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Increased nuchal translucency at 11–13 weeks' gestation and outcome in twin pregnancy

B. CIMPOCA, A. SYNGELAKI, E. LITWINSKA, A. MUZAFEROVIC and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

KEYWORDS: dichorionic twins; endoscopic laser surgery; fetal loss; first-trimester screening; monoamniotic twins; monochorionic twins; nuchal translucency; perinatal death; selective fetal growth restriction; twin pregnancy; twin–twin transfusion syndrome

CONTRIBUTION

What are the novel findings of this work?
In monochorionic diamniotic (MCDA) twin pregnancies with nuchal translucency thickness (NT) $\geq 95^{th}$ percentile, and more so in those with NT $\geq 99^{th}$ percentile, there is a substantially increased risk of fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation. In dichorionic (DC) twin pregnancies, the incidence of NT $\geq 95^{th}$ percentile in one or both fetuses is not significantly different between those with two survivors and those with fetal or perinatal death.

What are the clinical implications of this work?
In MCDA twin pregnancies with no major fetal abnormalities, measurement of NT at the 11–13-week scan is a poor screening test for adverse pregnancy outcome. However, the finding of high NT in one or both fetuses is associated with a high risk of fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation. The extent to which closer monitoring and earlier intervention in the high-risk group can reduce these complications remains to be determined.

ABSTRACT

Objective *To investigate the value of increased fetal nuchal translucency thickness (NT) at the 11–13-week scan in the prediction of adverse outcome in dichorionic (DC), monochorionic diamniotic (MCDA) and monochorionic monoamniotic (MCMA) twin pregnancies.*

Methods *This was a retrospective analysis of prospectively collected data on twin pregnancies undergoing routine ultrasound examination at 11–13 weeks' gestation between 2002 and 2019. In pregnancies with no major defects or chromosomal abnormalities, we examined the value of increased NT $\geq 95^{th}$ percentile in one or both fetuses in the prediction of, first, miscarriage or death of one or both fetuses at < 20 and < 24 weeks' gestation in DC, MCDA and MCMA twin pregnancies, second, death of one or both fetuses or neonates at ≥ 24 weeks in DC, MCDA and MCMA twin pregnancies, third, development of twin–twin transfusion syndrome (TTTS) or selective fetal growth restriction (sFGR) treated by endoscopic laser surgery at < 20 and ≥ 20 weeks' gestation in MCDA pregnancies, and, fourth, either fetal loss or laser surgery at < 20 weeks' gestation in MCDA pregnancies.*

Results *The study population of 6225 twin pregnancies included 4896 (78.7%) DC, 1274 (20.5%) MCDA and 55 (0.9%) MCMA pregnancies. The incidence of NT $\geq 95^{th}$ percentile in one or both fetuses in DC twin pregnancies was 8.3%; in MCDA twins the incidence was significantly higher (10.4%;* $P = 0.016$*), but in MCMA twins it was not significantly different (9.1%;* $P = 0.804$*) from that in DC twins. In DC twin pregnancies, the incidence of high NT was not significantly different between those with two survivors and those with adverse outcome. In MCMA twin pregnancies, the number of cases was too small for meaningful assessment of the relationship between high NT and adverse outcome. In MCDA twin pregnancies with at least one fetal death or need for endoscopic laser surgery at < 20 weeks' gestation, the incidence of NT $\geq 95^{th}$ percentile was significantly higher than in those with two survivors (23.5% vs 9.8%;* $P < 0.0001$*). Kaplan–Meier analysis in MCDA twin pregnancies showed that, in those with NT $\geq 95^{th}$ percentile, there was significantly lower survival at < 20 weeks' gestation than in those with NT $< 95^{th}$ percentile (*$P = 0.001$*); this was not the case for survival at ≥ 20 weeks (*$P = 0.960$*). The performance of screening*

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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by fetal NT ≥ 95th percentile for prediction of either fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation was poor, with a detection rate of 23.5% at a false-positive rate of 8.9%, and the relative risk, in comparison to fetal NT < 95th percentile, was 2.640 (95% CI, 1.854–3.758; P < 0.0001). In MCDA twin pregnancies, the overall rate of fetal loss or need for laser surgery at < 20 weeks' gestation was 10.7% but, in the subgroups with NT ≥ 95th and NT ≥ 99th percentiles, which constituted 10.4% and 3.3% of the total, the rates increased to 24.1% and 40.5%, respectively.

Conclusions *In MCDA twin pregnancies with no major fetal abnormalities, measurement of NT at the 11–13-week scan is a poor screening test for adverse pregnancy outcome. However, the finding in one or both fetuses of NT ≥ 95th percentile, and more so ≥ 99th percentile, is associated with a substantially increased risk of fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation. The extent to which closer monitoring and earlier intervention in the high-risk group can reduce these complications remains to be determined.*

INTRODUCTION

Increased fetal nuchal translucency thickness (NT) at 11–13 weeks' gestation is associated with chromosomal abnormalities and several major defects and genetic syndromes[1–5]. In chromosomally normal fetuses with no obvious defects, high NT is associated with an increased risk of fetal death, which is about 1% in those with NT between the 95th and 99th percentiles and > 5% in those with NT > 99th percentile; the majority of fetuses that die do so by 20 weeks and they usually show progression from increased NT to severe hydrops[4,5]. In addition to the measurement of fetal NT, the 11–13-week scan is useful in the early diagnosis of multiple pregnancy and determination of chorionicity and amnionicity, which are the main determinants of outcome in such pregnancies[6–9].

