Effect of monochorionicity on perinatal outcomes and growth discordance in triplet pregnancies: a collaborative multicentre study in England, 2000–2013

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Short title: Triplet outcomes by chorionicity

Keywords: triplets, monochorionic placentation, Northern Survey of Twin and Multiple Pregnancy (NorSTAMP), STORK collaboration, perinatal mortality, stillbirth, congenital anomalies

CONTRIBUTION

What are the novel findings of this work?

Monochorionic placentation in a triplet pregnancy was associated with a 5.4-fold increased risk of stillbirth, mainly due to feto-fetal transfusion syndrome, and with a higher risk of size discordance.

Gestational age at delivery (median=33 weeks of gestation) and neonatal outcomes did not differ by chorionicity type.

What are the clinical implications of this work?

Given the rarity of triplet pregnancies, in particular, few published data on pregnancy outcomes by chorionicity type, this collaborative data should be valuable for future studies aiming to build a robust evidence base for developing optimal management and timing of delivery in these pregnancies.

ABSTRACT

Objectives: To compare perinatal outcomes and growth discordance between trichorionic-triamniotic (TCTA) and dichorionic-triamniotic/monochorionic-triamniotic (DCTA/MCTA) triplets.

Methods: This multicentre cohort study used population-based data from 11 Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) and the Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple pregnancy cohort for 2000-2013. Perinatal outcomes (from ≥ 24 weeks' gestation to the first 28 days of life), inter-triplet fetal growth and birth weight discordance, and neonatal morbidity were analysed in relation to chorionicity.

Results: Monochorionic placentation in a triplet pregnancy (n=72) was associated with a significantly increased risk of perinatal mortality (RR=2.7, 1.3-5.5) compared with TCTA pregnancies (n=68), mainly due to a much higher stillbirth risk (RR=5.4, 1.6-18.2), in 57% resulting from feto-fetal transfusion syndrome. This persisted in pregnancies not affected by a major congenital anomaly, but there was no significant difference in neonatal mortality (*P*=0.60). DCTA/MCTA triplets had lower birth weights and demonstrated higher rates of birth weight discordance than TCTA triplets (*P*=0.049). Severe BW discordance of greater than 35% was also 2.5-fold higher in DCTA/MCTA (26.1% vs 10.4%), but this did not reach statistical significance (*P*=0.06) presumably due to low numbers. Triplets in both groups were delivered by caesarean section in over 95% of cases at a similar gestational age (median=33 weeks' gestation). The frequencies of respiratory (*P*=0.28) or infectious (*P*=0.08) neonatal morbidity were also similar.

Conclusions Despite close antenatal surveillance, monochorionic placentation in a triplet pregnancy was associated with a significantly increased stillbirth risk, mainly due to feto-fetal

transfusion syndrome and selective fetal growth restriction. For live born triplets there was no adverse effect of monochorionicity on neonatal outcomes.

INTRODUCTION

After a consistent increase in triplet rates from the early 1980-s mostly as a result of a wider use of assisted reproduction techniques (ART), from 1998 onwards triplet prevalence gradually declined in the UK,[1-3] similar to other developed countries,[4,5] due to the regulations of fertility treatment regimes. Triplets have a higher risk of adverse perinatal outcomes compared with singletons and twins mainly due to higher rates of preterm birth, low birth weight and congenital anomalies.[6,7] Consistent with data from twin pregnancies, perinatal risks might be expected to vary depending on chorionicity type, although there is a paucity of evidence to support this assumption. The risk of perinatal death in dichorionic triamniotic (DCTA) compared to trichorionic triamniotic (TCTA) triplets was found to be 5.5-fold higher in spontaneously conceived and 8-fold higher in ART-conceived UK cohorts.[8,9] However, the difference in risks of perinatal death between DCTA and TCTA triplets was not confirmed in studies from other countries,[10-13] likely due to lack of statistical power in most studies.

The UK 2011 NICE guideline on management of multiple pregnancy recommends specialist antenatal care for women with triplet pregnancies and referral to a tertiary centre for timely delivery to minimise the risks, but the evidence for optimal clinical management, in particular with regard to chorionicity, is scarce.[14] A recent systematic review of nine studies reporting a 3.3 higher risk of perinatal death in DCTA compared to TCTA pregnancies,[15] concluded that there is still insufficient evidence on the pregnancy outcome by triplet chorionicity from high quality epidemiological data.

We aimed to analyse perinatal outcomes, growth discordance and clinical management of triplet pregnancies using multicentre data from the NorSTAMP and from the Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple pregnancy cohort for 2000-2013.

METHODS

Data sources and study population

The NorSTAMP (established in 1998, data collection ceased 31st March 2015) collected data on multiple pregnancies in the North of England (North East and North Cumbria, population of approximately 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[16]) and then at the 20-week routine ultrasound and at delivery (details of the registration system are given elsewhere[17,18]). The records were maintained and held at the Regional Maternity Survey Office (RMSO), Public Health England (PHE), on a single database linked thorough the mother's details to other RMSO registers, including the Northern Congenital Abnormality Survey (NorCAS) and Perinatal Mortality Survey (PMS).[18] The RMSO data were cross-validated on a yearly basis with the Office for National Statistics (ONS) birth and death data. North of England maternity units follow the regional guidance, agreed and implemented in 2009,[19] which is consistent with the 2011 NICE recommendations for the antenatal management of twin and triplet pregnancies.[14] Information on type of conception is not recorded in the NorSTAMP.[18]

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 (each hospital's obstetric ultrasound and maternity records).[20] The STORK maternity units also follow the NICE recommendations.[14] Triplet data for this study were collected from the obstetric ultrasound and maternity databases of St George's University Hospital (SGH) only.

