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Interim report for BMFMS/TAMBA bursary (awarded January 2016 - £19,972)

Project title: Prevalence, birth outcomes and clinical management of monochorionic monoamniotic twin and all triplet pregnancies

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Introduction and Aim:

Monochorionic monoamniotic (MCMA) twin pregnancies occur in about 1 in 10,000 pregnancies overall (5% of MC pregnancies) (Shub et al, 2015). About 15-20% of these pregnancies result in perinatal death after 20 weeks (Hack KE et al, 2009; Morikawa M et al, 2012) and due to frequent complications, require intensive antenatal monitoring and specialist care (NICE clinical guideline 129, 2011; ACOG Practice Bulletin No. 144, 2014).

Triplet pregnancies (prevalence about 3 per 10,000 pregnancies (Tandberg A et al, 2010)) also have a high risk of adverse pregnancy outcomes, but the evidence for optimal clinical management is scarce, according to the current NICE guidance (NICE clinical guideline 129, 2011). As both MCMA twin pregnancies and triplets are rare, population-based data with accurate chorionicity information is required for meaningful analysis of their clinical management and pregnancy outcomes.

The aim of the project was to determine the prevalence of MCMA twin and triplet (any chorionicity) pregnancies using population-based data from the Northern Survey of Twin and Multiple Pregnancy (NorSTAMP) for 2000-2013, and to compare birth outcomes and clinical management of these pregnancies across the Northern England and with those from the Southwest Thames Region of London Obstetric Research Collaborative (STORK) multiple pregnancy cohort and also before and after the publication of the NICE guidelines.

Progress

MCMA twin pregnancies

Only twin pregnancies with a definite ultrasound diagnosis of MCMA chorionicity were included in both the NorSTAMP and STORK samples. Pregnancies with uncertain MCMA chorionicity were excluded from the initial sample of MCMA twins downloaded from NorSTAMP (n=108 during 2000-2013) if a different type of chorionicity (monochorionic diamniotic (MCDA) or dichorionic diamniotic) was confirmed by an experienced ultrasonographer in a tertiary centre. Confirmed MCMA twin pregnancies identified in the ultrasound databases of the tertiary centres, which were inaccurately recorded as MCDA in the NorSTAMP, were added to the initial sample, as well as MCMA twin pregnancies which were not in the initial NorSTAMP sample due to missing chorionicity.

Overall, in northern England there were 56 twin pregnancies during 2000-2013 with confirmed MCMA chorionicity by either both ultrasound scan and placenta pathology or by first trimester ultrasound scan only, including pregnancy resulting in early fetal losses of both co-twins (n=5) and TOPFA (n=13, among them 12 pregnancies with conjoined twins). Only MCMA twin pregnancies resulting in maternities with at least one live birth or stillbirth (fetal death at ≥24 weeks' gestation) were included in the prevalence calculation (38 among 442,281 maternities), which gave the prevalence rate of 0.9 per 10,000 all maternities, or 5.8 per 1000 twin maternities. There were a further nine pregnancies where chorionicity diagnosis was

based on placenta pathology only as no US scan results were available, but these were not included in the prevalence calculation as the reliability of these diagnoses was unclear.

Table 1: Pregnancy outcomes of MCMA twin pregnancies over 2000-2013 for both NorSTAMP and STORK cohorts

	NorSTAMP	STORK
Both live births	31	19
Both survived first 28 days	26	17
Both neonatal deaths	3	0
Neonatal death and survivor	2	2
Live birth and IUD	4	3
Both antepartum stillbirths (≥24 w)	2	
Both IUD before 24 weeks	5	8
TOPFA	1	6
Live birth and selective termination	1	1
IUD and selective termination	0	1
Total	**44**	**38**

Table footnote: IUD = intrauterine death; TOPFA = termination of pregnancy for fetal anomaly
Conjoined twins are not included.

For the analysis of fetal development and neonatal outcomes, we extracted data for the following indicators of pregnancy complications and neonatal morbidity for live births for both NorSTAMP and STORK cohorts recorded in Fetal Medicine Units (FMU) and Special Care Baby Units (SCBU) in Newcastle and London tertiary centres for 2000-2014 (this adds an additional 10 MCMA pregnancies):
Inter-twin discordance in estimated fetal weight (EFW) defined as ≥25% weight difference divided by the weight of the larger twin; selective fetal growth restriction (sFGR); cord entanglement; twin-to-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS); twin reversed arterial perfusion (TRAP) sequence; evidence of abnormal Doppler at the last ultrasound scan before delivery [umbilical artery (UA); congenital anomaly diagnosed antenatally.
Neonatal outcomes:
Inter-twin birthweight discordance defined as 25% or greater difference in birthweight with respect to the larger twin;, admission to SCBU (yes/no, if yes, number of days), resuscitation at birth (mask, intubation, none), mechanical ventilation (yes/no, if yes, number of days), 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), operations (yes/no). Major morbidity was defined as retinopathy of prematurity, necrotising enterocolitis, ventilator support, or intraventricular haemorrhage.

