Prasad Smriti (Orcid ID: 0000-0003-2329-4470)
Khalil Asma (Orcid ID: 0000-0003-2802-7670)

Neurodevelopmental Outcomes in Complicated Twin Pregnancies: Prospective Observational Study

S. Prasad[1], S. Beg[1], D. Badran[2], L. Masciullo[3], C. Huddy[4] and A. Khalil[1,5,6]

[1]Fetal Medicine Unit, St George's University Hospital, London, UK

[2]NHS Greater Glasgow and Clyde, Glasgow, UK.

[3]Department of obstetrics and Gynecology, Cristo Re Hospital, Via delle Calasanziane 25 00167 Rome

[4]Department of Neonatology, St George's University Hospital, London, UK

[5]Twins and Multiples Centre for Research and Clinical Excellence, London, UK

[6]Fetal Medicine Unit, Liverpool Women's Hospital, University of Liverpool, Liverpool, UK

CORRESPONDING AUTHOR:

Professor Asma Khalil, MBBCh MD FRCOG

Department of Obstetrics and Gynaecology, St. George's University Hospital, University of London, London, England, UK, SW17 0QT

Email: akhalil@sgul.ac.uk

RUNNING HEAD: Neurodevelopmental outcome in complicated twins

KEYWORDS: twin pregnancies, multiple, neurodevelopmental outcome, motor, monochorionic, twin to twin transfusion syndrome, selective fetal growth restriction, fetal intervention,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.27448

CONTRIBUTION

What are the novel findings of this work?

In this contemporary cohort, we report on long-term neurodevelopmental outcomes of survivors of complicated MCDA twin pregnancies compared to uncomplicated twins. Our study provides evidence that survivors of complicated MCDA twin pregnancies have a high rate of adverse neurodevelopmental outcomes compared to uncomplicated twin pregnancies.

What are the clinical implications of this work?

Complicated monochorionic twin pregnancies, especially those who had fetal intervention procedures or coexistent pathologies, are at higher risk of adverse neurodevelopmental outcomes. Our findings reiterate the importance of long-term neurodevelopment follow-up of these children to ensure timely optimal therapy can be initiated for those affected.

ABSTRACT

Objective: Twin pregnancies are associated with increased perinatal mortality and morbidity, but long-term neurodevelopmental outcomes remain under-investigated. The primary objective was to investigate the incidence of adverse neurodevelopment after one 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. Women with twin pregnancies culminating in at least one child surviving to at least 12 months up to 60 months (corrected for prematurity) at the time of assessment, were invited to complete the relevant Ages and Stages Questionnaires® test version 3 (ASQ-3). The two study groups were (1) complicated MCDA twin pregnancies and uncomplicated twin pregnancies (dichorionic and MCDA). Complicated twin pregnancies included those with twin-to-twin transfusion syndrome (TTTS), Twin Anaemia Polycythaemia Sequence (TAPS), selective Fetal Growth Restriction (sFGR), Twin Reversed Arterial Perfusion (TRAP) and single intrauterine demise (sIUD). The primary outcome measure was an abnormal ASQ-3 score, defined as a score of 2 standard deviations below the mean, for any one domain. Mixed-effects multivariable logistic regression was performed to determine whether a complicated MCDA twin pregnancy was independently associated with an abnormal ASQ-3 score. All analyses were performed using R v4.0 (R Foundation for Statistical Computing, Vienna, Austria)

Results: The study included 174 parents who completed the questionnaires, and therefore, 327 ASQ-3 questionnaires were available for analysis. Of those, 117/327 (35.8%) were classified as cases and 210/327 (64.2%) as controls. The overall incidence of an abnormal ASQ-3 score in children with complicated MCDA twin pregnancies was nearly double that in uncomplicated MCDA/DCDA twin pregnancies (14.5% versus 7.6%, p=0.056). Children born

of complicated MCDA twin pregnancies showed significantly higher gross motor domain impairment rates than the control group (8.5% versus 2.9%, p=0.022). Complicated MCDA twin pregnancies that underwent prenatal intervention had significantly higher rates of abnormal ASQ-3 scores compared to those that did not have any prenatal intervention (28.1% versus 1.7%, p=0.0001). On multilevel logistic regression analysis, complicated MCDA twin pregnancy was an independent predictor of abnormal ASQ-3 score in one or more domains (OR: 3.28 (95% CI: 3.27-3.29; p<0.001).

Conclusion: This study provides evidence that survivors of complicated MCDA twin pregnancies have a higher rate of adverse neurodevelopmental outcomes, independent of prematurity. Long-term neurodevelopmental follow-up in these pregnancies can ensure optimal timely management of those affected.

INTRODUCTION

Monochorionic twin pregnancies are associated with chorionicity specific complications including twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) and single fetal 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 the last few decades, there has been a paradigm shift in the immediate survival and short-term outcomes of these babies, attributable to both a clearer understanding of the pathophysiological processes and advances in fetal therapy and neonatal care.[5] However, there is a need to better elucidate the long-term neurodevelopmental outcomes as disability-free survival is the 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 to understand the long-term neurodevelopmental implications of these complications and 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 undergoing laser coagulation, 14% following serial amnio-reduction and 21% following expectant management.[10] Both donors and recipients are at risk of developing either ischaemic or haemorrhagic lesions. In a systematic review investigating the prognosis of the monochorionic co-twin following sIUD, the rate of abnormal postnatal cranial imaging was 34% compared with 16% for uncomplicated pregnancy, whilst the equivalent rates for neurodevelopmental impairment were 26% and 2%. Following sIUD the surviving monochorionic twin is 3 and 5 times more likely to have brain abnormalities and neurodevelopmental morbidity, respectively.[9] Furthermore, the incidence of severe cerebral injury in monochorionic twins complicated by sFGR is approximately 10% and

is associated with abnormal umbilical artery Doppler, larger twin, sIUD and lower gestational age (GA) at birth.[8] Lastly, it has been reported that 1 in 5 twin pregnancies complicated by TAPS are associated with adverse neurological outcome.[11,12]

