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Outcome of twin pregnancy with two live fetuses at 11–13 weeks' gestation

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

CONTRIBUTION

What are the novel findings of this work?
This study of 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation and no major abnormalities, first, compares overall survival, fetal loss at < 24 weeks' gestation, perinatal death at ≥ 24 weeks, delivery at < 37 and < 32 weeks, and birth weight < 5th percentile between dichorionic, monochorionic diamniotic and monochorionic monoamniotic twins, and, second, examines the potential impact of endoscopic laser surgery for severe twin–twin transfusion syndrome and/or selective fetal growth restriction on the outcome of monochorionic diamniotic twins.

What are the clinical implications of this work?
In twin pregnancy, determination of chorionicity and amnionicity at the routine 11–13-week scan is essential because this defines the subsequent pregnancy outcome and the need for surveillance and intervention.

ABSTRACT

Objectives *To report and compare pregnancy outcome in dichorionic (DC), monochorionic diamniotic (MCDA) and monochorionic monoamniotic (MCMA) twin pregnancies with two live fetuses at 11–13 weeks' gestation and to examine the impact of endoscopic laser surgery for severe twin–twin transfusion syndrome (TTTS) and/or selective fetal growth restriction (sFGR) on the outcome of MCDA twins.*

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 compared overall survival, fetal loss at < 24 weeks' gestation, perinatal death at ≥ 24 weeks, delivery at < 37 and < 32 weeks, and birth weight < 5th percentile between DC, MCDA and MCMA twins.*

Results *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 (20.5%) MCDA and 55 (0.9%) MCMA twins. In DC twins, the rate of loss at < 24 weeks' gestation in all fetuses was 2.3%; this rate was higher in MCDA twins (7.7%; relative risk (RR), 3.258; 95% CI, 2.706–3.923) and more so in MCMA twins (21.8%; RR, 9.289; 95% CI, 6.377–13.530). In DC twins, the rate of perinatal death at ≥ 24 weeks in all twins that were alive at 24 weeks was 1.0%; this rate was higher in MCDA twins (2.5%; RR, 2.456; 95% CI, 1.779–3.389) and more so in MCMA twins (9.3%; RR, 9.130; 95% CI, 4.584–18.184). In DC twins, the rate of preterm birth at < 37 weeks' gestation in pregnancies with at least one liveborn twin was 48.6%; this rate was higher in MCDA twins (88.5%; RR, 1.824; 95% CI, 1.760–1.890) and more so in MCMA twins (100%; RR, 2.060; 95% CI, 2.000–2.121). In DC twins, the rate of preterm birth at < 32 weeks was 7.4%; this rate was higher in MCDA twins (14.2%; RR, 1.920; 95% CI, 1.616–2.281) and more so in MCMA twins (26.8%; RR, 3.637; 95% CI, 2.172–6.089). In DC twin pregnancies with at least one liveborn twin, the rate of a small-for-gestational-age neonate among all liveborn twins was 31.2% and in MCDA twins this rate was higher (37.8%; RR, 1.209; 95% CI, 1.138–1.284); in MCMA twins, the rate was not significantly different (33.3%; RR, 1.067; 95% CI, 0.783–1.455). Kaplan–Meier analysis showed a significant difference in survival in MCDA and MCMA twins, compared to DC twins, for both the interval of 12 to < 24 weeks' gestation (log-rank test, P < 0.0001 for both) and that of ≥ 24 to 38 weeks (log-rank test, P < 0.0001 for both). Endoscopic laser ablation of intertwin communicating placental vessels*

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was carried out in 127 (10.0%) MCDA twin pregnancies for TTTS and/or sFGR and, in 111 of these, surgery was performed at < 24 weeks; both fetuses survived in 62 (55.9%) cases, one fetus survived in 25 (22.5%) cases and there were no survivors in 24 (21.6%) cases. On the extreme assumption that, had laser surgery not been carried out in these cases, all fetuses would have died, the total fetal loss rate at < 24 weeks' gestation in MCDA twins would have been 13.5%.

Conclusions *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 twins. In MCDA twins, the rate of fetal loss may have been reduced by endoscopic laser surgery in those that developed early TTTS and/or sFGR. These data would be useful in counseling parents as to the likely outcome of their pregnancy and in defining strategies for surveillance and interventions in the management of the different types of twin pregnancy.*

INTRODUCTION

In the 1990s, the finding of an association between increased fetal nuchal translucency thickness and chromosomal abnormalities, as well as several major defects and genetic syndromes, led to the widespread adoption of a routine ultrasound examination at 11–13 weeks' gestation[1–4]. It was subsequently shown that such a scan is useful in the early diagnosis of multiple pregnancy and determination of chorionicity and amnionicity, which are the main determinants of outcome of such pregnancies[5–9].

