The perinatal and obstetric outcomes of triplet conceptions at Groote Schuur Hospital in the five-year period: 1 January 2012 to 31 December 2016.

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Declaration

I, Jane Pauline Turner, hereby declare that the dissertation and all work conducted with compiling the dissertation is my own work, unless otherwise stated. I confirm that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university.

Signature Signed by candidate 14/12/2021

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List of Acronyms

AMA	Advanced Maternal Age
ART	Assisted Reproductive Technology
ASRM	American Society of Reproductive Medicine
CS	Caesarean Section
GDM	Gestational Diabetes
GSH	Groote Schuur Hospital
HELLP	Haemolysis, Elevated Liver enzymes and Low Platelets
IUFD	Intrauterine Fetal Death
IUGR	Intrauterine Growth Restriction
IVF	In Vitro Fertilisation
LBW	Low Birth Weight
NICU	Neonatal Intensive Care Unit
PROM	Premature Rupture of Membranes
PTL	Preterm Labour

SA	South Africa
TTTS	Twin to Twin Transfusion Syndrome
TRAP	Twin reversed arterial perfusion sequence
UK	United Kingdom

Definitions

Intrauterine growth restriction: a weight below the 10th centile for gestation and a 25% discordance in weight between the smallest and biggest triplet

Low birth weight: birth weight of less than 2500 g

Preterm rupture of membranes: rupture of the amniotic sac prior to 37 weeks gestation

Twin to twin transfusion syndrome: the diagnosis is made antenatally in a pregnancy with a single monochorionic placenta where there is ultrasonographic evidence of twin oligohydramnios/ polyhydramnios sequence. Exclusion of other disorders that could result in the differences in amniotic fluid volumes is required.

Twin reversed arterial perfusion syndrome: complication of a monochorionic twin pregnancy where one twin, with an absent or rudimentary heart (acardiac twin) is perfused by its co-twin (pump twin) via abnormal placental arterial anastomosis

Preterm delivery: delivery before the completion of 37 weeks gestation

Trichorionic triamniotic triplets: Each fetus has a separate placenta and amniotic sac

Dichorionic triamniotic triplets: One fetus has a separate placenta and the other two fetuses share a placenta. All three fetuses have separate amniotic sacs.

Dichorionic diamniotic triplets: one fetus has a separate placenta and amniotic sac the other two fetuses share a placenta and amniotic sac.

Monochorionic triamniotic triplets: all three fetuses share one placenta. All three fetuses have separate amniotic sacs.

Monochorionic diamniotic triplets: all three fetuses share one placenta. One fetus has a separate amniotic sac and the other two fetuses share an amniotic sac.

Monochorionic monoamniotic triplets: all 3 fetuses share one placenta and amniotic sac.

Abstract

Background:

Triplet pregnancy rates have increased over the past few decades due to the advancing maternal age at conception and assisted reproductive technology. It is well known that the risk to both the mother and fetus are greater in multiple pregnancy when compared to singleton pregnancy. Groote Schuur Hospital (GSH), as a tertiary hospital, is the main referral unit for patients with high risk pregnancies in the Metro West region of the Western Cape and provides care to women with triplet pregnancies. There are no studies in South Africa reviewing the outcomes of triplet pregnancies; this study provided the opportunity to do so.

Objectives:

The outcomes of all triplet pregnancies at GSH were reviewed from 1 January 2012 to 31 December 2016. The primary objective of the study was to review the fetal and neonatal outcomes of triplet pregnancies at GSH. Fetal complications included the prevalence of fetal abnormalities, miscarriage, twin to twin transfusion syndrome, intrauterine growth restriction and discordant growth, stillbirths, preterm delivery, premature rupture of membranes and low birth weight. Neonatal complications included respiratory distress syndrome or hyaline membrane disease, intraventricular haemorrhage and necrotising enterocolitis.

The secondary objective was to review maternal complications and outcomes, including anaemia, hyperemesis gravidarum, hypertensive disorders, gestational diabetes, preterm labour, antepartum and postpartum haemorrhage and operative complications. The demographic information, mode of conception and mode of delivery were also included.

Method

A quantitative retrospective folder review of all triplet pregnancies delivered at GSH between the period of 1 January 2012 and 31 December 2016 was conducted. A folder review was conducted; demographic information and outcomes were entered anonymously onto a data sheet and then reviewed. Triplets were analysed by chorionicity. Neonatal folders at Groote Schuur Hospital were reviewed to determine outcomes and length of hospital stay. Due to the small patient number only limited statistical analysis was possible.