Inclusion criteria and Definitions

All triplet maternities (i.e. pregnancies resulting in at least one stillbirth or live birth including those with a spontaneous early loss of one or two fetuses), plus initially triplet pregnancies that were reduced to a twin or singleton pregnancy, delivered during 1998-2013 and notified to the NorSTAMP, were included in the calculation of the triplet prevalence. Chorionicity of a triplet pregnancy was diagnosed both antenatally (at a first trimester ultrasound scan) in both centres and confirmed postnatally by placenta pathology or documentation of the three separate placentae for TCTA pregnancies (n=79 (71%) out of 112 NorSTAMP cases with diagnosed chorionicity and in all SGH cases of the STORK cohort). Chorionicity was verified and more detailed data on antenatal development were obtained from the serial ultrasound scans in the Fetal Medicine database of the Royal Victoria Infirmary (RVI), Newcastle tertiary centre. Women who refused to give consent to their confidential data to be held in the NorSTAMP were not included in the analysis of individual antenatal or neonatal data (n=8). The analysis of perinatal mortality and other outcomes by chorionicity using both NorSTAMP and STORK (SGH) triplet pregnancies was restricted to deliveries during 2000-2013 because a more standardised approach to antenatal surveillance of triplet pregnancies across the North of England maternity units was applied from 2000. 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.

The following indicators of fetal growth and wellbeing were analysed: inter-triplet BW discordance; inter-triplet discordance in estimated fetal weight (EFW); feto-fetal transfusion syndrome (FFTS) in a MC triplet pair, evidence of abnormal umbilical artery Doppler (pulsatility index >95th centile based on the reference ranges provided in the Viewpoint ultrasound reporting system[21] used in both RVI and SGH, absent or reversed end-diastolic flow) at the last ultrasound scan within two weeks before delivery. To define the inter-triplet discordance, we adopted the approach proposed by Blickstein et al[22] who defined concordant

sets as those with a difference in BW of less or equal to 25%, and differences of over 25% to 35% and 35% or more were defined as moderate and severe discordance, respectively. Following this approach, we also calculated the relative BW of the middle triplet by dividing the difference between the middle and the smallest triplets by the difference between the largest and the smallest triplets. The middle triplet was defined as symmetrical if the ratio was between 0.25 and 0.75 (i.e. within ±25% of the average between the largest and smallest triplet), low-skew if <0.25 (one large and two small triplets in a set) and high-skew if >0.75 (two large and one small triplets).[22] Inter-triplet discordance in EFW has been defined similar to the BW discordance.

The following maternal, obstetric and infant variables were used: maternal age, maternal body mass index (BMI) at booking, index of multiple deprivation (IMD) score (an area-based measure of socioeconomic position based on the maternal residential postcode, analysed in quintiles), mode of delivery, gestational age at delivery, birth weight (BW), sex, gestational age at diagnosis of multiple pregnancy, chorionicity type and pregnancy outcomes, including congenital anomalies.[23]

Data on the following neonatal conditions and interventions were collected for triplets who survived the first 28 days of life: admission to Special Care Baby Unit (SCBU) and number of days if admitted, mechanical ventilation, continuous positive airway pressure (CPAP), respiratory distress syndrome (RDS), necrotising enterocolitis, sepsis, intraventricular haemorrhage. The NorSTAMP data were complemented and verified by anonymised neonatal data from the RVI SCBU database after the linkage with obstetric ultrasound records and from other regional maternity units in response to the authors' request.

In the PMS[24] and NorSTAMP immediate causes of perinatal death were classified using clinico-pathological classification[25] based on the Wigglesworth classification.[26] All non-malformed stillbirths were arbitrarily classified as dying of antepartum anoxia/hypoxia unless

death was due to a specific recognisable condition such as idiopathic hydrops fetalis, FFTS etc, or there was evidence of a congenital anomaly, isoimmunisation, trauma or infection.[25] Data on congenital anomalies for the North of England population were available from the NorCAS, which collects data on all cases of major congenital anomaly (up to six individual congenital anomalies per case) irrespective of the outcome. Cases are notified from multiple sources and are included when first diagnosed at any age up to 12 years.[27] Coding and classification of major congenital anomalies according to European Surveillance of Congenital Anomalies (EUROCAT) criteria have been described previously.[23] Congenital anomalies in the STORK cohort were recorded based on ultrasound scan diagnosis confirmed at birth.

Statistical analysis

The triplet prevalence was estimated as the number of triplet maternities per 10,000 total maternities. The triplet prevalence at birth was estimated using triplet pregnancies resulting in all registered stillbirths or live births per 10,000 total maternities resulting in registered births. The 2-tailed Fisher exact test was used to compare the temporal change in the triplet prevalence between 1998-2005 and 2006-2013, as well as perinatal, stillbirth and neonatal mortality rates between chorionicity groups and over time. Differences in the distributions of continuous variables were compared using the Mann–Whitney *U*-test and medians with interquartile range (IQR) were reported. All analyses were performed using SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp). $P < 0.05$ was considered statistically significant.

