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Neurodevelopmental outcome in complicated twin pregnancy: prospective observational study

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KEYWORDS: Ages and Stages Questionnaire; ASQ; disability; fetal intervention; monochorionic; neurodevelopmental outcome; selective fetal growth restriction; twin pregnancy; twin–twin transfusion syndrome

CONTRIBUTION

What are the novel findings of this work?
In this contemporary cohort, we found that survivors of complicated monochorionic diamniotic (MCDA) twin pregnancies had a higher rate of adverse long-term neurodevelopmental outcome compared with uncomplicated twin pregnancies.

What are the clinical implications of this work?
Complicated MCDA twin pregnancies, especially those that underwent fetal intervention or presented with coexisting pathologies, were at higher risk of adverse neurodevelopmental outcome. Our findings reinforce the importance of long-term neurodevelopmental follow-up of these children to ensure timely initiation of therapy.

ABSTRACT

Objective *Twin pregnancy is associated with increased perinatal mortality and morbidity, but long-term neurodevelopmental outcome remains underinvestigated. The primary objective of this study was to investigate the incidence of adverse neurodevelopment after 1 year of age in complicated monochorionic diamniotic (MCDA) twin pregnancies compared with uncomplicated twin pregnancies.*

Methods *This was a prospective cohort study conducted at St George's University Hospital NHS Foundation Trust, London, UK. Women with a twin pregnancy culminating in at least one surviving child, aged between 12 and 60 months (corrected for prematurity) at the time of assessment, were invited to complete the relevant Ages and Stages Questionnaire® version 3 (ASQ-3) test. The two study groups were: (1) complicated MCDA twin pregnancies, including those with twin–twin transfusion syndrome, twin anemia–polycythemia sequence, selective fetal growth restriction, twin reversed arterial perfusion sequence and/or single intrauterine demise; and (2) uncomplicated MCDA and dichorionic diamniotic twin pregnancies. The primary outcome measure was an abnormal ASQ-3 score, defined as a score of more than 2 SD below the mean in any one of the five domains. Mixed-effects multivariable logistic regression analysis was performed to determine whether a complicated MCDA twin pregnancy was associated independently with an abnormal ASQ-3 score.*

Results *The study included 174 parents who completed the questionnaire for one or both twins; therefore, 327 ASQ-3 questionnaires were available for analysis. Of those, 117 (35.8%) were complicated MCDA twin pregnancies and 210 (64.2%) were controls. The overall rate of an abnormal ASQ-3 score in children born of a complicated MCDA twin pregnancy was nearly double that of those from uncomplicated twin pregnancies (14.5% vs 7.6%; P = 0.056). Children born of a complicated MCDA twin pregnancy had a significantly higher rate of impairment in the gross-motor domain compared with the control group (8.5% vs 2.9%; P = 0.031). Complicated MCDA twin pregnancies that underwent prenatal intervention had a significantly higher rate of abnormal ASQ-3 score compared with those that did not undergo prenatal intervention (28.1% vs 1.7%; P < 0.001). On multilevel logistic regression analysis,*

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complicated MCDA twin pregnancy was an independent predictor of abnormal ASQ-3 score (adjusted odds ratio, 3.28 (95% CI, 3.27–3.29); P < 0.001).

Conclusions *This study demonstrates that survivors of complicated MCDA twin pregnancies have a higher rate of adverse neurodevelopmental outcome, independently of prematurity. Long-term neurodevelopmental follow-up in these pregnancies can ensure timely and optimal management of those affected.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Monochorionic twin pregnancy is associated with chorionicity-specific complications, including twin–twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia–polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence and single intrauterine demise (sIUD)[1–4]. These complications are the sequelae of a single shared placenta with unbalanced vascular anastomoses and are associated with perinatal morbidity and mortality. Over recent decades, there has been a paradigm shift in the immediate survival and short-term outcome of these infants, attributable to both a clearer understanding of the underlying pathophysiological processes and advances in fetal therapy and neonatal care[5]. However, there is a need to better elucidate the long-term neurodevelopmental outcome, as disability-free survival is the ultimate goal. Guidelines and policymakers have highlighted the need for more evidence to provide parents with realistic counseling and appropriate follow-up[6]. Early investigations understandably focused on perinatal survival, but parents and clinicians now seek understanding of the long-term neurodevelopmental implications of these complications and associated prenatal interventions.

Several retrospective studies have demonstrated a significant association between the complications of monochorionic twin pregnancy (TTTS, sIUD for any reason, sFGR and TAPS) and neurological injury[7–10]. In pregnancies complicated by TTTS, cerebral abnormalities were identifiable on antenatal imaging in 5% of those that received laser coagulation, 14% of those that underwent serial amnioreduction and 21% of those that were managed expectantly[10]. Both donors and recipients are at risk of developing either ischemic or hemorrhagic lesions. In a systematic review investigating the prognosis of the monochorionic cotwin following sIUD, the rate of abnormal postnatal cranial imaging was 34%, compared with 16% for an uncomplicated pregnancy, while the respective rates for neurodevelopmental impairment were 26% and 2%[9]. Following sIUD, the surviving monochorionic twin is three and five times more likely, respectively, to have brain abnormalities and neurodevelopmental morbidity compared to a monochorionic twin pregnancy with two live fetuses[9]. Furthermore, severe cerebral injury affects approximately 10% of monochorionic twins complicated by sFGR and is associated with abnormal umbilical artery Doppler, the larger twin, sIUD and earlier gestational age (GA) at birth[8]. Lastly, it has been reported that one in five twin pregnancies complicated by TAPS is associated with adverse neurological outcome[11,12].