In a recent study of 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation and no major abnormalities, we found that the rates of fetal loss at < 24 weeks' gestation and perinatal death at ≥ 24 weeks were higher in monochorionic diamniotic (MCDA), and more so in monochorionic monoamniotic (MCMA), than in dichorionic (DC) twin pregnancies[10]. Early studies in twin pregnancies reported that the incidence of high NT in DC twins was similar to that in singleton pregnancies, but, in MCDA twins, the rate was higher and it was suggested that this may be an early manifestation of the circulatory imbalance associated with twin–twin transfusion syndrome (TTTS)[11,12]. However, subsequent studies that examined between 129 and 489 chromosomally and structurally normal MCDA twin pregnancies reported contradictory results concerning the value of NT in the prediction of TTTS or fetal loss at < 20 weeks' gestation[13–19].

The objectives of this study were to investigate the value of increased fetal NT at the 11–13-week scan in the prediction of, first, miscarriage or death of one or both fetuses at < 20 and < 24 weeks' gestation in DC, MCDA and MCMA twin pregnancies, second, death of one or both fetuses or neonates at ≥ 24 weeks in DC, MCDA and MCMA twin pregnancies, third, development of TTTS or selective fetal growth restriction (sFGR) treated by endoscopic laser surgery at < 20 and ≥ 20 weeks' gestation in MCDA pregnancies, and, fourth, either fetal loss or laser surgery at < 20 weeks' gestation in MCDA pregnancies.

METHODS

Study population and management

This was a retrospective analysis of prospectively collected data obtained from women undergoing routine ultrasound examination at 11–13 weeks' gestation at King's College Hospital or the Fetal Medicine Centre, London (January 2002 to February 2019), Medway Maritime Hospital, Gillingham (February 2007 to February 2019) or Southend University Hospital, Essex (March 2009 to February 2019), UK. The three participating hospitals are maternity units and offer routine ultrasound examination in all patients. The Fetal Medicine Centre is a private outpatient clinic of self-referred patients who deliver in many different hospitals. At the 11–13-week scan, gestational age was determined by the crown–rump length (CRL) of the larger twin[20] and chorionicity was determined from the number of placentas and the presence or absence of the lambda sign at the intertwin membrane–placenta junction[6]. NT was measured in each fetus and classified as ≥ 95th or < 95th percentile of our reference range for CRL[21]. All ultrasound scans were carried out according to standardized protocols by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in ultrasound examination for fetal abnormalities or by trainees under the supervision of certified sonographers. This study constitutes a retrospective analysis of data derived from a routine clinical service and did not require ethics committee approval.

The inclusion criteria for this study were DC, MCDA or MCMA twin pregnancy with two live fetuses at 11–13 weeks' gestation and known pregnancy outcome. We excluded pregnancies with known chromosomal abnormalities or major defects diagnosed prenatally or postnatally and those with twin reversed arterial perfusion sequence.

During the study period, the general policy was to, first, manage all pregnancies on an outpatient basis, unless there was a specific pregnancy complication such as pre-eclampsia, second, in addition to the 11–13-week scan, to carry out ultrasound assessment every 4 weeks from 20 weeks' gestation until delivery in DC twins and every 1–2 weeks from 16 weeks' gestation until delivery in MC twins, and, third, to recommend delivery at around 37 weeks' gestation for DC twins, 36 weeks for MCDA

twins and 32–33 weeks for MCMA twins, if there were no pregnancy complications necessitating earlier delivery.

Women with MCDA twin pregnancies and suspected TTTS and/or sFGR were referred to the fetal medicine unit at King's College Hospital for endoscopic laser ablation of intertwin communicating placental vessels[22–24]. sFGR was defined as ≥ 25% discordance in estimated weight between the two fetuses, with the smallest being < 5th percentile, and the condition was subdivided into Types I, II and III according to the Doppler finding of end-diastolic flow in the umbilical artery of the smaller fetus[25]. In TTTS, there was marked discordance in amniotic fluid volume with the deepest vertical pool being ≤ 2 cm in one sac and ≥ 8 cm at < 20 weeks and > 10 cm at ≥ 20 weeks in the other sac, and the condition was subdivided into Stages I–IV based on the Quintero classification[26]. Endoscopic laser surgery was carried out under local anesthesia as an outpatient procedure; selective coagulation of the intertwin communicating placental vessels with additional coagulation of the placenta between the coagulated vessels was performed. In cases with TTTS, amnioreduction of the polyhydramnios was undertaken.

Outcome measures

Data on pregnancy outcome were collected from the computerized records of the delivery ward and neonatal unit or the patients' general practitioners or the women themselves, and all prenatal and postnatal findings were recorded in a fetal database. The outcome measures were, first, miscarriage or death of one or both fetuses at < 20 and < 24 weeks' gestation in DC, MCDA and MCMA twin pregnancies, second, death of one or both fetuses or neonates at ≥ 24 weeks in DC, MCDA and MCMA twin pregnancies, third, development of TTTS or sFGR treated by endoscopic laser surgery at < 20 and ≥ 20 weeks' gestation in MCDA pregnancies, and, fourth, fetal loss or laser surgery at < 20 weeks' gestation in MCDA pregnancies.