RESULTS

Prevalence of triplet pregnancies (NorSTAMP, 1998-2013)

Among 505,096 total (singleton, twin, triplet and higher order) maternities during 1998-2013, 182 triplet pregnancies, including 17 resulting in a spontaneous or iatrogenic loss of all three fetuses (at <24 weeks of gestation), were notified to NorSTAMP (Figure 1). There were 165 triplet maternities that resulted in at least one registered birth, including eight pregnancies with a selective termination of pregnancy for a congenital anomaly (n=1) or a selective reduction of pregnancy (n=7), giving the triplet rate of 3.27 (95% CI 2.79-3.81) per 10,000 maternities. The triplet prevalence at birth was 2.48 (95% CI 2.06-2.95) per 10,000 maternities resulting in births of all triplets (125/504,701). The total triplet prevalence declined from 3.98 (95% CI 3.22-4.86) to 2.62 (95% CI 2.04-3.31) per 10,000 maternities between 1998-2005 and 2006-2013 (RR=0.66, 95% CI=0.48-0.90, *P* =0.008).

Pregnancy outcomes of triplet pregnancies (NorSTAMP and STORK, 2000-2013)

Overall, of 184 NorSTAMP and STORK triplet pregnancies delivered during 2000-2013, 168 pregnancies (NorSTAMP n=128 and SGH n=40) resulted in at least one stillbirth or live birth (Figure 1). Among 168 triplet maternities, nine were reduced to twins or singletons, which were excluded from further analysis leaving 159 (477 triplets) maternities with 444 triplets resulting in a registered birth (stillbirth or live birth). There were 68 TCTA triplet pregnancies, 59 DCTA, 13 MCTA, four dichorionic diamniotic (DCDA), three monochorionic diamniotic (MCDA) and 12 pregnancies with missing chorionicity data. There were no monoamniotic triplet pregnancies in this dataset. Maternal and pregnancy baseline characteristics of TCTA and DCTA/MCTA pregnancies are shown in Table 1.

The overall perinatal mortality was 83.3 per 1000 registered births (Table 2), with no significant decline over time (2007-2013 vs 2000-2006) in either stillbirth (RR=0.77, 95% CI

0.34-1.76, *P* =0.67) or neonatal mortality rates (RR=1.19, 95% CI 0.43-3.34, *P*=0.79). The presence of a monochorionic pair in a triplet pregnancy (DCTA/MCTA pregnancies) was associated with an increased risk of stillbirth (RR=5.41, 95% CI 1.61-18.16, *P*=0.002) and perinatal mortality (RR=2.65, 95% CI 1.27-5.53, *P*=0.007) compared with TCTA pregnancies, but there was no significant difference in neonatal mortality (RR=1.37, 95% CI 0.49-3.87, *P*=0.60).

Increased stillbirth and perinatal mortality rates in triplet pregnancies with a monochorionic placentation were mainly attributed to FFTS which caused 64.7% of stillbirths in DCTA/MCTA pregnancies and 56.5% of all stillbirths (n=13, with five double IUDs and one triple IUD). Overall, 25% of DCTA/MCTA pregnancies (9/36) were complicated by FFTS. The second common cause of antepartum stillbirth was antepartum hypoxia (n=8, 34.8%), with four IUDs in DCTA/MCTA, three IUDs in TCTA and one IUD in a pregnancy with uncertain chorionicity. The vast majority of neonatal deaths (n=12) were due to prematurity causes such as pulmonary immaturity (n=11) and intraventricular haemorrhage (n=1), with two deaths due to necrotising enterocolitis. The median gestational age at delivery in pregnancies resulting in at least one neonatal death was 24 gestational weeks (IQR=22.5-26.5).

In 159 triplet maternities, 18 single triplets were affected by a major congenital anomaly in three TCTA pregnancies (16.7%), 13 DCTA pregnancies (72.2%), one MCDA pregnancy and in one pregnancy with missing chorionicity. The affected pregnancies resulted in three IUDs, one feticide for a congenital anomaly and 14 live births. The prevalence of congenital anomalies in DCTA pregnancies was 4 times higher than in TCTA pregnancies (RR=4.09, 95% CI 1.18-14.15, *P*=0.02). The exclusion of two pregnancies with a twin-related anomaly (acardiac fetus) reduced the RR to 3.56 (95% CI 1.01-12.58, *P*=0.054). After exclusion of pregnancies affected by a congenital anomaly, the stillbirth (RR=5.59, 95% CI 1.65-18.95,

P=0.003) and perinatal mortality (RR=2.73, 95% CI 1.30-5.76, *P*=0.008) were still significantly higher in DCTA/MCTA (n=59) compared to TCTA (n=65) pregnancies.