However, most studies reporting on long-term neurological outcome are retrospective and lack appropriate controls, so are at high risk of bias and unable to answer several clinically important questions. It is not clear which of the abnormalities reported on antenatal or neonatal brain imaging will result in significant neurodevelopmental delay, and which other antenatal and neonatal parameters affect long-term neurodevelopment after a complicated twin pregnancy. The prevalence of neurodevelopmental delay in uncomplicated monochorionic and dichorionic twin pregnancies, and risk factors for long-term neurodevelopmental adverse outcome in complicated twin pregnancies, are yet to be established. We aimed to investigate prospectively the incidence of adverse neurodevelopment after 1 year of age in complicated monochorionic diamniotic (MCDA) twin pregnancies compared with uncomplicated monochorionic and dichorionic twin pregnancies. The secondary objective was to identify maternal or fetal risk factors that could be used to screen for adverse neurodevelopment in these complicated pregnancies.

METHODS

Study design and setting

This was a single-center prospective cohort study conducted at St George's University Hospital NHS Foundation Trust, London, UK, between 2015 and 2021. St George's Hospital is the regional tertiary referral unit for complex multiple pregnancies for the South West Thames region of the UK. We included children aged from 12 months up to 60 months (corrected for prematurity) at the time of assessment. The study population was divided into two groups: cases, which were MCDA twin pregnancies complicated by TTTS, sFGR, TAPS, TRAP sequence and/or sIUD; and controls, which were uncomplicated dichorionic diamniotic (DCDA) and MCDA twin pregnancies. DCDA twin pregnancies complicated by sFGR or sIUD were excluded. Pregnancies with major fetal anomaly, congenital infection or genetic abnormality were also excluded. Eligible survivor children were identified from the hospital records, and their mothers were invited to participate in the study. Only women who had a pregnancy in which one or both twins were born alive were contacted. If outcome data were not available in the hospital database, the mother was not contacted, as these high-risk pregnancies are at significant risk of bereavement.

Women who consented were asked to complete the relevant Ages and Stages Questionnaire® (ASQ) version 3 (ASQ-3) test. They were offered the choice of completing the form themselves and returning it by post or secure e-mail, completing it with a researcher over

the phone or attending the hospital to complete it in person with a healthcare professional. The ASQ-3 questionnaire comprises a series of 21 questions that can be completed by the parents, and contains 30 developmental items that are divided into five domains: communication, gross-motor, fine-motor, problem-solving and personal–social[13]. For these items, parents check 'yes' to indicate that the child performs the specified behavior, 'sometimes' to indicate an occasional or emerging response or 'not yet' to indicate that their child does not yet perform the behavior. The ASQ has been validated against the Bayley Scales of Infant Development as a screening tool for abnormal neurological development at 24 months of age[14–16]. The assessment and compilation of responses were performed by a researcher who was blinded to whether the pregnancy was complicated, to avoid potential investigator bias. The child's prematurity-corrected age was calculated for the purposes of analysis (http://bit.ly/ASQAgeCalc). Following the manufacturer's recommended cut-offs, a score of more than 2 SD below the mean score for term-born children in any one of the five domains was considered abnormal[17]. The ASQ is a screening test, not a diagnostic test, and this difference was made clear to the participants and reiterated if an abnormal result was returned. This study was approved by the Research Ethics Committee, London – Camden and Kings Cross Health Research Authority (19/LO/0295).

Demographic and clinical data, including maternal age, parity, mode of conception, chorionicity, amnionicity, clinical diagnosis, complications and details of prenatal intervention were extracted from ViewPoint database (ViewPoint Bildverarbeitung GmbH, Weßling, Germany). Perinatal outcomes, including fetal loss, mode of delivery, GA at birth, preterm birth (PTB) prior to 28, 32 and 34 weeks' gestation, birth weight, admission to the neonatal intensive care unit (NICU) and measures of neonatal morbidity (respiratory distress syndrome, need for resuscitation, jaundice requiring phototherapy or exchange transfusion, intraventricular hemorrhage, sepsis, necrotizing enterocolitis or persistent ductus arteriosus requiring intervention), were obtained from the electronic maternity information systems and the neonatal electronic database (BadgerNet; Clevermed Ltd, Edinburgh, UK). Estimates of birth weight $< 5^{th}$ centile were derived from twin chorionicity-specific population birth-weight charts[18]. Where available, long-term infant outcomes including chronic lung disease, pulmonary hypertension and bronchopulmonary dysplasia were also recorded.

