

Intertwin discordance in fetal size at 11–13 weeks' gestation and pregnancy outcome

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KEYWORDS: crown–rump length; dichorionic twins; endoscopic laser surgery; fetal loss; first-trimester screening; intertwin discordance; monoamniotic twins; monochorionic twins; perinatal death; preterm birth; selective fetal growth restriction; twin pregnancy; twin–twin transfusion syndrome

CONTRIBUTION

What are the novel findings of this work?

In both dichorionic (DC) and monochorionic diamniotic (MCDA) twin pregnancies, increased discordance in fetal crown–rump length (CRL) is associated with an increased risk of fetal death at <20 and <24 weeks' gestation, perinatal death at ≥24 weeks, preterm birth at <32 and <37 weeks, birth of at least one small-for-gestational-age neonate and birth-weight discordance of ≥20% and ≥25%, but CRL discordance is a poor screening test for adverse pregnancy outcome. However, in DC twins, CRL discordance of ≥15% is associated with a high risk of fetal loss at <20 and <24 weeks' gestation and, in MCDA twins, CRL discordance of ≥10%, and more so discordance of ≥15% and ≥20%, is associated with a very high risk of fetal loss at <20 and <24 weeks.

What are the clinical implications of this work?

In MCDA and DC twin pregnancies with large CRL discordance, the parents should be counseled on the increased risk of fetal loss and the need for early assessment and possible intervention.

ABSTRACT

Objective To investigate the value of intertwin discordance in fetal crown–rump length (CRL) 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 abnormalities, we examined the value of intertwin discordance in fetal CRL in DC, MCDA and

MCMA twins in the prediction of fetal loss at <20 and <24 weeks' gestation, perinatal death at ≥24 weeks, preterm delivery at <32 and <37 weeks, birth of at least one small-for-gestational-age (SGA) neonate with birth weight <5th percentile and intertwin birth-weight discordance of ≥20% and ≥25%.

Results First, the study population of 6225 twin pregnancies included 4896 (78.7%) DC, 1274 (20.4%) MCDA and 55 (0.9%) MCMA twin pregnancies. Second, median CRL discordance in DC twin pregnancies (3.2%; interquartile range (IQR), 1.4–5.8%) was lower than in MCDA twins (3.6%; IQR, 1.6–6.2%; $P=0.0008$), but was not significantly different from that in MCMA twins (2.9%; IQR, 1.2–5.1%; $P=0.269$). Third, compared to CRL discordance in DC twin pregnancies with two non-SGA live births at ≥37 weeks' gestation, there was significantly larger CRL discordance in both DC and MCDA twin pregnancies complicated by fetal death at <20 and <24 weeks' gestation, perinatal death at ≥24 weeks, preterm birth at <32 and <37 weeks, birth of at least one SGA neonate and birth-weight discordance ≥20% and ≥25%, and in MCDA twin pregnancies undergoing endoscopic laser surgery. Fourth, the predictive performance of CRL discordance for each adverse pregnancy outcome was poor, with areas under the receiver-operating-characteristics curves ranging from 0.533 to 0.624. However, in both DC and MCDA twin pregnancies with large CRL discordance, there was a high risk of fetal loss. Fifth, in DC twin pregnancies, the overall rate of fetal loss at <20 weeks' gestation was 1.3% but, in the small subgroup with CRL discordance of ≥15%, which constituted 1.9% of the total, the rate increased to 5.3%. Sixth, in MCDA twin pregnancies, the rate of fetal loss or endoscopic laser surgery at <20 weeks was about 11%, but, in the small subgroups with CRL discordance of ≥10%, ≥15% and ≥20%, which constituted 9%, <3% and <1% of the total, the risk was increased to about 32%, 49% and 70%, respectively. Seventh,

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in MCMA twin pregnancies, there were no significant differences in CRL discordance for any of the adverse outcome measures, but this may be the consequence of the small number of cases in the study population.

Conclusions In both DC and MCDA twin pregnancies, increased CRL discordance is associated with an increased risk of fetal death at <20 and <24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at <37 and <32 weeks, birth of at least one SGA neonate and birth-weight discordance $\geq 20\%$ and $\geq 25\%$, but CRL discordance is a poor screening test for adverse pregnancy outcome. However, in DC twins, CRL discordance of $\geq 15\%$ is associated with an increased risk of fetal loss at <20 and <24 weeks' gestation and, in MCDA twins, CRL discordance of $\geq 10\%$, and more so discordance of $\geq 15\%$ and $\geq 20\%$, is associated with a very high risk of fetal loss or endoscopic laser surgery at <20 and <24 weeks and this information is useful in counseling women and defining the timing for subsequent assessment and possible intervention. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

The 11–13-week scan is useful for screening for chromosomal abnormalities, diagnosis of major defects and detection of multiple pregnancy and determination of chorionicity and amnionicity, which are the main determinants of outcome in such pregnancies^{5–9}. A large study of twin pregnancies at 11–13 weeks' gestation reported that about 79% are dichorionic (DC), 20% are monochorionic diamniotic (MCDA) and 1% are monochorionic monoamniotic (MCMA), and that the rates of fetal loss at <24 weeks' gestation, perinatal death at ≥ 24 weeks and preterm birth are higher in MCDA, and more so in MCMA, twins than in DC twins⁹. Several studies, involving a minimum of 500 twin pregnancies, have reported contradictory results concerning the extent to which intertwin discordance in fetal crown–rump length (CRL) at the 11–13-week scan can predict adverse outcome, including early fetal loss, perinatal death, early preterm delivery and birth of a small-for-gestational-age (SGA) neonate^{10–15}.