Inter-triplet growth discordance in TCTA and DCTA/MCTA pregnancies

For comparison of growth discordance parameters and neonatal morbidity between TCTA and DCTA/MCTA triplets, pregnancies complicated by a major congenital anomaly of a triplet (n=18), resulting in an IUD at <24 weeks of gestation (n=25), pregnancies of patients who refused to give consent to held their confidential data in NorSTAMP (n=8) and those with other (n=6) or unknown (n=6) chorionicity, were excluded. This resulted in a final sample of 96 triplet pregnancies: 49 TCTA and 47 DCTA/MCTA (Table 3). No antenatal parameters of fetal growth were significantly different between TCTA and DCTA/MCTA triplet pregnancies. For example, severe EFW discordance was two-fold higher in triplet pregnancies with MC placentation (16.7%) compared to TCTA (6.9%) pregnancies but this was not statistically significant (*P*=0.39). In contrast, the distribution of the BW discordance between the smallest and the largest triplets was significantly different between these groups of triplets (*P*=0.049). Similarly, the BW distribution of the smallest (*P*=0.015) and the largest (*P*=0.023) triplet was different between the two groups, with the median BW of the smallest and the largest triplet being about 150g and 200g respectively larger in TCTA triplet pregnancies. Severe BW discordance was 2.5-fold higher in DCTA/MCTA (26.1%) than in TCTA triplets (10.4%), but it did not reach statistical significance (*P*=0.062). Moreover, the percentage of the *low-skew* middle triplets was significantly higher in DCTA/MCTA (23.9%) compared to TCTA triplets (4.2%, *P*=0.007) while the percentage of the symmetrical middle triplets was similar between the groups.

Modality of birth and neonatal morbidity in TCTA and DCTA/MCTA triplets

The vast majority of pregnancies in both triplet groups were delivered by Caesarean section (CS) (97.9% in TCTA and 95.7% in DCTA/MCTA triplets), with a significantly higher percentage of elective CS in TCTA triplets (P=0.038) compared with the higher percentage of deliveries by emergency CS in the other group. The median gestational age at delivery of 33 weeks was similar for both groups (Table 3). Neonatal outcomes were comparable between 139 neonates from 48 TCTA pregnancies and 115 neonates from 43 DCTA/MCTA pregnancies who survived the neonatal period. Over 88% of triplets in both groups were admitted to SCBU with the length of stay at around 20 days. The indicators of respiratory and infectious morbidity were also similar in both groups (Table 3).

DISCUSSION

Main findings

Using population-based NorSTAMP data, this study reports a significant decline in the triplet rates in the North of England between 1998-2005 and 2006-2013. Collaborative NorSTAMP and STORK triplet data showed that compared with TCTA pregnancies, the presence of a monochorionic pair in a triplet pregnancy was associated with a 5.4-fold increased risk of stillbirth, but no difference in neonatal mortality. FFTS, a complication of monochorionic placentation, was a major cause of stillbirth (56.5%) followed by antepartum hypoxia (34.8%). The magnitude of the higher risk of stillbirth and perinatal mortality for DCTA/MCTA pregnancies remained consistent after exclusion of pregnancies affected by a congenital anomaly. The indicators of BW discordance were more prominent in DCTA/MCTA than in TCTA triplets, although not all reached statistical significance. For example, severe BW discordance (>35%) was 2.5-fold higher in DCTA/MCTA than in TCTA triplets, but the p-value failed to reach statistical significance presumably due to small numbers. Triplets were delivered by CS in over 95% of cases in both groups at a similar gestational age of 33 weeks' gestation. The frequencies of respiratory or infectious neonatal morbidity were also comparable between the two groups.

Strengths and Limitations

A major strength of this collaborative study is that it was based on multicentre data from 11 NorSTAMP maternity units and the tertiary STORK hospital. Unique NorSTAMP features, such as ascertainment of multiple pregnancies from the earliest antenatal scan at which a multiple pregnancy was diagnosed, additional identification following miscarriage, link to other regional registers, including NorCAS, and annual cross-validation with the ONS, contributed to high case ascertainment, as well as completeness and accuracy of congenital

anomaly data. For the main analysis of outcomes, we excluded triplet pregnancies that underwent multifetal pregnancy reduction (MFPR), which is more commonly offered to women with MC/DC triplet pregnancies to avoid complications associated with a shared placenta.[28] Moreover, gestational age, BW and neonatal mortality were found to be significantly more favourable in pregnancies after MFPR,[29-31] therefore, inclusion of these pregnancies in the comparative analysis could introduce bias. For measuring inter-triplet growth discordance we used the approach introduced by Blickstein et al, 2003[22] that allows relative size assessment of all three triplets, giving more detailed information on the whole triplet set.

One of our study limitations is lack of data on mode of conception as the NorSTAMP could not capture ART data due to the restrictions by the Human Fertilisation and Embryology Acts.[18] In addition, data for some antenatal variables (e.g. EFW) and neonatal outcomes (e.g. days in SCBU, neonatal morbidity) were incomplete due to the retrospective nature of the study and the challenge in obtaining follow up data from all the participating hospitals. Although our study is multicentre, it lacks statistical power to provide robust statistical evidence of some associations (e.g. an increased rate of severe growth discordance in triplets with monochorionic placentation) due to the small sample size, which also did not allow subgroup analysis of DCTA and MCTA triplet pregnancies.

Interpretation and comparison with published studies

Our data showed a significant decline in triplet prevalence, consistent with the trends reported nationally from 1998[2] and in other developed countries.[1,4,5] Until a recent systematic review that summarised evidence from nine studies reporting perinatal outcomes of triplets by chorionicity,[15] the data showing a higher risk of perinatal death for DCTA compared to TCTA pregnancies from individual studies was inconsistent. This was likely due to differences in the triplet cohorts (e.g. spontaneously conceived triplets only,[8] iatrogenic triplets,[9] all triplets

irrespective of conception type,[10] DCTA only,[8,11,13] DCTA and MCTA combined[10,32]), small sample sizes and/or potential bias. There was no significant difference in stillbirth, neonatal mortality and perinatal mortality between DCTA and TCTA in a recent study from Portugal[11] but the sample sizes (n=44 and n=46, respectively) were relatively small. The systematic review using data for 1062 TCTA and 275 DCTA triplet pregnancies, reported a 3.3- and 4.6-fold higher risk of perinatal death and stillbirth, respectively.[15] Our findings of significantly higher risks of perinatal mortality and stillbirth in triplets with a monochorionic placentation are consistent with these findings.