Chorionicity was determined at the first-trimester ultrasound scan. The disease pathologies TTTS, sFGR, TRAP sequence and TAPS were defined according to standard criteria. TTTS was defined as a combination of oligohydramnios (deepest vertical pocket less than 2 cm) in the donor and polyhydramnios (deepest vertical pocket more than 8 cm if the pregnancy was < 20 weeks' gestation, or greater than 10 cm at ≥ 20 weeks' gestation) in the recipient twin[19]. The severity of TTTS was graded using Quintero's classification[19]. sFGR was defined according to the Delphi consensus criteria and classified according to the umbilical artery Doppler flow patterns of the smaller twin[20,21]. Active intervention (fetoscopic laser photocoagulation, selective feticide, intrafetal laser, amniodrainage or delivery) or expectant management was offered depending on individual cases as per unit protocol. Fetal brain magnetic resonance imaging was offered to all monochorionic twin pregnancies that had abnormal prenatal ultrasound or underwent active fetal intervention as per the hospital protocol.

The primary outcome measure was an abnormal ASQ-3 score, defined as a score of more than 2 SD below the mean for term-born children in one or more domains. If several questionnaires were completed for one child, then only the most recent one was considered for the analysis.

Power and sample size

In the UK, approximately 2% of all births are twin pregnancies. One third of twin pregnancies are monochorionic. TTTS affects 10–15% of monochorionic twin pregnancies, while sFGR affects 10–15% of monochorionic and 10% of dichorionic twin pregnancies. The other complications of interest are less common, hence the numbers of pregnancies affected by these complications were likely to be small. We planned to recruit 90 women whose MCDA pregnancy was complicated and 180 women who had an uncomplicated twin pregnancy as controls, to give a ratio of 1:2 and to allow for matching of the child's age and GA at birth.

Statistical analysis

Descriptive data are presented as mean ± SD for continuous variables and as n (%) for categorical variables. Comparisons for normally distributed continuous variables were made using Student's t-test, and for categorical variables using the χ-square test or Fisher's exact test. Mixed-effects multivariable logistic regression analysis was performed to determine whether a complicated MCDA twin pregnancy was associated independently with an abnormal ASQ-3 score. Clinically plausible risk factors were incorporated into the modeling approach as fixed effects, and the pregnancy was used as a random effect. Patients with incomplete data for explanatory variables were excluded from the analysis. Final model selection was performed through minimization of the Akaike information criterion and maximization of the C-statistic.

Propensity-score matching was used to investigate the association between complicated twin pregnancies and abnormal ASQ-3 and minimize selection bias between the two study groups (cases and controls). Full matching was used to allow multiple participants from each group (to avoid inappropriate discarding of data) to be matched together and weighted to achieve balance[22]. The balance in risk factors between the groups was assessed before and after matching, using the absolute standardized mean difference, and a value below 0.2 was considered

to indicate that a variable was well balanced between the groups. Subsequent doubly robust estimation was performed through risk adjustment using multivariable regression models, based on the same variables used to generate the propensity score[23].

All effect estimates are presented as odds ratios (OR) with 95% CI. Statistical significance was set *a priori* as $P < 0.05$. Statistical analysis was performed using R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria) with the tidyverse, finalfit and finalpsm packages.

RESULTS

Study population

This study included 174 parents who completed the questionnaire for one or both twins; 327 ASQ-3 questionnaires were available for analysis (Figure 1, Table S1). The study population included 69 complicated MCDA twin pregnancies (117 children) and 105 uncomplicated DCDA/MCDA twin pregnancies (210 children). The most prevalent pregnancy complication was TTTS ($n = 41$), followed by sFGR ($n = 32$), sIUD ($n = 15$), TAPS ($n = 5$) and TRAP sequence ($n = 3$).

The demographic and perinatal characteristics of the two groups are presented in Table 1. Maternal parity and body mass index (BMI) were similar between the two study groups ($P > 0.05$). However, women with a complicated MCDA twin pregnancy were significantly younger compared to those without complications (mean ± SD, 31.6 ± 5.0 years *vs* 33.5 ± 4.5 years; $P = 0.001$). The mean ± SD GA at birth was significantly lower in cases compared with controls (32.6 ± 2.8 weeks *vs* 35.8 ± 2.3 weeks; $P < 0.001$) and a similar trend was observed for birth weight (mean ± SD, 1742.9 ± 672.8 g *vs* 2342.2 ± 439.8 g; $P < 0.001$). A greater proportion of complicated MCDA twin pregnancies resulted in PTB before 32 weeks (29.0% *vs* 3.8%; $P < 0.001$) and PTB before 34 weeks (46.4% *vs* 15.2%; $P < 0.001$) compared with uncomplicated pregnancies. This was further reflected by the higher rates of NICU admission (48.7% *vs* 15.2%; $P < 0.001$) and neonatal morbidity (48.7% *vs* 13.3%; $P < 0.001$) in cases compared with controls. The mean age of the children at the time of completing the ASQ-3 questionnaire was 2.42 years and 2.95 years for cases and controls, respectively. Most of the children included in the study were 2 years of age or older (240/327 (73.4%)) (Table S1).

