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Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome

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KEYWORDS: first trimester; monochorionic twins; nuchal translucency; twin-to-twin transfusion syndrome

ABSTRACT

Objective *To examine in monochorionic pregnancies the possible value of intertwin discordance in nuchal translucency (NT) thickness in the prediction of early fetal death or severe twin–twin transfusion syndrome (TTTS).*

Methods *In 512 monochorionic twin pregnancies NT was measured at 11 to 13 + 6 weeks' gestation and regression analysis was used to determine the significance of the association between the intertwin discordance in NT and subsequent early fetal death or development of severe TTTS requiring endoscopic laser surgery.*

Results *In 412 (80.5%) pregnancies there was a normal outcome, in 58 (11.3%) there was severe TTTS requiring endoscopic laser surgery at 18–24 weeks, in 19 (3.7%) there was death of one or both fetuses at 13–18 weeks and in 23 (4.5%) there was fetal death at 21–38 weeks. In the four outcome groups the median discordance in NT was 11%, 22%, 35% and 7%, respectively. Significant prediction of early fetal death and severe TTTS was provided by the discordance in fetal NT, which was not significantly improved by including the discordance in crown–rump length. If the discordance in NT was 20% or more, the false positive rate was 20%, the detection rate of early fetal death was 63% and the detection rate of severe TTTS was 52%.*

Conclusions *Discordance in NT of 20% or more is found in about 25% of monochorionic twins and in this group the risk of early fetal death or development of severe TTTS is more than 30%. If the discordance is less than 20% the risk of complications is less than 10%. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The risk of fetal or neonatal death in monochorionic twin pregnancies is substantially higher than in dichorionic twins. In the combined data from two ultrasound screening studies in twins where both fetuses were alive at 10–14 weeks of gestation there was subsequent miscarriage or spontaneous death of at least one fetus before 24 weeks in 12.1% (21 of 174) of monochorionic and 2.5% (19 of 771) of dichorionic pregnancies[1,2]. The respective perinatal mortality rates were 4.4% (9 of 204) and 1.6% (19 of 1161). The much higher mortality before 24 weeks' gestation in monochorionic than dichorionic twins has been attributed to complications arising from the placental vascular anastomoses between the two fetoplacental circulations[1].

In about 30% of monochorionic twin pregnancies, imbalance in the net flow of blood across the placental vascular communications from one fetus, the donor, to the other, the recipient, results in twin-to-twin transfusion syndrome (TTTS). In about half of the cases of TTTS the disease is severe and by 16–24 weeks' gestation there is polyhydramnios in the sac of the polyuric recipient fetus and anhydramnios in the sac of the anuric donor twin[3]. Effective treatment for severe TTTS is provided by endoscopic laser coagulation of the communicating placental vessels[4–6].

Ultrasonographic features of the underlying hemodynamic changes in severe 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]. A study of 132 monochorionic twins reported that at 11 to 13 + 6 weeks there was a higher intertwin difference in NT, but not in crown–rump length (CRL), in the 16 pregnancies that subsequently developed severe TTTS compared with those without severe TTTS[7]. One study of an extended series of 287 monochorionic twin pregnancies, including 43 that developed severe TTTS at 16–24 weeks, reported that at 11 to 13 + 6 weeks the NT was above the 95th centile of the normal range in at least one of the fetuses in 28% of

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the TTTS group, compared to 10% in the non-TTTS group[8].

In this prospective study of monochorionic twin pregnancies undergoing ultrasound examination at 11 to 13 + 6 weeks' gestation we examined further the possible value of fetal NT and CRL in the prediction of subsequent early fetal death or development of severe TTTS.

PATIENTS AND METHODS

During a 5-year period (January 2001 to April 2006) we carried out ultrasound examination at 11 to 13 + 6 weeks' gestation of 560 monochorionic–diamniotic twin pregnancies as part of our policy of screening for chromosomal abnormalities by a combination of maternal age and fetal NT thickness[9]. Transabdominal ultrasound examination was performed to diagnose any major fetal defects and for measurement of the CRL and NT thickness of each twin. The pregnancies were diagnosed as being monochorionic because there was a single placental mass with no extension of placental tissue into the base of the intertwin membrane (lambda sign)[10].