Statistical analysis

Data for categorical variables are presented as *n* (%) and those for continuous variables as median and interquartile range. Comparisons of outcome measures between DC, MCDA and MCMA twin pregnancies were carried out using the χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Kaplan–Meier analysis was used to examine double survival in pregnancies with advancing gestational age according to NT ≥ 95th percentile in one or both fetuses *vs* NT < 95th percentile in both fetuses; the log-rank test was used to compare the difference in survival between the three types of twin pregnancy from 12 to 38 weeks' gestation and separately from 12 + 0 to 19 + 6 and 20 + 0 to 37 + 6 weeks. The relative risk for each outcome measure in pregnancies with NT ≥ 95th percentile, compared to those with NT < 95th percentile, was calculated. In MCDA pregnancies, performance of screening by NT ≥ 95th and ≥ 99th percentiles for either fetal loss or need for laser surgery at < 20 weeks' gestation was estimated. The statistical package SPSS version 24.0 for Windows (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

The study population of 6225 twin pregnancies included 4896 (78.7%) DC, 1274 (20.5%) MCDA and 55 (0.9%) MCMA pregnancies. The demographic characteristics and outcome in the three types of twin pregnancy are summarized in Table 1. In MCDA twins, compared to DC twins, median maternal age and weight were lower and there were more parous women, those of South and East Asian racial origin and natural conceptions. In MCMA twins, compared to DC twins, there were more natural conceptions. In MCMA and MCDA twins, compared to DC twins, there was a higher rate of fetal

Table 1 Demographic characteristics and outcome in 6225 twin pregnancies, according to chorionicity and amnionicity

Variable	*DC* (n = *4896*)	*MCDA* (n = *1274*)	*MCMA* (n = *55*)
MA (years)	34.1 (30.4–37.4)	32.1 (28.1–36.1)*	31.9 (25.9–35.5)
GA (weeks)	12.9 (12.5–13.3)	12.9 (12.5–13.3)	12.7 (12.4–13.0)
Weight (kg)	67.6 (60.4–77.6)	66.0 (59.0–76.3)*	69.2 (61.1–78.3)
Height (cm)	165 (161–170)	165 (160–169)	164 (160–170)
Racial origin			
White	4053 (82.8)	1023 (80.3)	44 (80.0)
Black	513 (10.5)	128 (10.0)	7 (12.7)
South Asian	188 (3.8)	78 (6.1)*	3 (5.5)
East Asian	61 (1.2)	28 (2.2)*	1 (1.8)
Mixed	81 (1.7)	17 (1.3)	0 (0.0)
Smoker	296 (6.0)	97 (7.6)	4 (7.3)
Parity			
Nulliparous	2638 (53.9)	584 (45.8)*	28 (50.9)
Parous	2258 (46.1)	690 (54.2)*	27 (49.1)
Conception			
Natural	2575 (52.6)	1141 (89.6)*	44 (80.0)*
IVF	2047 (41.8)	118 (9.3)*	11 (20.0)*
OI drugs	274 (5.6)	15 (1.2)*	0 (0)
IUFD < 20 weeks	62 (1.3)	82 (6.4)*	6 (10.9)*
One fetus	23 (0.5)	27 (2.1)*	0 (0)
Both fetuses	39 (0.8)	55 (4.3)*	6 (10.9)*
IUFD < 24 weeks	136 (2.8)	115 (9.0)*	12 (21.8)*
One fetus	42 (0.9)	35 (2.7)*	0 (0)
Both fetuses	94 (1.9)	80 (6.3)*	12 (21.8)*
PND ≥ 24 weeks	83 (1.7)	49 (3.8)*	5 (9.1)*
One baby	68 (1.4)	38 (3.0)*	2 (3.6)
Both babies	15 (0.3)	11 (0.9)*	3 (5.5)*
Laser surgery	—	127 (10.0)	—
< 20 weeks	—	84 (6.6)	—
≥ 20 weeks	—	43 (3.4)	—

Data are given as median (interquartile range) or *n* (%). *Compared with dichorionic (DC) twin pregnancies, *post-hoc* Bonferroni correction for multiple comparisons, $P < 0.0167$. GA, gestational age; IUFD, intrauterine fetal death; IVF, *in-vitro* fertilization; MA, maternal age; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; OI, ovulation induction; PND, perinatal death.

loss at < 20 weeks' gestation (10.9%, 6.4% and 1.3%, respectively), fetal loss at < 24 weeks (21.8%, 9.0% and 2.8%, respectively) and perinatal death at ≥ 24 weeks (9.1%, 3.8% and 1.7%, respectively).

Endoscopic laser ablation of intertwin communicating placental vessels was carried out in 127 (10.0%) MCDA twin pregnancies at a median gestational age of 18 (range, 16–27) weeks and the indications were TTTS ($n = 71$; 16 for Stage II, 54 for Stage III and one for Stage IV), sFGR ($n = 28$; 25 for Type II and three for Type III), TTTS and sFGR ($n = 25$; four for Stage II/Type I, two for Stage III/Type I and 19 for Stage III/Type II) and twin anemia–polycythemia sequence ($n = 3$); both babies survived in 74 (58.3%) cases, one baby survived in 29 (22.8%) cases and there were no survivors in 24 (18.9%) cases. Surgery was carried out at < 20 weeks' gestation in 84 MCDA pregnancies and the indications were TTTS ($n = 43$; six for Stage II and 37 for Stage III), sFGR ($n = 22$; 20 for Type II and two for Type III) and TTTS with sFGR ($n = 19$; four for Stage II/Type I, two for Stage III/Type I and 13 for Stage III/Type II); both babies survived in 45 (53.6%) cases, one baby survived in 20 (23.8%) cases and there were no survivors in 19 (22.6%) cases.