Primary outcome

The overall prevalence of an abnormal ASQ-3 score (defined as a score of more than 2 SD below the mean in any one of five domains) in cases was almost double that in controls (17/117 (14.5%) *vs* 16/210 (7.6%)), although the difference did not reach statistical significance ($P = 0.056$) (Table 2). Children born of a complicated MCDA twin pregnancy had a significantly higher rate of impairment

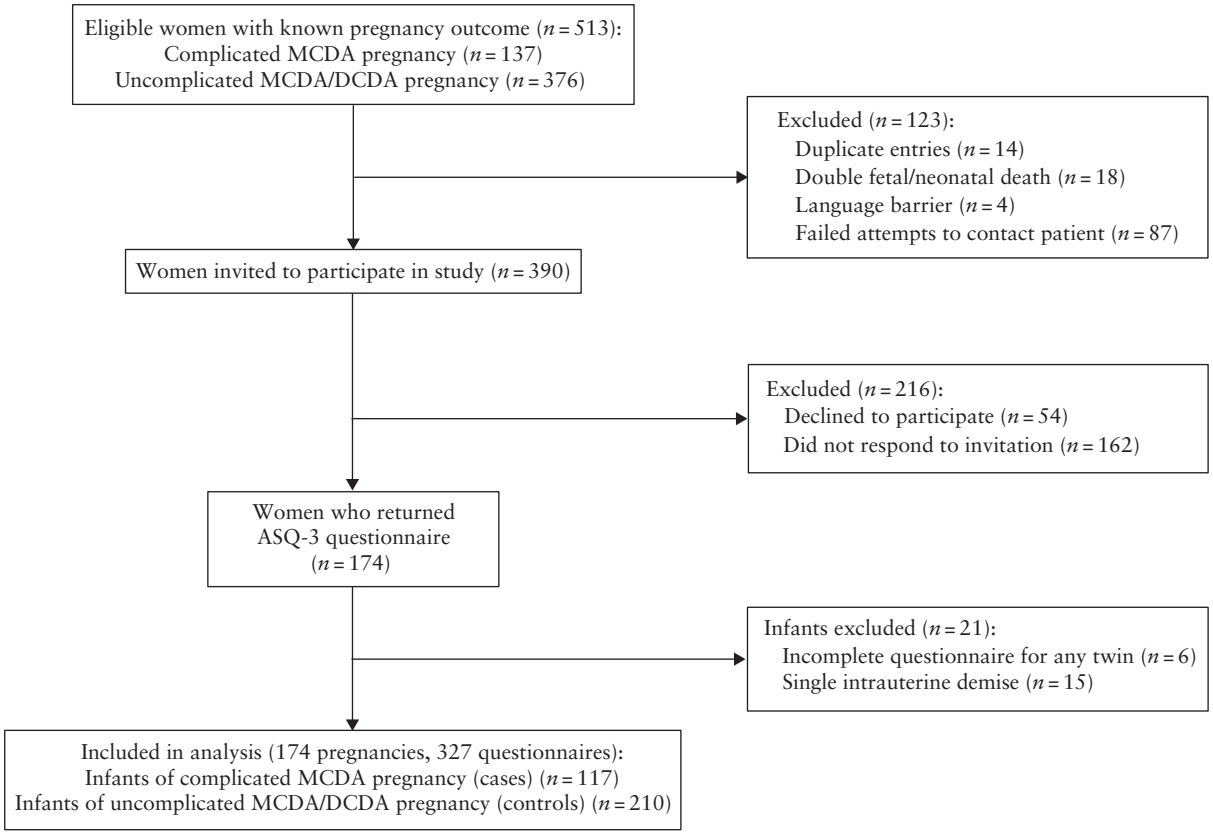

Figure 1 Flowchart summarizing eligibility and inclusion of participants in study. ASQ-3, Ages and Stages Questionnaire version 3; DCDA, dichorionic diamniotic; MCDA, monochorionic diamniotic.

in the gross-motor domain compared with the control group (10/117 (8.5%) *vs* 6/210 (2.9%); $P = 0.031$). No significant differences between the two study groups were noted for other individual domains of the ASQ-3 test, namely communication, fine-motor, problem-solving and personal–social skills.