Sebire *et al.* followed up 102 monochorionic diamniotic (MCDA) and 365 dichorionic (DC) twin pregnancies, diagnosed at the first-trimester scan, and reported that, in the MCDA group, there were higher rates of fetal loss at < 24 weeks' gestation (12.2% *vs* 1.8%) and perinatal death at ≥ 24 weeks (2.8% *vs* 1.6%)[9]. The authors suggested that, first, the previously unrecognized high rate of early mortality in monochorionic (MC) pregnancies is likely to be the consequence of the underlying chorioangiopagus and severe early-onset twin–twin transfusion syndrome (TTTS), and, second, reduction of the excess fetal loss can be achieved only through early identification of MC pregnancies and the development of appropriate methods of surveillance and intervention during the second trimester of pregnancy[9–12]. Subsequent studies confirmed that, in MCDA twin pregnancies, compared to DC twins, there was a higher rate of fetal loss at < 24 weeks' gestation, but there was a large discrepancy in the reported results (Carroll *et al.*[13], 6.3% *vs* 0%; Sperling *et al.*[14], 14.2% *vs* 2.6%; Oldenburg *et al.*[15], 4.4% *vs* 1.6%; D'Antonio *et al.*[16], 6.0% *vs* 0.7%).

The objectives of this study in 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation with no major abnormalities are to report and compare pregnancy outcome in DC, MCDA and monochorionic monoamniotic (MCMA) twins and to examine the impact of endoscopic laser surgery for severe TTTS and/or selective fetal growth restriction (sFGR) on the outcome of MCDA twins.

METHODS

This was a retrospective analysis of prospectively collected data obtained from women undergoing routine ultrasound examination at 11–13 weeks' gestation in the UK 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). 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. 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 abnormalities or major defects diagnosed prenatally or postnatally and those with twin reversed arterial perfusion (TRAP) sequence. At the 11–13-week scan, gestational age was determined by measurement of the crown–rump length of the larger twin[17] and chorionicity was determined from the number of placentas and the presence or absence of the lambda sign at the intertwin membrane–placenta junction[5]. 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.

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 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. 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, which was normal in Type I, absent or reversed (AREDF) in Type II or intermittent AREDF in Type III[18]. In TTTS, there was marked discordance in amniotic fluid volume,

with the deepest vertical pool being ≤ 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 classification[19]. 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 coexisting TTTS, amnioreduction of the polyhydramnios was undertaken.

Data on pregnancy outcome (survival of one or both twins, fetal loss < 24 weeks' gestation, stillbirth or neonatal death, gestational age at delivery or fetal death, and birth weight) 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. This study constitutes a retrospective analysis of data derived from a routine clinical service and did not require ethics committee approval. The same database used in this study was also used in our previous publications on the relationship of increased discordance in crown–rump length and increased nuchal translucency thickness with pregnancy outcome[20,21], first-trimester diagnosis of non-chromosomal fetal abnormalities[22] and the effect of one fetal death on pregnancy outcome[23].

Statistical analysis

Data for categorical variables are presented as *n* (%) and those for continuous variables as median and interquartile range (IQR). Comparisons of outcome measures between DC, MCDA and MCMA twin pregnancies were carried out using Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. Diagnosis of a small-for-gestational-age (SGA) neonate with birth weight < 5th percentile was derived from The Fetal Medicine Foundation fetal and neonatal population weight charts[24]. Kaplan–Meier analysis was used to examine survival of total number of fetuses with advancing gestational age; 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 to < 24 and ≥ 24 to 38 weeks. *Post-hoc* Bonferroni correction was used for multiple comparisons. The statistical package SPSS version 24.0 for Windows (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

The entry criteria were fulfilled by 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation, including 4896 (78.7%) DC, 1274 (20.5%) MCDA and 55 (0.9%) MCMA twin pregnancies. The demographic characteristics of the three types of twin pregnancy are shown in Table 1. In MCDA twins, compared to DC twins, median maternal age and weight were lower, 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.