Incidence of high NT in complicated pregnancies

Table 2 shows the incidence of NT ≥ 95th percentile in one or both fetuses in the three types of pregnancy, overall and in the subgroups of pregnancy complications. The main findings were: first, in MCDA twin pregnancies, the incidence of high NT (10.4%) was significantly higher than in DC twin pregnancies (8.3%); second, in MCDA twin pregnancies, the incidence of high NT was higher in those with one or more fetal deaths at < 20 and < 24 weeks, endoscopic laser surgery at < 20 weeks and either fetal death or laser surgery at < 20 weeks than in those with two survivors; and, third, in DC and MCMA twin pregnancies, the incidence of high NT was not significantly different between those with two survivors and those with one or more fetal or perinatal deaths.

Kaplan–Meier analysis

Kaplan–Meier analysis in DC twin pregnancies showed no significant difference in survival between those with NT ≥ 95th percentile in one or both fetuses *vs* those with NT < 95th percentile in both fetuses ($P = 0.205$; Figure 1).

In contrast, in MCDA twin pregnancies with NT ≥ 95th percentile, there was significantly lower survival than in those with NT < 95th percentile ($P < 0.031$; Figure 1); the difference was significant for survival < 20 weeks' gestation ($P = 0.001$) but not for survival ≥ 20 weeks ($P = 0.960$). In MCDA twin pregnancies, the relative risk for fetal loss and either fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation in those with NT ≥ 95th, compared to those with NT < 95th percentile,

Table 2 Incidence of fetal nuchal translucency thickness ≥ 95th percentile in one or both fetuses in 6225 twin pregnancies, overall and in subgroups of pregnancy outcome, according to chorionicity and amnionicity

Outcome subgroup	*DC (n = 4896)*	P	*MCDA (n = 1274)*	P	*MCMA (n = 55)*	P
Total population						
Fetuses	453/9792 (4.6)	—	156/2548 (6.1)	0.002†	5/110 (4.5)	0.968†
Pregnancies	404/4896 (8.3)	—	133/1274 (10.4)	0.016†	5/55 (9.1)	0.804†
Pregnancies with two survivors						
Fetuses	429/9356 (4.6)	—	129/2224 (5.8)	0.019†	5/76 (6.6)	0.400†
Pregnancies	381/4678 (8.1)	—	109/1112 (9.8)	0.082†	5/38 (13.2)	0.235†
Pregnancies with fetal death < 20 weeks						
Fetuses	8/124 (6.5)	0.283*	18/164 (11.0)	0.0167*	0/12 (0)	1.000*
Pregnancies	8/62 (12.9)	0.164*	17/82 (20.7)	0.004*	0/6 (0)	1.000*
Pregnancies with fetal death < 24 weeks						
Fetuses	15/272 (5.5)	0.462*	22/230 (9.6)	0.030*	0/24 (0)	1.000*
Pregnancies	15/136 (11.0)	0.265*	20/115 (17.4)	0.016*	0/12 (0)	1.000*
Pregnancies with perinatal death ≥ 24 weeks						
Fetuses	9/166 (5.4)	0.573*	5/98 (5.1)	1.000*	0/10 (0)	1.000*
Pregnancies	8/83 (9.6)	0.547*	4/49 (8.2)	1.000*	0/5 (0)	1.000*
Endoscopic laser surgery < 20 weeks						
Fetuses	—	—	25/168 (14.8)	< 0.0001*	—	—
Pregnancies	—	—	24/84 (28.6)	< 0.0001*	—	—
Endoscopic laser surgery < 28 weeks						
Fetuses	—	—	28/254 (11.0)	0.0025*	—	—
Pregnancies	—	—	27/127 (21.3)	0.0004*	—	—
Endoscopic laser surgery ≥ 20 weeks						
Fetuses	—	—	3/86 (3.5)	0.481*	—	—
Pregnancies	—	—	3/43 (7.0)	0.792*	—	—
Fetal death or laser surgery < 20 weeks						
Fetuses	—	—	35/272 (12.9)	< 0.0001*	—	—
Pregnancies	—	—	32/136 (23.5)	< 0.0001*	—	—

Data are given as *n/N* (%). *Comparison with pregnancies with two survivors within each type of pregnancy. †Comparison with dichorionic (DC) pregnancies. MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic.