Severe growth discordance (>35%) of 9.5% reported by Blickstein et al[22] for all triplets was comparable with that in TCTA triplets (10%) in our study, but not with a higher rate of 26% found in DCTA/MCTA triplets. A significantly higher percentage of BW discordance found in our study for DCTA/MCTA (median=23%) vs TCTA (17%) triplets is consistent with that in some published studies: medians 19% vs 15% in DCTA and TCTA respectively, in spontaneously conceived triplets (P<0.001),[8] medians 18% vs 17% respectively, in iatrogenic triplets, (P<0.001),[9] means 20.5% (DCTA/MCTA) vs 12.7% (TCTA) in all triplets.[10] EFW discordance was less prominent and statistically insignificant between DCTA (19%) and TCTA (14%) triplets.

Gestational age at delivery at a median of 33 weeks was comparable with a large Japanese study reporting no significant differences in median gestational age between TCTA and DCTA or MCTA pregnancies,[12] as well as with the summary results of the systematic review that were affected by the results of this largest study.[15] The findings from a recent US study which was not included in the systematic review also support our findings in relation to median gestational age at delivery for both groups, although the percentage of those delivered at <30 weeks was significantly higher for DC pregnancies.[13] Other studies reported significantly lower gestational age at delivery for DCTA triplets.[8,9,11,33]

Overall, CS delivery was similarly common in both triplet groups (>95%) in our cohort, with elective CS being more frequent in TCTA pregnancies. A very high rate of CS in both triplet groups was consistent with some recent studies from Japan and Portugal[11,12] but earlier UK studies reported lower CS rates in both iatrogenic (62%) and spontaneously conceived DCTA (77%) triplets compared to 88% in TCTA triplets in respective groups.[8,9] Neonatal mortality and the indicators of neonatal morbidity available in our study were not statistically different between the compared triplet groups. Respiratory morbidity associated with preterm delivery was the most frequent neonatal complication in triplet neonates.

Conclusion

Our multicentre study of triplet pregnancies during 2000-2013 provided additional evidence that monochorionic placentation in a triplet pregnancy was associated with a significantly increased risk of perinatal mortality and stillbirth, mainly due to feto-fetal transfusion syndrome, and with a higher risk of size discordance. For live born triplets, there was no adverse effect of monochorionicity on neonatal outcomes. In view of the rarity of some of these multiple pregnancies, this data should be valuable for future studies aiming to build a robust evidence base for developing optimal management and timing of delivery in these pregnancies.

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.

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Disclosure of interests

None declared. Completed Disclosure of Interests form available to view online as supporting information.

Details of ethics approval and patients' consent

The RMSO had Regional Multicentre Research Ethics Committee's approval (04/MRE04/25) for using the RMSO registers' data, including the NorSTAMP, for research studies. In line with the UK regulations, since 2005 a system of informed consent has been introduced for women's identifying details to be held by the NorSTAMP.[17] 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.

References

1. Blickstein I, Keith LG. The decreased rates of triplet births: temporal trends and biologic speculations. *Am J Obstet Gynecol* 2005; **193**: 327-331.
2. Simmons R, Doyle P, Maconochie N. Dramatic reduction in triplet and higher order births in England and Wales. *BJOG* 2004; **111**: 856-858.
3. Smith LK, Manktelow BN, Draper ES, Boyle EM, Johnson SJ, Field DJ. Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: population-based cohort study. *BMJ Open* 2014; **4**: e004514.
4. Martin JA, Osterman MJ, Thoma ME. Declines in Triplet and Higher-order Multiple Births in the United States, 1998-2014. *NCHS Data Brief* 2016: 1-8.
5. Tandberg A, Bjorge T, Nygard O, Bordahl PE, Skjaerven R. Trends in incidence and mortality for triplets in Norway 1967-2006: the influence of assisted reproductive technologies. *BJOG* 2010; **117**: 667-675.
6. Luke B, Brown MB. The changing risk of infant mortality by gestation, plurality, and race: 1989-1991 versus 1999-2001. *Pediatrics* 2006; **118**: 2488-2497.
7. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, Wilson EC. Births: final data for 2009. *Natl Vital Stat Rep* 2011; **60**: 1-70.
8. Adegbite AL, Ward SB, Bajoria R. Perinatal outcome of spontaneously conceived triplet pregnancies in relation to chorionicity. *Am J Obstet Gynecol* 2005; **193**: 1463-1471.
9. Bajoria R, Ward SB, Adegbite AL. Comparative study of perinatal outcome of dichorionic and trichorionic iatrogenic triplets. *Am J Obstet Gynecol* 2006; **194**: 415-424.
10. Geipel A, Berg C, Katalinic A, Plath H, Hansmann M, Germer U, Gembruch U. Prenatal diagnosis and obstetric outcomes in triplet pregnancies in relation to chorionicity. *BJOG* 2005; **112**: 554-558.