Our policy for the follow-up of monochorionic twins includes ultrasound examinations at 16–18 weeks and 4-weekly thereafter, unless there is evidence of TTTS, in which case the frequency of examinations is increased as necessary. In cases of severe TTTS endoscopic laser coagulation of the communicating placental vessels is performed[4,5]. The indications for such treatment are firstly, ultrasound diagnosis of polyhydramnios in one twin and anhydramnios in the other, and secondly, absent or reversed end-diastolic flow in either the umbilical artery or ductus venosus in one or both fetuses.

Demographic details, ultrasound findings, fetal interventions and pregnancy outcome were entered into a computer database. Pregnancy outcome was obtained from the maternity units or the patients themselves.

Statistical analysis

In each pregnancy the intertwin discordance in NT and CRL was calculated as the difference in each measurement between the two fetuses (NT_1-NT_2 and CRL_1-CRL_2, respectively) expressed as a percentage of the larger measurement. The distribution of measurements in three groups of pregnancies was determined and compared. The first group was that of pregnancies with a normal outcome in which both babies were liveborn without antenatal intervention, the second group was that of pregnancies undergoing fetoscopic laser coagulation for severe TTTS, and the third group comprised pregnancies complicated by the death of one or both fetuses in the absence of antenatal intervention. Regression analysis was used to determine the significance of the association between discordance in measurements and gestational age at which the relevant event – i.e. live birth, fetoscopic laser coagulation, or fetal death – occurred. Prediction of an adverse outcome was derived by logistic regression analysis with backwards elimination of variables that were not significant ($P < 0.05$).

RESULTS

During the study period we examined 560 monochorionic–diamniotic twin pregnancies at 11 to 13 + 6 weeks. However, we excluded from further analysis 48 cases because we diagnosed chromosomal or major structural defects ($n = 28$) or we could not get data on pregnancy outcome ($n = 20$). In the remaining 512 cases, there were 412 (80.5%) with a normal outcome, 58 (11.3%) with severe TTTS treated by endoscopic laser surgery and 42 (8.2%) with the death of one ($n = 13$) or both ($n = 29$) fetuses.

In the normal outcome group, each pregnancy resulted in two live births at a median gestational age of 35 (range, 26–40) weeks. At 11 to 13 + 6 weeks, the median discordance in NT was 11% and in CRL it was 3.6% (Figures 1 and 2, Tables 1 and 2). There was no significant association between gestational age at delivery and either discordance in NT ($r = 0.013$, $P = 0.789$) or discordance in CRL ($r = 0.038$, $P = 0.439$).

In the group treated by laser for severe TTTS, endoscopy was carried out at a median gestation of 18 (range, 16–24) weeks. The stage of TTTS according to the method of Quintero *et al.*[11] was II in 13 (22.4%) and III in 45 (77.6%) of the cases. These pregnancies resulted in the live birth of two babies in 30 (51.7%) and of one baby in 12 (20.7%) cases at a median gestation of 32 (range, 27–40) weeks. At 11 to 13 + 6 weeks, the median discordance in NT was 22% and in CRL it was 6% (Figure 1, Tables 1 and 2). There was a significant association between gestational age at endoscopic laser treatment and discordance in NT ($r = 0.46$, $P < 0.001$; Figure 2), but no discordance in CRL ($r = 0.254$, $P = 0.054$).

In the group with fetal deaths there was a significant inverse association between discordance in NT and gestation at fetal death ($r = 0.48$, $P < 0.001$; Figure 2). In the 19 pregnancies with fetal death at or before 18 weeks (median 16 (range, 13–18) weeks), at the 11 to 13 + 6 weeks' scan the median discordance in NT was 35.3% and in CRL it was 5.9% (Figure 1, Tables 1 and 2). There was a significant association between gestational age at death and discordance in both NT ($r = 0.640$, $P = 0.003$) and CRL ($r = 0.514$, $P = 0.024$). In the 23 pregnancies with fetal death after 18 weeks (median 25 (range, 21–38) weeks), at the 11 to 13 + 6 weeks' scan the median discordance in NT was 7.1% and in CRL it was 3.1%. There was no significant association between gestational age at death and discordance in either NT ($r = 0.192$, $P = 0.381$) or CRL ($r = 0.170$, $P = 0.439$).