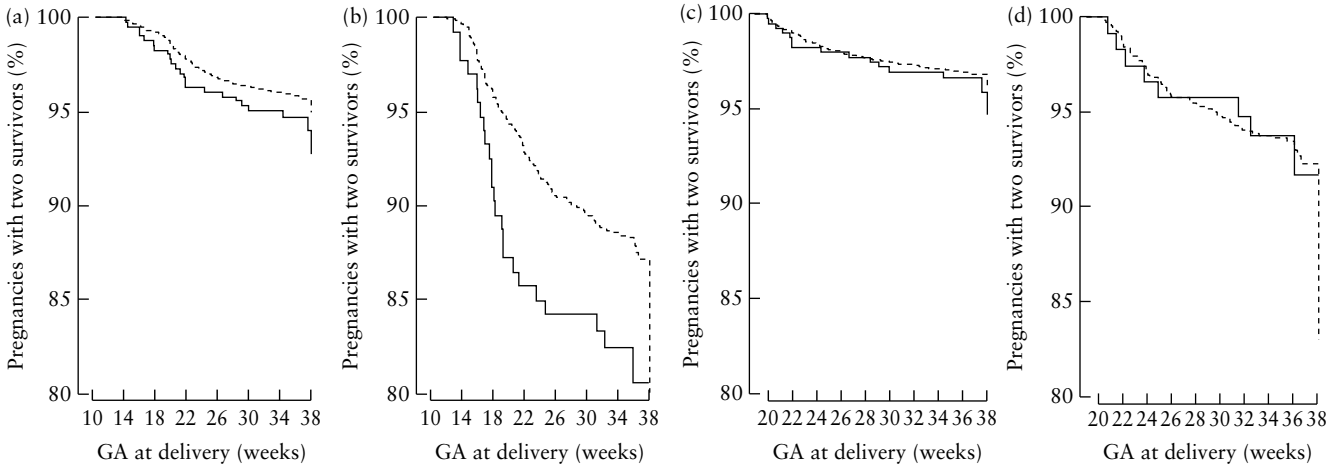

Figure 1 Kaplan–Meier analysis of double survival, overall (a,b) and at ≥ 20 weeks' gestation (c,d), in dichorionic (a,c) and monochorionic diamniotic (b,d) twin pregnancies with advancing gestational age (GA), according to nuchal translucency thickness (NT) ≥ 95th percentile in one or both fetuses (——) or NT < 95th percentile in both fetuses (- - - -).

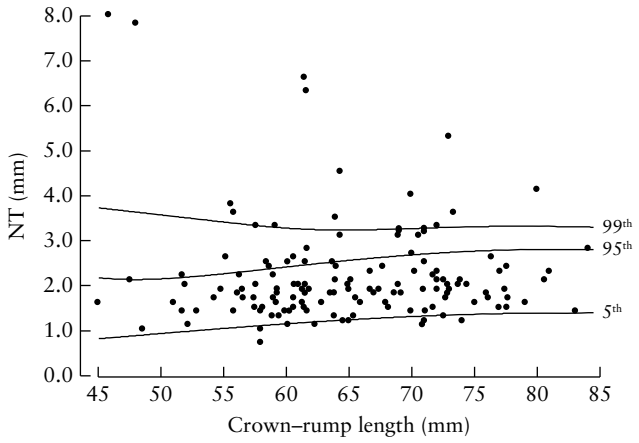

Figure 2 Fetal nuchal translucency thickness (NT) in monochorionic diamniotic twin pregnancies with fetal loss or laser surgery at < 20 weeks' gestation, plotted on reference range of fetal NT for crown–rump length[20]. In each pregnancy, fetus with highest NT was selected.

was 2.244 (95% CI, 1.357–3.710; $P = 0.0016$) and 2.640 (95% CI, 1.854–3.758; $P < 0.0001$), respectively.

Performance of screening for fetal loss and need for laser surgery at < 20 weeks

Fetal NT in MCDA twin pregnancies with fetal loss or laser surgery at < 20 weeks' gestation, plotted on the reference range of fetal NT according to CRL[20], is shown in Figure 2. The performance of screening of fetal NT ≥ 95th and ≥ 99th percentiles in the prediction of fetal loss and need for endoscopic laser surgery at < 20 weeks' gestation is summarized in Table 3. For fetal loss, the detection rates at NT ≥ 95th and ≥ 99th percentiles were 20.7% and 12.2%, respectively, at false-positive rates of 9.7% and 2.7%, respectively. The respective detection rates for prediction of either fetal loss or need for laser surgery at < 20 weeks were 23.5% and 12.5% at false-positive rates of 8.9% and 2.2%, respectively.

Table 3 Performance of fetal nuchal translucency thickness (NT) ≥ 95th and ≥ 99th percentiles in prediction of fetal loss or endoscopic laser surgery at < 20 weeks' gestation in monochorionic diamniotic twin pregnancies

Parameter	*Loss < 20 weeks*	*Laser < 20 weeks*	*Loss or laser < 20 weeks*
NT ≥ 95th percentile			
Detection rate	17/82; 20.7 (12.6–31.1)	24/84; 28.6 (19.2–39.5)	32/136; 23.5 (16.7–31.6)
False-positive rate	116/1192; 9.7 (8.2–11.6)	109/1190; 9.2 (7.7–10.9)	101/1138; 8.9 (7.4–10.7)
Positive likelihood ratio	2.13 (1.35–3.37)	3.12 (2.13–4.57)	2.65 (1.86–3.78)
Negative likelihood ratio	0.88 (0.78–0.98)	0.79 (0.69–0.90)	0.84 (0.76–0.92)
Positive predictive value	12.8 (8.5–18.8)	18.1 (13.1–24.4)	24.1 (18.2–31.1)
Negative predictive value	94.3 (93.7–94.9)	94.7 (94.0–95.4)	90.9 (90.1–91.6)
NT ≥ 99th percentile			
Detection rate	10/82; 12.2 (6.0–21.3)	12/84; 14.3 (7.6–23.6)	17/136; 12.5 (7.5–12.3)
False-positive rate	32/1192; 2.7 (1.9–3.8)	30/1190; 2.5 (1.2–3.6)	25/1138; 2.2 (1.5–3.2)
Positive likelihood ratio	4.54 (2.32–8.91)	5.67 (3.01–10.66)	5.69 (3.15–10.26)
Negative likelihood ratio	0.90 (0.83–0.98)	0.88 (0.81–0.96)	0.89 (0.84–0.95)
Positive predictive value	23.8 (13.7–38.0)	28.6 (17.5–42.9)	40.5 (27.4–55.1)
Negative predictive value	94.2 (93.7–94.6)	94.2 (93.7–94.6)	90.3 (89.8–90.9)