The frequency of an abnormal ASQ-3 score for the subcategories of complicated MCDA twin pregnancy is presented in Table S2. In twin pregnancies complicated by TTTS, 20.3% (14/69) of the children had an abnormal ASQ-3 score, while the rate was 13.3% (8/60) in children born of pregnancies complicated by sFGR. One-third (9/28) of children born of MCDA twin pregnancies complicated by more than one pathology had an abnormal ASQ-3 score. Table 3 presents the frequency of abnormal ASQ-3 scores in the subgroups according to clinical features, donor/recipient status or smaller/larger twin. For TTTS survivors, the occurrence of an abnormal ASQ-3 score was almost double in the donor twin compared with the recipient twin (9/33 (27.3%) *vs* 5/36 (13.9%)), although the difference did not reach statistical significance ($P = 0.171$). Monochorionic twin pairs affected by sFGR demonstrated a similar distribution of abnormal ASQ-3 scores among larger and smaller twins (4/32 (12.5%) *vs* 4/28 (14.3%); $P = 0.840$). Complicated

Table 2 Frequency of abnormal domains attained on Ages and Stages Questionnaire version 3 (ASQ-3) by infants from uncomplicated *vs* complicated twin pregnancies

Domain	*Uncomplicated MCDA/DCDA twins* (n = *210*)	*Complicated MCDA twins* (n = *117*)	P
One abnormal domain	16 (7.6)	17 (14.5)	0.056
Two abnormal domains	11 (5.2)	8 (6.8)	0.624
Abnormal communication	9 (4.3)	9 (7.7)	0.212
Abnormal gross-motor	6 (2.9)	10 (8.5)	0.031
Abnormal fine-motor	6 (2.9)	5 (4.3)	0.531
Abnormal problem-solving	8 (3.8)	7 (6.0)	0.413
Abnormal personal–social	9 (4.3)	8 (6.8)	0.314

Data are given as *n* (%). Abnormal domain was defined as score of more than 2 SD below mean. Overall abnormal ASQ-3 score was defined as abnormal score in any one of five domains. Some infants had > 2 abnormal domains. DCDA, dichorionic diamniotic; MCDA, monochorionic diamniotic.

Table 1 Baseline characteristics and perinatal outcomes of uncomplicated *vs* complicated twin pregnancies

Parameter	*Uncomplicated MCDA/DCDA twin pregnancy* (n = *105) (210 twins)*	*Complicated MCDA twin pregnancy* (n = *69) (117 twins)*	P
Maternal age (years)	33.5 ± 4.5	31.6 ± 5.0	0.001
Nulliparous	53 (50.5)	37 (53.6)	0.757
Body mass index at presentation (kg/m^2)	26.6 ± 6.2	25.5 ± 4.7	0.083
Spontaneous conception	80 (76.2)	62 (89.9)	0.028
Index of multiple deprivation			
Quintile 1 (most deprived)	22 (21.0)	12 (17.4)	0.570
Quintile 2	15 (14.3)	13 (18.8)	0.430
Quintile 3	36 (34.3)	26 (37.7)	0.648
Quintile 4	24 (22.9)	10 (14.5)	0.173
Quintile 5 (least deprived)	8 (7.6)	8 (11.6)	0.373
Single intrauterine demise	0 (0)	15 (21.7)	NE
GA at birth (weeks)	35.8 ± 2.3	32.6 ± 2.8	< 0.001
Missing data	7 (6.7)	14 (20.3)	
Preterm birth			
< 28 weeks	2 (1.9)	4 (5.8)	0.1690
< 32 weeks	4 (3.8)	20 (29.0)	< 0.001
< 34 weeks	16 (15.2)	32 (46.4)	< 0.001
Missing data	7 (6.7)	13 (18.8)	
Mode of delivery			< 0.001
Vaginal*	46 (21.9)	9 (7.7)	
Emergency Cesarean*	46 (21.9)	44 (37.6)	
Elective Cesarean*	98 (46.7)	30 (25.6)	
Missing data*	20 (9.5)	34 (29.1)	
Birth weight (g)	2342.2 ± 439.8	1742.9 ± 672.8	< 0.001
Missing data*	20 (9.5)	27 (23.1)	
Birth weight < 5th centile*	3 (1.4)	15 (12.8)	< 0.001
Missing data*	20 (9.5)	27 (23.1)	
Female gender*	93 (44.3)	45 (38.5)	0.087
Missing data*	17 (8.1)	43 (36.8)	
NICU admission*	32 (15.2)	57 (48.7)	< 0.001
Missing data*	14 (6.7)	19 (16.2)	
Neonatal morbidity*†	28 (13.3)	57 (48.7)	< 0.001
Missing data*	14 (6.7)	19 (16.2)	
Age of child at ASQ-3 (months)	35.4 ± 14.0	29.1 ± 11.2	< 0.001

Data are given as mean ± SD or *n* (%). *Denominator is number of children. †Neonatal morbidity includes any of: respiratory distress syndrome, need for resuscitation, jaundice requiring phototherapy or exchange transfusion, intraventricular hemorrhage, sepsis, necrotizing enterocolitis and persistent ductus arteriosus requiring intervention. ASQ-3, Ages and Stages Questionnaire version 3; DCDA, dichorionic diamniotic; GA, gestational age; MCDA, monochorionic diamniotic; NE, not estimable; NICU, neonatal intensive care unit.

MCDA twin pregnancies that underwent prenatal intervention (fetoscopic laser photocoagulation, bipolar cord coagulation or intrafetal laser) had a significantly higher rate of abnormal ASQ-3 score compared with those that did not undergo prenatal intervention (16/57 (28.1%) *vs* 1/60 (1.7%); $P < 0.001$). Similarly, complicated MCDA twin pregnancies that had two or more coexisting pathologies had a significantly higher rate of abnormal ASQ-3 score compared to those affected by a single pathology (9/28 (32.1%) *vs* 8/89 (9.0%); $P = 0.003$).