Table 1 Demographic characteristics of 6225 twin pregnancies with two live fetuses at 11–13 weeks, according to chorionicity and amnionicity

Variable	*Dichorionic (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)
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)

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

Results on pregnancy outcome of the three types of twin pregnancy are shown in Table 2. In DC twins, the rate of loss in all fetuses at < 24 weeks' gestation was 2.3%; this rate was higher in MCDA twins (7.7%; relative risk (RR), 3.258; 95% CI, 2.706–3.923) and more so in MCMA twins (21.8%; RR, 9.289; 95% CI, 6.377–13.530). In DC twins, the rate of perinatal death at ≥ 24 weeks in all twins that were alive at 24 weeks was 1.0%; this rate was higher in MCDA twins (2.5%; RR, 2.456; 95% CI, 1.779–3.389) and more so in MCMA twins (9.3%; RR, 9.130; 95% CI, 4.584–18.184). In DC twins, the rate of preterm birth at < 37 weeks' gestation in pregnancies with at least one liveborn twin was 48.6%; this rate was higher in MCDA twins (88.5%; RR, 1.824; 95% CI, 1.760–1.890) and more so in MCMA twins (100%; RR, 2.060; 95% CI, 2.000–2.121). In DC twins, the rate of preterm birth at < 32 weeks was 7.4%; this rate was higher in MCDA twins (14.2%; RR, 1.920; 95% CI, 1.616–2.281) and more so in MCMA twins (26.8%; RR, 3.637; 95% CI, 2.172–6.089). In DC twin pregnancies with at least one liveborn twin, the rate of a SGA neonate among all liveborn twins was 31.2% and in MCDA twins this rate was higher (37.8%; RR, 1.209; 95% CI, 1.138–1.284); in MCMA twins, the rate was not significantly different (33.3%; RR, 1.067; 95% CI, 0.783–1.455).

In DC twins conceived by assisted reproduction, compared to those conceived naturally, the rate of fetal loss

Table 2 Pregnancy outcome in 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation, according to chorionicity and amnionicity

Outcome	*Dichorionic (n = 4896)*	*MCDA (n = 1274)*		*MCMA (n = 55)*	
		Value	*RR* (95% CI)*	*Value*	*RR* (95% CI)*
Fetal death < 24 weeks					
One twin	42/4896 (0.9)	35/1274 (2.7)	3.203 (2.054–4.994)	0/55 (0)	1.029 (0.064–16.511)
Both twins	94/4896 (1.9)	80/1274 (6.3)	3.271 (2.443–4.378)	12/55 (21.8)	11.364 (6.630–19.479)
Overall†	230/9792 (2.3)	195/2548 (7.7)	3.258 (2.706–3.923)	24/110 (21.8)	9.289 (6.377–13.530)
Perinatal death ≥ 24 weeks					
Pregnancies with two live fetuses at 24 weeks					
One twin	67/4760 (1.4)	36/1159 (3.1)	2.207 (1.479–3.292)	2/43 (4.7)	3.304 (0.836–13.057)
Both twins	15/4760 (0.3)	11/1159 (0.9)	3.012 (1.387–6.540)	3/43 (7.0)	22.139 (6.650–73.705)
Overall†	97/9520 (1.0)	58/2318 (2.5)	2.456 (1.779–3.389)	8/86 (9.3)	9.130 (4.584–18.184)
Pregnancies with one live fetus at 24 weeks	1/42 (2.4)	2/35 (5.7)	2.400 (0.227–25.373)	—	—
Pregnancies with at least one liveborn twin‡					
GA at delivery (weeks)	37.0 (35.3–37.7)	35.6 (33.6–36.4)	—	32.9 (31.9–33.1)	—
Delivery < 37 weeks	2330/4799 (48.6)	1050/1186 (88.5)	1.824 (1.760–1.890)	41/41 (100)	2.060 (2.000–2.121)
Delivery < 32 weeks	354/4799 (7.4)	168/1186 (14.2)	1.920 (1.616–2.281)	11/41 (26.8)	3.637 (2.172–6.089)
Birth weight < 5th percentile†	2971/9514 (31.2)	874/2315 (37.8)	1.209 (1.138–1.284)	27/81 (33.3)	1.067 (0.783–1.455)
Pregnancies with two survivors¶					
GA at delivery (weeks)	37.0 (35.4–37.7)	35.7 (33.9–36.4)	—	32.9 (32.1–33.5)	—
Delivery < 37 weeks	2244/4678 (48.0)	993/1112 (89.3)	1.862 (1.796–1.930)	38/38 (100)	2.085 (2.023–2.148)
Delivery < 32 weeks	297/4678 (6.3)	135/1112 (12.1)	1.912 (1.577–2.319)	8/38 (21.1)	3.316 (1.774–6.198)
Birth weight < 5th percentile					
Both twins	736/4678 (15.7)	225/1112 (20.2)	1.286 (1.125–1.471)	7/38 (18.4)	1.171 (0.598–2.294)
At least one twin	2204/4678 (47.1)	624/1112 (56.1)	1.191 (1.122–1.265)	17/38 (44.7)	0.950 (0.666–1.354)
Pregnancies with one survivor¶					
GA at delivery (weeks)	34.1 (27.8–37.8)	33.3 (29.6–36.4)	—	24.1 and 27.0	—
Delivery < 37 weeks	71/108 (65.7)	52/69 (75.4)	1.146 (0.946–1.389)	2/2 (100)	1.521 (1.328–1.743)
Delivery < 32 weeks	45/108 (41.7)	29/69 (42.0)	1.009 (0.707–1.440)	2/2 (100)	2.400 (1.920–3.000)
Birth weight < 5th percentile	21/108 (19.4)	19/69 (27.5)	1.416 (0.824–2.435)	1/2 (50.0)	2.571 (0.610–10.833)