Data are given as *n*/*N*; % (95% CI) or value (95% CI).

In MCDA twin pregnancies, the overall rate of either fetal loss or need for laser surgery at < 20 weeks' gestation was 10.7% (136/1274); in the subgroups with NT $\geq 95^{th}$ and NT $\geq 99^{th}$ percentiles, which constituted 10.4% (133/1274) and 3.3% (42/1274) of the total, the rates increased to 24.1% (32/133) and 40.5% (17/42), respectively, whereas, in those with NT $< 95^{th}$ percentile in both fetuses, which constituted 89.6% (1141/1274) of the total, the rate decreased to 9.1% (104/1141).

DISCUSSION

Main findings

The findings of this study of 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation and no major abnormalities have demonstrated that: first, in MCDA, but not in MCMA twin pregnancies, the incidence of NT $\geq 95^{th}$ percentile in one or both fetuses is higher than in DC twin pregnancies; second, in DC twin pregnancies, the incidence of high NT is not significantly different between those with two survivors and those with adverse outcome; third, in MCMA twin pregnancies, the number of cases was too small for meaningful assessment of the relationship between high NT and adverse outcome; fourth, in MCDA twin pregnancies with one or more fetal deaths at < 20 weeks' gestation and those requiring endoscopic laser surgery for TTTS and/or sFGR at < 20 weeks, the incidence of NT $\geq 95^{th}$ percentile is higher than in those with two survivors; fifth, in MCDA twin pregnancies with NT $\geq 95^{th}$ percentile, compared to those with NT $< 95^{th}$ percentile, survival at < 20 weeks' gestation is lower, but survival ≥ 20 weeks is not significantly different; and, sixth, the performance of screening by fetal NT $\geq 95^{th}$ for prediction of either fetal loss or need for endoscopic laser surgery at < 20 weeks' gestation is poor, but, in the subgroup with high NT, the risk for these complications is substantially increased.

Comparison with findings from previous studies

Previous studies have not reported on the relationship between high NT and adverse outcome in DC and MCMA twin pregnancies unaffected by major fetal abnormalities. Our findings in this large series of 1274 MCDA twin pregnancies that high NT in one or both fetuses is found in 29% (24/84) of those that develop severe TTTS *vs* 9% in the non-TTTS group is almost the same as the respective rates of 28% (12/43) and 10% reported in our first series of 287 MCDA pregnancies[13]. These findings contradict those of a retrospective study that compared 64 pregnancies that developed TTTS and 72 without TTTS and found no difference in the incidence of high NT between the two groups[14]. In a subsequent study, we examined the discordance in NT between the two fetuses, expressed as a percentage of the larger NT, and reported that NT discordance of ≥ 20% was found in about 25% of 512 MCDA twin pregnancies and, in this group, the risk of early fetal death < 18 weeks' gestation or development of severe TTTS was > 30%, whereas, in those with NT discordance of < 20%, the risk of these complications was < 10%[15]. Essentially, the study highlighted the association of high NT with both severe TTTS and early, but not late, fetal death[15]. However, there is a problem with the use of NT discordance rather than percentile cut-offs of NT for CRL, because, first, discordance in NT may be a mere consequence of discordance in CRL, since NT normally increases with CRL, and, second, there may be large NT discordance between two measurements within the normal range (such as 1 mm and 2 mm at CRL of 65 mm, corresponding to NT discordance of 50%) and smaller discordance between two measurements when one is $> 95^{th}$ percentile (such as 2.6 mm and 2.2 mm at CRL of 65 mm, corresponding to NT discordance of 15%) or two measurements which are both $> 95^{th}$ percentile (such as 2.8 mm and 2.6 mm at CRL of 65 mm, corresponding to NT discordance of 7%). Three studies, which included only 16–19 cases of TTTS, reported that median NT discordance or rate of discordance ≥ 20% was not significantly different between TTTS and non-TTTS pregnancies[16–18]. Memmo *et al.* reported that median NT discordance was not significantly different between 102 pregnancies that developed TTTS and 104 controls with normal outcome; in this study, NT discordance was expressed as a percentage of the smaller NT (NT of 1 mm and 2 mm at CRL of 65 mm, corresponding to NT discordance of 100%, and NT of 2.8 mm and 2.6 mm at CRL of 65 mm, corresponding to NT discordance of 8%)[19].