Results:

A total of 29 triplet pregnancies were identified during the period. Four patients were excluded from the study due to missing folders in 3 patients and one patient who delivered at another hospital. The mean maternal age was found to be 31.4 years (range 21-43 years). The majority of patients were multiparous (n=21) and conceived spontaneously. The majority of patients presented to the antenatal clinic in the second trimester making assessment of chronicity a challenge and possibly resulting in an over diagnosis of monochorionic and dichorionic triplets. There were 5 monochorionic, 6 dichorionic pairs, and 10 trichorionic pregnancies identified and 4 patients had undetermined chorionicity. Twenty one patients delivered by caesarean section and 4 women had normal vaginal deliveries. Preterm labour was diagnosed in 60% and preterm rupture of membranes in 20% of patients in the study. Other comorbidities diagnosed during these pregnancies included hypertension (28%), gestational diabetes (20%) and anaemia (20%). Low birth weight was found in 96% of triplets born at GSH with 69.3% of neonates requiring admission to the neonatal intensive care unit (NICU). The overall survival rate was shown to be 81% in our setting.

Conclusion:

Triplet pregnancies are seen infrequently but clinicians should be aware of the increased maternal, fetal and neonatal risks associated with these pregnancies. A multidisciplinary team, including a neonatologist and fetal medicine specialist, is required in the management of multiple pregnancies. Our study found that preterm labour occurred in 60% of patients and the average birth weight was 1.6kg. Neonatal admission to the nursery or NICU occurred in 96.3% of triplets with an survival rate of 81%. A multicentre national study, including evaluation of neurodevelopment, will provide a better comprehensive perspective in South Africa.

CHAPTER 1: Introduction and Literature Review

The incidence of triplet pregnancies has increased over the past 30 years worldwide.[1,2,4,5,6,28] Multiple pregnancies account for approximately 3% of live births.[1,14] Multiple pregnancies in the United Kingdom (UK) have increased from 10 per 1000 in 1980 to 16 per 1000 in 2009.[1] A study in sub-Saharan Africa found the multiple birth rate to be 17.1 per 1000 births.[14] However, data for the South African multiple birth rate is lacking. The incidence of multiple pregnancies has increased due to assisted fertility and the advancing age before childbearing (women desiring to pursue a career first).[1,2,5,8,21,28,35] The probability of a multiple birth in sub-Saharan Africa was shown to be increased with advanced maternal age, parity and maternal height.[14] The greatest increase in multiple pregnancies has been seen in patients who are 40 years and older and, secondly, in women between the ages of 30 and 40 years.[7,17] In Africa, a high incidence of spontaneous multiple births exists, especially in West African patients.[14,24]

Assisted fertility has become available to more patients desiring fertility and there are more techniques available. In recent years there has been an increase in the number of pregnancies resulting from assisted reproduction; often these pregnancies result in multiples. A 1989 UK study consisting of 156 triplet, 12 quadruplet and 1 quintuplet delivery, showed that 31% were conceived naturally, 34% as result of ovarian stimulation and 35% from *in vitro* fertilisation (IVF). According to the American Society of Reproductive Medicine (ASRM) 20% of triplets are due to spontaneous conception, 39-67% to ovulation induction and 13-44% to ART.[32] Groote Schuur Hospital offers assisted reproduction/infertility treatment to patients and therefore multiple pregnancies may result. The current practice at Groote Schuur Hospital is to transfer a maximum of 2 embryos in patients

undergoing IVF treatment. Cases of higher order multiple pregnancy have been found after the division of an embryo where 2 embryos were inserted, including at the GSH fertility clinic.[2,5,12,32]

Early determination of chorionicity and amnionicity are of great importance; this is done by ultrasound assessment in early pregnancy. Chorionicity and amnionicity help with planning of delivery and screening for complications such as twin to twin transfusion syndrome (TTTS).[1,4,5] Screening for fetal abnormalities should also be performed as congenital abnormalities are more common than in singleton pregnancies (4.9% more common); this may be linked to older women conceiving triplets.[1,4,5,17] Congenital malformations, especially neural tube defects and structural gastrointestinal malformations, are increased in multiple pregnancies.[15] The rate of major fetal malformations is 9.3% for monochorionic and 5.5% for trichorionic triplet pregnancies. The rates of aneuploidy are 6.2% in monochorionic versus 2.8% in trichorionic triplets.[21] A 1996 study looking at neonatal outcomes reported a 7.1% incidence of major congenital abnormalities.[27]