Data are given as *n/N* (%) or median (interquartile range). *Compared with dichorionic pregnancy. †Expressed as proportion of fetuses or neonates. ‡Includes neonatal deaths. ¶Excludes neonatal deaths. GA, gestational age; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; RR, relative risk.

at < 24 weeks was significantly higher (2.8% (128/4642) *vs* 2.0% (102/5150); $P = 0.013$), but the rate of perinatal death at ≥ 24 weeks was not different (1.0% (46/4514) *vs* 1.0% (52/5048)). In MCDA twins conceived by assisted reproduction, compared to those conceived naturally, the rate of fetal loss at < 24 weeks and perinatal death at ≥ 24 weeks was not significantly different (7.5% (20/266) *vs* 7.7% (175/2282); $P = 1.000$ and 3.3% (8/246) *vs* 2.5% (52/2107); $P = 0.519$, respectively). The number of MCMA twins was too small for meaningful comparisons of outcome according to method of conception.

Kaplan–Meier analysis showed a significant difference in survival in MCDA and MCMA twins compared to DC twins for both the intervals of 12 to < 24 weeks' gestation (log-rank test, $P < 0.0001$ for both) and ≥ 24 to 38 weeks (log-rank test, $P < 0.0001$ for both) (Figure 1).

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. The indications for intervention were TTTS Stage IV ($n = 1$), Stage III ($n = 54$), Stage II ($n = 11$) and Stage I ($n = 5$), sFGR Type II ($n = 25$) and Type III ($n = 3$), sFGR Type II and TTTS Stage III ($n = 19$), sFGR

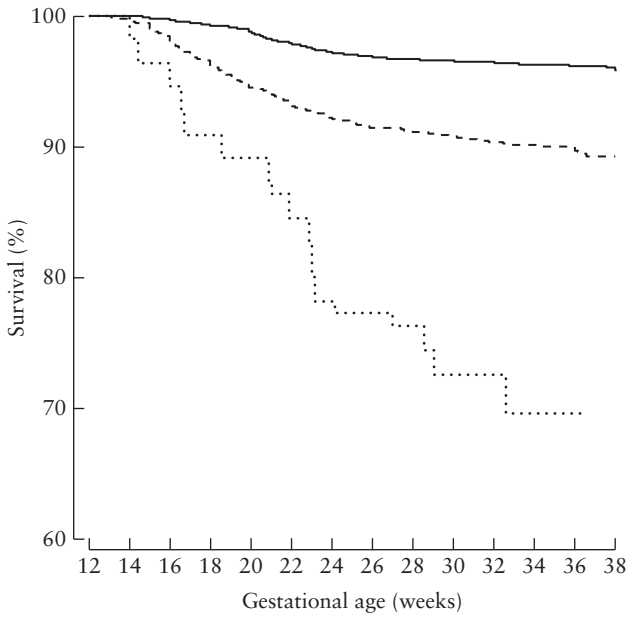

Figure 1 Kaplan–Meier analysis of fetal survival in dichorionic (——), monochorionic diamniotic (- - -) and monochorionic monoamniotic (·····) twin pregnancies from 12 to 38 weeks' gestation.

Type I and TTTS Stage III ($n = 2$) and Stage II ($n = 4$), and twin anemia–polycythemia sequence ($n = 3$). Both fetuses survived in 74 (58.3%) cases, one fetus survived in 29 (22.8%) cases and there were no survivors in 24 (18.9%) cases. In the subgroup of 111 pregnancies with laser surgery at < 24 weeks' gestation, both fetuses survived in 62 (55.9%) cases, one fetus survived in 25 (22.5%) cases and there were no survivors in 24 (21.6%) cases; on the extreme assumption that, had laser surgery not been carried out in these cases, all fetuses would have died, the total fetal loss rate at < 24 weeks' gestation in MCDA twins would have been 13.5% (344/2548, including the 195 that died without surgery and the 149 survivors after surgery).