Implications for clinical practice

The essential components of the 11–13-week scan in multiple pregnancies are, first, establishment of gestational age from the measurement of CRL of the larger twin, second, assessment of chorionicity and amnionicity[6], third, examination of the fetal anatomy for early diagnosis of major defects[27], and, fourth, measurement of fetal NT as part of combined screening for trisomies[11,28–32]. As in singleton pregnancies, the finding of increased NT should, first, stimulate further assessment for fetal defects, especially those of the heart and great arteries[4,5,27], second, lead to counseling of the parents concerning the risk for chromosomal abnormalities and offer of invasive testing or cell-free DNA testing[33–35], and, third, arrange follow-up scans in the subsequent 2–3 weeks for further assessment of the fetal anatomy and evolution of the increased NT.

The recommended policy for the management of MCDA twin pregnancies includes ultrasound examination at 11–13 weeks' gestation and subsequent scans every 2 weeks from 16 weeks' gestation until delivery[36]. One implication of our findings is that, in pregnancies with NT $\geq 95^{th}$ percentile in one or both fetuses, the parents should be counseled regarding the increased risk of early fetal loss and possible development of TTTS and/or sFGR requiring endoscopic laser surgery and a scan should be offered at 14 weeks' gestation, in addition

to the recommended one at 16 weeks. In most cases, the scan would be reassuring but, in a high proportion of cases, there could be evidence of severe early TTTS or sFGR; should that be the case, early endoscopic laser surgery at 14–15 weeks could be considered despite the associated increased risk of procedure-related preterm prelabor rupture of membranes and miscarriage[37].

Strengths and limitations

The main strength of our study is the large population of DC and MCDA twin pregnancies which provided sufficient numbers of the various adverse outcome measures for valid conclusions to be drawn concerning their association with high NT. However, the number of MCMA pregnancies was very small and it is therefore uncertain whether the incidence of high NT is increased or whether this measurement can predict adverse outcomes. Similarly, the number of cases of laser surgery was small and it was therefore not possible to examine possible associations between high NT and severity of TTTS and/or sFGR.

The main limitation of this study is that it was retrospective with an inherent risk of bias. Another limitation is that, for pregnancies delivering in hospitals other than the three at which the routine first-trimester scan was carried out, pregnancy outcome was essentially obtained from the patients themselves; however, it is reasonable to assume that the basic outcome measures for this study (prenatal and postnatal survival, laser surgery and gestational age at delivery) are likely to be correct. A third limitation of this study is that, in cases of early fetal loss, no pathological examination was carried out and it is therefore not possible to know the cause of death or whether the fetus was indeed normal, as was thought to be the case prenatally.

Conclusions

In DC twin pregnancies with no major fetal abnormalities, the incidence of NT $\geq 95^{th}$ percentile in one or both fetuses is not significantly different between those with two survivors and those with fetal or perinatal death. In MCDA twin pregnancies, measurement of NT at the 11–13-week scan is a poor screening test for adverse pregnancy outcome. However, the finding in one or both fetuses of NT $\geq 95^{th}$ percentile, and more so NT $\geq 99^{th}$ percentile, is associated with a substantially increased risk of fetal loss or need for endoscopic laser surgery at <20 weeks' gestation. 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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REFERENCES