It is well known that multiple pregnancies are high-risk pregnancies, with risks to both the mother and fetuses.[1,4,14,15,36] The mother will require close monitoring during the pregnancy (2-weekly follow up in uncomplicated triplet pregnancy) and may require admission to hospital to ensure wellbeing.[1,15] The mother has an increased risk for miscarriage, anaemia, hyperemesis gravidarum, hypertension or pre-eclampsia, gestational diabetes, placenta praevia, antepartum and postpartum haemorrhage and preterm labour.[1,4,6,13-15] Preterm labour is the most common complication, followed by anaemia.[27] The demands on the healthcare system (individuals, hospital and resources) are increased in terms of care for both mother and babies.[1,4, 28] A multidisciplinary team will be required to manage the pregnancy and neonatal period.[18]

When compared to singletons, maternal morbidity and mortality is increased in multiple pregnancies.[17, 21-23] Studies in Europe have shown a 3 times higher mortality and 2 times higher intensive care admission rate in multiple pregnancy. This may be explained by the increased incidence of pregnancy-related hypertension, including pre-eclampsia and eclampsia, and haemorrhage.[15,17] There have been few studies assessing the outcomes of multiple pregnancies in an African setting. A study in rural Malawi between 1987 and 1990 showed a maternal death rate of 11.5% in patients with multiple pregnancies. As previously mentioned, obstetric complications are also more common in multiple pregnancies.[14] In a study published in 2004, Wen et al. compared obstetric complications and maternal morbidity in twin, triplet and higher-order multiple pregnancies. They showed that the risks of pregnancy-associated hypertension, diabetes mellitus and placental abruption increased with triplet and higher-order pregnancies when compared with twins, with no difference in chronic hypertension in each group.[23] Postpartum haemorrhage also occurs commonly, often requiring blood transfusion. A study by Albrecht et al. showed rates of pre-eclampsia, HELLP syndrome, and gestational diabetes of 33.3%, 14% and 10.5%, respectively.[27] Mothers who have multiple pregnancies are often older, which may also be related to the increased complication rate.[23]

The mode of delivery in triplet pregnancies is caesarean section in the vast majority of cases. Caesarean section rates vary between 94 and 100%.[15, 23, 25, 28] At Groote Schuur Hospital, it is policy to deliver all triplet pregnancies by caesarean section. Operative delivery may result in an increase in the risk of operative complications, as well as postpartum haemorrhage and blood transfusion. [1,3,15, 23, 25] The Saving Mothers Report 2011-2013 showed obstetric haemorrhage to be the second leading cause of death in South Africa, with a third of these deaths being linked to bleeding at or after caesarean section.[30]

Early fetal loss and miscarriage occur much more frequently in triplet than in singleton pregnancies. The loss may be of one, two or the entire pregnancy, e.g. 'spontaneous' reduction or total loss. Miscarriage before 24 weeks gestation was found in 20% of triplet pregnancies compared to 8% of singleton pregnancies.[6] Rates of miscarriage vary according to chorionicity. Monochorionic triplet miscarriage rates are higher than in trichorionic triplet pregnancies: 9.7% and 5.5%, respectively.[21] In an article published in 2017, miscarriage rates after embryo reduction versus expectant management were compared for trichorionic and dichorionic triplet pregnancies.[26] Trichorionic triamniotic triplet pregnancies had a 7.4% miscarriage rate in patients managed expectantly versus 8.1% in those who had an embryo reduction. Dichorionic triamniotic triplet pregnancies managed expectantly had an 8.5% risk of miscarriage compared to 13.3% in those triplet pregnancies undergoing embryo reduction.[26] Fetal reduction increases the rates of miscarriage in both di-and-trichorionic pregnancies, with an increasing rate of miscarriage when pregnancy is reduced to one fetus. Monochorionic and dichorionic triplets have a worse prognosis than trichorionic triplets. Spontaneous conceptions often resulted in monochorionic placentation, while triplets conceived via assisted reproductive techniques result in trichorionic placentation.[21]