DISCUSSION

Main findings

The main findings of this study of 6225 twin pregnancies with two live fetuses at 11–13 weeks' gestation and no major abnormalities are, first, 79% of the pregnancies were DC, 20% were MCDA and 1% were MCMA, second, in MCMA and MCDA twins, compared to DC twins, there was a higher rate of fetal loss at < 24 weeks' gestation (21.8%, 7.7% and 2.3% of all fetuses, respectively), perinatal death at ≥ 24 weeks (9.3%, 2.5% and 1.0% of all twins that were alive at 24 weeks, respectively), and delivery at < 37 weeks' gestation (100%, 88.5% and 48.6%, respectively) and < 32 weeks (26.8%, 14.2% and 7.4%, respectively) in pregnancies with at least one liveborn twin, third, the rate of birth of a SGA neonate in MCDA twins (37.8%), but not in MCMA twins (33.3%), was significantly higher than in DC twins (31.2%), and, fourth, in MCDA twins, the rate of fetal loss may have been reduced by endoscopic laser surgery in those that developed early TTTS and/or sFGR.

Comparison with findings from previous studies

Our findings on the risk of fetal loss at < 24 weeks' gestation in DC and MCDA twins are consistent with those of our first study following the introduction of the 11–13-week scan[9]; the lower rate of fetal loss in MCDA twins in the current than in the previous study (7.7% *vs* 12.2%) is likely to be the consequence of endoscopic laser surgery for severe early TTTS and/or sFGR. Our finding that the rates of fetal loss and perinatal death are higher in MCDA than in DC twins (7.7% *vs* 2.3% and 2.5% *vs* 1.0%, respectively) is consistent with the results of previous studies. However, the proportion of such adverse events varied considerably between the studies, presumably because, in some, the number of patients examined was very small and among the larger ones there may have been differences in the characteristics of the study populations, selection criteria, management and ascertainment of outcome. Carroll *et al.* examined 32 MC and 107 DC twins between 1998 and 2000 and reported that the respective rates of fetal loss were 6.3% and 0% and those of perinatal death were 10.0% and 0%[13]. Sperling *et al.* performed a multicenter study in Denmark between 1999 and 2003 which included 74 MC and 421 DC twins without exclusion of fetal abnormalities; the respective rates of fetal loss were 14.2% and 2.6% and those of perinatal death were 2.4% and 1.1%[14]. In a subsequent multicenter study in Denmark between 2003 and 2006, Oldenburg *et al.* examined 281 MC and 1757 DC twins without exclusion of fetal abnormalities; the respective rates of fetal loss were 4.4% and 1.6% and those of perinatal death were 3.2% and 1.4%[15]. In a multicenter study in England between 2000 and 2009, D'Antonio *et al.* examined 605 MC and 2512 DC twins and reported that the respective rates of fetal loss were 6.0% and 0.7% and those of perinatal death were 2.6% and 0.8%; survival analysis showed a significant difference between MC and DC twins for early fetal loss, but not for loss at ≥ 24 weeks[16]. There is also one study of 48 MC and 190 DC twins examined between 1996 and 1998, which reported that the rates of fetal loss (2.1% and 3.2%, respectively) and perinatal death (3.3% and 2.2%, respectively) were similar in the two types of twin pregnancy[25].

We found that, in DC twins conceived by assisted reproduction, compared to those conceived naturally, the rate of fetal loss at < 24 weeks was significantly higher (2.8% *vs* 2.0%), but the rate of perinatal death at ≥ 24 weeks was not different (both 1%); in MCDA twins conceived by assisted reproduction, compared to those conceived naturally, the rates of fetal loss and perinatal death were not significantly different. These findings contradict the results of the multicenter Danish study of Sperling *et al.*, who reported that 14% of their MCDA twins and 61% of DC twins were conceived by assisted reproduction and, in these pregnancies, the rate of fetal loss < 24 weeks' gestation was lower than in naturally conceived pregnancies (1.6% *vs* 4.2% for DC twins and 0% *vs* 16.4% for MC twins); the rate of perinatal death was 0.6% *vs* 1.6% for DC twins and 5.8% *vs* 2.8% for MC twins[14].