However, most studies reporting long-term neurological outcomes 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 abnormalities reported on antenatal or neonatal brain imaging will result in significant neurodevelopmental delay and what other antenatal and neonatal parameters have an impact on long-term neurodevelopment after complicated twin pregnancies. The prevalence of neurodevelopmental delay in uncomplicated monochorionic and dichorionic twin pregnancies, and risk factors for long-term neurodevelopmental adverse outcomes in complicated twin pregnancies are yet to be established. We aimed to prospectively investigate the incidence of adverse neurodevelopment after one year of age in complicated monochorionic diamniotic (MCDA) twin pregnancies compared to 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 at St George's University Hospital NHS Foundation Trust, London between 2015-2021. St George's Hospital is the regional tertiary referral unit for complex multiple pregnancies for the South-west Thames region of the United Kingdom. We included children from 12 months up to 60 months of age (corrected for prematurity) at the time of assessment. The study population was divided into two groups: Cases - MCDA twin pregnancies complicated by TTTS, sFGR, TAPS, TRAP or sIUD, and Controls – uncomplicated DCDA and MCDA twin pregnancies. DCDA twin pregnancies complicated by sFGR or sIUD were excluded. Pregnancies with major fetal anomalies, congenital infections or genetic abnormalities 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 pregnancies where 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 Questionnaires® (ASQ) test - version 3 (ASQ-3). They were offered the choice of completing the form themselves and returning it by post or secure email, 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.[14,15,16] The assessment and compilation of responses were performed by a

researcher who was blinded to whether this pregnancy was complicated, to avoid potential investigator bias. The child's age corrected for prematurity 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 was considered abnormal.[17] The ASQ is a screening test, not a diagnostic test, and this difference was made clear to the participants and re-iterated if an abnormal result was returned. This study was approved by the Research Ethics Committee, London – Camden and Kings Cross Heath 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 5.6.8.428, ViewPoint Bildverarbeitung GmbH, Weßling, Germany software). Perinatal outcomes including fetal loss, mode of delivery, gestational age (GA) at birth, preterm birth (PTB) prior to 28, 32 and 34 weeks' gestation, birthweight, neonatal intensive care unit (NICU) admission and measures of neonatal morbidity (respiratory distress syndrome (RDS), need for resuscitation, jaundice requiring phototherapy or exchange transfusion, intraventricular hemorrhage (IVH), sepsis, necrotizing enterocolitis (NEC), persistent ductus arteriosus (PDA) requiring intervention) were obtained from the electronic maternity information systems and the neonatal electronic database (Badgernet). Estimates of birthweight <5th centile were derived from twin chorionicity-specific population birthweight charts.[18] Where available, long-term neonatal outcomes including chronic lung disease, pulmonary hypertension and bronchopulmonary dysplasia were also recorded.

Chorionicity was determined at the first trimester ultrasound. The disease pathologies TTTS, sFGR, TRAP 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 less than 20

weeks', or greater than 10 cm if more than 20 weeks' gestation) in the recipient twin.[19] The severity of TTTS was graded using Quintero's classification. 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 (laser photocoagulation/selective feticide/ intrafetal laser/ amnio drainage/ delivery) or expectant management was offered depending on individual cases as per unit protocol. Fetal brain MRI was offered in all monochorionic twin pregnancies that had an abnormal prenatal ultrasound or active fetal intervention as per the hospital protocol.

The primary outcome measure was an abnormal ASQ-3 score, defined as a score of 2 standard deviations below the mean, for 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, and the numbers of pregnancies affected by these complications were likely to be small. The plan was to recruit 90 women whose MCDA pregnancies were complicated and 180 women who had uncomplicated twin pregnancies as controls, to give a ratio of 1:2, and to allow for matching for the child's age and GA at birth.

Statistical analysis

Descriptive data were presented as the mean and standard deviation for continuous variables, and as numbers and percentages for categorical variables. Comparisons for normally distributed continuous variables were made using Student's t-tests, and for categorical variables using $\chi 2$-tests and Fisher exact-tests. Mixed-effects multivariable logistic regression was performed to determine whether a complicated twin pregnancy was associated

independently with abnormal ASQ-3. Clinically plausible risk factors were incorporated into the modelling approach as fixed effects, and the pregnancy was used as a random effect. Patients who had incomplete data for explanatory variables were excluded from the analysis. Final model selection was performed through minimization of the Akaike information criterion and maximisation of C-statistic.

Propensity score matching was used to investigate the association between complicated twin pregnancies and abnormal ASQ-3, to 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 groups was assessed before and after using the absolute standardized mean difference, and a value below 0.2 was considered to indicate that a variable was well-balanced between 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 were presented as odds ratios (ORs) with 95% confidence intervals. Statistical significance was set *a priori* as $P < 0.05$. All analyses were performed using R v4.0 (R Foundation for Statistical Computing, Vienna, Austria) with the tidyverse, finalfit, and finalpsm packages.