On univariable analysis, complicated MCDA twin pregnancy was associated with double the odds (OR, 2.06 (95% CI, 1.00–4.29); $P = 0.050$) of having an abnormal ASQ-3 score (Table 4). Multivariable mixed-effects regression analysis demonstrated that a complicated MCDA twin pregnancy (adjusted OR (aOR), 3.28 (95% CI, 3.27–3.29); $P < 0.001$) and higher maternal BMI (aOR, 1.08 (95% CI, 1.08–1.09); $P < 0.001$) were associated significantly with an increased chance of an abnormal ASQ-3 score, while emergency Cesarean birth (aOR, 0.29 (95% CI, 0.29–0.29); $P < 0.001$), elective Cesarean birth (aOR, 0.15 (95% CI, 0.02–0.78); $P = 0.022$) and higher GA at birth (aOR, 0.78 (95% CI, 0.77–0.78); $P < 0.001$) were associated significantly with a lower chance of an abnormal ASQ-3 score (Table 4). Propensity-score matching produced balanced, well matched groups (Table S3). This association between complicated MCDA twin pregnancy and abnormal ASQ-3 score was even more pronounced following propensity-score matching, as infants born of complicated MCDA pregnancies were almost four times as likely to have an abnormal ASQ-3 score than were those without complication (matched OR, 3.95 (95% CI, 1.13–13.72); $P = 0.031$) (Table 5).

Table 3 Frequency of abnormal scores attained on Ages and Stages Questionnaire version 3 (ASQ-3) by infants from complicated monochorionic diamniotic twin pregnancies, according to donor/recipient status, discordant fetal size, prenatal intervention and coexisting pathology

Clinical feature	n	*Abnormal ASQ-3*	P
TTTS			0.171
Donor	33	9 (27.3)	
Recipient	36	5 (13.9)	
sFGR			0.840
Smaller twin	28	4 (14.3)	
Larger twin	32	4 (12.5)	
Prenatal intervention*			< 0.001
Yes	57	16 (28.1)	
No	60	1 (1.7)	
Number of pathologies			0.003
Multiple	28	9 (32.1)	
Single	89	8 (9.0)	

Data are given as *n* or *n* (%). Abnormal ASQ-3 score was defined as score of more than 2 SD below mean in any one of five domains. *Fetoscopic laser photocoagulation, bipolar cord coagulation or intrafetal laser. sFGR, selective fetal growth restriction; TTTS, twin–twin transfusion syndrome.

DISCUSSION

Summary of key findings

In our cohort, the survivors of a complicated MCDA twin pregnancy had nearly four-fold higher odds of overall adverse neurodevelopmental outcome compared with uncomplicated twins. Among complicated MCDA twins, the incidence of adverse neurodevelopmental outcome was significantly higher in survivors following a prenatal intervention or if there were two or more coexisting pathologies. Of note, 14.5% of complicated twin pregnancies and 7.6% of uncomplicated twin pregnancies had an abnormal ASQ-3 score in one or more domains.

Interpretation of findings and comparison with the literature

One unique aspect of our study, compared with the existing literature, is the comparison of the neurodevelopmental outcome of survivors of complicated MCDA twin pregnancies with that of a group of uncomplicated twin pregnancies. We did not find a significant difference

Table 4 Multilevel model of factors associated with abnormal Ages and Stages Questionnaire version 3 (ASQ-3) score in twin pregnancy

Variable	*OR (95% CI)*	P	*aOR (95% CI)**	P
Study group				
Control	1.00 (ref)	—	1.00 (ref)	—
Case	2.06 (1.00–4.29)	0.050	3.28 (3.27–3.29)	< 0.001
Maternal BMI†	1.03 (0.97–1.09)	0.273	1.08 (1.08–1.09)	< 0.001
Mode of delivery				
Vaginal	1.00 (ref)	—	1.00 (ref)	—
Emergency CS	0.56 (0.22–1.47)	0.235	0.29 (0.29–0.29)	< 0.001
Elective CS	0.22 (0.07–0.63)	0.006	0.15 (0.02–0.78)	0.022
GA at birth‡	0.86 (0.77–0.98)	0.017	0.78 (0.77–0.78)	< 0.001
Fetal gender				
Female	1.00 (ref)	—	1.00 (ref)	—
Male	1.28 (0.57–2.92)	0.553	1.17 (0.68–2.42)	0.472

Number in model, 258; number of groups, 136; Akaike information criterion, 140.7; C-statistic, 0.991. Abnormal ASQ-3 score was defined as score of more than 2 SD below mean in any one of five domains. *Adjusted for combination of maternal body mass index (BMI), mode of delivery, gestational age (GA) at birth and fetal gender, as appropriate. †Per 1-kg/m^2 increase. ‡Per 1-week increase. aOR, adjusted odds ratio; CS, Cesarean section; OR, odds ratio; ref, reference.