Regression analysis demonstrated that significant prediction of early fetal death and severe TTTS requiring endoscopic laser treatment was provided by both the discordance in fetal NT and the discordance in CRL at 11 to 13 + 6 weeks (Table 3). However, the prediction provided by the discordance in NT, expressed as the c-index (area under the receiver–operating characteristics

Table 1 Discordance in nuchal translucency thickness at 11 to 13 + 6 weeks' gestation and subsequent outcome of pregnancy in the normal group ($n = 412$), the group that had endoscopic laser treatment ($n = 58$) and the group in which early fetal death occurred ($n = 19$)

Discordance	*Normal*	*Endoscopic laser treatment group*		*Early fetal death group*	
(%)	*group* (n *(%))*	n *(%)*	*OR (95% CI)*	n *(%)*	*OR (95% CI)*
Median	11.1%	22.2%	—	35.3%	—
0–9	185 (44.9)	15 (25.9)	0.47 (0.27–0.82)	4 (21.1)	0.34 (0.12–1.01)
10–19	134 (32.5)	10 (17.2)	0.47 (0.25–0.91)	3 (15.8)	0.40 (0.12–1.36)
20–29	63 (15.3)	13 (22.4)	1.50 (0.85–2.64)	2 (10.5)	0.66 (0.16–2.80)
30–39	17 (4.1)	6 (10.3)	2.24 (1.08–4.67)	2 (10.5)	2.55 (0.64–10.25)
40–49	9 (2.2)	5 (8.6)	3.07 (1.46–6.49)	3 (15.8)	6.55 (2.20–19.50)
≥ 50	4 (1.0)	9 (15.5)	6.46 (4.12–10.11)	5 (26.3)	16.75 (7.69–36.49)

OR, odds ratio.

Table 2 Discordance in crown–rump length at 11 to 13 + 6 weeks' gestation and subsequent outcome of pregnancy in the normal group ($n = 412$), the group that had endoscopic laser treatment ($n = 58$) and the group in which early fetal death occurred ($n = 19$)

Discordance	*Normal*	*Endoscopic laser treatment group*		*Early fetal death group*	
(%)	*group* (n *(%))*	n *(%)*	*OR (95% CI)*	n *(%)*	*OR (95% CI)*
Median	3.6%	6.0%	—	5.9%	—
0–4	271 (65.8)	24 (41.4)	0.42 (0.26–0.88)	8 (42.1)	0.40 (0.16–0.96)
5–9	106 (25.7)	21 (36.2)	1.53 (0.93–2.52)	4 (21.1)	0.78 (0.26–2.30)
10–14	29 (7.0)	8 (13.8)	1.87 (0.96–3.65)	6 (31.6)	5.22 (2.12–12.89)
15–19	5 (1.2)	3 (5.2)	3.15 (1.25–7.97)	—	—
≥ 20	1 (0.2)	2 (3.4)	5.56 (2.41–12.84)	1 (5.3)	11.92 (2.77–51.20)

OR, odds ratio.

(ROC) curve) was not significantly improved by including the discordance in CRL (early fetal death: c-index for NT 0.727, 95% CI 0.576–0.877; c-index for NT and CRL 0.741, 95% CI 0.593–0.888; severe TTTS: c-index for NT 0.691, 95% CI 0.607–0.774, c-index for NT and CRL 0.716, 95% CI 0.638–0.795). If the discordance in NT was 20% or more, the false positive rate was 20% and the detection rate of early fetal death was 63% and of severe TTTS it was 52% (Figure 3).

On the basis of these results and after exclusion of the late fetal deaths we can assume that in 1000 monochorionic twins seen at 11 to 13 + 6 weeks' gestation, approximately 843 would subsequently have a normal outcome, 39 would result in early fetal death and 118 would develop severe TTTS. Discordance in NT of 20% or more would be found in 169 (20.0% of 843) of the normal outcome group, 25 (64.1% of 39) of the early fetal death group and 61 (51.7% of 118) of the severe TTTS group. Therefore, the risk of a serious complication is 33.7% (86 of 255) in the pregnancies with discordance in NT of 20% or more, compared to 9.5% (71 of 745) in those with a smaller discordance.

In the pregnancies with discordance in NT of 20% or more the fetus with the higher NT also had a higher CRL in 62 of the 93 (66.7%) of the normal outcome group, 11 of the 12 (91.7%) of the early fetal death group and 27 of the 33 (81.8%) of the severe TTTS group.

DISCUSSION

The findings of this study demonstrate that in monochorionic–diamniotic twin pregnancies presenting with two live fetuses at 11 to 13 + 6 weeks' gestation about 4% will subsequently result in the death of one or both twins before the 18th week of gestation, and about 12% will develop severe TTTS requiring endoscopic laser surgery. The results also demonstrate that the risk of developing these complications can be predicted from the intertwin discordance in fetal NT at 11 to 13 + 6 weeks. The risk is more than 30% in those pregnancies with discordance in NT of 20% or more, compared to less than 10% in those with a smaller discordance.