Preterm labour is the most common complication seen in multiple pregnancies.[27] The World Health Organisation data states that 15 million babies are born prematurely each year; 1 million babies die due to complications of prematurity. Survival rates differ around the world. Low-income areas have a 50% mortality rate for babies born at or less than 32 weeks gestation due to lack of feasible or cost-effective care.[8] This is in contrast to the almost 100% survival in developed countries.[6] In South Africa there are limited resources available in the state sector resulting in management of patients would differ when compared to a developed country. Preterm labour occurs in about 90%

of triplets.[1,17,18,28,36] The risk of delivery of a multiple pregnancy before 32 weeks of gestation is 3.3 times higher than in twin pregnancies and 24.1 times higher than in singleton pregnancies.[28] The average birth weight of triplets was found to be 1596g compared to 2300g in twins.[18] Another study showed the average birth weight of triplets to be 1800g compared to 3300g in singleton pregnancies.[15] The main risk factors for mortality and morbidity in triplet pregnancies are preterm delivery and low birth weight.[17] Premature infants require a specialist unit for their care. The mean gestation at delivery for triplet pregnancies is 32 weeks and the majority are low birth weight (<2500 g). The mean gestational age at delivery in monochorionic triplets is 30 weeks with a mean birth weight of 1330g, compared to 31 weeks and a mean birth weight of 1570g in trichorionic triplets.[21] Dichorionic triplets tend to deliver 2 weeks earlier than trichorionic triplets (31 weeks versus 33 weeks).[31] The duration of hospitalisation is longer in triplets than in twins.[18] In South Africa, 8 out of 100 babies are born prematurely, and South Africa is ranked 24th out of 184 countries for number of neonatal deaths due to complications of prematurity with respiratory distress.[10,27] According to the Saving Babies Report the perinatal mortality rate for babies born with a birth weight of more than 1000g is 15.68% and the early neonatal death rate is 3.43% in the Western Cape.[11] There is a paucity of data comparing the outcomes of triplet or twin pregnancies to singleton deliveries in South Africa.

There is an association between intrauterine fetal death (IUFD) and monochorionicity. Complications of TTTS, twin reversed arterial perfusion sequence (TRAP), and selective intrauterine growth restriction (sIUGR) occur in multiple pregnancies. Differentiating between TTTS and intrauterine growth restriction is linked to chorionicity.[1,2,13] Chasen et al. showed a prevalence of TTTS of 17.6% in monochorionic triplets. IUFD occurs in 8.8% of monochorionic triplets compared to 1.5% of trichorionic pregnancies. Complications (IUFD, TTTS, TRAP, and

IUGR) occur more frequently in monochorionic triplets (38.2% vs 21% in monochorionic and trichorionic triplet pregnancies, respectively).[21] Monochorionic pregnancies are at risk of arterial and venous anastomoses between fetuses which may result in TTTS and stillbirth.[17] Monochorionic triplet pregnancies have been associated with lower birth weight (mean 1810g compared to 2125g).[29]

The perinatal morbidity and mortality are increased in multiple pregnancy, including triplet conceptions.[1,4,5,17] The take-home-baby rate in triplet pregnancies is 85%.[28] Risks to the fetus can occur during the antenatal, intrapartum and neonatal periods. These risks include stillbirth, fetal abnormalities, IUGR, small for gestation/low birth weight infants, TTTS, preterm labour with sequelae of prematurity e.g. hyaline membrane disease, necrotising enterocolitis and intraventricular haemorrhage.[1,6] Neonatal complications are associated with prematurity and IUGR.[17,21,31] Long-term neurological complications should be taken into account, with an increased risk of cerebral palsy in triplets. The risk of neurodevelopmental delay has also been shown to be higher when compared to singleton pregnancies.[17,28] Studies in the 1980s showed that triplet pregnancies had a 20 times higher relative risk for cerebral palsy than singletons.[17] More recent data shows rates of cerebral palsy of 44.8 per 1000 in triplets compared to 2.3 per1000 in singletons and 12.6 per1000 in twins.[28] Improvement in neurodevelopmental outcome may be achieved by reducing preterm delivery, which may be accomplished by embryo/fetal reduction.[7, 21] The risk of miscarriage should be considered in fetal reduction.

Groote Schuur Hospital provides care for triplet pregnancies in the Cape Town Metro West region as well as to patients from further afield who are referred for specialist care. An infertility unit is based at Groote Schuur Hospital; pregnancies from this unit may result in multiple pregnancies.

Data from this study will provide information as to whether triplet pregnancies occur more commonly from assisted fertility procedures or spontaneous conception at Groote Schuur Hospital. As previously mentioned, data from triplet pregnancies in South Africa is lacking; this study aims to review maternal morbidity and mortality and compare the gestation, birth weight at delivery and outcomes of triplets born at GSH. Review of data collected will give an indication of the risk of a triplet pregnancy in a South African context and contribute to patient counselling.