RESULTS

Study population

The study included 174 parents who completed the questionnaires, and therefore, 327 ASQ-3 questionnaires were available for analysis (Figure 1 and 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 (n=3).

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

Primary outcome

The overall prevalence of an abnormal ASQ-3 score (defined as score < 2 SD below the mean in any one of five domains) in cases was almost double that in controls (14.5%; 17/117 versus

7.6%;16/210, p=0.056) (Table 2). Children born of a complicated MCDA twin pregnancy also had significantly higher rates of impairment of the gross motor domain compared to the control group (8.5%; 10/117 versus 2.9%; 6/210, p=0.031). No significant differences between the two study groups were noted for other individual domains of the ASQ-3 questionnaire, including communication, fine motor, problem-solving and personal social skills.

The prevalence of an abnormal ASQ-3 score for the subcategories of complicated MCDA twin pregnancies 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 prevalence was 13.6% (8/59) in children born of pregnancies complicated by sFGR. One third 32.1% (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 incidence 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 to the recipient twin (27.3%; 9/33 versus 13.9%; 5/36, p=0.17), although the difference did not reach statistical significance. In our cohort of cases, the monochorionic twin pairs affected by sFGR demonstrated a similar distribution of an abnormal ASQ-3 score among the larger and smaller twins (14.3% in the smaller vs 12.5% in the larger twin, p=0.840). Complicated MCDA twin pregnancies that underwent prenatal intervention (fetoscopic laser, bipolar cord coagulation, intrafetal laser) had significantly higher rates of abnormal ASQ-3 score compared to those that did not have any prenatal intervention (28.1%; 16/57 versus 1.7%; 1/60, p<0.001).

On univariable analysis, complicated MCDA twin pregnancies were associated with double the odds (OR 2.06 (95% CI 1.00-4.29), p=0.05) of having an abnormal ASQ-3 in one or more domains (Table 4). Multivariable mixed effects regression analysis demonstrated that a complicated MCDA twin pregnancy (adjusted OR 3.28; 95%CI 3.27-3.29, p<0.001) and maternal BMI (adjusted OR 1.08; 95% CI 1.08-1.09, p<0.001) were significantly associated with an increased chance of abnormal ASQ-3 in one or more domains, while emergency Caesarean birth (adjusted OR 0.29; 95% CI 0.29-0.29, p<0.001), elective Caesarean birth

(adjusted OR 0.15; 95% CI 0.02-0.78, p=0.022), and higher GA at birth (adjusted OR 0.78; 95% CI 0.77-0.78, p<0.001) were significantly associated with a lower chance of abnormal ASQ-3 (Table 4). Propensity score matching produced balanced, well-matched groups (Table S3). This association between complicated MCDA twin pregnancy and abnormal ASQ-3 was even more pronounced following propensity score matching as babies of pregnancies with complicated MCDA were almost four times as likely to have an abnormal ASQ-3 than those without complication (matched OR 3.95; 95%CI: 1.13-13.72, p=0.031) (Table 5).

DISCUSSION

Summary of the key findings

In our cohort, the survivors of complicated MCDA twin pregnancies had nearly four-fold higher overall adverse neurodevelopment outcome compared to the uncomplicated twins. Amongst complicated MCDA twins, the incidence of adverse neurodevelopment outcome was significantly higher in survivors following a prenatal intervention or if there were two co-existent pathologies. Of note, 7.6% of uncomplicated twin pregnancies had abnormal ASQ-3 in one or more domains.

Strengths and limitations

The primary strength of our study is the presence of a comparator cohort of uncomplicated twin pregnancies and that neurodevelopmental outcomes were collected prospectively. We have uniformly employed ASQ-3 questionnaires in our study which is a simple, validated parent-completed tool.

There are few limitations to our study. Firstly, the sample size was inadequate for subgroup analysis for rare pathologies like TAPS, TRAP, and single demise. Secondly, we cannot rule out selection bias as the study centre is a tertiary referral unit for complex multiple pregnancies; however, it can be argued that this enabled us to compare our results with previous studies whose populations were also mostly derived from specialist units. As participation in the study was voluntary, there is a possibility of non-response bias. Women with uncomplicated twin pregnancies were more likely to non-response compared to women with complicated MC pregnancies (147/162; 90.7% versus 15/162; 9.2%). The overall non-response rate of 41.5% is like other studies which employed parent administered ASQ-3 scores.[30]

As ASQ-3 questionnaires are parent-administered, the bias introduced by either under- or over-estimating a child's capabilities based on parental expectations and perceptions cannot be completely ruled out. Lastly, in our study, we have not analysed the effect of a child's

environment, especially parental education, and socioeconomic status on their neurodevelopmental outcomes, which are potential residual confounding factors.

Interpretation of study findings and comparison with published literature

One unique aspect of our study, compared to the existing literature, is the fact that we compared the neurodevelopmental outcomes of survivors of complicated MCDA twin pregnancies to those in a group of uncomplicated twin pregnancies. We did not find a significant difference in prevalence of an abnormal ASQ-2 score between the uncomplicated DCDA and MCDA twin pregnancies (9/136, 6.62% versus 7/74, 9.46%; p =0.460) in our study. Therefore, we decided to include both DCDA and MCDA twin pregnancies as a single comparison group. A further subgroup analysis is unlikely to be productive owing to the smaller number of the primary outcomes in the uncomplicated DCDA and MCDA, if they were to be considered separately.