The objective of this study of 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation with no major abnormalities, was to investigate further the value of CRL discordance in DC, MCDA and MCMA twins in the prediction of fetal loss at <20 and <24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at <32 and <37 weeks, birth of at least one SGA neonate and intertwin birth-weight discordance of $\geq 20\%$ and $\geq 25\%$.

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 measurement of the CRL of the larger twin¹⁶ and chorionicity was determined from the number of placentas and the presence or absence of the lambda sign at the intertwin membrane–placental junction⁵. All ultrasound examinations 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 ethical committee approval.

During the study period, the general policy was, first, to 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 a MCDA twin pregnancy and suspected twin–twin transfusion syndrome (TTTS) and/or selective fetal growth restriction (sFGR) were referred to the fetal medicine unit at King's College Hospital for endoscopic laser ablation of intertwin communicating placental vessels. sFGR was defined as $\geq 25\%$ 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 fetus¹⁷. In TTTS, there was marked discordance in amniotic fluid volume with the deepest vertical pool of ≤ 2 cm in one sac and ≥ 8 cm before 20 weeks and >10 cm after 20 weeks in the other sac and the condition was subdivided into Stages I–IV based on the Quintero classification¹⁸. 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 the cases with coexisting TTTS, amnioreduction of the polyhydramnios was undertaken.

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 chromosomal abnormality or a major defect diagnosed prenatally or postnatally and those with twin reversed arterial perfusion sequence. The

same database used in this study was also used in our previous publications on the outcome of MC and DC twins⁹, the relationship between increased nuchal translucency thickness and pregnancy outcome¹⁹, first-trimester diagnosis of non-chromosomal fetal abnormalities²⁰ and the effect of one fetal death on pregnancy outcome²¹.

Outcome measures

Data on pregnancy outcome were collected from 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 miscarriage or death of one or both fetuses at < 20 and < 24 weeks' gestation, death of one or both fetuses or neonates at ≥ 24 weeks, endoscopic laser surgery at < 20 weeks and at any gestational age in MCDA twin pregnancies, and, in pregnancies with two live births, delivery at < 32 and < 37 weeks, birth of at least one SGA neonate with birth weight < 5th percentile²² and intertwin birth-weight discordance of $\geq 20\%$ and $\geq 25\%$.

Statistical analysis

Data from categorical variables are presented as *n* (%) and from continuous variables as median and interquartile range (IQR). Comparisons of outcome measures between DC, MCDA and MCMA twin pregnancies were carried out by χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney *U*-test for continuous variables. Kaplan-Meier analysis was used to examine double survival in pregnancies with advancing gestational age according to CRL discordance of < 10%, $\geq 10\%$, $\geq 15\%$ or $\geq 20\%$; log-rank test was used to compare the difference in survival between the three types of twin pregnancies from 12 to 38 weeks' gestation. CRL discordance (%) and birth-weight discordance (%) were calculated as (larger twin - smaller twin) $\times 100$ /larger twin. The predictive performance of CRL discordance for each outcome measure was assessed using receiver-operating-characteristics (ROC) curve analysis. The statistical package SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

The study population of 6225 twin pregnancies with two live fetuses at 11-13 weeks' gestation with no major abnormalities, included 4896 (78.7%) DC, 1274 (20.4%) MCDA and 55 (0.9%) MCMA twin pregnancies. Demographic characteristics and outcome in the three types of twin pregnancies 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 and those of South and East Asian racial origin and more 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 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), perinatal death at ≥ 24 weeks (9.1%, 3.8% and 1.7%, respectively), and, in pregnancies with two live births, delivery at < 32 weeks (25.0%, 13.2% and 7.0%, respectively) and < 37 weeks' gestation (100%, 89.5% and 48.4%, respectively). In pregnancies with two live births, the rate of at least one SGA neonate in DC twins (47.0%) was lower than in MCDA twins (55.9%) but was not significantly different from that in MCMA twins (47.5%); there was no significant difference between the three types of pregnancy in birth-weight discordance $\geq 20\%$ or $\geq 25\%$.

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 weeks (range, 16-27 weeks); surgery was carried out at < 20 and < 24 weeks' gestation in 84 and 111 pregnancies, respectively. 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.

Median CRL discordance and pregnancy complications

Median CRL discordance in DC twin pregnancies (3.2%; IQR, 1.4-5.8%) was significantly lower than in MCDA twins (3.6%; IQR, 1.6-6.2%; $P = 0.0008$), but was not significantly different compared with in MCMA twins (2.9%; IQR, 1.2-5.1%; $P = 0.269$). Compared with DC twin pregnancies with two non-SGA livebirths at ≥ 37 weeks' gestation (median, 3.0%; IQR, 1.3-5.3%), median CRL discordance was significantly larger in both DC and MCDA twin pregnancies complicated by fetal death at < 20 and < 24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at < 32 and < 37 weeks, birth of at least one SGA neonate and birth-weight discordance $\geq 20\%$ and $\geq 25\%$, and in MCDA twin pregnancies undergoing endoscopic laser surgery; in MCMA twin pregnancies there were no significant differences in CRL discordance for any of the outcome measures (Table 2).

