Prevalence, antenatal management and perinatal outcomes of monochorionic monoamniotic twin pregnancies: a collaborative multicentre study in England, 2000-2013

Svetlana V Glinianaia,[1]* Judith Rankin,[1] Asma Khalil,[2] Julia Binder,[2,3] Gareth Waring,[4] Stephen N Sturgiss,[4] Basky Thilaganathan,[2] Therese Hannon[4]

[1]Institute of Health & Society, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom

[2]Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

[3]Department of Obstetrics and Fetomaternal Medicine, Medical University of Vienna, Austria.

[4]Department of Fetal Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

***Address for correspondence**: Dr Svetlana Glinianaia, Institute of Health & Society, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, United Kingdom; [svetlana.glinianaia@ncl.ac.uk], Tel: +44 191 208 5891.

Short title: outcomes of monoamniotic twin pregnancies

Keywords: Monochorionic monoamniotic twins, Northern Survey of Twin and Multiple Pregnancy (NorSTAMP), STORK collaboration, antenatal surveillance, perinatal mortality

Abstract

Objectives: To determine the prevalence of monochorionic monoamniotic (MCMA) twin pregnancies and to describe perinatal outcomes and clinical management of these pregnancies.

Methods: This multicentre cohort study used population-based data on MCMA twin pregnancies from 11 Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) maternity units for the prevalence estimation of MCMA twinning. Pregnancy outcomes at <24 weeks' gestation, antenatal parameters and perinatal outcomes (from ≥24 weeks to the first 28 days of life) were analysed using combined data on pregnancies with confirmed MCMA chorionicity from the NorSTAMP and the Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple pregnancy cohort for 2000-2013.

Results: The estimated total prevalence of MCMA twin pregnancies in the North of England was 8.2 per 1000 total twin pregnancies, the birth prevalence was 0.08 per 1000 all (singleton and multiple) pregnancies. The rate of a spontaneous or iatrogenic fetal death at <24 weeks' gestation was 31.8%; the overall perinatal mortality was 14.7%, ranging from 69.2% at <30 weeks to 4.3% at 33-34 weeks' gestation. MCMA twins who survived *in utero* beyond 24 weeks were delivered, usually by caesarean section, at a median of 33 weeks of gestation (interquartile range=32-34).

Conclusions: In MCMA twins surviving beyond 24 weeks of gestation, there was a higher survival rate compared to previous decades presumably due to early diagnosis, close surveillance and elective birth around 32-34 weeks of gestation. High perinatal mortality at early gestations was mainly attributed to extreme prematurity due to preterm spontaneous labour.

Introduction

Monozygotic twinning is more stable than dizygotic twinning, similar across countries and little affected by factors such as fertility treatment, increasing maternal age and obesity, major contributors to the increased twinning rates in recent decades.[1-3] Monochorionic (MC) twins (about 20% of all twins) are at a higher risk of perinatal death than dichorionic (DC) twins[4-9] due to higher prematurity rates, selective fetal growth restriction (sFGR), congenital anomalies and twin-twin transfusion syndrome (TTTS).[10,11] MC monoamniotic (MCMA) twins that also share the same amniotic sac are rarer, occurring in about 5% of MC pregnancies, or in one in 10,000 all pregnancies.[9] They carry an additional risk for perinatal death due to twin-related congenital anomalies and cord-related complications, resulting in about 15% of deaths after 20 weeks of pregnancy.[12,13] Although the perinatal mortality of MCMA twins has strikingly reduced during the last two decades compared to extremely high rates up to 70% reported previously,[14] it remains relatively high despite improved surveillance and care.[12]

As MCMA twinning is very uncommon, randomised controlled evidence of the best management of MCMA twin pregnancies is lacking[9] and, until recently, there were no consistent recommendations on the optimal timing or method of delivery.[15] For example, the National Institute for Health and Clinical Excellence (NICE) guidance (England & Wales, 2011) on the antenatal management of twin and triplet pregnancies highlighted that there was insufficient evidence for effective clinical management of MCMA twin pregnancies, and that there was need for further research to inform future provision of NHS services.[15] There is some evidence from a recent multicentre cohort study,[16] which supports the American College[17] and Royal College[10] of Obstetricians and Gynaecologists recommendations for delivery of MCMA twins by caesarean section at 32-34 weeks, but more studies of these rare multiple pregnancies are needed.

This collaborative study aimed: to determine the prevalence of MCMA twin pregnancies using population-based data from the Northern Survey of Twin and Multiple Pregnancy (NorSTAMP), 2000-2013, and to describe perinatal outcomes and clinical management of these pregnancies using data from the NorSTAMP and the Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple birth cohort.

Methods

Data sources and study population, 2000-2013

The NorSTAMP (established in 1998, data collection ceased 31st March 2015) captured data on multiple pregnancies of women resident in the North of England (North East and North Cumbria), which has a population of around 3 million and 32,000 annual deliveries. The ascertainment was from the earliest antenatal scan at which a multiple pregnancy was diagnosed (recommended at 10–13 weeks in the UK[18]) and then at the 20-week routine ultrasound anomaly scan and at delivery (details of the notification system are presented elsewhere[19,20]). The records were maintained and held at the Regional Maternity Survey Office (RMSO), on a single database linked through the mother's details to other RMSO registers, including the Northern Congenital Abnormality Survey (NorCAS).[20] The RMSO data were annually cross-validated with the Office for National Statistics (ONS) birth and death data through the external linkage built into the database. The NorSTAMP collected data on maternal, obstetric and infant variables, including maternal age, index of multiple deprivation (IMD) score (an area-based measure of socio-economic position based on the maternal residential postcode, analysed in quintiles), pregnancy outcomes [spontaneous fetal loss (<16 completed weeks of gestation), selective feticide, miscarriage (16-23 weeks), termination of pregnancy (TOP), stillbirth (fetal death delivered at ≥24 weeks of gestation), early neonatal death (0-6 days of life), late neonatal death (7-27 days of life) and post-

neonatal death (28-365 days of life), alive at 1 year] and chorionicity type. The final diagnosis of chorionicity for like-sex twin pregnancies is based on placental examination and histology, and where unavailable, on the appropriate first trimester ultrasound determination. Chorionicity diagnosis was verified and detailed antenatal data were obtained from the serial ultrasound scans in the Department of Fetal Medicine database of the Royal Victoria Infirmary (RVI), the regional tertiary centre in Newcastle upon Tyne. Information on zygosity as well as type of conception is not recorded in the NorSTAMP.[20] Anonymised data on neonatal morbidity and care were obtained from the RVI Special Care Baby Unit (SCBU) database after the linkage with obstetric ultrasound records.

The STORK multiple pregnancy cohort covers multiple pregnancies registered for routine antenatal care in ten hospitals (46,500 annual births) and collects matched data on antenatal care, including ultrasound scan, and pregnancy outcomes from two computer databases.[21] The STORK regional hospitals, including the tertiary hospital St George's University of London (SGH), had unified protocols for antenatal management. Ultrasound scans were performed every two weeks from 16 weeks until the end of the pregnancy, which included assessment of fetal biometry, amniotic fluid volume and umbilical artery Doppler waveforms. Routine antenatal admission for fetal monitoring was not advocated as these pregnancies were managed as outpatient, and were admitted for obstetric indications mainly. Neonatal outcome data were collected from the SGH and other STORK hospitals where possible.