In our cohort, we have demonstrated that survivors of complicated MCDA twin pregnancies have higher rates of adverse neurodevelopmental outcomes compared to their counterparts from a mixed cohort of uncomplicated DCDA/MCDA twin pregnancies. It is imperative that any data on neurodevelopmental outcomes are examined in the light of the higher background rates of adverse neurodevelopmental outcomes reported for twins compared to singletons in large population-based studies.[24] There is substantial evidence from the existing literature that once controlled for potential covariates and monochorionity-specific complications, the long-term neurodevelopment outcome for DCDA and MCDA twins are unlikely to be different. Tosello et al reported similar rates of neurodevelopmental impairment in preterm twins irrespective of their chorionicity.[25] Similarly, in their comparison of MCDA twins and matched DCDA twins (weight and age at delivery, gender, ethnicity of the mother and study centre), Hack et al did not find differences in the rate of cerebral palsy and neurodevelopmental adverse outcomes.[26] More recently, a systematic review and meta-analysis by Yan et al

demonstrates that MC twins and DC twins did not significantly differ in neurodevelopment impairment (OR, 1.21; 95% CI, 0.95–1.54, I^2 = 0%) and cerebral palsy (OR, 1.12; 95%CI, 0.80–1.57, I^2 = 62%) when MC twins with TTTS were exculded.[27] The overall rate of an abnormal ASQ-3 score for the complicated MCDA twins was 14.5% in our study. Around 7% of the uncomplicated twins in our cohort had an abnormal ASQ-3 score.

The overall prevalence of an abnormal ASQ-3 score in survivors of TTTS, irrespective of Quintero stage and prenatal intervention, was 20.6% in our study, which is higher than in other cohorts reported by Gray[28] et al (14/113, 12.4%) and Lopriore[29] et al (50/278, 18%). In a recent meta-analysis to study the prenatal risk factors associated with neurodevelopmental impairment in TTTS survivors following fetoscopic laser surgery, Hessami[30] et al reported an overall incidence of 14.0% (95% CI, 9.0-18.0%, 9 studies, 1499 TTTS survivors). It is difficult to compare results from different studies as different assessment tools and definitions of neurodevelopmental impairment have been employed. Among studies, there is a heterogeneity in the populations analysed, namely, single fetal demise cases versus double survivors; unsurprisingly, the rates of adverse neurodevelopmental outcomes are greater in studies where single survivors have been included. Sananes[31] et al used the ASQ-3 tool and reported an abnormal ASQ-3 score rate 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 to the recipients (27.3% vs 13.9%) although the difference did not reach statistical significance owing to small sample size, but we believe this finding is clinically significant and warrants mention. Although the early cohort studies report differences in the rates of neurodevelopmental impairment according to donor/recipient status, the recent meta-analysis by Hessami[30] et al did not find any significant association between donor/recipient status, Quintero staging, and associated growth restriction/demise.

Our second largest subgroup was MCDA twin pregnancies with sFGR, in whom 13.6% 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 % versus 12.5%, p=0.840). Groene[32] et al, in their systematic review, acknowledged the paucity of evidence regarding the long-term neurodevelopmental outcomes for MCDA twins with sFGR. Of note, they could find only five relevant articles[33-37], with heterogenous case definitions, and variable assessment tools and outcome measures. In their recent report of 47 twin pairs (LEMON cohort)[38], Groene et al reported an increased prevalence of mild neurodevelopmental impairment among the growth-restricted twin compared to the larger twin (36% versus 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 scores among the subgroups of complicated MCDA twins with more than one pathology (e.g., coexistence of TTTS with sFGR/TAPS/sIUD or any of these combinations) or who 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 handicap. In our cohort, 1 out of 5 survivors of a co-twin demise had an abnormal ASQ-3 score. Hillman[9] et al in their meta-analysis of co-twin prognosis following sIUD reported a 26% rate of neurodevelopmental impairment for MCDA surviving co-twins. We could not derive any meaningful conclusions for adverse neurodevelopmental outcomes for the TRAP and TAPS subgroups in our cohort due to the small numbers.

Clinical and research implications

Early identification of neurodevelopmental impairment and stratification of the risk enable effective surveillance and early intervention, as well as accurate prenatal counselling of parents. Older studies quote higher rates of neurodevelopmental impairment, and it is important to generate new evidence from more recent cohorts to assess 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 the child's neurodevelopment. Further research should use uniform and strict case definitions such that results can be pragmatically applied and compared. There is still a large gap in evidence regarding the neurodevelopmental outcomes stratified according to the time of onset (early versus late) for both TTTS and sFGR, management strategy (Solomon versus selective technique for fetoscopic laser), classification of sFGR according to umbilical artery waveform patterns, and for rarer outcomes like TAPS and TRAP. Studies on the correlation of abnormal prenatal brain imaging with postnatal neurodevelopmental outcomes are also warranted, particularly in cases with subtle/equivocal findings.

Conclusions

In this contemporary cohort, we report on long-term neurodevelopmental outcomes of survivors of complicated MCDA twin pregnancies compared to uncomplicated twins. Our study provides evidence that survivors of complicated MCDA twin pregnancies have a high rate of adverse neurodevelopmental outcomes compared to uncomplicated twin pregnancies. Our findings reiterate the importance of long-term neurodevelopment follow-up of these children to ensure timely optimal therapy can be initiated for those affected.

ACKNOWLEDGEMENT

This study was funded by a grant from the Twins Trust charity and British Maternal Fetal Medicine Society.