Increased CRL discordance and pregnancy complications

There was no significant difference between DC and MCDA or MCMA twin pregnancies in the incidence of CRL discordance $\geq 10\%$ (7.9%, 9.4% and 5.5%; $P = 0.086$ and $P = 0.799$, respectively), CRL discordance $\geq 15\%$ (1.9%, 2.7% and 1.8%; $P = 0.078$ and $P = 1.000$, respectively) or CRL discordance $\geq 20\%$ (0.6%, 0.8% and 0%; $P = 0.314$ and $P = 1.000$, respectively) (Figure 1).

The incidence of CRL discordance $\geq 10\%$ and $\geq 15\%$ in DC twin pregnancies with two non-SGA live births at ≥ 37 weeks' gestation was 5.4% and 0.8%, respectively; compared to these pregnancies, the incidence of CRL discordance $\geq 10\%$ and $\geq 15\%$, respectively, was significantly higher in both DC and MCDA twin pregnancies complicated by fetal death at < 20 and

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

Variable	DC (n = 4896)	MCDA (n = 1274)	MCMA (n = 55)
Maternal age (years)	34.1 (30.4–37.4)	32.1 (28.1–36.1)*	31.9 (25.9–35.5)
Gestational age (weeks)	12.9 (12.5–13.3)	12.9 (12.5–13.3)	12.7 (12.4–13.0)
Maternal weight (kg)	67.6 (60.4–77.6)	66.0 (59.0–76.3)*	69.2 (61.1–78.3)
Maternal 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)
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)
Method of conception			
Natural	2575 (52.6)	1141 (89.6)*	44 (80.0)*
<i>In-vitro</i> fertilization	2047 (41.8)	118 (9.3)*	11 (20.0)*
Ovulation induction drugs	274 (5.6)	15 (1.2)*	0 (0)
Fetal death < 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)*
Fetal death < 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)*
Perinatal death ≥ 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)*
Two live births	4715 (96.3)	1129 (88.6)*	40 (72.7)*
Preterm birth < 32 weeks	330 (7.0)	149 (13.2)*	10 (25.0)*
Preterm birth < 37 weeks	2282 (48.4)	1010 (89.5)*	40 (100)*
BW of at least one baby < 5 th percentile	2215 (47.0)	631 (55.9)*	19 (47.5)
BW discordance ≥ 20%	732 (15.5)	190 (16.8)	2 (5.0)
BW discordance ≥ 25%	384 (8.1)	100 (8.9)	1 (2.5)
Endoscopic laser for TTTS or sFGR			
All	0 (0)	127 (10.0)	0 (0)
< 20 weeks	0 (0)	84 (6.6)	0 (0)

Data are given as median (interquartile range) or *n* (%). *Compared with DC pregnancies, *post-hoc* Bonferroni correction for multiple comparisons, $P < 0.0167$. BW, birth weight; DC, dichorionic; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; sFGR, selective fetal growth restriction; TTTS, twin–twin transfusion syndrome.

< 24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at < 37 weeks and < 32 weeks (except for MCDA pregnancies with CRL discordance ≥ 10%), birth of at least one SGA neonate and birth-weight discordance of ≥ 20% and ≥ 25%, and in MCDA pregnancies undergoing endoscopic laser surgery (Table 3). In MCMA twin pregnancies, the number of cases with CRL discordance ≥ 10% and ≥ 15% was too small for meaningful comparisons with DC twin pregnancies.

The ROC curves for the predictive performance of CRL discordance of each outcome measure are shown in Figure 2. The best performance was for prediction of fetal loss at < 20 and < 24 weeks' gestation and perinatal death at ≥ 24 weeks in MCDA twins but, in general, the performance of screening was poor.

Kaplan–Meier analysis

Kaplan–Meier analysis in MCDA twin pregnancies showed a significant difference in survival between those with CRL discordance ≥ 10% *vs* < 10% ($P < 0.0001$),

≥ 15% *vs* < 15% ($P < 0.0001$) and ≥ 20% *vs* < 20% ($P < 0.0001$) (Figure 3). Thus, by 20 weeks' gestation, the percentage of pregnancies with fetal deaths was 4.8%, 22.5%, 34.3% and 60.0% for CRL discordance of < 10%, ≥ 10%, ≥ 15% and ≥ 20%, respectively; the respective values for fetal loss at < 24 weeks were 7.4%, 25.0%, 37.1% and 60.0%. The relative risk for fetal loss at < 20 and < 24 weeks' gestation in those with CRL discordance of ≥ 10%, compared to those with CRL discordance of < 10%, was 4.721 (95% CI, 3.100–7.188; $P < 0.0001$) and 3.394 (95% CI, 2.341–4.210; $P < 0.0001$), respectively. The respective values for CRL discordance ≥ 15% *vs* < 15% were 6.069 (95% CI, 3.637–10.126; $P < 0.0001$) and 4.512 (95% CI, 2.822–7.214; $P < 0.0001$), and for CRL discordance ≥ 20% *vs* < 20% they were 9.979 (95% CI, 5.752–17.314; $P < 0.0001$) and 6.958 (95% CI, 4.067–11.903; $P < 0.0001$).