There was a significant association between both early fetal death and severe TTTS with discordance in CRL. However, in the prediction of these events the discordance in CRL did not improve the prediction provided by the discordance in NT. In the case of fetal deaths after 18 weeks' gestation there was no association with discordance in either NT or CRL and in addition there was no second-trimester sonographic evidence for TTTS, suggesting that in these cases the cause of death is unrelated to TTTS.

In both the early fetal loss and the endoscopic laser groups, where there was a large discordance in NT the larger measurement was usually found in the fetus with the greater CRL. It could therefore be assumed that in both groups the most likely explanation for the discordance in NT is severe early onset TTTS. Although

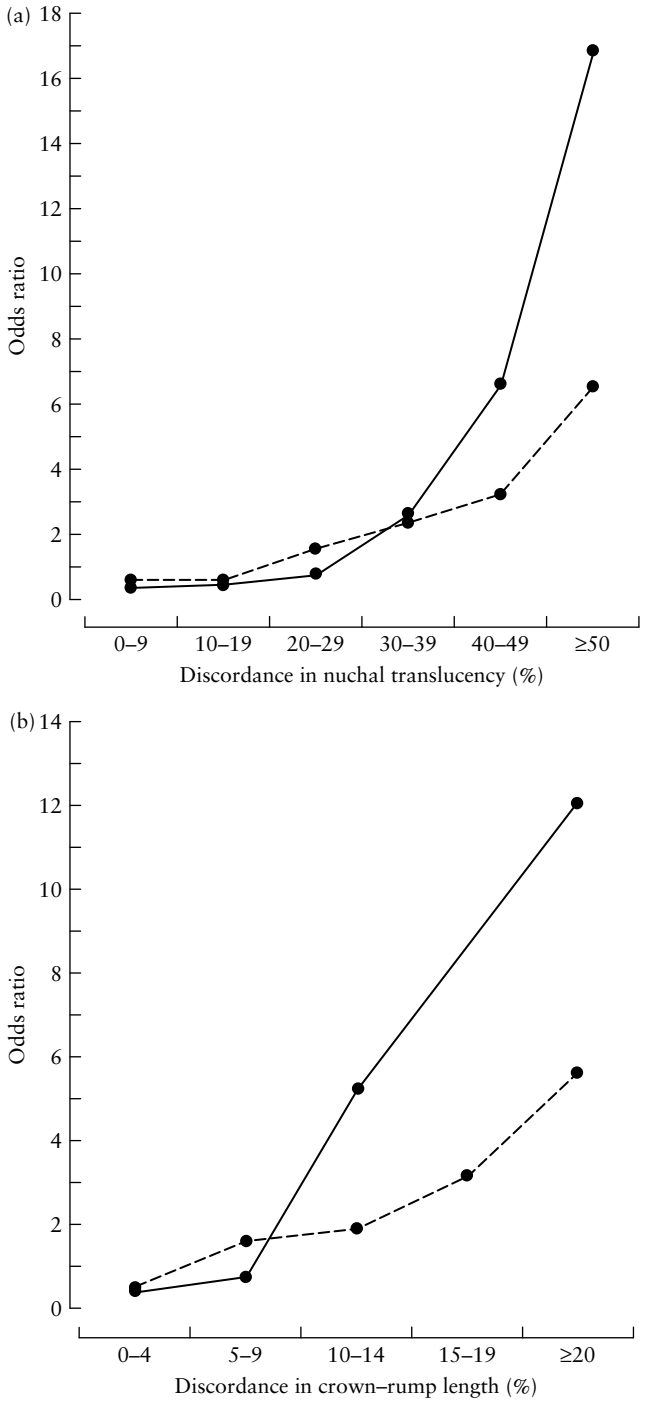

Figure 1 Discordance in nuchal translucency thickness (a) and crown–rump length (b) at 11 to 13 + 6 weeks' gestation, and odds ratio for fetal death before 18 weeks (——) or development of severe twin-to-twin transfusion syndrome (– – –).