All maternity units in both the NorSTAMP and STORK cohorts follow the 2011 NICE recommendations for the antenatal management of twin and triplet pregnancies.[15] The North of England regional guidance, agreed and implemented in 2009, is consistent with the NICE principles.[22] Those units that do not have a nominated multidisciplinary team for management of MCMA twin pregnancy referred these patients to the RVI where closer fetal surveillance was undertaken at ≥24 weeks. Routine practice for management of MCMA pregnancies in

both RVI and STORK centres was similar in relation to frequency of ultrasound scans (fortnightly from 16 weeks of gestation for uncomplicated pregnancies or more frequently from 24 weeks, if necessary) and prescription of a course of corticosteroids for fetal lung maturation before elective caesarean section at about 32-34 weeks of gestation. However, in contrast to the management of MCMA pregnancies as outpatients in the STORK cohort, the RVI followed the principles of active management which would offer admission to an antenatal ward, computerised cardiotocograms (CTGs) three times a day, weekly ultrasound scans for Doppler measurements with fetal biometry every two weeks (Figure S1). The timing of active management differs for different patients depending on the gestation at which patients would opt for elective delivery if there were concerns about fetal wellbeing, but usually from 28 weeks.

Inclusion criteria and Definitions

Only twin pregnancies with a definite diagnosis of MCMA chorionicity were included in both cohorts. An initial NorSTAMP cohort was refined by excluding confirmed MCDA pregnancies and complemented by additional MCMA pregnancies identified in the RVI ultrasound database. Women who refused to give consent for their confidential data to be held in the NorSTAMP were excluded from the analyses of antenatal and neonatal data (n=6, Figure 1). Neonatal death was defined as death during the first 0-27 days after live birth. Perinatal death included both stillbirth (fetal death at ≥24 weeks' gestation) and neonatal death. Twin maternities were defined as pregnancies resulting in at least one live birth or stillbirth and were used for the population-based birth prevalence estimation and for the calculation of perinatal mortality.

The following indicators of fetal growth and wellbeing/development were recorded and analysed: sFGR [(fetal size discordance defined as difference in estimated fetal weight, EFW, (using Hadlock formula) at the last scan before delivery of >20%];[10] inter-twin birthweight

discordance (defined as difference in birthweight of >20%); small for gestational age (SGA) at birth (defined as birthweight <10th percentile using birthweight-by-gestation and sex standards from a population of Scottish twins[23]); EFW-based SGA (defined as EFW <10th percentile using fetal growth curves from the USA ultrasound data[24] adjusted to fit the Scottish reference dataset[23] following our previously used approach[25]). Other variables included diagnosis of cord entanglement, TTTS, twin reversed arterial perfusion (TRAP) sequence, evidence of abnormal umbilical artery Doppler (pulsatility index >95th centile, absent or reversed end-diastolic flow) at the last ultrasound scan within two weeks before delivery and congenital anomaly diagnosed prenatally.

Data on the following neonatal outcomes were collected for infants who survived the neonatal period: respiratory distress syndrome (RDS) (yes/no), necrotising enterocolitis (yes/no), intraventricular haemorrhage (yes/no), congenital anomalies (yes/no, and if yes, final diagnosis), sepsis (yes/no), admission to SCBU (yes/no, if yes, number of days), mechanical ventilation (yes/no, if yes, number of days), continuous positive airway pressure (CPAP).

The North of England data on congenital anomalies were obtained from the NorCAS, a member of the European Surveillance of Congenital Anomalies (EUROCAT). NorCAS collects data on major congenital anomalies (up to six individual congenital anomalies per case) occurring in late miscarriages (20-23 weeks gestation), termination of pregnancy (TOP) for fetal anomaly (any gestation), stillbirths or live births, whether diagnosed antenatally or not.[26] Cases are notified from multiple sources and are included when first diagnosed at any age up to 12 years.[26] All major congenital anomalies were coded according to the WHO International Classification of Diseases 10th Revision (ICD-10[27]) and categorised using the EUROCAT criteria into group (the organ system affected), subtype (the specific condition) and syndrome.[28,29] Cases with more than one ICD code were assigned a primary diagnosis

using a hierarchical approach described elsewhere.[30] Congenital anomalies in the STORK cohort were recorded based on ultrasound scan diagnosis confirmed at birth.

Statistical analysis

The MCMA twin birth prevalence for 2000-2013 was estimated as the number of MCMA twin maternities for the North of England population per 1000 total pregnancies resulting in registered births (live or stillbirths) obtained from the ONS. The total prevalence was estimated using the number of all MCMA twin pregnancies per 1000 all twin pregnancies recorded in NorSTAMP. Descriptive statistics were used to characterise and compare baseline characteristics of MCMA twin pregnancies between the NorSTAMP and STORK cohorts. Differences in the distributions of continuous variables were compared using Mann-Whitney U test and medians with interquartile ranges (IQR) were reported. Percentages were presented for categorical variables and compared using the X^2 test (Fisher exact test). Perinatal mortality was calculated using combined NorSTAMP and STORK data per 1000 individuals from MCMA maternities, including those with one fetal loss before 24 weeks gestation. Antenatal parameters and obstetric outcomes were analysed using data for stillbirths and live births, while the analysis of neonatal outcomes was restricted to neonatal survivors.

All analyses were performed using SPSS Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp). P <0.05 was considered statistically significant.

Results

Prevalence of MCMA twin pregnancies (NorSTAMP, n=59 twin pregnancies)

Overall, there were 59 twin pregnancies in the North of England during 2000-2013, with MCMA chorionicity confirmed by either both ultrasound scan and placental pathology (54.2%), where available, or by the first trimester ultrasound scan only (45.8%), including pregnancies resulting in early fetal losses of both co-twins (n=22) (Figure 1). The estimated

MCMA birth prevalence was 0.08 (37/442,624) per 1000 total pregnancies (singleton and multiple), or 5.7 (37/6536) per 1000 twin pregnancies, resulting in registered births. The total prevalence was 8.2 per 1000 total twin pregnancies (59/7170) (Figure 1).

Pregnancy outcomes of MCMA twin pregnancies (NorSTAMP and STORK, n=85 pregnancies)

Table 1 shows baseline characteristics for 85 MCMA pregnancies (excluding conjoined twins) from the NorSTAMP and STORK cohorts. There were no significant differences in median maternal BMI at booking, as well as the percentage of nulliparous women, prenatal diagnosis of chorionicity or deliveries by caesarean section between the two cohorts. However, the mothers were older and the percentage of pregnancies with female fetal sex was significantly higher in the STORK cohort, while the percentage of women living in the most deprived areas (5^{th} quintile) was significantly higher in the NorSTAMP cohort (Table 1).