In a high proportion of MCMA twin pregnancies diagnosed at 11–13 weeks' gestation, there are major abnormalities, including conjoined twins, TRAP sequence and body-stalk anomaly. Sebire *et al.* examined 12 MCMA twin pregnancies at 11–13 weeks and in eight (66.7%) there were conjoined twins or major abnormalities in one of the fetuses[8]. In our study of 55 MCMA twin pregnancies with no major abnormalities recruited at 11–13 weeks' gestation, the rate of fetal loss at < 24 weeks was 21.8% and the rate of perinatal death at ≥ 24 weeks was 9.3%. These high rates of adverse outcome are consistent with those in previous studies but the actual rates varied considerably between studies, presumably reflecting the small numbers of patients in each study. Dias *et al.* reported on 15 MCMA twin pregnancies with no major abnormalities recruited at 9–14 weeks' gestation between 1997 and 2008; the

rates of fetal loss and perinatal death were 20.0% and 4.2%, respectively[26]. The authors suggested that, once fetal abnormalities are excluded, the survival of MCMA twins is not significantly different from that of MCDA twins[26]. Prefumo *et al.* reported on 16 MCMA twin pregnancies with no major abnormalities, recruited at < 16 weeks' gestation between 2004 and 2013; the rates of fetal loss and perinatal death were 37.5% and 10.0%, respectively[27]. Madsen *et al.,* in a multicenter study from Denmark, reported on 46 MCMA twin pregnancies with no major abnormalities, recruited at < 17 weeks' gestation between 2004 and 2013; the rates of fetal loss and perinatal death were 26.1% and 11.8%, respectively[28]. Glinianaia *et al.* used two multicenter datasets in England, which covered births between 2000 and 2013, to report on 61 MCMA twin pregnancies with no major abnormalities in which chorionicity had been determined by ultrasound at a median gestational age of 13 (IQR, 12–14) weeks; the rates of fetal loss and perinatal death were 18.9% and 12.1%, respectively[29].

Implications for clinical practice

In multiple pregnancy, 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 outcome between DC, MCDA and MCMA twins and there is therefore a need for appropriate counseling of parents and planning of subsequent pregnancy management.

In DC twins, the rates of fetal loss at < 24 weeks and perinatal death at ≥ 24 weeks are about 2% and 1%, respectively, the rate of early preterm delivery < 32 weeks is about 7% and the rate of birth of a SGA neonate is about 30%. We have also reported previously that, in twins, compared to singletons, the risk of preterm pre-eclampsia is 9-times higher[30,31]. In singleton pregnancies, the risks of preterm pre-eclampsia and early SGA are substantially reduced by first-trimester screening and prophylactic therapy with aspirin (150 mg/day from 11–14 until 36 weeks' gestation)[32,33]. The extent to which the same would be true for twin pregnancies remains to be determined. Similarly, in singleton pregnancies, the risk of early preterm birth is reduced by mid-trimester screening by cervical-length measurement and the prophylactic use of vaginal progesterone for those with a short cervix[34,35]. There is some evidence that the same may be true for twin pregnancies with a short cervix[36]; a multicenter trial is currently investigating the use of vaginal progesterone started from 12 weeks' gestation in unselected twin pregnancies.

In MCDA twins, the risks of early fetal loss, perinatal death and early preterm birth are substantially higher than in DC twins and this excess can to a great extent be attributed to the development of TTTS, sFGR and twin anemia–polycythemia sequence. These risks can be reduced by intensive antenatal surveillance and endoscopic laser surgery. As in the case of DC twins, the effectiveness of prophylactic use of low-dose aspirin and vaginal progesterone for reduction of the risks of pre-eclampsia and preterm birth, respectively, are being investigated in randomized trials.

In MCMA twins identified as such at the 11–13-week scan, the first objective is to exclude commonly associated major fetal defects. The parents can then be counseled that, on the basis of our findings and those of previous studies, in MCMA twins without major abnormalities, the rates of fetal loss at < 24 weeks and perinatal death at ≥ 24 weeks are about 20% and 10%, respectively. The risk of early fetal loss cannot be prevented. As for the risk of perinatal death, this can be reduced by aiming to deliver at around 32 weeks' gestation[37,38]. The outcome may not be different if monitoring after 26 weeks' gestation is carried out on an outpatient basis compared to hospitalization[39–41].

Strengths and limitations

The main strength of our study is the large population of DC, MCDA and MCMA pregnancies with no major abnormalities, which provided sufficient numbers of the various adverse outcome measures for valid conclusions to be drawn concerning differences between these three types of twin pregnancy. Another strength is the inclusion of MCDA twins treated with endoscopic laser surgery which allowed assessment of the impact of surveillance and fetal therapy.

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.

Conclusions

The rates of fetal loss, perinatal death and preterm birth are higher in MCDA and more so in MCMA twins than in DC twins; in MCDA twins, the incidence of SGA is increased. In MCDA twins, the rate of fetal loss may have been reduced by endoscopic laser surgery in those that developed early TTTS and/or sFGR. These data would be useful in counseling parents as to the likely outcome of their pregnancy and in defining strategies for surveillance and interventions in the management of the different types of twin pregnancy.