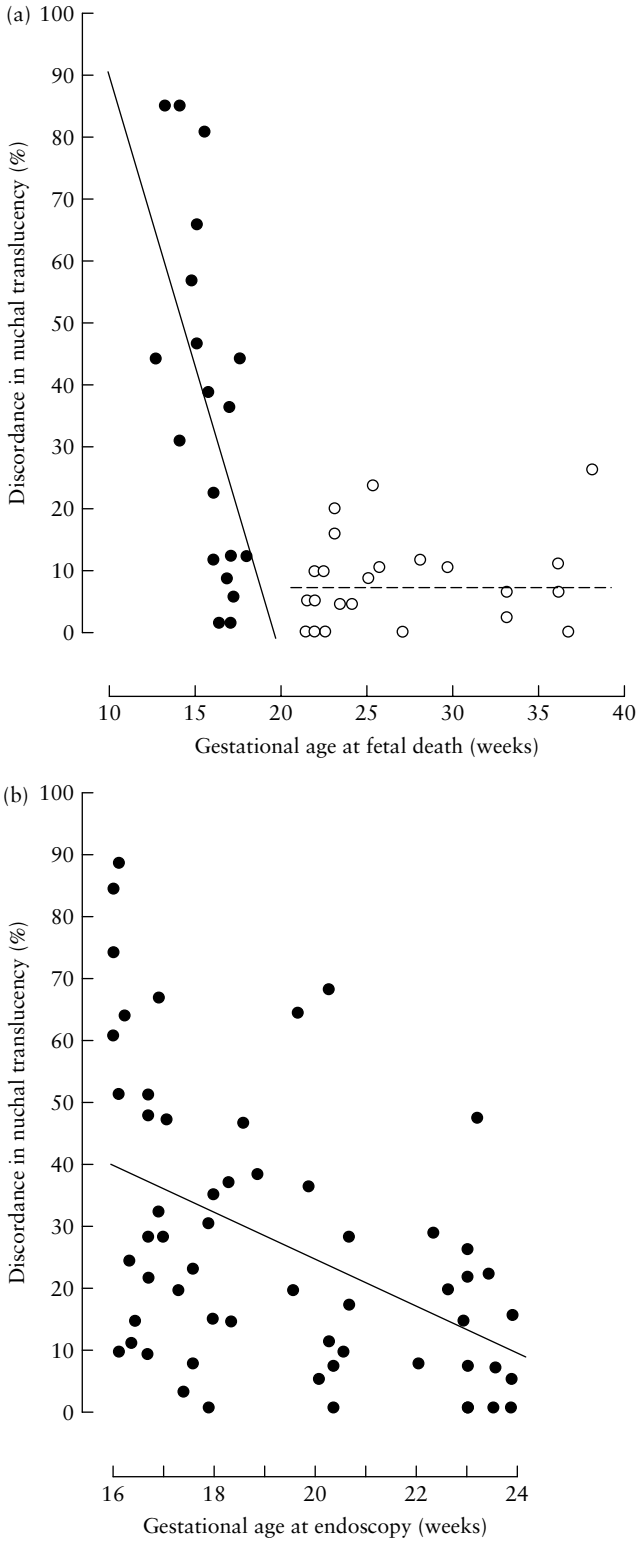

Figure 2 Relationship between discordance in nuchal translucency (NT) thickness and gestational age at fetal death in (a) pregnancies that did not have antenatal intervention and (b) those that developed severe twin-to-twin transfusion syndrome and underwent endoscopic laser treatment. In the fetal death group there was a significant association of NT thickness with gestational age at death before 18 weeks (●) but not after 18 weeks (○).

we did not formally assess discordance in amniotic fluid at the 11 to 13 + 6 weeks' scan, our subjective impression was that in at least some of the pregnancies resulting in early fetal death or severe TTTS by 16–24 weeks, the amniotic fluid volume in the sac of the bigger fetus with the higher NT was greater than in that of the co-twin. We did not, however, observe anhydramnios in any of the cases because at 11 to 13 + 6 weeks a substantial proportion of amniotic fluid is derived from the placenta rather than fetal urination; anhydramnios is not found before 16 weeks even in cases of bilateral renal agenesis.