Tables 2a and b show pregnancy outcomes for these 85 pregnancies. Thirty pregnancies resulted in a spontaneous or iatrogenic intrauterine death (IUD) before 24 weeks gestation (IUD rate 31.8%): spontaneous IUD (n=17) or TOP (n=7) of both fetuses, and six with either a spontaneous IUD (n=3) or selective termination (n=3) (Table 2a). Among further 55 pregnancies, the majority (n=49) were both live births [in 43 (88%) both survived the neonatal period], while six resulted in either a single or double IUD at ≥24 weeks (Table 2b).

Perinatal mortality in MCMA twins (NorSTAMP and STORK, n=116 registered twin births)

Table 3 shows stillbirth and neonatal mortality among MCMA twins with known causes of death. The overall perinatal mortality was 14.7% differing by gestational age windows: 69.82%, 11.8%, 4.3% and 4.8% at <30 weeks, 30-32, 33-34 and ≥35weeks of gestation respectively. The excess perinatal mortality at <30 weeks was mainly attributed to neonatal deaths due to extreme prematurity as a result of spontaneous labour at 22-26 weeks (n=6,

among those one twin with complex congenital heart defect) and antepartum stillbirths at 24 and 27 weeks (n=3). According to the post-mortem examination, antepartum hypoxia was the leading cause of stillbirth (3/8 due to presumed cord entanglement) with double IUDs in two pregnancies (Tables 2 and 3).

Antenatal parameters and obstetric outcomes of MCMA twins (NorSTAMP and STORK, n=45 pregnancies)

Figure 1 shows the derivation of the cohort eligible for the analysis of MCMA pregnancies that survived beyond 24 weeks' gestation. Table 4 shows antenatal indicators of fetal development and wellbeing, and obstetric outcomes for live and stillborn MCMA twins, whose mothers gave consent for their confidential data to be held in the NorSTAMP. In over two thirds (33/45, 73.3%) of pregnancies, MCMA placentation was diagnosed in the first trimester of pregnancy (≤13 weeks gestation). None of the fetuses who had recorded umbilical artery Doppler at the last scan ≤2 weeks before delivery (n=53) had abnormal parameters despite the majority (86%) with definite cord entanglement diagnosis. However, in one pregnancy with double IUD, there were normal Doppler parameters and no apparent knotting between the adjacent cords a week before IUDs were diagnosed. In all five pregnancies complicated by a major congenital anomaly the diagnosis was made by an antenatal ultrasound scan. The inter-twin discordance in the EFW at the last scan ≤2 weeks before delivery was a good predictor of the inter-twin birthweight discordance (regression coefficient [ß]=0.63, 95% CI=0.22-0.72, p=0.001) in an univariate model. The inter-twin birthweight discordance (>20%) was diagnosed in four pregnancies (9%). The vast majority (93.3%). of MCMA twins were delivered by caesarean section. Most twins (86.4%) were delivered at ≤34 weeks [median=33.0 (IQR=32.0-34.0) weeks; gestational age at delivery was insignificantly lower among the NorSTAMP patients [median=32.0 (IQR=31.0-34.0 vs STORK median=34.0 (IQR=32.5-34.0) weeks), p=0.061].

Neonatal morbidity of MCMA twins (n=73 neonatal survivors)

Five neonatal deaths were excluded from the analysis of neonatal morbidity (Table 4). Most twins (74% of 73 neonatal survivors) were admitted to SCBU for about 17 days with RDS as a most common diagnosis (58.7%) For infants with RDS, mechanical ventilation and/or CPAP were used for respiratory support in 15% and 55% of infants respectively.

Discussion

Summary of study findings

We estimated the prevalence of MCMA twin pregnancies in an English region using population-based NorSTAMP data, 2000-2013, to inform future provision of obstetric and neonatal services. The total MCMA twin prevalence in the North of England was 8.2/1000 twin pregnancies; the birth prevalence was 0.08/1000 all pregnancies. Over a third of pregnancies resulted in a spontaneous or iatrogenic IUD at <24 weeks of gestation (IUD rate 31.8%). The overall perinatal mortality was 14.7%. The majority of MCMA twins were delivered by elective caesarean section at a median of 33 gestational weeks. The inter-twin birthweight discordance (>20%) was rare (9%). Neonatal morbidity was mostly associated with conditions related to preterm delivery, RDS being the most common diagnosis.

Strengths and limitations

This study used multicentre data sources from 10 STORK and 11 NorSTAMP maternity units. The NorSTAMP was unique in Europe by ascertaining a multiple pregnancy from the earliest antenatal scan. Accuracy of chorionicity diagnosis was ensured at the first trimester ultrasound scan by an experienced Fetal Medicine ultrasonographer in both the NorSTAMP and STORK tertiary centres. Only twin pregnancies with a definite MCMA diagnosis were included in the analysis. This study analysed early fetal losses in addition to perinatal outcomes, including congenital anomalies, and collected detailed antenatal data from the

serial ultrasound scans linked to the outcome data. In the North of England, congenital anomalies data were collected in the population-based NorCAS, linked with NorSTAMP, assuring completeness and accuracy of congenital anomaly data. Our study also has some limitations. The retrospective nature of the study led to challenges in obtaining all the necessary detail on the antenatal and neonatal data for all pregnancies in both collaborative centres, particularly for the early study years, resulting in incomplete follow up and some missing data. While both centres followed region-specific unified protocols for the management of MCMA twin pregnancies, consistent during the study period, there were some differences in relation to out- and in-patient antenatal management. Nevertheless, this did not significantly affect the timing of elective delivery, although gestational age at delivery was non-significantly lower among the NorSTAMP patients, possibly due to the RVI active management from about 28 weeks. Whilst detailed RVI antenatal scan data were extracted, full information regarding in/outpatient management and frequency of CTG monitoring was unavailable for all NorSTAMP pregnancies. Although one of the largest studies on MCMA twins in Europe, our sample size was still small.

Interpretation of study findings and comparison with existing literature

Females predominated in MCMA pairs with known fetal sex (67% from combined NorSTAMP and STORK data), consistent with previous studies,[12,13,31-34] reporting a variation between 55%[13]-92%.[34] The percentage of female MCMA pairs was significantly higher in the STORK cohort; likely due to a three-fold increased percentage of pregnancies with missing sex among early fetal losses (34.2% vs 10.6% in NorSTAMP), assuming a proposed higher rate of early fetal mortality among male MCMA pregnancies.[31] Expected differences between the cohorts existed in maternal age and deprivation scores. Thus the reported higher maternal age in the STORK cohort can be attributed to the known geographical differences in maternal age distribution in England & Wales, characterised by the highest percentage of mothers aged

≥35 years in London (26.6% vs 15.1% in North East) and the two-fold higher percentage of younger mothers (<25 years) in the North East (2013 data).[35] A significantly higher percentage of women from the most deprived residential areas were found in the NorSTAMP cohort as the North of England has a large proportion of areas amongst the most deprived in England.[36] Our estimated MCMA twin prevalence of 0.8 per 10,000 all pregnancies in the North of England is consistent with published estimates.[9] It is encouraging that in our study, as in the large recent study by Van Mieghem et al,[16] MCMA pregnancies were diagnosed much earlier (at about 13 weeks' gestation) than in the past[37] which gives more room for earlier fetal monitoring and management. Few studies reported pregnancy outcomes in MCMA pregnancies before 20 weeks gestation as the majority excluded early fetal losses from their analyses. The rate of spontaneous IUD (16.3%) in the above study[16] was comparable with our study (23%, if excluding pregnancies with TRAP sequence as in the referred study). Pregnancies affected by a major congenital anomaly in our study constituted 27%, similar to 23%[16] and 28%[37] in previous studies.