CHAPTER 2: Methods

Aims and Objectives

Primary Objective:

The primary objective was to review the incidence of fetal and neonatal complications in triplet pregnancies. These complications included fetal abnormalities, miscarriage, twin to twin transfusion syndrome, intrauterine growth restriction and discordant growth, stillbirths, preterm delivery, premature rupture of membranes and low birth weight. Complications in the neonatal period included respiratory distress syndrome and pneumonia, hypoxic ischaemic encephalopathy, necrotising enterocolitis, intraventricular haemorrhage, sepsis, jaundice, retinopathy of prematurity, patent ductus arteriosus, anaemia, hypothermia and hypoglycaemia. Birth weight and gestation were linked to outcomes.

Secondary Objective:

The secondary objective was to review maternal outcomes, including the incidence of anaemia, hyperemesis gravidarum, hypertensive disorders, gestational diabetes, preterm labour, antepartum and postpartum haemorrhage and operative complications, and maternal death. The mode of conception was recorded for each triplet pregnancy.

Research Plan and Methods

Study Design

The study was a retrospective descriptive folder review. The study population consisted of all women with triplet pregnancies who attended and delivered at GSH during the period 1 January 2012 to 31 December 2016. Information was obtained from patients' folders, and from the Astraia

database of all women recorded as having triplet conceptions at GSH over this five-year period. Neonatal folders were reviewed to determine neonatal outcomes. Mode of conception (spontaneous or assisted reproduction), mode of delivery and demographic information were included. GSH Neonatal folders were reviewed to determine neonatal outcomes.

Inclusion and Exclusion Criteria

The inclusion criteria were all patients with a triplet pregnancy who delivered at GSH between 1 January 2012 and 31 December 2016. This included patients with both spontaneous and assisted conceptions.

The exclusion criteria were:

- women with singleton and twin pregnancies
- women with triplet pregnancies who did not follow up or deliver at GSH
- women whose folders were missing

The folders of all women with triplet pregnancies seen and delivered at GSH during the period of January 2012 to December 2016 who met the study criteria were reviewed.

Data Collection and Analysis

A data collection sheet was used to capture data. Data collected was entered onto a collection sheet with a unique number assigned to each triplet conception. The data was then entered into an Excel spreadsheet for analysis purposes. Information was kept anonymous. Analysis was done with the help of a statistician. Descriptive data was not tested.

Ethics

Approval for data collection from patients' files was obtained from Groote Schuur Hospital prior to commencing data collection. Ethical approval was requested from the University of Cape Town's Human Research Committee (HREC Ref: 589/2018)

Strengths and Limitations

As this was a retrospective study, data was collected from patients' folders, allowing the study to be completed in a shorter time period. Multiple variables and outcomes were reviewed. Minimal costs were incurred. It was not necessary for consent to be obtained from individual patients for participation.