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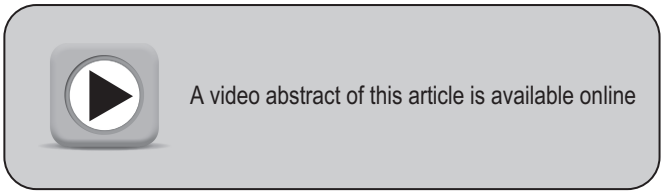

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Resultado del embarazo de gemelos con dos fetos vivos a las 11–13 semanas de gestación

RESUMEN

Objetivos Informar y comparar el resultado de embarazos de gemelos dicoriales (DC), monocoriales diamnióticos (MCDA) y monocoriales monoamnióticos (MCMA) con dos fetos vivos a las 11–13 semanas de gestación y examinar la repercusión de la cirugía endoscópica con láser para los casos graves del síndrome de transfusión gemelo a gemelo (STGG) y/o la restricción selectiva del crecimiento fetal (RsCF) en el resultado de gemelos MCDA.

Métodos Este estudio fue un análisis retrospectivo de datos recogidos prospectivamente sobre embarazos de gemelos sometidos a un examen ecográfico rutinario a las 11–13 semanas de gestación entre 2002 y 2019. En los embarazos sin anomalías importantes, se comparó la supervivencia general, la pérdida del feto a <24 semanas de gestación, la muerte perinatal a ≥24 semanas, el parto a <37 y <32 semanas, y el peso al nacer <5º percentil entre gemelos DC, MCDA y MCMA.

Resultados La población de estudio fue de 6225 embarazos de gemelos con dos fetos vivos a las 11–13 semanas de gestación sin anomalías importantes y estaba formada por 4896 (78,7%) gemelos DC, 1274 (20,5%) gemelos MCDA y 55 (0,9%) gemelos MCMA. En los gemelos DC, la tasa de pérdida a <24 semanas de gestación, en el total de los fetos fue del 2,3%; esta tasa fue más alta en gemelos MCDA (7,7%; riesgo relativo (RR), 3,258; IC 95%, 2,706–3,923) y mayor aun en gemelos MCMA (21,8%; RR, 9,289; IC 95%, 6,377–13,530). En los gemelos DC, la tasa de muerte perinatal a ≥24 semanas en todos los gemelos que estaban vivos a las 24 semanas fue del 1,0%; esta tasa fue mayor en gemelos MCDA (2,5%; RR, 2,456; IC 95%, 1,779–3,389) y mayor aun en los gemelos MCMA (9,3%; RR, 9,130; IC 95%, 4,584–18,184). En los gemelos DC, la tasa de parto pretérmino a <37 semanas de gestación en embarazos con al menos un gemelo nacido vivo fue del 48,6%; esta tasa fue mayor en gemelos MCDA (88,5%; RR, 1,824; IC 95%, 1,760–1,890) y mayor aun en los gemelos MCMA (100%; RR, 2,060; IC 95%, 2,000–2,121). En los gemelos DC, la tasa de parto pretérmino a <32 semanas de gestación fue del 7,4%; esta tasa fue mayor en gemelos MCDA (14,2%; RR, 1,920; IC 95%, 1,616–2,281) y mayor aun en los gemelos MCMA (26,8%; RR, 3,637; IC 95%, 2,172–6,089). En los embarazos de gemelos DC con al menos un gemelo nacido vivo, la tasa de un recién nacido pequeño para la edad gestacional entre todos los gemelos nacidos vivos fue del 31,2% y en los gemelos MCDA esta tasa fue mayor (37,8%; RR, 1,209; IC 95%, 1,138–1,284); en los gemelos MCMA, la tasa no fue significativamente diferente (33,3%; RR, 1,067; IC 95%, 0,783–1,455). El análisis de Kaplan-Meier mostró una diferencia significativa en la supervivencia de los gemelos MCDA y MCMA, en comparación con los gemelos DC, tanto para el intervalo de 12 a <24 semanas de gestación (prueba logarítmico-ordinal, P<0,0001 para ambos) como para el de ≥24 a 38 semanas (prueba logarítmico-ordinal, P<0,0001 para ambos). La ablación endoscópica con láser de los vasos placentarios comunicantes entre gemelos se llevó a cabo en 127 (10,0%) embarazos de gemelos MCDA para STGG y/o RsCF y, en 111 de ellos, la cirugía se realizó a <24 semanas; en 62 (55,.9%) casos sobrevivieron ambos fetos, en 25 (22,5%) casos sobrevivió uno de los fetos y en 24 (21,6%) casos no hubo sobrevivientes. En la suposición extrema de que, si no se hubiera utilizado la cirugía láser en estos casos, todos los fetos habrían muerto, la tasa de pérdida fetal total a <24 semanas de gestación in gemelos MCDA hubiera sido del 13,5%.