REFERENCES

1. Sebire NJ, Snijders RJ, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynaecol. 1997 Oct;104(10):1203–7.

2. Joseph KS, Demissie K, Platt RW, Ananth C V., McCarthy BJ, Kramer MS. A parsimonious explanation for intersecting perinatal mortality curves: Understanding the effects of race and of maternal smoking. BMC Pregnancy Childbirth. 2004;4(July 2003).

3. Hack KEA, Derks JB, Elias SG, Franx A, Roos EJ, Voerman SK, Bode CL, Koopman-Esseboom C, Visser GHA. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. Br J Obstet Gynaecol. 2008;115(1):58-67

4. Southwest Thames Obstetric Research Collaborative (STORK) ST. Prospective risk of late stillbirth in monochorionic twins: a regional cohort study. Ultrasound Obstet Gynecol. 2012 May;39(5):500–4.

5. Spruijt MS, Lopriore E, J Steggerda S, Slaghekke F, Van Klink JMM. Twin-twin transfusion syndrome in the era of fetoscopic laser surgery: antenatal management, neonatal outcome and beyond. Expert Rev Hematol. 2020;13(3):259-267.

6. Khalil A, Townsend R, Reed K, Lopriore E. Call to action: long-term neurodevelopment in monochorionic twins. Ultrasound Obstet Gynecol. 2021;58(1):5–10.

7. Hoffman M, Habli M, Donepudi R, Boring N, Johnson A, Moise KJ, Papanna R. Perinatal outcomes of single fetal survivor after fetal intervention for complicated monochorionic twins. Prenat Diagn. 2018;38(7):511-516.

8. Inklaar MJ, van Klink JMM, Stolk TT, van Zwet EW, Oepkes D, Lopriore E. Cerebral injury in monochorionic twins with selective intrauterine growth restriction: a systematic review. Prenat Diagn. 2014 Mar;34(3):205–13.

9. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. Obstet Gynecol. 2011 Oct;118(4):928–40.

10. Quarello E, Molho M, Ville Y. Incidence, mechanisms, and patterns of fetal cerebral lesions in twin-to-twin transfusion syndrome. J Matern Fetal Neonatal Med. 2007 Aug 7;20(8):589–97.

11. Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, Walther FJ, Vandenbussche FPHA, Lopriore E. Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther. 2010;27(4):181-190.

12. Tollenaar LSA, Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Haak MC, Klumper FJCM, Tan RNGB, Rijken M, Van Klink JMM. High risk of long-term neurodevelopmental impairment in donor twins with spontaneous twin anemia-polycythemia sequence. Ultrasound Obstet Gynecol. 2020;55(1):39-46

13. ASQ-3 [Internet]. Ages and Stages. [cited 2022 Oct 26]. Available from: https://agesandstages.com/products-pricing/asq3/

14. Gollenberg AL, Lynch CD, Jackson LW, McGuinness BM, Msall ME. Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample. Child Care Health Dev. 2010;36(4):485-490.

15. Drotar D, Stancin T, Dworkin PH, Sices L, Wood S. Selecting Developmental Surveillance and Screening Tools. Pediatrics In Review. 2008 Oct 1;29(10):e52–8.

16. Schonhaut L, Pérez M, Armijo I, Maturana A. Comparison between Ages & Stages Questionnaire and Bayley Scales, to predict cognitive delay in school age. Early Hum Dev. 2020;141:104933.

17. Kerstjens JM, Nijhuis A, Hulzebos CV, van Imhoff DE, van Wassenaer-Leemhuis AG, van Haastert IC, Lopriore E, Katgert T, Swarte RM, van Lingen RA, Mulder TL, Laarman CR, Steiner K, Dijk PH. The Ages and Stages Questionnaire and Neurodevelopmental Impairment in Two-Year-Old Preterm-Born Children. PLoS One. 2015;10(7):e0133087.

18. Briffa C, Stirrup O, Huddy C, Richards J, Shetty S, Reed K, Khalil A. Twin chorionicity-specific population birth-weight charts adjusted for estimated fetal weight. Ultrasound Obstet Gynecol. 2021;58(3):439-449.

19. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol. 1999 Dec;19(8 Pt 1):550–5.

20. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure - Khalil - 2019 - Ultrasound in Obstetrics & Gynecology - Wiley Online Library [Internet]. [cited 2022 Oct 26]. Available from: https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.19013

21. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. Ultrasound Obstet Gynecol. 2007;30(1):28-34.

22. Stuart EA, Green KM. Using full matching to estimate causal effects in nonexperimental studies: examining the relationship between adolescent marijuana use and adult outcomes. Dev Psychol 2008;44:395–406

23. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. Am J Epidemiol 2011;173:761–767

24. Lorenz, J., 2012. Neurodevelopmental Outcomes of Twins. Seminars in Perinatology, 36(3), pp.201-212.

25. Tosello B, Garbi A, Blanc J, Lorthe E, Foix-L'Hélias L, D'Ercole C, Winer N, Subtil D, Goffinet F, Kayem G, Resseguier N, Gire C, EPIPAGE-2 Obstetric Writing Group. The impact of chorionicity on pregnancy outcome and neurodevelopment at 2 years old among twins born preterm: the EPIPAGE-2 cohort study. BJOG. 2021;128(2):281-291.

26. Hack KEA, Koopman-Esseboom C, Derks JB, Elias SG, de Kleine MJK, Baerts W, Go ATJI, Schaap AHP, van der Hoeven MAHBM, Eggink AJ, Sollie KM, Weisglas-Kuperus N, A.Visser GH. Long-Term Neurodevelopmental Outcome of Monochorionic and Matched Dichorionic Twins. PLoS One. 2009;4(8):e6815

27. Yan S, Wang Y, Chen Z, Zhang F. Chorionicity and neurodevelopmental outcomes in twin pregnancy: a systematic review and meta-analysis. J Perinatol. 2023 Feb;43(2):133–46.