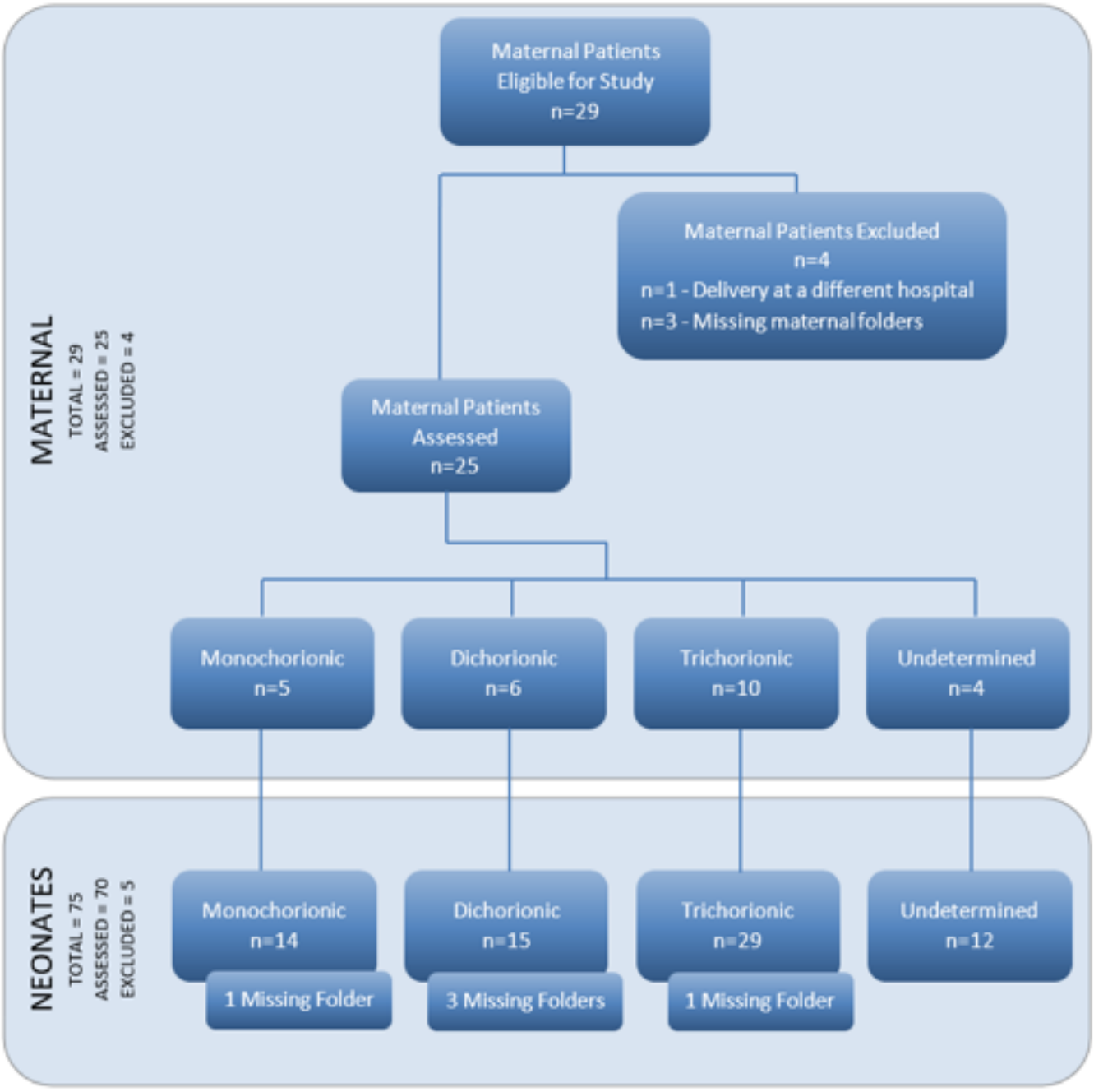
Limitations

As this was a retrospective study we had to rely on the accuracy and completeness of patients' notes during data collection. Only a small number of patients with triplet pregnancies were identified during our study time frame which influenced the statistical significance. Determination of chorionicity was inaccurate due to the late gestation at booking in most patients identified. This may have led to skewed outcomes based on chronicity.

CHAPTER 3: Results

During the period from January 2012 to December 2016 a total of 29 triplet pregnancies were identified at Groote Schuur Hospital. There 4 maternal patients who were excluded and outcomes from 5 neonates could not be reviewed due to missing folders. This is shown in the flow diagram below.

Diagram 1: Flow Diagram showing patients eligible for the study and excluded patients.



Demographic data

The mean maternal age was 31.4 years with a range of 21 to 43 years. The majority of patients were multiparous (n=21) and conceived spontaneously. Assisted reproduction techniques were used in 2 triplet pregnancies during the study period; 1 resulted in monochorionic and the other in trichorionic triplets. The initial antenatal presentation occurred most commonly in the second trimester (n=14). Demographic information is shown in Table 1.

Table 1: Demographic Information

Variables	Monochorionic n=5	Dichorionic n=6	Trichorionic n=10	Unknown Chorionicity n=4
Mean Maternal Age	32.6 (30-37)	32.5 (23-43)	30.6 (21-38)	30.2 (27-32)
Parity (n, %)				
Primiparous	1 (20%)	1 (16.7%)	2 (20%)	0
Multiparous	4 (80%)	5 (83.3%)	8 (80%)	4 (100%)
Booking Gestation (n, %)				
1st Trimester	2 (40%)	1 (16.7%)	4 (40%)	0
2nd Trimester	2 (40%)	4 (66.7%)	6 (60%)	2 (50%)
3rd Trimester	1 (20%)	1 (16.7%)	0	1 (25%)
Unbooked	0	0	0	1 (25%)
Conception (n, %)				
Spontaneous	4 (80%)	6 (100%)	9 (90%)	4 (100%)
ART	1 (20%)	0	1 (10%)	0
Amnionicity (n, %)				
Undetermined	1 (20%)	0	0	3 (75%)
Monoamniotic	0	0	0	0
Diamniotic	1 (20%)	2 (33.3%)	0	0
Triamniotic	3 (60%)	4 (66.7%)	10 (100%)	1 (25%)
Mode of Delivery				
NVD	1 (20%)	1 (16.7%)	2 (20%)	0
Elective C/Section	2 (40%)	1 (16.7%)	2 (20%)	0
Emergency C/Section	2 (40%)	4 (66.7%)	6 (60%)	4 (100%)

ART, assisted reproductive technology; NVD, normal vaginal delivery; C/section, caesarean section

We identified 4 patients who delivered by means of an NVD. The circumstances of each delivery is briefly described in Table 2.