In MCDA twin pregnancies, the relative risk for fetal loss or need of endoscopic laser surgery at < 20 and < 24 weeks' gestation in those with CRL discordance of ≥ 10%, compared to those with

Table 2 Crown–rump length (CRL) discordance in 6225 twin pregnancies, according to chorionicity and pregnancy outcome

Outcome	DC (n = 4896)			MCDA (n = 1274)			MCMA (n = 55)		
	n	CRL discord (%)	P*	n	CRL discord (%)	P*	n	CRL discord (%)	P*
Total	4896	3.2 (1.4–5.8)	—	1274	3.6 (1.6–6.2)	—	55	2.9 (1.2–5.1)	—
Two live births	1338	3.0 (1.3–5.3)	—	51	4.0 (1.6–5.4)	0.451	0	—	—
≥ 37 weeks with BW > 5 th percentile									
Fetal death < 20 weeks	62	4.3 (2.1–8.0)	0.003	82	4.9 (2.1–11.7)	< 0.0001	6	2.8 (1.7–3.1)	0.507
One fetus	23	4.0 (2.2–6.4)	0.075	27	3.9 (2.3–11.3)	0.015	0	—	—
Both fetuses	39	7.7 (1.9–8.0)	0.018	55	5.7 (2.2–12.2)	< 0.0001	6	2.8 (1.7–3.1)	0.507
Fetal death < 24 weeks	136	4.1 (1.9–7.4)	< 0.0001	115	4.7 (2.2–10.7)	< 0.0001	12	2.8 (1.3–3.3)	0.389
One fetus	42	3.8 (2.3–6.0)	0.014	35	3.9 (2.6–9.5)	0.009	0	—	—
Both fetuses	94	4.4 (1.4–7.5)	0.014	80	5.1 (2.0–10.9)	< 0.0001	12	2.8 (1.3–3.3)	0.389
Perinatal death ≥ 24 weeks	83	4.1 (1.5–8.1)	0.006	49	5.1 (1.9–10.6)	< 0.0001	5	3.1 (2.8–10.6)	0.843
One baby	68	4.3 (1.5–8.2)	0.013	38	4.5 (1.7–9.1)	0.013	2	0.1 and 5.7	0.621
Both babies	15	3.9 (1.9–7.2)	0.245	11	12.1 (3.6–12.6)	0.002	3	3.1 (2.1–4.9)	0.882
Two live births	4715	3.1 (1.4–5.7)	0.032	1129	3.5 (1.5–5.9)	0.0009	40	2.9 (1.2–5.2)	0.912
PTB < 32 weeks	330	3.9 (1.7–6.8)	< 0.0001	149	3.8 (1.6–6.4)	0.008	10	3.3 (2.3–4.3)	0.986
PTB < 37 weeks	2282	3.2 (1.4–6.0)	0.002	1010	3.5 (1.5–6.0)	0.0005	40	2.9 (1.2–5.2)	0.912
BW of at least one baby < 5 th percentile	2215	3.3 (1.4–6.1)	0.0003	631	3.6 (1.8–6.6)	< 0.0001	19	3.6 (1.4–5.5)	0.593
BW discord ≥ 20%	732	3.7 (1.6–7.2)	< 0.0001	190	4.5 (2.0–8.1)	< 0.0001	2	3.6 and 6.1	0.356
BW discord ≥ 25%	384	3.9 (1.7–7.6)	< 0.0001	100	5.2 (2.6–10.1)	< 0.0001	1	3.6	—
Endoscopic laser for TTTS or sFGR									
All	0	—	—	127	4.5 (2.2–9.3)	< 0.0001	0	—	—
< 20 weeks	0	—	—	84	4.8 (2.8–10.0)	< 0.0001	0	—	—

Data are given as median (interquartile range). *Compared with DC twin pregnancies with two non-small-for-gestational-age live births at ≥ 37 weeks' gestation. BW, birth weight; DC, dichorionic; discord, discordance; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; PTB, preterm birth; sFGR, selective fetal growth restriction; TTTS, twin–twin transfusion syndrome.

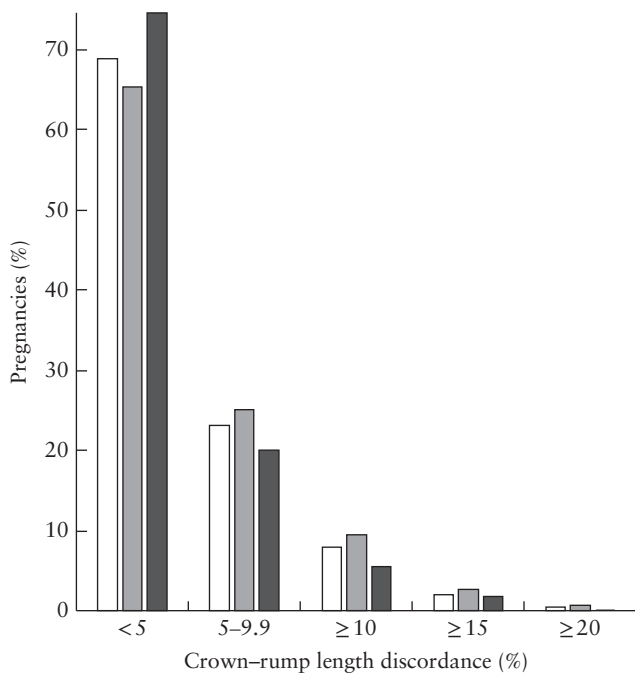


Figure 1 Distribution of discordance in crown–rump length in dichorionic (□), monochorionic diamniotic (■) and monochorionic monoamniotic (■) twin pregnancies at 11–13 weeks' gestation.