28. Gray PH, Poulsen L, Gilshenan K, Soong B, Cincotta RB, Gardener G. Neurodevelopmental outcome and risk factors for disability for twin-twin transfusion syndrome treated with laser surgery. Am J Obstet Gynecol. 2011 Feb;204(2):159.e1-6.

29. Lopriore E, Ortibus E, Acosta-Rojas R, Le Cessie S, Middeldorp JM, Oepkes D, Gratacos E, Vandenbussche FPHA, Deprest J, Walther FJ, Lewi L. Risk factors for neurodevelopment impairment in twin-twin transfusion syndrome treated with fetoscopic laser surgery. Obstet Gynecol. 2009;113(2 Pt 1):361-366.

30. Hessami K, Nassr AA, Sananès N, Castillo J, Castillo HA, Sanz Cortes M, Espinoza J, Donepudi RV, Sun RC, Krispin E, Belfort MA, Shamshirsaz AA. Perinatal risk factors of neurodevelopmental impairment after fetoscopic laser photocoagulation for twin-twin transfusion syndrome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2021;58(5):658-668.

31. Sananès N, Gabriele V, Weingertner AS, Ruano R, Sanz-Cortes M, Gaudineau A, Langer B, Nisand I, Akladios CY, Favre R. Evaluation of long-term neurodevelopment in twin-twin transfusion syndrome after laser therapy. Prenat Diagn. 2016;36(12):1139-1145.

32. Groene SG, Tollenaar LSA, Oepkes D, Lopriore E, van Klink JMM. The Impact of Selective Fetal Growth Restriction or Birth Weight Discordance on Long-Term Neurodevelopment in Monochorionic Twins: A Systematic Literature Review. J Clin Med. 2019 Jun 28;8(7):E944.

33. Adegbite, A.L.; Castille, S.; Ward, S.; Bajoria, R. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. Am. J. Obstet. Gynecol. 2004, 190, 156–163.

34. Edmonds, C.J.; Isaacs, E.B.; Cole, T.J.; Rogers, M.H.; Lanigan, J.; Singhal, A.; Birbara, T.; Gringras, P.; Denton, J Lucas, A. The effect of intrauterine growth on verbal IQ scores in childhood: A study of monozygotic twins. Pediatrics 2010, 126, e1095–e1101.

35. Halling, C.; Malone, F.D.; Breathnach, F.M.; Stewart, M.C.; McAuli_e, F.M.; Morrison, J.J.; Dicker, P. Manning, F.; Corcoran, J.D. Perinatal Ireland Research Consortium. Neuro-developmental outcome of a large cohort of growth discordant twins. Eur. J. Pediatr. 2016, 175, 381–389.

36. Rustico MA, Consonni D, Lanna M, Faiola S, Schena V, Scelsa B, Introvini P, Righini A, Parazzini C, Lista G, Barretta F, Ferrazzi E. Selective intrauterine growth restriction in monochorionic twins: changing patterns in umbilical artery Doppler flow and outcomes. Ultrasound Obstet Gynecol. 2017;49(3):387-393

37. Swamy, R.S.; McConachie, H.; Ng, J.; Rankin, J.; Korada, M.; Sturgiss, S.; Embleton, N.D. Cognitive outcome in childhood of birth weight discordant monochorionic twins: The long-term effects of fetal growth restriction. Arch. Dis. Child. Fetal Neonatal Ed. 2018, 103, 512–516

38. Groene SG, Stegmeijer KJJ, Tan RNGB, Steggerda SJ, Haak MC, Slaghekke F, Roest AAW, Heijmans BT, Lopriore E, Klink JMM van. Long-term effects of selective fetal growth restriction (LEMON): a cohort study of neurodevelopmental outcome in growth

discordant identical twins in the Netherlands. The Lancet Child & Adolescent Health. 2022;6(9):624-632.

FIGURE LEGENDS

Figure 1. Flow chart showing eligibility and inclusion of participants in the study.

Table 1. Baseline characteristics and perinatal outcomes of the two study populations.

	Uncomplicated twin pregnancies (n=105 pregnancies; 210 children)	**Complicated monochorionic twin pregnancies (n = 69 pregnancies; 117 children)**	**P value**
Maternal age in years, (mean ± SD)	33.5 ± 4.5	31.6 ± 5.0	0.001
Nulliparous, n (%)	53 (50.5)	37 (53.6)	0.757
Body mass index (kg/m^2), (mean ± SD)	26.6 ± 6.2	25.5 ± 4.7	0.083
Spontaneous conception, n (%)	80 (76.2)	62 (89.9)	0.028
Index of multiple deprivation, n (%)			
1st Quintile (most deprived)	22 (20.9%)	12 (17.4%)	0.570
2nd Quintile	15 (14.3%)	13 (18.8%)	0.430
3rd Quintile	36 (34.3%)	26 (37.7%)	0.648
4th Quintile	24 (22.9%)	10 (14.5%)	0.173
5th Quintile (least deprived)	8 (7.6%)	8 (11.6%)	0.373