11. Simoes T, Queiros A, Goncalves MR, Periquito I, Silva P, Blickstein I. Perinatal outcome of dichorionic-triamniotic as compared to trichorionic triplets. *J Perinat Med* 2016; **44**: 875-879.
12. Kawaguchi H, Ishii K, Yamamoto R, Hayashi S, Mitsuda N, Perinatal Research Network Group in J. Perinatal death of triplet pregnancies by chorionicity. *Am J Obstet Gynecol* 2013; **209**: 36 e31-37.
13. Lopes Perdigao J, Straub H, Zhou Y, Gonzalez A, Ismail M, Ouyang DW. Perinatal and obstetric outcomes of dichorionic vs trichorionic triplet pregnancies. *Am J Obstet Gynecol* 2016; **214**: 659 e651-655.
14. National Institute for Health and Clinical Excellence (NICE). Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period. *NICE clinical guideline* **129**. NICE: London, 2011. https://www.nice.org.uk/guidance/cg129
15. Curado J, D'Antonio F, Papageorghiou A, Bhide A, Thilaganathan B, Khalil A. Perinatal mortality and morbidity in triplet pregnancies according to chorionicity: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **54**: 589-595.
16. National Institute for Health and Clinical Excellence (NICE). Antenatal care: routine care for the healthy pregnant woman. *NICE clinical guideline* **62**. NICE: London, 2008. http://guidance.nice.org.uk/CG62/NiceGuidance/pdf/English
17. 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.
18. 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.

19. 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.

20. 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.

21. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. *Am J Obstet Gynecol* 2005; **192**: 937-944.

22. Blickstein I, Jacques DL, Keith LG. A novel approach to intertriplet birth weight discordance. *Am J Obstet Gynecol* 2003; **188**: 1026-1030.

23. Glinianaia SV, Rankin J, Khalil A, Binder J, Waring G, Sturgiss SN, Thilaganathan B, Hannon T. Prevalence, antenatal management and perinatal outcome of monochorionic monoamniotic twin pregnancy: a collaborative multicenter study in England, 2000-2013. *Ultrasound Obstet Gynecol* 2019; **53**: 184-192.

24. Bell R, Glinianaia SV, Rankin J, Wright C, Pearce MS, Parker L. Changing patterns of perinatal death, 1982-2000: a retrospective cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F531-536.

25. Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal factors. *Br J Obstet Gynaecol* 1986; **93**: 1213-1223.

26. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. *Lancet* 1980; **2**: 684-686.

27. Richmond S, Atkins J. A population-based study of the prenatal diagnosis of congenital malformation over 16 years. *BJOG* 2005; **112**: 1349-1357.

28. 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.

29. 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.

30. Abel JS, Flock A, Berg C, Gembruch U, Geipel A. Expectant management versus multifetal pregnancy reduction in higher order multiple pregnancies containing a monochorionic pair and a review of the literature. *Arch Gynecol Obstet* 2016; **294**: 1167-1173.

31. Zipori Y, Haas J, Berger H, Barzilay E. Multifetal pregnancy reduction of triplets to twins compared with non-reduced triplets: a meta-analysis. *Reprod Biomed Online* 2017; **35**: 296-304.

32. Downing M, Sulo S, Parilla BV. Perinatal and Neonatal Outcomes of Triplet Gestations Based on Chorionicity. *AJP Rep* 2017; **7**: e59-e63.

33. Spencer JV, Ingardia CJ, Nold CJ, Borgida AF, Herson VC, Egan JF. Perinatal and neonatal outcomes of triplet gestations based on placental chorionicity. *Am J Perinatol* 2009; **26**: 587-590.

FIGURE LEGEND

Figure 1 Derivation of study cohort of triplet pregnancies using population-based North of England regional data from Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) and multicenter Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple birth cohorts.

Notes: *Maternity defined as pregnancy with at least one live birth or stillbirth (fetal death ≥24 weeks of gestation), including pregnancies with one early fetal loss.
†Total prevalence, derived from NorSTAMP data, of 3.27 (95% CI 2.79-3.81) per 10,000 maternities (165/505,096).
IUD, intrauterine death, TCTA, trichorionic triamniotic, DCTA, dichorionic triamniotic, MCTA, monochorionic triamniotic.