Table 5 Logistic regression model of factors associated with abnormal Ages and Stages Questionnaire version 3 (ASQ-3) score in twin pregnancy after propensity-score matching

Variable	*Normal ASQ-3*	*Abnormal ASQ-3*	*Univariable OR (95% CI)*	P	*Matched OR (95% CI)*	P
Study group						
Control	171 (92.4)	14 (7.6)	1.00 (ref)	—	1.00 (ref)	—
Case	61 (83.6)	12 (16.4)	2.40 (1.04–5.49)	0.037	3.95 (1.13–13.72)	0.031
Parity						
Nulliparous	123 (91.8)	11 (8.2)	1.00 (ref)	—	1.00 (ref)	—
Parous	109 (87.9)	15 (12.1)	1.54 (0.68–3.57)	0.303	0.61 (0.12–3.03)	0.550
Maternal BMI*	26.7 ± 5.9	28.0 ± 5.8	1.04 (0.97–1.10)	0.270	1.27 (1.03–1.57)	0.027
GA at birth†	35.2 ± 2.6	33.7 ± 3.5	0.84 (0.74–0.96)	0.008	0.77 (0.50–1.18)	0.236
Fetal gender						
Female	121 (91.0)	12 (9.0)	1.00 (ref)	—	1.00 (ref)	—
Male	111 (88.8)	14 (11.2)	1.27 (0.56–2.91)	0.562	4.41 (0.70–27.85)	0.114

Data are given as *n* (%), where denominator is row total, or mean ± SD, unless stated otherwise. *Per 1-kg/m^2 increase. †Per 1-week increase. BMI, body mass index; GA, gestational age; OR, odds ratio; ref, reference.

in the prevalence of an abnormal ASQ-3 score between the uncomplicated DCDA and MCDA twin pregnancies in our study (9/136 (6.6%) *vs* 7/74 (9.5%); $P = 0.460$). Therefore, we decided to include both DCDA and MCDA twin pregnancies in a single comparison group. A further subgroup analysis in which DCDA and MCDA twin pregnancies were considered separately was unlikely to be productive, owing to the few occurrences of the primary outcome in these pregnancies.

In our cohort, we demonstrated that survivors of complicated MCDA twin pregnancies have higher rates of adverse neurodevelopmental outcome compared with their counterparts from a mixed cohort of uncomplicated DCDA/MCDA twin pregnancies. It is imperative that any data on neurodevelopmental outcome are examined in light of the higher background rates of adverse neurodevelopmental outcome reported for twins compared with singletons in large population-based studies[24]. There is substantial evidence in the literature that, once controlled for potential covariates and monochorionicity-specific complications, the long-term neurodevelopmental outcome for DCDA and MCDA twins are unlikely to differ. Tosello *et al.*[25] reported similar rates of neurodevelopmental impairment in preterm twins irrespective of their chorionicity. Similarly, in their comparison of MCDA and DCDA twins (matched by weight and age at delivery, gender, ethnicity of the mother and study center), Hack *et al.*[26] found no difference in the rate of cerebral palsy and neurodevelopmental adverse outcome. More recently, a systematic review and meta-analysis by Yan *et al.*[27] demonstrated that monochorionic twins and dichorionic twins did not differ significantly in the rate of neurodevelopment impairment (OR, 1.21 (95% CI, 0.95–1.54); $I^2 = 0\%$) or cerebral palsy (OR, 1.12 (95% CI, 0.80–1.57); $I^2 = 62\%$) when monochorionic twins with TTTS were excluded. The rate of an abnormal ASQ-3 score for complicated MCDA twins in our study was 14.5%, and that for uncomplicated twins was 7.6%.

The overall prevalence of an abnormal ASQ-3 score in survivors of TTTS, irrespective of Quintero stage and prenatal intervention, was 20.3% in our study, which is higher than that in other cohorts reported by Gray *et al.*[28] (14/113 (12.4%)) and Lopriore *et al.*[29] (50/278 (18.0%)). In a recent meta-analysis to study the prenatal risk factors associated with neurodevelopmental impairment in TTTS survivors following fetoscopic laser surgery, Hessami *et al.*[30] reported an overall incidence of 14.0% (95% CI, 9.0–18.0%) (nine studies; 1499 TTTS survivors). It is difficult to compare results between studies as different assessment tools and definitions of neurodevelopmental impairment were employed. There was also significant heterogeneity between studies in the populations analyzed, namely, cases of sIUD *vs* double survivors. Unsurprisingly, the rates of adverse neurodevelopmental outcome are higher in studies in which single survivors were included. Sananès *et al.*[31] reported a rate of abnormal ASQ-3 score of 13.5% in their cohort of 126 survivors of TTTS following fetoscopic laser photocoagulation of the placental communicating blood vessels.