Perinatal mortality in our study (14.7%) was almost identical to the total perinatal mortality reported by Baxi, 2010,[34] for eight studies covering 1990-2007 (15%),[12,32,33,37-41] being more similar (15%-19%) to larger multi-centre studies.[12,39] Perinatal mortality for non-anomalous MCMA twins in our study (12.4%) was also similar to the total perinatal mortality for non-anomalous pregnancies from six studies in their review (12.7%).[34] Both perinatal (14.7%) and neonatal mortality (8.3%) in our study were comparable to those (19% and 10% respectively) from the biggest of the reviewed studies (n=92, Netherlands, 2000-2007[12]), as well as to the perinatal mortality (13.9%) reported in a large recent Japanese study for 2002-2009 (n=101).[13] However, there are differences in the stillbirth definition between our and previous studies: ≥24 weeks versus ≥20[12,34,37] and ≥22 weeks' gestation[13] respectively. The use of an earlier stillbirth definition would have slightly increased our perinatal mortality rate. The largest

study on MCMA twins to date (2003-2012: 193 MCMA pregnancies, 295 live births)[16] reported neonatal mortality of 5.8% comparable with our study (8.3%).

Clinical and research implications

There is no consistency regarding optimal timing of elective delivery of MCMA twin pregnancies and the effect of cord entanglement on perinatal outcomes. Some authors advocate expectant management after 20 weeks, predicting a good prognosis for uncomplicated MCMA twin pregnancies despite the existence of cord entanglement.[42,43] This would suggest reassessing the practice of elective very preterm delivery (≤32 weeks).[42] There is evidence that IUD in MCMA twins can occur after 32 weeks,[12,32,39,40] which is also confirmed by our findings. Whilst most MCMA pregnancies surviving beyond 24 weeks' gestation with definite diagnosis of cord entanglement had good perinatal outcomes, the risk for fetal death after 32 weeks was shown to be 4 in 100 MCMA pregnancies compared to 1 in 100 for neonatal death associated with preterm birth at 32 weeks.[12,44] The largest study to date also demonstrated that the prospective risk of an IUD in MCMA twins outweighs the risk of a non-respiratory neonatal complication at 32 4/7 weeks of gestation concluding that optimal timing for elective delivery is about 33 gestational weeks.[16]

Conclusions

Our study confirms that the perinatal survival of MCMA twins has improved compared to previous decades presumably due to early diagnosis, careful fetal surveillance and elective birth by caesarean section at 32-34 weeks. Fetal losses at <24 weeks are common as a result of spontaneous loss and congenital anomalies. Future research investigating pregnancy outcomes and antenatal development of these rare high risk twin pregnancies should aim at a multicentre prospective approach to establish survival from the first trimester and the consequences of early elective delivery, including the long-term developmental outcomes.

Disclosure of interests

None declared.

Contribution to authorship

TH, SVG and JR conceived the project and designed the study. TH, SVG, JR, AK, SNS and BT obtained funding for the study. BT set up the STORK collaboration. SVG, JR, TH, AK, JB and GW participated in the acquisition of the data. SVG cleaned and prepared the dataset for the analysis, conducted the statistical analysis and drafted the report. All authors critically reviewed the manuscript and approved the final manuscript before submission.

Ethics approval and patients' consent

Informed consent was sought for women's identifying details to be held by the NorSTAMP.[19,20] STORK Institutional Review Boards confirmed that for a retrospective analysis of routinely collected data no specific ethics consent was required.

Funding

SVG was funded by a 2015-16 bursary from the British Maternal & Fetal Medicine Society (BMFMS) and the Twins and Multiple Births Association (TAMBA). The funding body had no role in the study design, data collection, data analysis, data interpretation and in writing the manuscript.

Acknowledgements

We are grateful to all the district convenors and coordinators in the north of England for their collaboration and support of NorSTAMP and NorCAS. We also thank the staff at the RMSO for their help in data tracing and checking. We are very grateful to Dr Alan Fenton for providing RVI SCBU data for the RVI deliveries and to the clinical staff of all the North of

England maternity units for providing data for our study. We thank the Research and Clinical Midwifes at SGH, especially Jennika Chauhan and Uzma Khan, for helping with data tracing.

STORK contributors:

St George's University of London

St Peter's Hospital

Frimley Park Hospital

St Helier's Hospital

Epsom General Hospital

East Surrey Hospital

Mayday University Hospital

Royal Surrey County Hospital

Worthing Hospital

Kingston Hospital

References

1. Reddy UM, Branum AM, Klebanoff MA. Relationship of maternal body mass index and height to twinning. *Obstet Gynecol* 2005; **105**: 593-597.
2. Black M, Bhattacharya S. Epidemiology of multiple pregnancy and the effect of assisted conception. *Semin Fetal Neonatal Med* 2010; **15**: 306-312.
3. Human Fertilisation and Embryology Authority. The best possible start to life. A consultation document on multiple births after IVF. https://ifqlive.blob.core.windows.net/umbraco-website/1312/the_best_possible_start_to_life.pdf. [Accessed 10 August 2017].
4. Loos R, Derom C, Vlietinck R, Derom R. The East Flanders Prospective Twin Survey (Belgium): a population-based register. *Twin Res* 1998; **1**: 167-175.
5. Dubé J, Dodds L, Armson BA. Does chorionicity or zygosity predict adverse perinatal outcomes in twins? *Am J Obstet Gynecol* 2002; **186**: 579-583.
6. Machin GA. The phenomenon of monozygosity. In *Multiple pregnancy: epidemiology, gestation & perinatal outcome*, I. Blickstein, L. G. Keith (eds). Taylor & Francis: Oxford, UK, 2005, 204.
7. Glinianaia SV, Obeysekera MA, Sturgiss S, Bell R. Stillbirth and neonatal mortality in monochorionic and dichorionic twins: a population-based study. *Hum Reprod* 2011; **26**: 2549-2557.
8. Southwest Thames Obstetric Research Collaborative (STORK). Prospective risk of late stillbirth in monochorionic twins: a regional cohort study. *Ultrasound Obstet Gynecol* 2012; **39**: 500-504.
9. Shub A, Walker SP. Planned early delivery versus expectant management for monoamniotic twins. *Cochrane Database Syst Rev* 2015; **4**: CD008820.