Table 2: Characteristics of patients who had a normal vaginal delivery

Patients	Patient Characteristics
Patient 1	Miscarriage < 24/40
Patient 2	IUGR with TTTS at 24+ weeks
Patient 3	IUGR at 30 weeks
Patient 4	Presented in advanced labour at 32 weeks gestation and delivered soon after arrival at GSH

IUGR, intrauterine growth restriction; TTTS, twin-to-twin transfusion syndrome

Maternal Complications

The most common complication was preterm labour; this occurred in 15 (60%) patients. No maternal deaths were recorded during this period. One patient was admitted to the ICU with a postpartum haemorrhage and required blood products. The average duration of postpartum hospitalisation for mothers was 2 to 5 days. Maternal complications are shown in Table 3.

Table 3: Maternal Complications

Variables	Number (n=25)	Percentage (%)
Preterm Labour	15	60
Preterm Rupture of Membranes	5	20
Anaemia	5	20
Hyperemesis	0	0
Hypertensive Disorders	11	44
Gestational Diabetes	5	20
Antepartum Haemorrhage	1	4
Postpartum Haemorrhage	1	4
Operative Complications	1	4
Requiring Blood Products	3	12
ICU Admission	1	4

Recurrent Admissions	9	36

ICU, intensive care unit

Neonatal Complications

Neonatal outcomes have been linked to chorionicity and can be seen in Table 4.

Table 4: Fetal and neonatal complications and outcomes according to chorionicity

	Monochorionic (n=5)	**Dichorionic (n=6)**	**Trichorionic (n=10)**	**Undetermined (n=4)**
Number of Neonates	14	15	29	12
Average birth weight	1653g	1738g	1616g	1608g
Median birth weight	1835g	1790g	1752g	1872g
Range of birth weight	270-2680g	570-2935	575-2350g	785-1985g
Average Gestation at delivery	32-36 weeks	32-36 weeks	32-36 weeks	32-36 weeks
Admission to NICU	9	11	21	11
Respiratory Distress Syndrome	5	5	16	9
NEC	0	0	0	0
IVH	0	1	2	2
Other*	7	5	8	10
ENND	1	1	1	0
LNND	0	1	1	0
Stillborn	1 (2 fetuses)	1	1	0
IUGR	2	1	4	0
Vascular Malformations **	1	1	0	0
Congenital Abnormalities	0	1	0	0
Average length of hospital stay in days	2-7 days	> 14 days	> 7days	>7days

NICU, neonatal intensive care unit; NEC, necrotizing enterocolitis; IVH, intraventricular haemorrhage; ENND, early neonatal death; LNND, late neonatal death; IUGR, intrauterine growth restriction
*Other: Sepsis, neonatal jaundice, feeding intolerance, hypoglycaemia
** Vascular Malformation: TTTS, TRAP

Monochorionic

Five monochorionic triplet pregnancies were identified; 1 pregnancy resulted from ART. In the monochorionic group, 1 pregnancy resulted in no live births. This pregnancy was complicated by TTTS and resulted in a vaginal delivery prior to 28 weeks gestation with no surviving fetuses. The fetal birth weights in this pregnancy ranged from 270g to 620g. The duration of neonatal hospital admission was 2 to 7 days in this group.

Dichorionic

A dichorionic pair was identified in 6 triplet pregnancies. One patient delivered via normal vaginal delivery at approximately 30 weeks gestation. This pregnancy was complicated by intrauterine growth restriction with birth weights ranging from 540g to1080g and only 1 of the triplets survived. In another patient, an early fetal demise occurred in 2 of the 3 fetuses and they were resorbed. The third fetus was born by emergency caesarean section at >36 weeks gestation. A TRAP sequence with an acardiac twin was identified in 1 pregnancy. Neonatal hospital admission was on average more than 14 days.

Trichorionic

In this cohort we identified 10 trichorionic triplet pregnancies. A second trimester miscarriage was noted in this group (delivery <24 weeks) resulting in 2 stillbirths and 1 late neonatal death. The average length of hospitalisation was > 7 days for neonates in this group.

Undetermined

Chorionicity was not determined in 4 triplet pregnancies. In these pregnancies, patients presented to the hospital for the first consultation during the second or third trimester, with one patient presenting in labour. The patients were all multiparous and conception was spontaneous. One patient delivered before 28 weeks gestation. The average neonatal hospital stay was between 2 and 7 days.