Conclusiones Las tasas de pérdida fetal a <24 semanas de gestación, de muerte perinatal a ≥24 semanas y de parto pretérmino son mayores en gemelos MCDA y más aun en gemelos MCMA que en gemelos DC. En los gemelos MCDA, la tasa de pérdida fetal podría haberse reducido mediante la cirugía endoscópica láser en aquellos que desarrollaron STGG y/o RsCF de forma temprana. Estos datos podrían ser útiles para asesorar a los padres en cuanto al resultado probable de su embarazo y para definir las estrategias de vigilancia e intervenciones en el tratamiento de los diferentes tipos de embarazo de gemelos.

妊娠11-13周有两个活胎的双胎妊娠的结局

摘要

目的 报告和比较妊娠11-13周有两个活胎的双胎(DC)、单绒毛膜双胎(MCDA)和单绒毛膜单胎(MCMA)的双胎妊娠的妊娠结局，并检查内镜激光手术治疗严重双胎输血综合征(TTTS)和/或选择性胎儿生长受限(sFGR)对MCDA双胎结局的影响。

方法这是对2002年至2019年间在妊娠11-13周接受常规超声检查的双胎妊娠前瞻性收集数据的回顾性分析。在没有重大异常的妊娠中，我们比较了DC、MCDA和MCMA双胞胎的总体存活率、妊娠< 24周时的胎儿丢失率、妊娠≥24周时的围产儿死亡率、妊娠< 37周和< 32周时的分娩率以及出生体重<第五百分位数。

结果 6225名双胎妊娠的研究人群中有两个活胎，妊娠11-13周且无重大异常，包括4896名(78.7%) DC、1274名(20.5%) MCDA和55名(0.9%) MCMA双胎。在DC双胞胎中，所有胎儿在妊娠< 24周时的丢失率为2.3%；这一比率在MCDA双胞胎(7.7%；相对风险 (RR)，3.258；95%CI，2.706 - 3.923)中更高，在MCMA双胞胎(21.8%；RR，9.289；95%CI，6.377 - 13.530)中更是如此。在DC双胞胎中，24周时存活的所有双胞胎中≥24周时的围产期死亡率为1.0%；这一比率在MCDA双胞胎(2.5%；RR，2.456；95%CI，1.779-3.389)中更高，在MCMA双胞胎中更是如此(9.3%；RR，9.130；95%CI，4.584 - 18.184)。在DC双胞胎中，在至少有一个活产双胞胎的妊娠中，小于37周的早产率为48.6%；
MCDA双胞胎的这一比率更高(88.5%；RR，1.824；95%CI，1.760-1.890)，MCMA双胞胎更是如此
(100%；RR，2.060；95%CI，2.000 - 2.121)。在DC双胞胎中，小于32周的早产率为7.4%；MCDA双胞胎的这一比率更高(14.2%；RR，1.920；95%CI，1.616 - 2.281)，在MCMA双胞胎中更是如此
(26.8%；RR，3.637；95%CI，2.172-6.089)。在至少有一个活产双胞胎的DC双胎妊娠中，
所有活产双胞胎中小于胎龄儿的比率为31.2%，在MCDA双胎中这一比率更高(37.8%；RR，1.209；95%CI，1.138 - 1.284)；在MCMA双胞胎中，这一比率没有显著差异(33.3%；RR，1.067；95%CI，0.783 - 1.455)。Kaplan - Meier分析显示，在妊娠12至< 24周的时间间隔(对数秩检验，两者均< 0.0001)和≥24至38周的时间间隔(对数秩检验，两者均< 0.0001)，MCDA和MCMA双胞胎的存活率与DC双胞胎相比有显著差异。在127例(10.0%) MCDA双胎妊娠中，对TTTS和/或sFGR的胎儿进行了子宫内膜间沟通胎盘血管的激光内窥镜消融，其中111例在< 24周时进行了手术；62例(55.9%)双胎存活，25例(22.5%)单胎存活，24例(21.6%)无存活者。在极端假设下，如果在这些病例中不进行激光手术，
所有胎儿都会死亡，MCDA双胞胎在妊娠<24周时的总胎儿丢失率将为13.5%。

结论MCDA双胎妊娠<24周胎儿丢失率、24周以上围产儿死亡率及早产率均高于DC双胎，MCMA双胎的早产率高于DC双胎。在MCDA双胞胎中，早期TTTS和/或sFGR的胎儿通过内窥镜激光手术可能降低了胎儿丢失率。这些数据将有助于就父母怀孕的可能结果向他们提供咨询，并有助于确定监控和干预不同类型双胎妊娠的策略。

