logistic regression analysis, the probability of TTTS development for a certain % of NT discordance was calculated (Figure 2). If the NTs of the two fetuses are similar the risk for development of TTTS was 8.9%. The probability of TTTS development increased gradually with increasing NT discordance. If NT discordance 20% of more was used as a categorical variable (yes/no) logistic regression analysis demonstrated a significant association with TTTS development, p = .006, OR 6.4 (95% CI 1.7–23.9).

Discussion

Our study confirms a previously suggested association between NT discordance in monochorionic twins with subsequent development of TTTS (Kagan et al., 2007; Sebire et al., 1997; Sebire et al., 2000). We found the optimal cut-off for NT discordance to be 20% or more. The current research shows that a larger NT discordance is associated with higher chance of TTTS development. In the group with 20% or more NT discordance, the risk for later chance of development of TTTS was more than 5 times higher (50% versus 9%) than in twins with identical measurement of the NT.

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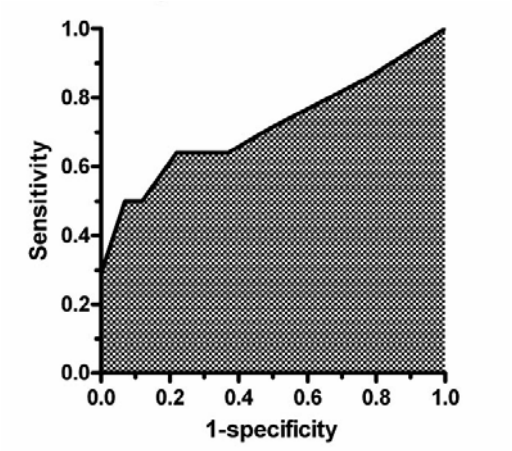

Figure 1

Receiver operating characteristics (ROC) curve: relationship between sensitivity and specificity in the prediction of Twin-to-Twin Transfusion Syndrome by discordance in nuchal translucency measurements.

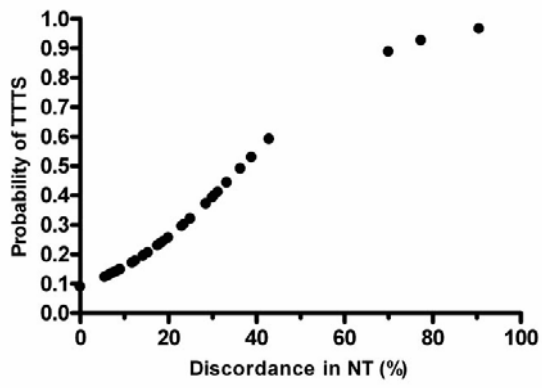

Figure 2

Probability of Twin-to-Twin Transfusion Syndrome at different cut-off levels of discordance in nuchal translucency measurements (%).

The use of NT measurements is general practice in screening for trisomies (Nicolaides et al., 1992). Finding discordance in NT in monochorionic twins is a challenge for the counsellor. Several cases have been described of monochorionic twin pairs concordant for a chromosomal abnormality but with dissimilar NT values (Pandya et al., 1995; Sebire et al., 2000; Vandecruys et al., 2005). In addition, although monozygotic twins are considered genetically 'identical', a small number of discordances for chromosomal abnormalities have been described (Gilbert et al., 2002; Nieuwint et al., 1999). To account for heterokaryotypic twinning, individual fetal karyotyping should be considered in monochorionic twins. Amniocentesis with individual aspiration of each fetal sac may provide more reliable test results compared to chorionic villus sampling (Chen et al., 2003; Gentilin et al., 2008). Postponing invasive diagnostics to a more advanced gestation age might be beneficial since structural fetal abnormalities can be more easily visualized and signs of TTTS can become present in the mean time.

Fetal structural abnormalities are more frequently seen in monozygotic twins compared to singletons and discordance in structural abnormalities has been described (Hall, 2003). Since increased NT is also associated with structural fetal abnormalities, mostly cardiac abnormalities, targeted structural ultrasonography with echocardiography is indicated (Hyett et al., 1997; Souka et al., 2005).