10. Kilby MD, Bricker L. on behalf of the Royal College of Obstetricians and Gynaecologists. Management of Monochorionic Twin Pregnancy: Green-top Guideline No. 51. *BJOG* 2017; **124**: e1-e45.
11. Glinianaia SV, Rankin J, Wright C. Congenital anomalies in twins: a register-based study. *Hum Reprod* 2008; **23**: 1306-1311.
12. Hack KE, Derks JB, Schaap AH, Lopriore E, Elias SG, Arabin B, Eggink AJ, Sollie KM, Mol BW, Duvekot HJ, Willekes C, Go AT, Koopman-Esseboom C, Vandenbussche FP, Visser GH. Perinatal outcome of monoamniotic twin pregnancies. *Obstet Gynecol* 2009; **113**: 353-360.
13. Morikawa M, Yamada T, Sato S, Minakami H. Prospective risk of intrauterine fetal death in monoamniotic twin pregnancies. *Twin Res Hum Genet* 2012; **15**: 522-526.
14. Beasley E, Megerian G, Gerson A, Roberts NS. Monoamniotic twins: case series and proposal for antenatal management. *Obstet Gynecol* 1999; **93**: 130-134.
15. National Institute for Health and Clinical Excellence. Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period. NICE clinical guideline 129. London: National Institute for Health and Clinical Excellence, 2011.
16. Van Mieghem T, De Heus R, Lewi L, Klaritsch P, Kollmann M, Baud D, Vial Y, Shah PS, Ranzini AC, Mason L, Raio L, Lachat R, Barrett J, Khorsand V, Windrim R, Ryan G. Prenatal management of monoamniotic twin pregnancies. *Obstet Gynecol* 2014; **124**: 498-506.
17. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 144: Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol* 2014; **123**: 1118-1132.

18. National Institute for Health and Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman. NICE clinical guideline 62. http://guidance.nice.org.uk/CG62/NiceGuidance/pdf/English. [Accessed 27 June 2012].
19. Ward Platt MP, Glinianaia SV, Rankin J, Wright C, Renwick M. The North of England Multiple Pregnancy Register: five-year results of data collection. *Twin Res Hum Genet* 2006; **9**: 913-918.
20. Glinianaia SV, Rankin J, Sturgiss SN, Ward Platt MP, Crowder D, Bell R. The North of England Survey of Twin and Multiple Pregnancy. *Twin Res Hum Genet* 2013; **16**: 112-116.
21. D'Antonio F, Khalil A, Dias T, Thilaganathan B, Southwest Thames Obstetric Research C. Early fetal loss in monochorionic and dichorionic twin pregnancies: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 632-636.
22. NorSTAMP Steering Group. Northern Survey of Twin and Multiple Pregnancy (NorSTAMP): Standards of Care for Multiple Pregnancies. Final Version – July 2009. http://www.nepho.org.uk/uploads/doc/vid_3497_Twins%20standards-Final%20version.pdf. [Accessed 23 July 2015].
23. Anonymous. Birthweight, Head Circumference and Length for Gestational Age. Edinburgh: Information and Statistics Division of the Scottish Health Service, Common Services Agency, 1991.
24. Min SJ, Luke B, Gillespie B, Min L, Newman RB, Mauldin JG, Witter FR, Salman FA, O'sullivan MJ. Birth weight references for twins. *Am J Obstet Gynecol* 2000; **182**: 1250-1257.

25. Glinianaia SV, Jarvis S, Topp M, Guillem P, Platt MJ, Pearce MS, Parker L, SCPE Collaboration of European Cerebral Palsy Registers. Intrauterine growth and cerebral palsy in twins: a European multicenter study. *Twin Res Hum Genet* 2006; **9**: 460-466.
26. Richmond S, Atkins J. A population-based study of the prenatal diagnosis of congenital malformation over 16 years. *BJOG* 2005; **112**: 1349-1357.
27. World Health Organization. Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99). In *International statistical classification of diseases and related health problems: 10th revision*. World Health Organization: Geneva, Switzerland, 2010.
28. European Surveillance of Congenital Anomalies. EUROCAT syndrome guide: definition and coding of syndromes. www.eurocat-network.eu/content/EUROCAT-Syndrome-Guide-6-2008.pdf. [Accessed 12 February 2014].
29. European Surveillance of Congenital Anomalies. Chapter 3.3: EUROCAT Subgroups of Congenital Anomalies (Version 2014). In *EUROCAT Guide 14 and reference documents*. EUROCAT Central Registry: Newtownabbey, UK, 2013.
30. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *Lancet* 2010; **375**: 649-656.
31. Derom C, Vlietinck R, Derom R, Van den Berghe H, Thiery M. Population-based study of sex proportion in monoamniotic twins. *N Engl J Med* 1988; **319**: 119-120.
32. DeFalco LM, Sciscione AC, Megerian G, Tolosa J, Macones G, O'Shea A, Pollock MA. Inpatient versus outpatient management of monoamniotic twins and outcomes. *Am J Perinatol* 2006; **23**: 205-211.
33. Cordero L, Franco A, Joy SD. Monochorionic monoamniotic twins: neonatal outcome. *J Perinatol* 2006; **26**: 170-175.

34. Baxi LV, Walsh CA. Monoamniotic twins in contemporary practice: a single-center study of perinatal outcomes. *J Matern Fetal Neonatal Med* 2010; **23**: 506-510.

35. Office for National Statistics. Table 2 Live births (numbers and rates): age of mother and administrative area of usual residence, England and Wales, 2013. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsbyareaofusualresidenceofmotheruk. [Accessed 17 August 2017].

36. Department for Communities and Local Government. The English Indices of Deprivation 2010. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6871/1871208.pdf. [Accessed 14 June 2017].

37. Allen VM, Windrim R, Barrett J, Ohlsson A. Management of monoamniotic twin pregnancies: a case series and systematic review of the literature. *BJOG* 2001; **108**: 931-936.

38. Demaria F, Goffinet F, Kayem G, Tsatsaris V, Hessabi M, Cabrol D. Monoamniotic twin pregnancies: antenatal management and perinatal results of 19 consecutive cases. *BJOG* 2004; **111**: 22-26.

39. Heyborne KD, Porreco RP, Garite TJ, Phair K, Abril D, Obstetrix/Pediatrix Research Study Group. Improved perinatal survival of monoamniotic twins with intensive inpatient monitoring. *Am J Obstet Gynecol* 2005; **192**: 96-101.

40. Ezra Y, Shveiky D, Ophir E, Nadjari M, Eisenberg VH, Samueloff A, Rojansky N. Intensive management and early delivery reduce antenatal mortality in monoamniotic twin pregnancies. *Acta Obstet Gynecol Scand* 2005; **84**: 432-435.

41. Pasquini L, Wimalasundera RC, Fichera A, Barigye O, Chappell L, Fisk NM. High perinatal survival in monoamniotic twins managed by prophylactic sulindac, intensive

494 ultrasound surveillance, and Cesarean delivery at 32 weeks' gestation. *Ultrasound Obstet*
495 *Gynecol* 2006; **28**: 681-687.
496 42. Dias T, Mahsud-Dornan S, Bhide A, Papageorghiou AT, Thilaganathan B. Cord
497 entanglement and perinatal outcome in monoamniotic twin pregnancies. *Ultrasound*
498 *Obstet Gynecol* 2010; **35**: 201-204.
499 43. Rossi AC, Prefumo F. Impact of cord entanglement on perinatal outcome of
500 monoamniotic twins: a systematic review of the literature. *Ultrasound Obstet Gynecol*
501 2013; **41**: 131-135.
502 44. Lewi L. Cord entanglement in monoamniotic twins: does it really matter? *Ultrasound*
503 *Obstet Gynecol* 2010; **35**: 139-141.