1. Nicolaides KH, Azar GB, Byrne D, Mansur CA, Marks K. Nuchal translucency: ultrasound screening for chromosomal defects in the first trimester of pregnancy. *BMJ* 1992; **304**: 867–869.
2. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998; **352**: 343–346.
3. Hyett J, Moscoso G, Papapanagiotou G, Perdu M, Nicolaides KH. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol* 1996; **7**: 245–250.
4. Souka AP, Snijders RJ, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 1998; **11**: 391–400.
5. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol* 2001; **18**: 9–17.
6. Sepulveda W, Sebire NJ, Hughes K, Odibo A, Nicolaides KH. The lambda sign at 10–14 weeks as a predictor of chorionicity in twin pregnancies. *Ultrasound Obstet Gynecol* 1996; **7**: 421–423.
7. Sepulveda W, Sebire NJ, Odibo A, Psarra A, Nicolaides KH. Prenatal determination of chorionicity in triplet pregnancy by ultrasonographic examination of the ipsilon zone. *Obstet Gynecol* 1996; **88**: 855–858.
8. Sebire NJ, A Souka, H Skentou, L Geerts, KH Nicolaides. First trimester diagnosis of monoamniotic twin pregnancies. *Ultrasound Obstet Gynecol* 2000; **16**: 223–225.
9. Sebire NJ, Snijders RJM, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. *Br J Obstet Gynaecol* 1997; **104**: 1203–1207.
10. Litwinska E, Syngelaki A, Cimpoca B, Frei L, Nicolaides KH. Outcome of twin pregnancies with two live fetuses at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2019; **55**: 32–38.
11. Sebire NJ, Snijders RJ, Hughes K, Sepulveda W, Nicolaides KH. Screening for trisomy 21 in twin pregnancies by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Br J Obstet Gynaecol* 1996; **103**: 999–1003.
12. Sebire NJ, Hughes K, D'Ercole C, Souka A, Nicolaides KH. Increased fetal nuchal translucency at 10–14 weeks as a predictor of severe twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 1997; **10**: 86–89.
13. Sebire NJ, Souka A, Skentou H, Geerts L, Nicolaides KH. Early prediction of severe twin-to-twin transfusion syndrome. *Hum Reprod* 2000; **15**: 2008–2010.
14. El Kateb A, Nasr B, Nassar M, Bernard JP, Ville Y. First-trimester ultrasound examination and the outcome of monochorionic twin pregnancies. *Prenat Diagn* 2007; **27**: 922–925.
15. Kagan KO, Gazzoni A, Sepulveda-Gonzalez G, Sotiriadis A, Nicolaides KH. Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2007; **29**: 527–532.
16. Lewi L, Lewi P, Diemert A, Jani J, Gucciardo L, Van Mieghem T, Doné E, Gratacós E, Huber A, Hecher K, Deprest J. The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies. *Am J Obstet Gynecol* 2008; **199**: 493.e1–7.
17. Allaf MB, Vintzileos AM, Chavez MR, Wax JA, Ravangard SF, Figueroa R, Borgida A, Shamshirsaz A, Markenson G, Davis S, Habenicht R, Haeri S, Ozhand A, Johnson J, Sangi-Haghpeykar H, Spiel M, Ruano R, Meyer M, Belfort MA, Ogburn P, Campbell WA, Shamshirsaz AA. First-trimester sonographic prediction of obstetric and neonatal outcomes in monochorionic diamniotic twin pregnancies. *J Ultrasound Med* 2014; **33**: 135–140.
18. Fratelli N, Prefumo F, Fichera A, Valcamonico A, Marella D, Frusca T. Nuchal translucency thickness and crown–rump length discordance for the prediction of outcome in monochorionic diamniotic pregnancies. *Early Hum Dev* 2011; **87**: 27–30.
19. Memmo A, Dias T, Mahsud-Dornan S, Papageorghiou AT, Bhide A, Thilaganathan B. Prediction of selective fetal growth restriction and twin-to-twin transfusion syndrome in monochorionic twins. *BJOG* 2012; **119**: 417–421.
20. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
21. Wright D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. A mixture model of nuchal translucency thickness in screening for chromosomal defects. *Ultrasound Obstet Gynecol* 2008; **31**: 376–383.
22. Ville Y, Hecher K, Ogg D, Warren R, Nicolaides KH. Successful outcome after Nd-YAG laser separation of chorioangiopagus-twins under sonoendoscopic control. *Ultrasound Obstet Gynecol* 1992; **2**: 429–431.
23. Ville Y, Hyett J, Hecher K, Nicolaides KH. Preliminary experience with endoscopic laser surgery for severe twin–twin transfusion syndrome. *NEJM* 1995; **332**: 224–227.
24. Peeva G, Bower S, Orosz L, Chaveeva P, Akolekar R, Nicolaides KH. Endoscopic Placental Laser Coagulation in Monochorionic Diamniotic Twins with Type II Selective Fetal Growth Restriction. *Fetal Diagn Ther* 2015; **38**: 86–93.
25. Gratacos E, Lewi L, Munoz M, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**: 28–34.
26. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin–twin transfusion syndrome. *J Perinatol* 1999; **19**: 550–555.
27. Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities at routine ultrasound examination at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2019; **54**: 468–478.

28. Spencer K, Nicolaides KH. First trimester prenatal diagnosis of trisomy 21 in discordant twins using fetal nuchal translucency thickness and maternal serum free beta-hCG and PAPP-A. *Prenat Diagn* 2000; **20**: 683–684.
29. Spencer K, Nicolaides KH. Screening for trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years experience. *BJOG* 2003; **110**: 276–280.
30. Vandecruys H, Faiola S, Auer M, Sebire N, Nicolaides KH. Screening for trisomy 21 in monochorionic twins by measurement of fetal nuchal translucency thickness. *Ultrasound Obstet Gynecol* 2005; **25**: 551–553.
31. Spencer K, Kagan KO, Nicolaides KH. Screening for trisomy 21 in twin pregnancies in the first trimester: an update of the impact of chorionicity on maternal serum markers. *Prenat Diagn* 2008; **28**: 49–52.
32. Madsen HN, Ball S, Wright D, Tørring N, Petersen OB, Nicolaides KH, Spencer K. A reassessment of biochemical marker distributions in trisomy 21-affected and unaffected twin pregnancies in the first trimester. *Ultrasound Obstet Gynecol* 2011; **37**: 38–47.
33. Gil MM, Galeva S, Jani J, Konstantinidou L, Akolekar R, Plana MN, Nicolaides KH. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **53**: 734–742.
34. Galeva S, Gil MM, Konstantinidou L, Akolekar R, Nicolaides KH. First-trimester screening for trisomies by cfDNA testing of maternal blood in singleton and twin pregnancies: factors affecting test failure. *Ultrasound Obstet Gynecol* 2019; **53**: 804–809.
35. Galeva S, Konstantinidou L, Gil MM, Akolekar R, Nicolaides KH. Routine first-trimester screening for fetal trisomies in twin pregnancy: cell-free DNA test contingent on results from combined test. *Ultrasound Obstet Gynecol* 2019; **53**: 208–213.
36. National Institute for Health and Care Excellence. Twin and triplet pregnancy. NICE guideline (NG137), 2019.
37. Stirnemann J, Djaafri F, Kim A, Mediouni I, Bussieres L, Spaggiari E, Veluppillai C, Lapillonne A, Kermorvant E, Magny JF, Colmant C, Ville Y. Preterm premature rupture of membranes is a collateral effect of improvement in perinatal outcomes following fetoscopic coagulation of chorionic vessels for twin–twin transfusion syndrome: a retrospective observational study of 1092 cases. *BJOG* 2018; **125**: 1154–1162.