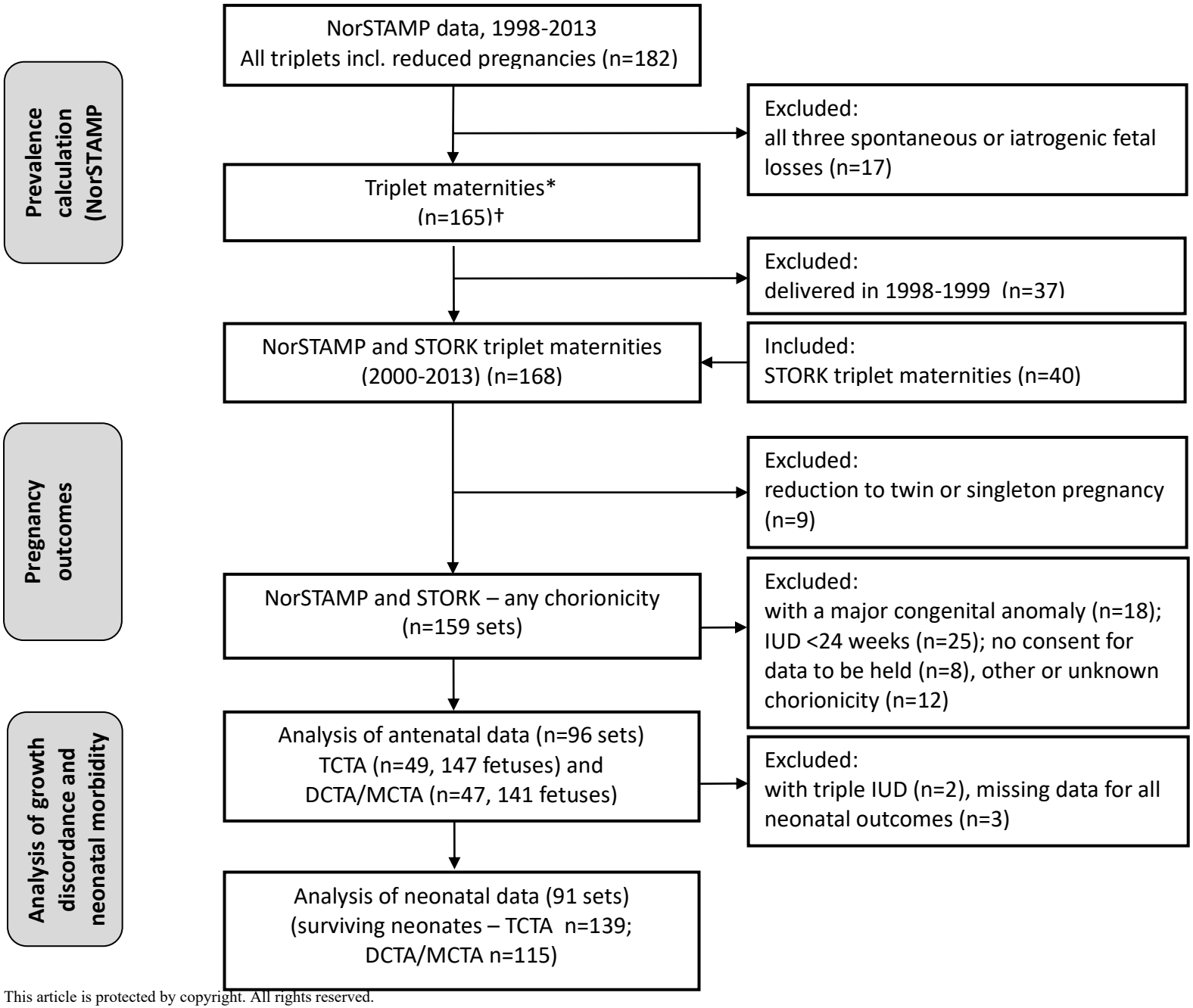

Table 1 Baseline characteristics in TCTA and DCTA/MCTA triplet pregnancies, 2000-2013

	TCTA *n*=68	DCTA/MCTA *n*=72	P value
Maternal age (years)	34.0 (30.0-37.0)*	31.5 (27.3-35.0)	**0.013**
Maternal BMI at booking (kg/m^2)	25.3 (22.5-28.5)†	23.3 (21.9-26.6)‡	**0.042**
Most deprived quintile (IMD score) ††	11/62 (17.0)§	16/64 (25.0)¶	0.39
Nulliparous	41/60 (68.3)¶	43/66 (65.2)§	0.85
Diagnosis of multiple pregnancy (weeks)	11.0 (9.0-12)**	11 (8.5-13)‡‡	0.68
Pregnancies affected by a major congenital anomaly	3/68 (4.4)	13/72 (18.1)§§	**0.015**

Data given as median (interquartile range) or *n* (%). Mann–Whitney *U*-test was used for comparing continuous variables between cohorts and Fisher's exact test was used for comparing categorical variables.

Data missing in: *one case; †25 cases; ‡13 cases; §six cases; ¶eight cases; **five cases, ‡‡three cases.

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

§§including two pregnancies with a twin-related anomaly (acardiac fetus)

Table 2 Stillbirth, neonatal and perinatal mortality of triplets by chorionicity, 2000-2013

	Triplet pregnancies (n=159)				
	TCTA (n=189)	DCTA&MCTA (n=198)	Other‡ (n=21)	Unknown (n=36)	Total (n=444)
Stillbirth n (per 1000 total births)*	3 (15.9)	17 (85.9)§	2 (95.2)	1 (27.8)	23 (51.8)
Neonatal death n (per 1000 live births)*	6 (32.3)	8 (44.2)	—	—	14 (33.3)
Perinatal death n (per 1000 total births)†	9 (47.6)	25 (126.3)§	2 (95.2)	1 (27.8)	37 (83.3)

*Stillbirth and perinatal mortality rates are calculated per 1000 births in triplet pregnancies resulting in at least one registered birth (stillbirth or live birth), excluding fetal losses at <24 weeks of gestation; Neonatal mortality is calculated per 1000 triplet live births.
†Perinatal deaths include stillbirths (≥24 weeks of gestation) and neonatal (0-27 days) deaths.
TCTA=trichorionic triamniotic (n=68), DCTA=dichorionic triamniotic (n=59), MCTA=monochorionic triamniotic (n=13) pregnancies.
‡Other chorionicity includes dichorionic diamniotic (n=4) and monochorionic diamniotic (n=3) triplet pregnancies.
§ *P* value <0.05 (2-tailed Fisher exact test) for comparison with TCTA.