Table 1. Baseline characteristics in monochorionic monoamniotic twin pregnancies, NorSTAMP and STORK, 2000-2013

	NorSTAMP n=47	STORK n=38	P value
Maternal age (y)*	27.0 (22.3-31.8)	30.5 (27.8-33.0)	0.035
Maternal BMI at booking (kg/m^2)	24.1 (22.8-31.5)†	24.3 (22.5-28.3)†	0.53
Most deprived quintile (IMD score)	17/36 (47.2)†	4/37 (10.8)	0.001
Female sex	24/42 (57.1)	21/25 (84.0)	0.03
Nulliparous	23/42 (54.8)	22 (57.9)	0.82
Prenatal diagnosis	47 (100.0)	38 (100.0)	n/a
Pregnancies affected by a major congenital anomaly‡	10 (21.3)	13 (34.2)	0.22
Caesarean delivery§	28/36 (77.8)§	21/22 (95.5)	0.13

Mann-Whitney U test was used for testing differences in distribution of continuous variables between the cohorts reporting medians (interquartile range, IQR), the X^2 test (Fisher exact test) was used for testing differences in categorical variables reporting n (%).

*Maternal age was recorded at delivery in NorSTAMP and at booking in STORK.

†There were missing data in some variables (NorSTAMP: sex n=5; parity n=5; BMI n=16, IMD score n=11, maternal age n=3; STORK: BMI n=8)

‡There were pregnancies where both twins were affected by a congenital anomaly: NorSTAMP – n=3, STORK – n=3.

§Presented for pregnancies resulting in at least one registered birth: NorSTAMP: 8 women had spontaneous vertex delivery: 2 resulted in both antepartum stillbirths, three births were at <28 weeks of gestation: one at 22 and two at 26 weeks of gestation; and there were 3 pregnancies with an early fetal loss: STORK: one pregnancy with a single antepartum stillbirth had a vaginal delivery.

IMD=Index of multiple deprivation, an area-based measure of socio-economic position, based on the maternal residential postcode; quintile groups were calculated using the categories given in the IMD tool by the National Perinatal Epidemiology Unit (NPEU), University of Oxford https://tools.npeu.ox.ac.uk/imd/**.** Most deprived group was defined as the 5th quintile of the IMD score (≥34.18).

524 **Table 2.** Pregnancy outcomes with causes of death of monochorionic monoamniotic twin pregnancies, NorSTAMP and STORK, 2000-2013

525 **a) Pregnancies with intrauterine death (IUD) at <24 weeks**

	n	Cause/ Indication	Co-twin
Pregnancies with IUD at <24 weeks			
Live birth and IUD	**3**		
	1	TRAP, acardiac twin	Alive at 12 months
	1	TRAP, acardiac twin	Alive at 12 months, VSD
	1	PROM at 21+2wk, born at 25 wk - ENND (pulmonary immaturity)	IUD at 23+2 wk, IUGR, placental insufficiency
Double IUD (<16 wks)	**11**		
	4	Missed abortion	
	1	Double IUD at 14 wk, TTTS	
	1	Double IUD at 11+6 wk	
	3	TRAP, acardiac twin	IUD at 12-14 wk
	2	Urinary anomaly	IUD at 12-14 wk
Double IUD (16-23 wks)	**6**		
	1	AP hypoxia at 21 wk	pURSM sequence
	1	Placenta insufficiency, placenta abruption, reverse EDF at 19+5 wk, IUD at 20+5 wk	Placenta insufficiency, IUD at 17+5 wk
	2	Double IUD (unexplained) at 19+2 wk and at 22 wk	
	1	TTTS at 23 wk	
	1	Unexplained IUD at 18wk	
TOP	**7**		
	1	Copper storage disorder (both twins)	
	1	Body stalk anomaly (both twins)	
	1	Body stalk anomaly	Bladder exstrophy
	1	Increased NT	Body stalk anomaly

	1	Amniotic bands	Orofacial cleft
	2	No fetal anomaly (either twin)	
Selective feticide and live birth	**3**		
	1	Encephalocele	Alive at 12 months
	1	Multiple anomalies (spina bifida, exomphalos)	Alive at 28 days
	1	Hydrocephalus	Alive at 28 days
Total	**30**		

b) Live births and pregnancies with IUD at ≥24 weeks

	n deaths	**Cause/ Indication**	**Co-twin**
Live births and pregnancies with IUD at ≥24 weeks			
Double AP stillbirths	**2**		
	1	Unexplained AP hypoxia at 24 wk (both twins)	
	1	AP hypoxia due to cord entanglement* at 32 wk (both twins)	
Live birth and IUD	**4**		
	1	AP hypoxia due to cord entanglement* (27 wk)	Alive at 12 months
	3	AP hypoxia	Alive at 28 days
Both live births	**49**		
Both survived first 28 days	43	n/a	n/a
Single neonatal death			
	1	Diaphragmatic hernia, secondary hypoplasia of lungs (delivered at 34 wk)	Alive at 12 months
	2	CHD	Alive at 28 days
	1	HMD, extensive IVH, sepsis, seizures, renal failure (26 wk)	HMD, alive at 12 months
Both neonatal deaths			

	1	Extreme prematurity (26 wk), HMD, complex CHD	Extreme prematurity, HMD, IVH
	1	Extreme prematurity (22 wk), severe HMD (both twins)	
Total	**55**		

Table footnote: pregnancies with conjoined twins are not included

*This cause of death was specified if the definite post-mortem diagnosis was available.

AP = antepartum, IUD = intrauterine death; TOP = termination of pregnancy, NT = nuchal translucency; pURSM sequence = Partial urorectal septum malformation sequence (or 'persistent cloaca'); TTTS= twin-twin transfusion syndrome; EDF = end-diastolic flow on umbilical artery Doppler; ENND= early neonatal death; HMD = hyaline membrane disease; CHD =Congenital heart disease, IVH = intraventricular haemorrhage.

534 **Table 3.** Perinatal mortality with cause of death in monochorionic monoamniotic (MCMA)

535 twin pregnancies, NorSTAMP and STORK, 2000-2013

Cause of death	Stillbirth* n (rate per 1000 total twin births)	Neonatal death n (rate per 1000 twin live births)	Perinatal death† n (rate per 1000 total twin births)
Congenital anomaly		4 (37.0)	4 (34.5)
Antepartum hypoxia (cord entanglement n=3)	8 (69.0)		8 (69.0)
Prematurity‡		5 (46.3)	5 (43.1)
Total	8 (69.0)	9 (83.3)§	17 (146.6)
Total MCMA twins (n)	116	108	116

536 *Stillbirth rate is calculated per 1000 registered births in MCMA twin maternities, excluding
537 single fetal losses at <24 weeks of gestation (n=6) in pregnancies resulting in a single live
538 birth.
539 †Perinatal deaths include stillbirths (≥24 weeks of gestation) and neonatal (0-27 days) deaths.
540 ‡Prematurity category includes related cause codes: severe pulmonary immaturity, hyaline
541 membrane disease and intraventricular haemorrhage.
542 §Four pregnancies resulted in neonatal deaths at <27 weeks of gestation: two co-twins at 22
543 weeks of gestation (both early neonatal deaths, ENNDs), one ENND at 25 weeks, two co-
544 twins (ENND with complex congenital heart disease and late neonatal death due to severe
545 hyaline membrane disease) and one single late neonatal death at 26 weeks.