Fetal loss of one twin, n (%)	0/105	15/69 (21.7)	NE
Gestational age at birth in weeks, (mean ± SD)	35.8 ± 2.3	32.6 ± 2.8	<0.001
Missing data	7	14	
Mode of delivery, n (%)			<0.001
Vaginal	46 (21.9)	9 (7.7)	
Emergency Caesarean birth	46 (21.9)	44 (37.6)	
Elective Caesarean birth	98 (46.7)	30 (25.6)	
Missing data	20 (9.5)	34 (29.1)	
Preterm birth < 28weeks, n (%)	2 (1.9)	4 (5.8)	0.1690
Preterm birth < 32 weeks, n (%)	4 (3.8)	20 (29.0)	<0.001
Preterm birth < 34 weeks, n (%)	16 (15.2)	32 (46.4)	<0.001
Missing data, n (%)	7 (6.7)	13 (18.8)	
Birthweight (grams), (mean ± SD)	2342.2 ± 439.8	1742.9 ± 672.8	<0.001
Missing data, n (%)	20 (9.5)	27 (23.1)	
Birthweight < 5th centile, n (%)	3 (1.4)	15 (12.8)	<0.001

Missing data, n (%)	20 (9.5)	27 (23.1)	
Female gender, n (%)	93 (48.2)	45 (60.8)	0.087
Neonatal unit admission, n (%) Missing data	32 (15.2) 14 (6.7)	57 (48.7) 19 (16.2)	<0.001
Neonatal morbidity*, n (%) Missing data, n (%)	28 (13.3) 14 (6.7)	57 (48.7) 19 (16.2)	<0.001
Age of the child at ASQ-3 questionnaire in months, (mean ± SD)	35.4 ± 14.0	29.1 ± 11.2	<0.001

SD: standard deviation; ASQ-3: Ages and Stages Questionnaires® test version 3.

* Neonatal morbidity includes respiratory distress syndrome (RDS), need for resuscitation, jaundice requiring phototherapy or exchange transfusion, intraventricular hemorrhage (IVH), sepsis, necrotizing enterocolitis (NEC), persistent ductus arteriosus (PDA) requiring intervention

Table 2. Prevalence of abnormal Ages and Stages Questionnaire® (ASQ) 3 scores (defined as score <2 SD below mean in any one of five domains) in the study population.

	Uncomplicated twin pregnancies (n=210 children)	**Complicated monochorionic twin pregnancies (n=117 children)**	**P value**
Abnormal ASQ-3	16 (7.6)	17 (14.5)	0.056
One abnormal domain	16 (7.6)	17 (14.5)	0.056
Two abnormal domains	11 (5.2)	8 (6.8)	0.624
Communication < 2 SD	9 (4.3)	9 (7.7)	0.212
Gross motor < 2 SD	6 (2.9)	10 (8.5)	0.031

Fine motor < 2 SD	6 (2.9)	5 (4.3)	0.531
Problem solving < 2 SD	8 (3.8)	7 (6.0)	0.413
Personal and social skills < 2 SD	9 (4.3)	8 (6.8)	0.314

SD: standard deviation

Data are shown as numbers (percentage

Table 3. Prevalence of abnormal Ages and Stages Questionnaire® (ASQ) 3 scores (defined as score <2 SD below mean in any one of five domains) in the complicated monochorionic diamniotic (MCDA) twin pregnancies stratified according to donor/recipient status, discordant fetal size, prenatal intervention, and co-existent pathologies.

Twin-to-twin transfusion syndrome (TTTS)	**TTTS donor (n=33)**	**TTTS recipient (n=36)**	**P value**
Abnormal ASQ-3, n (%)	9 (27.3)	5 (13.9)	0.171
Selective fetal growth restriction	**Smaller twin (n=28)**	**Larger twin (n=32)**	
Abnormal ASQ-3, n (%)	4 (14.3)	4 (12.5)	0.840
Prenatal intervention*	**Cases with prenatal intervention (n=57)**	**Cases without intervention (n=60)**	
Abnormal ASQ-3, n (%)	16 (28.1)	1 (1.7)	< 0.001

Single or multiple pathologies	**More than one pathology (n=28)**	**Single pathology (n=89)**	
Abnormal ASQ-3, n (%)	9 (32.1)	8 (9.0)	0.003

*Fetoscopic laser/ bipolar cord coagulation/ radiofrequency ablation

Table 4. Multilevel model demonstrating the association between complicated monochorionic diamniotic (MCDA) twin pregnancies and abnormal Ages and Stages Questionnaire® (ASQ) 3 scores (defined as score <2 SD below mean in any one of five domains)

	Odds ratio (95% CI)	**P value**	**Adjusted odds ratio (95%CI)**	**P value**
Complicated MCDA twin pregnancies	2.06 (1.00-4.29)	0.050	3.28 (3.27-3.29)	<0.001
Maternal body mass index (kg/m^2)	1.03 (0.97-1.09)	0.273	1.08 (1.08-1.09)	<0.001
Emergency Caesarean section	0.56 (0.22-1.47)	0.235	0.29 (0.29-0.29)	<0.001
Elective Caesarean section	0.22 (0.07-0.63)	0.006	0.15 (0.02-0.78)	0.022
Gestational age in weeks	0.86 (0.77-0.98)	0.017	0.78 (0.77-0.78)	<0.001
Male gender	1.28 (0.57-2.92)	0.553	1.17 (0.68-2.42)	0.472

Number in model = 258, Number of groups = 136, AIC = 140.7, C-statistic = 0.991

CI: confidence interval

Table 5. Logistic regression model after propensity-score matching.