CRL discordance of < 10%, was 3.729 (95% CI, 2.697–5.156; $P < 0.0001$) and 2.912 (95% CI, 2.191–3.871; $P < 0.0001$), respectively. The respective values for CRL discordance ≥ 15% *vs* < 15% were 4.913 (95% CI, 3.342–7.222; $P < 0.0001$) and 3.936 (95% CI, 2.802–5.529; $P < 0.0001$) and those for CRL discordance ≥ 20% *vs* < 20% were 6.859 (95% CI, 4.429–10.623; $P < 0.0001$) and 4.971 (95% CI, 3.240–7.626; $P < 0.0001$).

Kaplan–Meier analysis in DC twin pregnancies showed a significant difference in survival between those with CRL discordance ≥ 10% *vs* < 10% ($P = 0.007$), ≥ 15% *vs* < 15% ($P < 0.0001$) and ≥ 20% *vs* < 20% ($P = 0.010$) (Figure 3). Thus, by 20 weeks' gestation, the percentage of pregnancies with fetal deaths was 1.2%, 2.3%, 5.3% and 3.7% for CRL discordance of < 10%, ≥ 10%, ≥ 15% and ≥ 20%, respectively; the respective values for fetal loss at < 24 weeks were 2.7%, 4.1%, 9.5% and 3.7%. The relative risk for fetal loss at < 20 and < 24 weeks' gestation in those with CRL discordance of ≥ 10%, compared to those with CRL discordance of < 10%, was 1.973 (95% CI, 0.981–3.961; $P = 0.057$) and 1.549 (95% CI, 0.929–2.583; $P = 0.093$), respectively. The respective values for CRL discordance ≥ 15% *vs* < 15% were 4.811 (95% CI, 1.838–10.924; $P = 0.001$) and

Table 3 Incidence of crown–rump length (CRL) discordance $\geq 10\%$ and $\geq 15\%$ in 6225 twin pregnancies, according to chorionicity and pregnancy outcome

Outcome	DC (n = 4896)		MCDA (n = 1274)		MCMA (n = 55)	
	n/N (%)	P*	n/N (%)	P*	n/N (%)	P*
CRL discordance $\geq 10\%$						
Total	388/4896 (7.9)	—	120/1274 (9.4)	—	3/55 (5.5)	—
Two live births ≥ 37 weeks with BW $> 5^{\text{th}}$ percentile	72/1338 (5.4)	—	1/51 (2.0)	0.516	0/0 (0)	—
Fetal death < 20 weeks	9/62 (14.5)	0.008	27/82 (32.9)	0.0001	0/6 (0)	—
One fetus	4/23 (17.4)	0.035	8/27 (29.6)	0.0001	0/0 (0)	—
Both fetuses	5/39 (12.8)	0.062	19/55 (34.5)	0.0001	0/6 (0)	—
Fetal death < 24 weeks	16/136 (11.8)	0.007	30/115 (26.1)	0.0001	1/12 (8.3)	—
One fetus	8/42 (19.0)	0.002	8/35 (22.9)	0.0006	0/0 (0)	—
Both fetuses	8/94 (8.5)	0.239	22/80 (27.5)	0.0001	1/12 (8.3)	0.488
Perinatal death ≥ 24 weeks	14/83 (16.9)	0.0003	13/49 (26.5)	0.0001	0/5 (0)	—
One baby	13/68 (19.1)	0.0001	6/38 (15.8)	0.018	0/2 (0)	—
Both babies	1/15 (6.7)	0.567	7/11 (63.6)	0.0001	0/3 (0)	—
Two live births	364/4715 (7.7)	0.003	81/1129 (7.2)	0.078	2/40 (5.0)	1.000
Preterm birth < 32 weeks	41/330 (12.4)	0.0001	13/149 (8.7)	0.096	0/10 (0)	—
Preterm birth < 37 weeks	208/2282 (9.1)	0.0001	76/1010 (7.5)	0.039	2/40 (5.0)	1.000
BW of at least one baby $< 5^{\text{th}}$ percentile	212/2215 (9.6)	0.0001	64/631 (10.1)	0.0002	0/19 (0)	—
BW discordance $\geq 20\%$	99/732 (13.5)	0.0001	33/190 (17.4)	0.0001	0/2 (0)	—
BW discordance $\geq 25\%$	62/384 (16.1)	0.0001	26/100 (26.0)	0.0001	0/1 (0)	—
Endoscopic laser for TTTS or sFGR						
All	0/0 (0)	—	25/127 (19.7)	0.0001	0/0 (0)	—
< 20 weeks	0/0 (0)	—	21/84 (25.0)	0.0001	0/0 (0)	—
CRL discordance $\geq 15\%$						
Total	94/4896 (1.9)	—	35/1274 (2.7)	—	1/55 (1.8)	—
Two live births ≥ 37 weeks with BW $> 5^{\text{th}}$ percentile	11/1338 (0.8)	—	0/51 (0)	—	0/0 (0)	—
Fetal death < 20 weeks	5/62 (8.1)	0.0004	12/82 (14.6)	0.0001	0/6 (0)	—
One fetus	2/23 (8.7)	0.019	3/27 (11.1)	0.002	0/0 (0)	—
Both fetuses	3/39 (7.7)	0.006	9/55 (16.4)	0.0001	0/6 (0)	—
Fetal death < 24 weeks	9/136 (6.6)	0.0001	13/115 (11.3)	0.0001	0/12 (0)	—
One fetus	4/42 (9.5)	0.0008	4/35 (11.4)	0.0004	0/0 (0)	—
Both fetuses	5/94 (5.3)	0.003	9/80 (11.3)	0.0001	0/12 (0)	—
Perinatal death ≥ 24 weeks	8/83 (9.6)	0.0001	0/49 (0)	—	0/5 (0)	—
One baby	7/68 (10.3)	0.0001	0/38 (0)	—	0/2 (0)	—
Both babies	1/15 (6.7)	0.126	0/11 (0)	—	0/3 (0)	—
Two live births	80/4715 (1.7)	0.021	22/1129 (1.9)	0.021	1/40 (2.5)	0.299
Preterm birth < 32 weeks	11/330 (3.3)	0.002	6/149 (4.0)	0.004	0/10 (0)	—
Preterm birth < 37 weeks	52/2282 (2.3)	0.0009	21/1010 (2.1)	0.011	1/40 (2.5)	0.299
BW of at least one baby $< 5^{\text{th}}$ percentile	58/2215 (2.6)	0.0001	19/631 (3.0)	0.0005	0/19 (0)	—
BW discordance $\geq 20\%$	38/732 (5.2)	0.0001	13/190 (6.8)	0.0001	0/2 (0)	—
BW discordance $\geq 25\%$	26/384 (6.8)	0.0001	11/100 (11)	0.0001	0/1 (0)	—
Endoscopic laser for TTTS or sFGR						
All	0/0 (0)	—	11/127 (8.7)	0.0001	0/0 (0)	—
< 20 weeks	0/0 (0)	—	9/84 (10.7)	0.0001	0/0 (0)	—