In the TTTS group, we found a higher rate of abnormal ASQ-3 scores in the donors compared with the recipients (27.3% *vs* 13.9%); although this difference did not reach statistical significance, owing to the small sample size, we believe that this finding is clinically significant and warrants mention. Whilst some early cohort studies[32,33] report differences in the rates of neurodevelopmental impairment according to donor/recipient status, the recent meta-analysis by Hessami *et al.*[30] did not find any significant association between donor/recipient status, Quintero staging and associated growth restriction/demise.

Our second largest subgroup of complicated MCDA twin pregnancies was those with sFGR, in which 13.3% of survivors had an abnormal ASQ-3 score, but the distribution of abnormal ASQ-3 scores amongst the smaller and larger twins was similar (14.3% *vs* 12.5%; $P = 0.840$). In their systematic review, Groene *et al.*[34] acknowledged the paucity of evidence regarding the long-term neurodevelopmental outcome for MCDA twins with sFGR. Of note, they could find only five relevant articles[35–39], with heterogeneous case definitions and variable assessment tools and outcome measures. In their recent report of 47 twin pairs (LEMON cohort), Groene *et al.*[40] reported an increased prevalence of mild

neurodevelopmental impairment in the growth-restricted twin compared to the larger twin (36% *vs* 11%; OR, 4.8 (95% CI, 1.6–14.1); $P = 0.005$), but similar rates of severe neurodevelopmental impairment.

The higher rates of abnormal ASQ-3 score in the subgroups of complicated MCDA twins with more than one pathology (for example, coexistence of TTTS with sFGR, TAPS or sIUD, or any of these combinations) or that underwent prenatal intervention is likely to be a marker of the severity of the disease. Expectant management is the norm in the early stages, regardless of the phenotype, and intervention is offered only when there are signs of progression indicative of risk of demise or disability. In our cohort, one in five survivors of the demise of a cotwin had an abnormal ASQ-3 score. In their meta-analysis of cotwin prognosis following sIUD, Hillman *et al.*[9] reported a 26% rate of neurodevelopmental impairment for surviving cotwins in MCDA pregnancies. We could not derive any meaningful conclusions for adverse neurodevelopmental outcome for the TRAP sequence and TAPS subgroups in our cohort owing to the small numbers affected.

Clinical and research implications

Early identification of neurodevelopmental impairment and stratification of risk enable effective surveillance and early intervention, as well as accurate prenatal counseling of parents. Older studies quote higher rates of neurodevelopmental impairment, and it is important to generate new evidence from more recent cohorts to ascertain if advances in the management of these complicated pregnancies have translated into better long-term outcomes. The ASQ-3 assessment also offers parents an opportunity to voice their concerns about any area of their child's neurodevelopment. Further research should use uniform and strict case definitions, such that results can be applied pragmatically and compared. There is still a lack of evidence regarding neurodevelopmental outcome stratified by time of onset (early *vs* late) for TTTS and sFGR, by management strategy (Solomon *vs* selective technique for fetoscopic laser) and by umbilical artery waveform patterns for sFGR, and for rarer complications like TAPS and TRAP sequence. Studies on the correlation of abnormal prenatal brain imaging with postnatal neurodevelopmental outcome are also warranted, particularly in cases with subtle/equivocal findings.

Strengths and limitations

The primary strengths of our study include the enrolment of a comparator cohort of uncomplicated twin pregnancies and the prospective collection of neurodevelopmental outcome data. We uniformly employed the ASQ-3 questionnaire, which is a simple, validated, parent-completed tool.

There are a few limitations to our study. Firstly, the sample size was inadequate for subgroup analysis for rare pathologies, such as TAPS, TRAP sequence and sIUD. Secondly, we cannot rule out selection bias, as the study center is a tertiary referral unit for complex multiple pregnancy; however, it can be argued that this enabled us to compare our findings with those of previous studies whose populations were also derived mostly from specialist units. As participation in the study was voluntary, there is a possibility of non-response bias. Women with an uncomplicated twin pregnancy were more likely to not respond compared with women with a complicated MCDA pregnancy (147/162 (90.7%) *vs* 15/162 (9.3%)). The overall non-response rate of 41.5% is consistent with that of other studies that employed parent-administered ASQ-3 scores[30]. As ASQ-3 questionnaires are parent-administered, the bias introduced by either under- or overestimating a child's capabilities based on parental expectations and perceptions cannot be ruled out completely. Lastly, we did not analyze the effect of a child's environment, especially parental education and socioeconomic status, on their neurodevelopmental outcome, which could be a source of residual confounding.

Conclusions

In this contemporary cohort, we found that survivors of complicated MCDA twin pregnancies had a higher rate of adverse long-term neurodevelopmental outcome compared with uncomplicated twin pregnancies. Our findings reinforce the importance of long-term neurodevelopmental follow-up of these children to ensure that therapy can be initiated for those affected in a timely manner.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Distribution of Ages and Stages Questionnaire® version 3 (ASQ-3) tests in study population

Table S2 Frequency of abnormal scores attained on Ages and Stages Questionnaire® version 3 (ASQ-3) by infants from complicated monochorionic diamniotic twin pregnancies, according to type of complication (not mutually exclusive)

Table S3 Balance table for characteristics of patients before and after propensity-score matching