Table 3 Regression analysis in the prediction of severe twin-to-twin transfusion syndrome (TTTS) requiring endoscopic laser treatment and fetal death by the discordance in fetal nuchal translucency thickness (NT) and crown–rump length (CRL) at 11 to 13 + 6 weeks' gestation

	Univariate analysis		*Multivariate analysis*	
Prediction	*OR (95% CI)*	P	*OR (95% CI)*	P
Severe TTTS by discordance in NT	1.06 (1.04–1.08)	< 0.001	1.05 (1.03–1.07)	< 0.001
Severe TTTS by discordance in CRL	1.15 (1.08–1.23)	< 0.001	1.10 (1.02–1.18)	0.012
Early death by discordance in NT	1.07 (1.05–1.10)	< 0.001	1.07 (1.05–1.10)	< 0.001
Early death by discordance in CRL	1.18 (1.08–1.30)	< 0.001	1.06 (0.95–1.20)	0.304

OR, odds ratio.

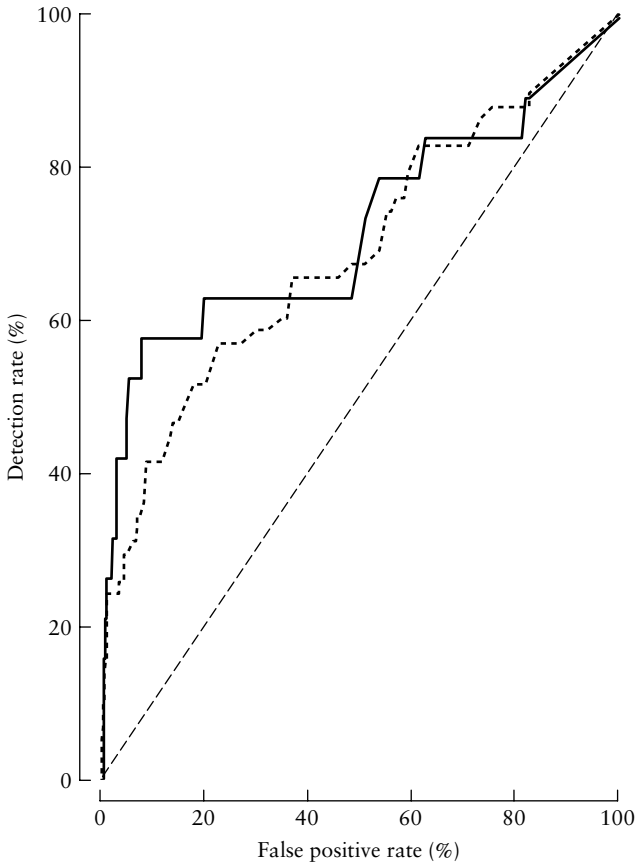

Figure 3 Relationship between detection and false positive rates in the prediction of early fetal death (——) and development of severe twin-to-twin transfusion syndrome (- - - -) by the discordance in fetal nuchal translucency at 11 to 13 + 6 weeks' gestation.

Consequently, the criteria for the diagnosis of severe TTTS that would potentially benefit from surgical intervention before 16 weeks remain to be determined.

We found that firstly, only some (about 30%) of the pregnancies with evidence of TTTS in the first trimester progressed to fetal death or severe TTTS in the second trimester and secondly, only some (about 60%) of the pregnancies presenting with severe TTTS in the second trimester had evidence of the syndrome from the first trimester. A possible explanation for these findings is provided by the hypothesis of 'asymmetric reduction in placental anastomoses'[12]. According to this hypothesis in all monochorionic twins in early pregnancy, there is a large of number of bidirectional arteriovenous connections but with advancing gestation there is progressive spontaneous closure or disruption of these anastomoses, which occurs at random. Clinical features of TTTS occur when there is asymmetry in the arteriovenous anastomoses so that there is a net flow of blood in favor of one of the fetuses and at the expense of its co-twin. It is therefore possible that in some pregnancies with asymmetrical flow at 11 to 13 + 6 weeks, causing a large discordance in NT, with advancing gestation the random disruption of arteriovenous anastomoses restores symmetry in flow and therefore spontaneous resolution of the early signs of TTTS. In contrast, in some cases with symmetrical flow and therefore concordance in NT at 11 to 13 + 6 weeks, the subsequent disruption of arteriovenous anastomoses is asymmetrical, resulting in the development of TTTS during the second trimester.

In monochorionic twin pregnancies with two live fetuses at 12 weeks the risk of fetal death or development of severe TTTS in the subsequent 12 weeks is about 15%. Discordance in NT of 20% or more would be found in about 25% of cases, and in this group the risk of developing these complications is more than 30%. If the discordance in NT is less than 20% the risk of complications is less than 10%. The extent to which closer monitoring and earlier intervention in the high-risk group can reduce these complications remains to be determined.

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