*Compared with DC twin pregnancies with two non-small-for-gestational-age live births at ≥ 37 weeks' gestation. BW, birth weight; DC, dichorionic; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; sFGR, selective fetal growth restriction; TTTS, twin–twin transfusion syndrome.

3.620 (95% CI, 1.900–6.897; $P = 0.0001$), and those for CRL discordance $\geq 20\%$ vs $< 20\%$ were 2.956 (95% CI, 0.425–20.561; $P = 0.273$) and 1.288 (95% CI, 0.187–8.891; $P = 0.797$).

Risk of fetal loss at < 20 and < 24 weeks according to CRL discordance

In DC twin pregnancies, the overall rate of fetal loss at < 20 weeks' gestation was 1.3% (62/4896), but, in the small subgroup with CRL discordance of $\geq 15\%$, which

constituted 1.9% (94/4896) of the total, the rate increased to 5.3% (5/94); the overall rate of fetal loss at < 24 weeks was 2.8% (136/4896) and this increased to 9.6% (9/94) in the subgroup with CRL discordance of $\geq 15\%$.

In MCDA twin pregnancies, the overall rate of fetal loss at < 20 weeks' gestation was 6.4% (82/1274), but, in the subgroups with CRL discordance of $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$, which constituted 9.4% (120/1274), 2.7% (35/1274) and 0.8% (10/1274) of the total, respectively, the rates increased to 22.5% (27/120), 34.3% (12/35) and 60.0% (6/10); the overall rate of fetal loss at