Increased NT measurements are more frequently seen in chromosomally normal monochorionic twin pregnancies in comparison to dichorionic twins and singletons (Sebire et al., 1996). The earliest reports on the association between increased NT (defined as NT > 95th centile) and early TTTS described a positive predictive value of 38% and negative predictive value of 91% (Sebire et al., 1997). In monochorionic twin fetuses with increased NT (defined as NT > 95th centile) a more than three-fold increase in risk for TTTS development was described (Sebire et al., 2000). However, a study by El et al. found no significant association between increased NT (defined as NT > 95th centile) and TTTS development, but only a tendency for TTTS development in those cases with increased NT, namely 20% versus 4% in those with NT < 95th centile (El Kateb et al., 2007). Recently Kagan et al., in a large series monochorionic twins, found a detection rate of 52% for TTTS and 63% for early fetal death using NT discordance as parameter with a cut-off of 20% or more. If NT discordance was less than 20% the risk of complications was less than 10% (Kagan et al., 2007). Sperling et al. found no relationship between NT discordance and subsequent TTTS development, however they studied only the absolute NT difference of 0,5 mm between both fetuses and not NT discordance as percentage of delta NT of the largest measurement (Sperling et al., 2007).

An interesting and new finding in our study was that in TTTS cases with NT discordance less than 20% (Table 2, Case X-XIV) fetuses generally presented with TTTS symptoms after 20 weeks of gestation. This is in contrast to the group with NT discordance of 20% or more in which the earliest case was diagnosed at 14+3 wks and median gestational age at diagnosis was 17+5 wks.

Monochorionic twin pregnancies are characterized by the presence of vascular anastomoses between the two fetoplacental circulations (Robertson & Neer, 1983). Sebire et al. hypothesized that in monochorionic twins, the mechanism for increased NT as an early manifestation of TTTS is likely to be cardiac dysfunction due to hypervolaemic congestion in the recipient twin (Sebire et al., 2000). The placental vascular pattern is thought to be dynamic in the first trimester, with 'asymmetric reduction in placental anastomoses'. According to this hypothesis in early pregnancy, all monochorionic twins have a large

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number of bidirectional arteriovenous connections but with advancing gestation there is progressive spontaneous closure or disruption of these anastomoses (Kagan et al., 2007; Sebire et al., 2001). This hypothesis is in accordance with the findings of our study, as not all monochorionic twins with NT discordance of more than 20% developed TTTS. We observed two pregnancies with development of TTTS in which the subsequent donor fetus presented with an extreme enlarged NT and smaller CRL. Although in literature the increased NT is assigned to the recipient fetus, due to the placental dynamics in the first trimester this phenomenon, increased NT in the smaller donor fetus, could also be seen as support for the asymmetric reduction theory. Possibly, Kagan et al. already described this phenomenon since only 27 of the 33 of their TTTS cases represented with the higher NT in the fetus with higher CRL. However, information concerning identification of recipient/donor fetus was lacking (Kagan et al., 2007).

From our results, although a relatively small number of twins were studied, one may conclude that NT discordance of more than 20% in monochorionic twin pregnancies should raise a high level of suspicion for subsequent development of TTTS. Intensive ultrasound follow-up or even referral to a specialized clinic is advisable. Biweekly ultrasound examinations combined with detailed patient instructions for rapidly increasing abdominal girth or premature contractions can aid in the timely diagnosis of TTTS and is a safe monitoring program for monochorionic twins (Sueters et al., 2006). Fetal outcome benefits from early and timely TTTS diagnosis and treatment (Huber et al., 2006; Middeldorp et al., 2007; Senat et al., 2004). In the future, standardized NT measurements might be considered for all monochorionic twins as TTTS screening tool besides aneuploidy screening. Larger prospective studies on monochorionic twins including NT and hemodynamic profiles are necessary to evaluate the benefit for TTTS screening.

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