546 **Table 4.** Antenatal parameters and obstetric and neonatal outcomes of monochorionic
547 monoamniotic (MCMA) twins, NorSTAMP and STORK, 2000-2013

Antenatal parameters (45 pregnancies: 5 stillbirths and 85 live births)	
Gestational age at US chorionicity diagnosis median (IQR)	13.0 (12.0-14.0)
Estimated fetal weight (EFW) *n*=25 median (IQR)*	
The smaller twin	1711.0 (1443.5-1910.5)
The bigger twin	1850.0 (1580.5-2070.0)
SGA based on EFW (<10 percentile†) *n %*	1 (4.0)
Inter-twin EFW discordance median (IQR) (%)	6.8 (3.3-16.5)
sGR (EFW discordance (>20%) n (%)	5 (20.0)
Diagnosis of TTTS *n* (%)	2/45 (4.9)
Definite diagnosis of cord entanglement *n* (%)‡	40/44 (90.1)
Diagnosis of inter-twin growth discordance *n* (%)	2/45 (4.4)
Antenatal diagnosis of a major congenital anomaly *n* fetuses (%)	5/90 (5.6)
Evidence of abnormal Doppler parameters at the last scan* *n* fetuses (%)	0/53 (0.0)
Obstetric outcomes (45 pregnancies: 5 stillbirths and 85 live births)	
Elective CS *n* (%)	33 (73.3)
Emergency CS *n* (%)	9 (20.0)
Gestational age at delivery *n*=44 median (IQR)	33 (32-34)
<34 weeks *n* deliveries (%)	25 (56.8)
<32 weeks *n* deliveries (%)	7 (15.9)
<30 weeks *n* deliveries (%)	2 (4.5)
Birthweight median *n*=44 (IQR) (g)	
The smaller twin	1800 (1542.3-2004.5)
The bigger twin	1964.5 (1659.5-2150.3)
SGA (<10 percentile)† *n* %	4/86 (4.7)
Inter-twin birthweight discordance median (IQR) (%)	6.4 (1.9-12.8)
Inter-twin birthweight discordance (>20%) *n* %	4 (9.1)
Birthweight discordance (>15%) *n* %	8 (18.2)
Neonatal death *n* (% of live births)	5 (5.9)
Pregnancies complicated by a major congenital anomaly *n* %	5 (11.1)
Resulting in neonatal death with congenital anomaly as a major cause	3 (6.7)
Neonatal outcomes (n=73 neonatal survivors)§	
Admitted to SCBU *n* (%)	54 (74.0)
Days at SCBU	
Twin 1 median (IQR)¶	18.5 (6.0-28.3)
Twin 2 median (IQR)¶	16.5 (6.0-35.0)
Mechanical ventilation *n* (%)	11 (15.1)
CPAP *n* (%)$	23/42 (54.8)
Respiratory distress syndrome *n* (%) $	27/46 (58.7)
Necrotising enterocolitis[f] *n* (%) $	1/55 (1.8)
Sepsis (confirmed or suspected/treated with antibiotics) *n* (%)$	2/55 (3.6)
Intraventricular haemorrhage *n*=36 (%)$	0 (0.0)

548 * Only estimated fetal weights (EFW) and Doppler parameters examined at gestational age of
549 2 weeks or less prior to delivery are included.
550 † Birthweight <10th percentile was calculated to define small for gestational age (SGA)
551 infants using birthweight-by-gestation and sex standards from a population of Scottish
552 twins;[23] EFW <10th percentile was calculated to define SGA *in utero* using fetal growth
553 curves from the USA ultrasound data[24] adjusted to fit the Scottish reference dataset.[23]
554 ‡ In one pregnancy resulting in both early neonatal deaths (22 wks of gestation) there was no
555 comment on cord conditions.
556 § STORK pregnancies with missing data on neonatal outcomes are excluded (n=4).
557 ¶ missing data for 7 of 29 1st twins and for 9 of 25 2nd twins admitted to SCBU.
558 $Calculated using complete data for this parameter.
559 CS=caesarean section; CPAP=continuous positive airway pressure; SCBU=Special Care
560 Baby Unit; sFGR= selective fetal growth restriction defined as difference in EFW of greater
561 than 20%.[10]

Figure legends

Figure 1. Derivation of the study cohort of monochorionic monoamniotic (MCMA) twin pregnancies using population-based North of England data from the Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) and data from the multicentre Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple birth cohort, 2000-2013

Figure 1 footnote:

*Pregnancies with conjoined twins are excluded (n=12 in NorSTAMP, n=4 in STORK); IUD=intrauterine death; TOPFA= termination of pregnancy for fetal anomaly.

Maternities are defined as pregnancies with at least one live birth or stillbirth (fetal death at ≥24 weeks of gestation), including pregnancies with one early fetal loss.

Figure S1. Principles of active management of patients with monochorionic monoamniotic (MCMA) pregnancy in the Department of Fetal Medicine, Royal Victoria Infirmary (RVI), Newcastle upon Tyne

Figure 1. Derivation of the study cohort of monochorionic monoamniotic (MCMA) twin pregnancies using population-based North of England data from the Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) and data from the multicentre Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple birth cohort, 2000-2013