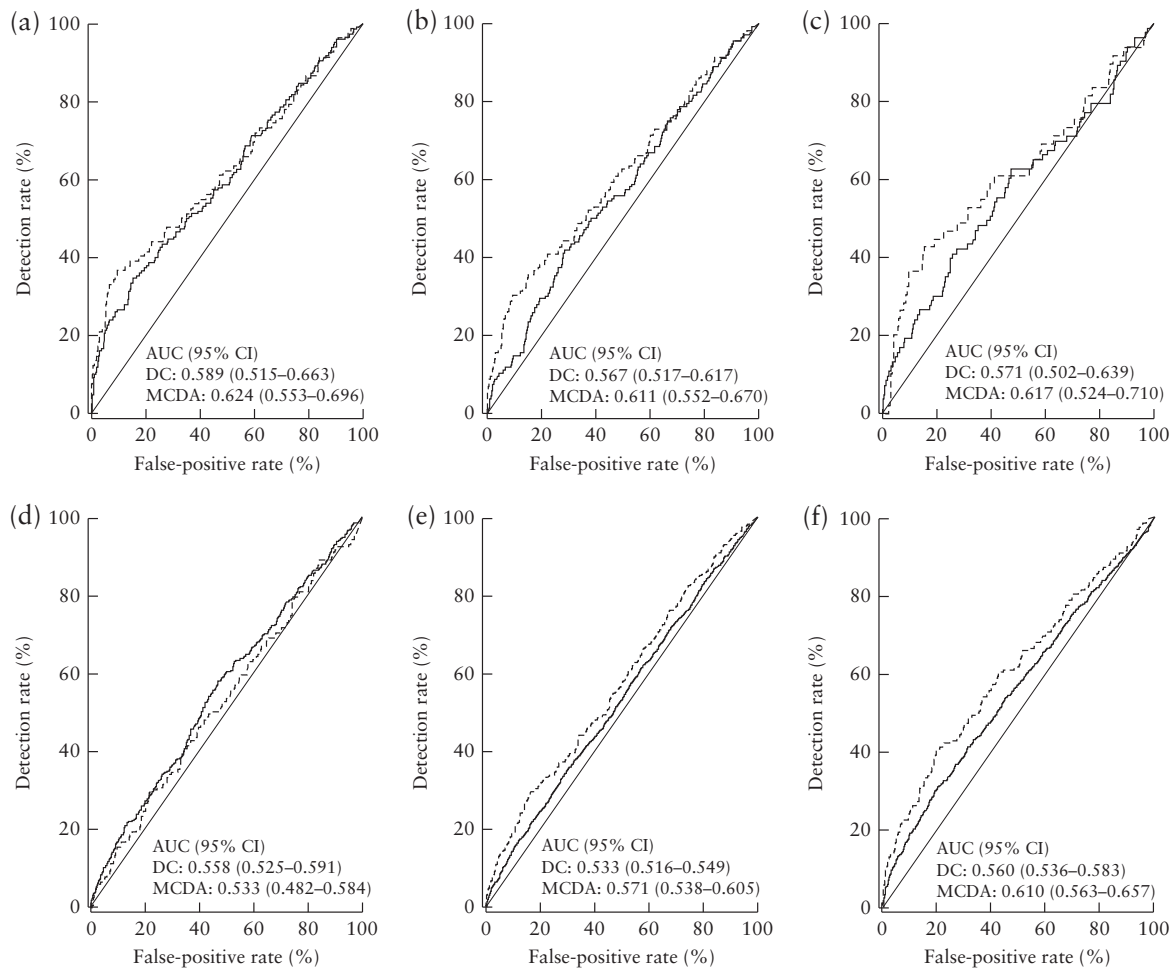


Figure 2 Receiver-operating-characteristics curves for prediction of pregnancies with at least one fetal loss at < 20 (a) and < 24 (b) weeks' gestation, perinatal death at ≥ 24 weeks (c), delivery at < 32 weeks (d), birth of at least one small-for-gestational-age neonate (e) and birth-weight discordance of ≥ 20% (f) from crown-rump length discordance at 11–13 weeks' gestation, in dichorionic (DC) (—) and monochorionic diamniotic (MCDA) (---) twin pregnancies. AUC, area under the curve.

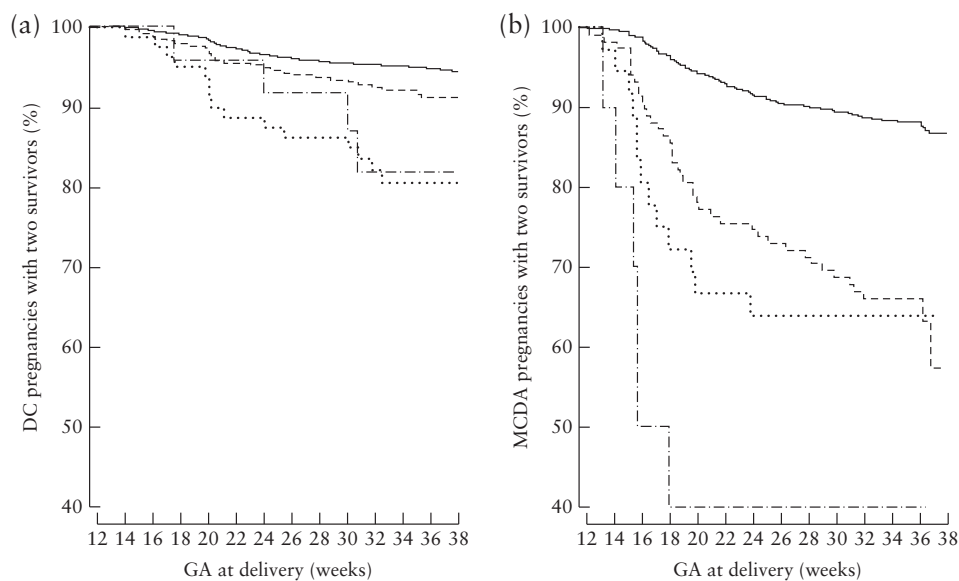


Figure 3 Kaplan-Meier analysis for double survival in dichorionic (DC) (a) and monochorionic diamniotic (MCDA) (b) twin pregnancies with advancing gestational age (GA) according to crown-rump length discordance of < 10% (—), ≥ 10% (---), ≥ 15% (····) and ≥ 20% (-.-).

< 24 weeks' gestation was 9.0% (115/1274) and the rates in the subgroups with CRL discordance of $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ were 25.0% (30/120), 37.1% (13/35) and 60.0% (6/10), respectively.

Risk of fetal loss or laser surgery at < 20 weeks in MCDA twins

In MCDA twin pregnancies, the rate of fetal loss or endoscopic laser surgery at < 20 weeks' gestation was 10.7% (136/1274). For the groups with CRL discordance of < 10%, $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$, which constituted 90.6% (1154/1274), 9.4% (120/1274), 2.7% (35/1274) and 0.8% (10/1274) of the total, respectively, the rates were 8.5% (98/1154), 31.7% (38/120), 48.6% (17/35) and 70.0% (7/10).

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, CRL discordance is increased in both DC and MCDA twin pregnancies complicated by fetal death at < 20 and < 24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at < 32 and < 37 weeks, birth of at least one SGA neonate and birth-weight discordance of $\geq 20\%$ and $\geq 25\%$, and in MCDA twin pregnancies undergoing endoscopic laser surgery; second, the predictive performance of CRL discordance for each adverse pregnancy outcome is poor, with areas under the ROC curves ranging from 0.533 to 0.624; third, in DC twin pregnancies, the rate of fetal loss at < 20 weeks' gestation is about 1%, but in the small subgroup with CRL discordance of $\geq 15\%$, which constitutes < 2% of the total, the risk is increased to 5%; fourth, in MCDA twin pregnancies, the rate of fetal loss or endoscopic laser surgery at < 20 weeks is about 11%, but, in the small subgroups with CRL discordance of $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$, which constitute 9%, < 3% and < 1% of the total, respectively, the risk is increased to about 32%, 49% and 70%; and, fifth, in MCMA twin pregnancies, there were no significant differences in CRL discordance for any of the adverse outcome measures, but this may be the consequence of the small number of cases in the study population.