We will analyse these outcomes (Table 1) and their association with antenatal complications, management and mode and timing of delivery in addition to maternal and fetal factors.

Triplet pregnancies

For the triplet prevalence calculation we included 179 triplet pregnancies notified to the NorSTAMP during 1998-2013, including 16 which resulted in an early miscarriage (at <24 weeks of gestation, n=15) or termination of pregnancy (n=1) of all fetuses (Table 2). There were 163 triplet maternities that resulted in at least one registered birth, including six pregnancies which were reduced to either twin or singleton pregnancy, giving the triplet rate of 3.2 per 10,000 maternities. The triplet prevalence at birth was 2.5 per 10,000 maternities resulting in births of all triplets.

Table 2: Pregnancy outcomes of triplet pregnancies, NorSTAMP 1998-2013

Outcome	Number (%)
All TOP (no congenital anomaly recorded)	1 (0.6)
All miscarriages (<24 weeks' gestation)	13
Reduction of pregnancy (feticide) and a live birth	8 (4.5)
Reduction of pregnancy (feticide) and a miscarriage (<24 wks)	2 (1.1)
At least one stillbirth or live birth and a spontaneous fetal loss	30 (16.8)
All registered births	125 (69.8)
Total	**179 (100)**

TOP=termination of pregnancy
There are further 15 triplet pregnancies for this period identified in the FMU of the tertiary centre that were not matched to the register data (checking is ongoing).

For triplet pregnancies that resulted in registered births during 2000-2014, we will analyse birth outcomes by chorionicity type:
NorSTAMP: n=128
STORK: n=58 (follow up for pregnancy outcomes of 12 pregnancies is still ongoing).

The following prenatal indicators of fetal growth and wellbeing/development were recorded and will be analysed for live births for both NorSTAMP and STORK cohorts for 2000-2014: Inter-triplet discordance in estimated fetal weight (EFW); selective fetal growth restriction (sFGR); twin-to-twin transfusion syndrome (TTTS) in a MC triplet pair, twin anemia polycythemia sequence (TAPS); evidence of abnormal Doppler at the last ultrasound scan before delivery (umbilical artery Doppler); congenital anomaly diagnosed antenatally. To define the inter-triplet discordance we adopted the approach proposed by Blickstein et al, 2003, who defined concordant sets as those with a difference in weight of less than 25%, and differences of 25% to 35% and 35% and more were defined as moderate and severe discordance, respectively. Following their approach, we also calculated the relative weight 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 0.27 and 0.75, low-skew if <0.25 and high-skew if >0.75. Interfetal discordance in EFW has been similarly defined.

Neonatal outcomes:
Inter-triplet birthweight discordance (25% or greater difference in birthweight); admission to SCBU (yes/no, if yes, number of days), resuscitation at birth (mask, intubation, none), mechanical ventilation (yes/no, if yes, number of days), 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), operations (yes/no). Major

morbidity was defined as retinopathy of prematurity, necrotising enterocolitis, ventilator support, or intraventricular haemorrhage.

We will analyse these outcomes and their association with antenatal complications, management and mode and timing of delivery in addition to maternal and fetal factors.

Challenges

The data collection and verification of chorionicity for both MCMA twin and triplet pregnancies has been much more challenging than anticipated and has required longer in both collaborating centres. We were interested in much more detailed data from antenatal US scans throughout pregnancy than was available in the NorSTAMP, therefore we have contacted individual maternity units in the Northern region and individual hospitals from the STORK collaborative to trace the pregnancy outcomes and neonatal morbidity in addition to the US scan data from the tertiary centres. It was challenging to achieve for many pregnancies with the dates of delivery going back to 2000 as the data were not available in electronic format in many maternity units and the obstetric and neonatal notes were not easily accessible. As a result, after the verification of chorionicity in the FMUs of the Newcastle and London tertiary centres (St George's Hospital) and due to follow up problems, we obtained data on a smaller sample of MCMA twins and triplets than initially estimated. Despite these challenges, the project will still be reporting on time and to budget.

Outputs

Two papers for publication in an Obstetrics journal are in preparation:

1) Prevalence, antenatal management and perinatal outcomes in monochorionic monoamniotic twin pregnancies: a collaborative multicentre study in England
2) Prevalence, antenatal management and perinatal outcomes of triplet pregnancies.
3) The results of the project will be presented at national conferences (e.g. BMFMS)
4) Summary of the key findings published on the BMFMS and TAMBA websites (after seeking permission)