Table 3 Antenatal parameters and obstetric and neonatal outcomes of non-malformed TCTA and DCTA/MCTA triplet pregnancies, 2000-2013

	TCTA (n=49)	DCTA&MCTA (n=47)	P-value
Antenatal parameters			
EFW*			
EFW smallest triplet (g)	1603 (1352-1870)	1409 (942-1691)	0.104
EFW largest triplet (g)	1873 (1570-2232)	1653 (1370-2078)	0.108
Relative EFW of the middle triplet			
Low-skew	13/29 (44.8)	8/24 (33.3)	0.42
High-skew	2/29 (6.9)	6/24 (25.0)	0.12
Inter-triplet EFW discordance (between the smallest and the largest triplet) (%)	13.9 (8.0-20.2)	19.0 (12.7 27.6)	0.086
Moderate EFW discordance (between >25% and ≤35%) (%)	4/29 (13.8)	4/24 (16.7)	1.00
Severe EFW discordance (>35%)	2/29 (6.9)	4/24 (16.7)	0.39
Diagnosis of FFTS	—	9/36 (25.0)	n/a
Evidence of abnormal Doppler parameters at the last scan†	5/25 (20.0)	8/28 (28.6)	0.54
Obstetric outcomes			
Elective CS	30/48 (62.5)	18/46 (39.1)	**0.038**
Emergency CS	17/48 (35.4)	26/46 (56.5)‡	0.062
Gestational age at delivery	33 (31.5-34)	33 (30-34)	0.101
<34 weeks	25/49 (51.0)	32/47 (68.1)	0.101
<32 weeks	12/49 (24.5)	19/47 (40.4)	0.127
<30 weeks	6/49 (12.2)	11/47 (23.4)	0.187
Birth weight			
Weight of smallest triplet (g)	1665 (1268-1920)	1513 (978-1677)	**0.015**
Weight of largest triplet (g)	2059 (1669-2295)	1860 (1528-2139)	**0.023**
Relative birth weight of the middle triplet			
Low-skew	2/48 (4.2)	11/46 (23.9)	**0.007**
High-skew	19/48 (39.6)	10/46 (21.7)	0.076

Inter-triplet birth weight discordance (between the smallest and the largest triplet) (%)	17.1 (10.2-27.6)	23.0 (14.0-35.8)	**0.049**
Moderate birth weight discordance (between >25% and ≤35%)	11/48 (22.9)	6/46 (13.0)	0.286
Severe birth weight discordance (>35%)	5/48 (10.4)	12/46 (26.1)	0.062
Antepartum stillbirth§	1/147 (0.68)	15/141 (10.6)	**0.0001**
Neonatal death (of live born)§	4/146 (2.7)	5/126 (4.0)	0.74
Neonatal outcomes**			
Admitted to SCBU	123/139 (88.5)	105/115 (91.3)	0.54
Length of stay in SCBU (days)††	23 (14-33)	19 (13-30)	0.26
Mechanical ventilation¶	17/110 (15.5)	11/84 (13.1)	0.69
CPAP¶	29/89 (32.6)	26/62 (41.9)	0.30
Respiratory distress syndrome¶	34/97 (35.1)	33/76 (43.4)	0.28
Necrotizing enterocolitis¶	2/95 (2.1)	2/78 (2.6)	1.00
Sepsis (confirmed or suspected/treated with antibiotics)¶	8/96 (8.3)	1/79 (1.3)	0.08
Intraventricular haemorrhage¶	2/96 (2.1)	1/75 (1.3)	1.00

Note:

Data given as median (interquartile range) or *n*/*N* (%). All numbers expressed as percentage of pregnancies, unless indicated otherwise. Mann–Whitney *U*-test was used for comparing continuous variables between cohorts and χ^2 test or Fisher's exact test was used for comparing categorical variables. *Only estimated fetal weights (EFW) examined ≤ 2weeks prior to delivery are included (TCTA *N* =29: DCTA/MCTA *N*=24). †Umbilical artery Doppler abnormalities (pulsatility index >95th centile based on the reference ranges provided in the Viewpoint ultrasound reporting system[21] used in both collaborating centres, absent or reversed end-diastolic flow) reported for any fetus no earlier than at ≤ 2 weeks prior to delivery are included. ‡in 24 DCTA/MCTA pregnancies, all triplets were delivered by emergency CS, in 2 pregnancies the second and the third triplets were delivered by emergency CS after the first fetus was delivered vaginally by forceps.

§Number expressed as percentage of individual triplets. **Data for 254 neonatal survivors (9 neonatal deaths were excluded from the analysis of neonatal outcomes, but two postneonatal deaths were included) from 91 triplet pregnancies (pregnancies with triple IUDs (*n*=2) and pregnancies with missing data on all neonatal outcomes were excluded (*n* = 3)). ††Data missing for 31 of 139 (22.3%) TCTA and for 26 of 115 (22.6%) DCTA/MCTA surviving triplets. ¶Including only cases with complete data for this parameter. CPAP, continuous positive airway pressure; CS, Cesarean section; SCBU, special care baby unit; FFTS, feto-fetal transfusion syndrome.