Comparison with findings from previous studies

Some of the findings of our study, which included 4896 DC and 1274 MCDA twin pregnancies, are consistent with those of previous smaller studies, while others are not. Six previous studies involving a minimum of 500 twin pregnancies have examined the relationship between CRL discordance and adverse outcome^{10–15}. Sebire *et al.* examined 416 DC and 123 MCDA twin pregnancies and reported that, in DC, but not in MCDA, twin pregnancies resulting in fetal loss, CRL discordance was higher than in those with two live births¹⁰. Kagan *et al.* examined 512

MCDA twin pregnancies and reported that, compared to those with normal outcome, pregnancies resulting in fetal loss at ≤ 18 weeks and those requiring endoscopic laser surgery for TTTS, but not those with fetal death at > 18 weeks, had larger CRL discordance and that the risks for these adverse outcomes increased with increasing CRL discordance¹¹. Bhide *et al.* examined 382 DC and 125 MCDA twin pregnancies and reported that, in MCDA, but not in DC, pregnancies resulting in fetal loss, CRL discordance was higher than in those with two live births; additionally, in DC, but not in MCDA, pregnancies, there was a significant association between CRL and birth-weight discordance¹². Harper *et al.* examined 610 DC twin pregnancies and reported that CRL discordance of $\geq 11\%$ was associated with an increased risk of fetal loss at < 20 weeks' gestation; the risk of stillbirth, preterm birth at < 34 weeks or birth of a SGA neonate was not increased, but the authors acknowledged that this may be the consequence of the small number of patients¹³. D'Antonio *et al.* examined 1735 DC and 420 MCDA twin pregnancies and reported that, in both types of pregnancy, CRL discordance is a poor predictor of early fetal loss, perinatal loss, preterm birth at < 34 weeks, birth of a SGA neonate and birth-weight discordance; they concluded that CRL discordance should not be used to identify twin pregnancies at high risk of adverse perinatal outcome¹⁴. Johansen *et al.* examined 1733 DC and 260 MCDA twin pregnancies and reported that CRL discordance of $\geq 10\%$ was associated with an increased risk of birth-weight discordance of $\geq 20\%$ in both types of pregnancies and preterm birth at < 34 weeks in DC twins; there was no significant association with fetal or neonatal death¹⁵.

Implications for clinical practice

In multiple pregnancies, assessment of chorionicity and amnionicity at the routine 11–13-week scan is essential because there are large differences in the incidence of adverse pregnancy outcomes between DC, MCDA and MCMA twins and there is therefore a need for appropriate counseling of parents and planning of subsequent pregnancy management^{5,9}.

This study has demonstrated that, although CRL discordance at the 11–13-week scan is not a good screening test for subsequent adverse pregnancy outcome, large discordance is associated with a high risk for fetal loss. The recommended policy for the management of twin pregnancies includes ultrasound examination at 11–13 weeks' gestation and subsequent scans every 4 weeks from 20 weeks' gestation until delivery in DC twins and every 2 weeks from 16 weeks' gestation until delivery in MC twins²³. One implication of our findings is that, in DC twin pregnancies with CRL discordance of $\geq 15\%$, a scan should be offered at 16 weeks' gestation, in addition to the recommended one at 20 weeks, to examine whether the finding from the 12-week scan that the fetuses were anatomically normal is true and to monitor fetal growth. In most cases, the scan would be reassuring but, in a few cases, an abnormality requiring

further investigation could be identified or there might be evidence of deteriorating growth in an anatomically normal fetus. In the latter case, there may not be a useful intervention to improve the fetal condition but the parents could be counseled as to the increased risk of fetal demise and the need for more intensive surveillance.

In MCDA twin pregnancies with CRL discordance of $\geq 15\%$, and possibly those with discordance of $\geq 10\%$, the parents should be counseled on the increased risk of early fetal loss and development of severe 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 could be considered despite the associated increased risk of procedure-related preterm premature rupture of membranes and miscarriage²⁴.

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 CRL discordance.

The main limitation of the 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 in 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 (survival or not, gestational age at delivery and birth weight) are likely to be correct. A third limitation of the study is that, in the case 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 fetuses were normal.

Conclusions

In both DC and MCDA twin pregnancies, increased CRL discordance is associated with increased risk of fetal death at < 20 and < 24 weeks' gestation, perinatal death at ≥ 24 weeks, preterm birth at < 32 and < 37 weeks, birth of at least one SGA neonate and birth-weight discordance of $\geq 20\%$ and $\geq 25\%$, but CRL discordance is a poor screening test for adverse pregnancy outcome. However, in DC twins, CRL discordance of $\geq 15\%$ is associated with increased risk of fetal loss at < 20 and < 24 weeks' gestation, and, in MCDA twins, CRL discordance of $\geq 10\%$, and more so discordance of $\geq 15\%$ and $\geq 20\%$, is associated with a very high risk of fetal loss or endoscopic laser surgery at < 20 and < 24 weeks and this information is useful in counseling women and defining the timing for subsequent assessment and possible intervention.

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