		Abnormal ASQ-3 in one or more domain			
		No	Yes	Univariable OR (95% CI)	Matched OR (95% CI)
Group	Control	171 (92.4)	14 (7.6)	1·00 (reference)	1·00 (reference)
	Case	61 (83.6)	12 (16.4)	2.40 (1.04-5.49, p=0.037)	3.95 (1.13-13.72, p=0.031)
Parity	Nulliparous	123 (91.8)	11 (8.2)	1·00 (reference)	1·00 (reference)
	Multiparous	109 (87.9)	15 (12.1)	1.54 (0.68-3.57, p=0.303)	0.61 (0.12-3.03, p=0.550)
Maternal BMI (kg/m^2)	Mean (SD)	26.7 (5.9)	28.0 (5.8)	1.04 (0.97-1.10, p=0.270)	1.27 (1.03-1.57, p=0.027)

		Abnormal ASQ-3 in one or more domain			
		No	Yes	Univariable OR (95% CI)	Matched OR (95% CI)
Gestational age (weeks)	Mean (SD)	35.2 (2.6)	33.7 (3.5)	0.84 (0.74-0.96, p=0.008)	0.77 (0.50-1.18, p=0.236)
Gender	Female	121 (91.0)	12 (9.0)	1·00 (reference)	1·00 (reference)
	Male	111 (88.8)	14 (11.2)	1.27 (0.56-2.91, p=0.562)	4.41 (0.70-27.85, p=0.114)

BMI: body mass index; ASQ-3: Ages and Stages Questionnaires® test version 3; SD: standard deviation; BMI: body mass index; OR: odds ratio; CI: confidence intervals.

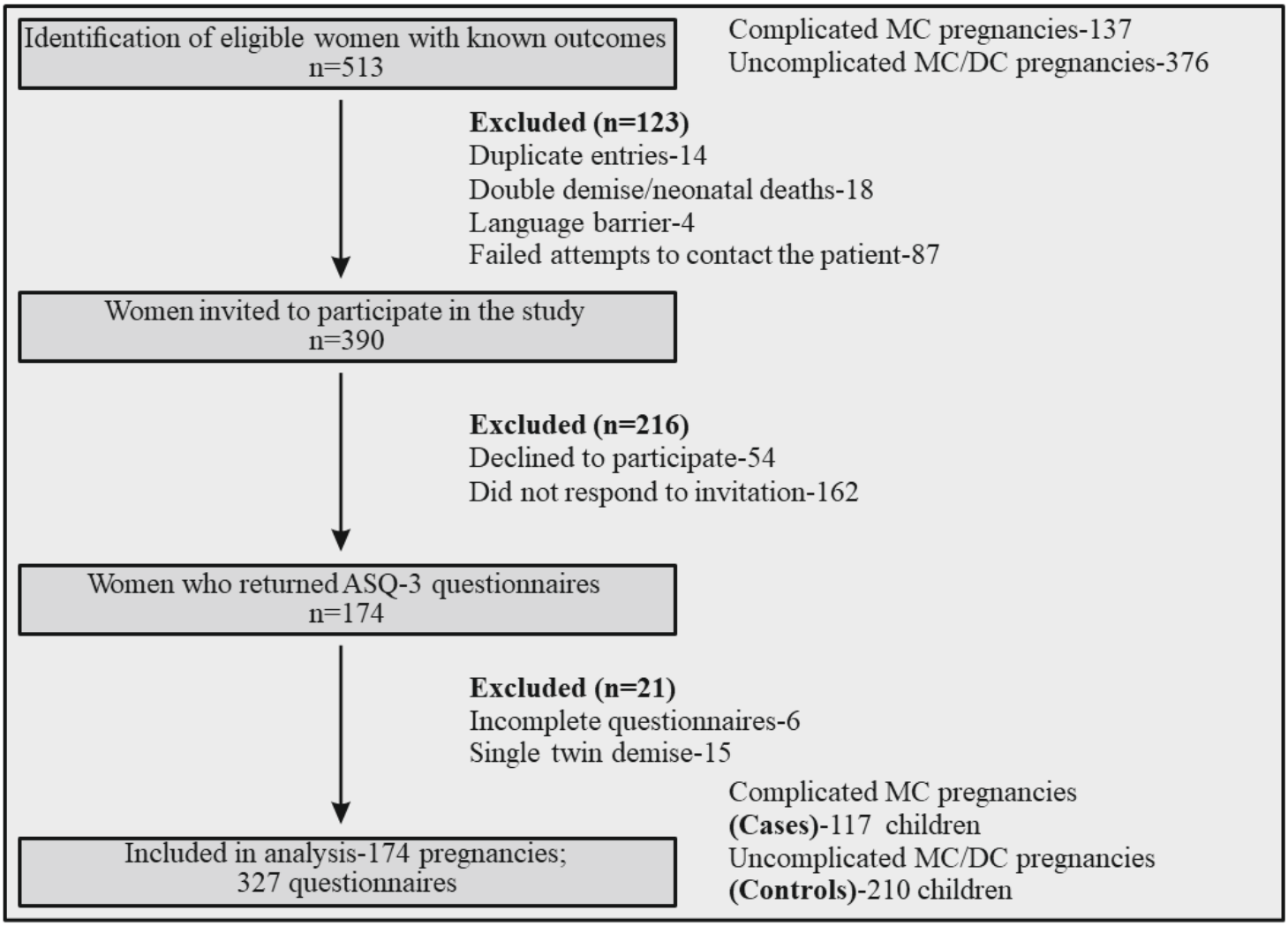

Figure 1.tif