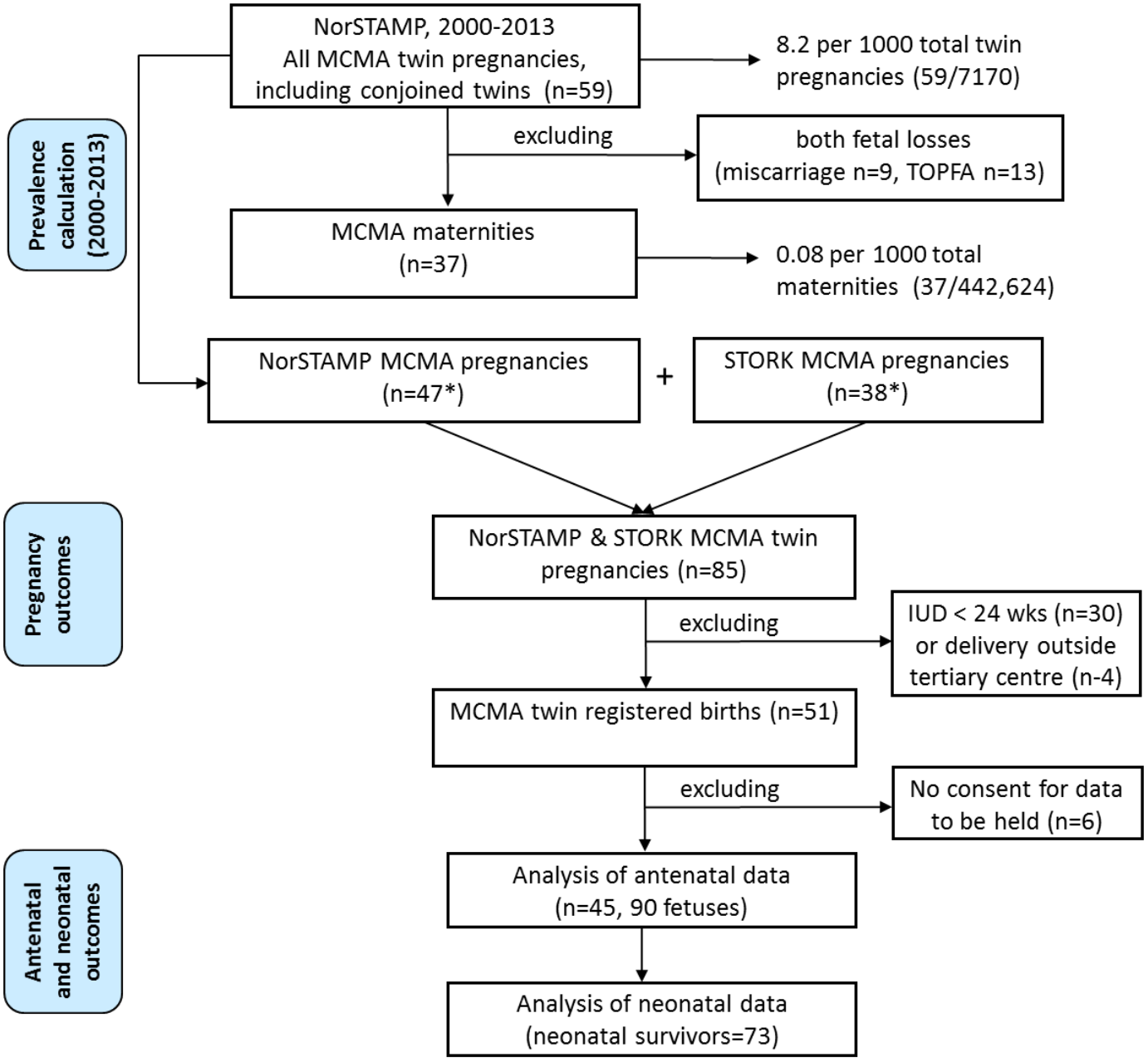
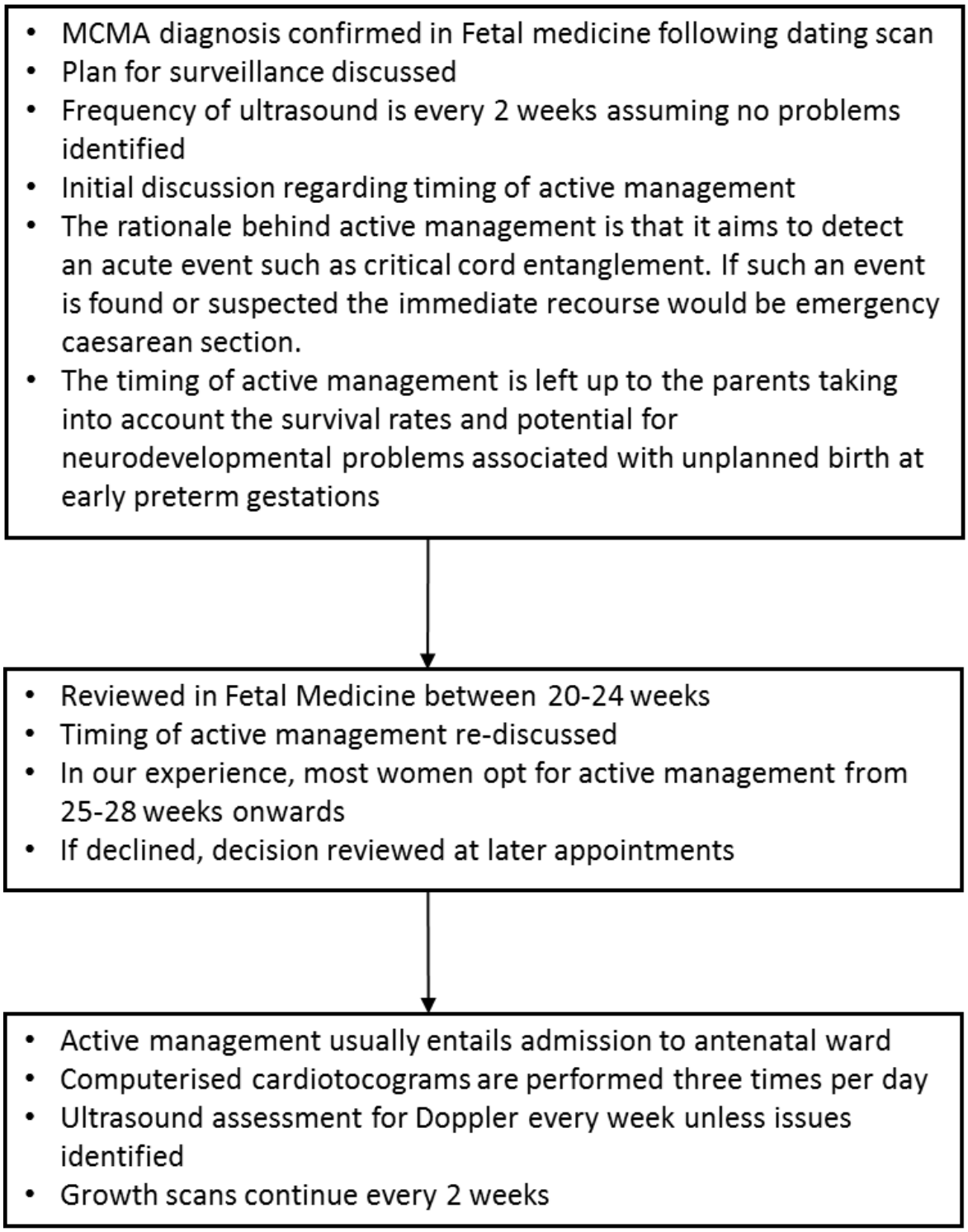


Figure footnote:
*Pregnancies with conjoined twins are excluded (n=12 in NorSTAMP, n=4 in STORK);
IUD=intrauterine death; TOPFA= termination of pregnancy for fetal anomaly.
Maternities are defined as pregnancies with at least one live birth or stillbirth (fetal death at ≥24 weeks of gestation), including pregnancies with one early fetal loss.

590 **Figure S1**. Principles of active management of patients with monochorionic monoamniotic
591 (MCMA) pregnancy in the Department of Fetal Medicine, Royal Victoria Infirmary (RVI),
592 Newcastle upon Tyne

593



594
595