Table 5 provides a summary of both the maternal and neonatal outcomes for the triplet pregnancies seen at GSH during our study period.

Table 5: Maternal and Neonatal outcomes of triplet pregnancies at Groote Schuur Hospital.

Variables	Monochorionic	Dichorionic	Trichorionic	Undetermined	Total
Number of Maternal patients	5	6	10	4	25
Anaemia	1 (20%)	2 (33.3%)	1 (10%)	1 (25%)	5 (20%)
Preterm Labour	2 (40%)	4 (66.6%)	5 (50%)	4 (100%)	15 (60%)
PROM	0	1 (16.7%)	3 (30%)	1 (25%)	5 (20%)
Hypertensive disorders	1 (20%)	2 (33.3%)	3 (30%)	1 (25%)	9 (28%)
Gestational Diabetes	4 (80%)	0	1 (10%)	0	5 (20%)
Postpartum Haemorrhage	1 (20%)	0	0	0	1 (4%)
Number of Neonates	14	15	29	12	70
Low Birth Weight (<2500 g)	14 (93.3%)	13 (72.2%)	30 (100%)	12 (100%)	69 (96%)
Admission NICU	9 (60%)	11 (61.1%)	21 (70%)	11 (91.6%)	52 (69.3%)
Congenital Abnormalities	0	1 (16.6%)	0	0	1 (4%)
Intrauterine Growth Restriction	2 (40%)	1 (16.7%)	4 (40%)	0	7(10%)

Vascular Malformations **TTTS** **TRAP**	1 (20%) 0	0 1(16.7%)	0 0	0 0	2 (2.9%) 1(1.4%) 1(1.4%)
Survival	10 (71%)	10 (66.7%)	25(86%)	12 (100%)	57 (81%)

This table shows data of maternal and fetal complications. Neonates were divided into groups based on the predominant triplet chorionicity

Triplet pregnancy containing a MC Pair (n=5) with 14 neonates assessed (1 missing neonatal folder)

Triplet pregnancy containing a DC pair (n=6) with 15 neonates assessed (3 missing neonatal folders)

Triplet pregnancy containing a TC (n=10) with 29 neonates assessed (1 missing neonatal folder)

Triplet pregnancy containing a Undetermined chorionicity with 12 neonates assessed

CHAPTER 4: Discussion

Triplet pregnancies are not common as can be appreciated by the number (n=25) of patients seen at GSH over the five-year study period. Internationally, higher order multiple pregnancies are reported as being primarily due to ovulation induction and ART, with only about 20% of triplets conceived spontaneously. According to the ASRM, 20% of triplets are due to spontaneous conception, 39-67% to ovulation induction and 13-44% to ART.[32] Our study showed a different relationship, with 92% (n=23) of triplets conceived spontaneously and only one pregnancy resulting from ovulation induction and one from IVF. This may be due to the practice in our unit of transferring a maximum of 2 embryos in IVF and offering contraception to patients with multiple dominant follicles during ovulation induction. Another reason for this low rate of ART triplets at GSH might be that patients attended antenatal care in the private sector and thus were not included in our study. Some patients would find ART at GSH a financially feasible option compared to the higher costs applicable in the private sector. These patients may continue their antenatal care in the private sector. Ethnicity has not been considered in this study; according to the literature the incidence of triplet pregnancies is higher in Nigeria compared to Europe, US and Japan.[32]

Data obtained from the GSH cohort was compared to international literature as shown in table 6. The rate of NICU admission in our study was 69.3% compared to the studies from Beijing (39.4%) and India (80%).[16,33] The average birth weight in the literature ranges from 1500 to 1800g, with 90% of triplets having a birth weight of less than 2500g; this is in keeping with the results seen in the GSH cohort where the average weight was 1669g.[1,15,17,18,28] Survival rate in our cohort of triplets was 81% which is similar to the literature of 85%take-home-baby rate.[28] The average duration of hospitalisation for neonates in our study was > 7 days. This duration of hospitalisation is longer with more resource usage than neonates born with normal weights or at term.[1,4,28]

Table 6 shows data from GSH compared to data for other international studies reviewing triplet pregnancy outcomes.

Table 6: Maternal and Neonatal outcomes compared to International literature

Variables	GSH n=25	India[33] n=82	Triplet Pregnancy Outcomes[38] n=42	Wen et al[23] n=5491	Santema et al[37] n=40
Anaemia	5 (20%)	33 (40.2%)		173 (3.2%)	15 (38%)
Preterm Labour	15 (60%)	24 (29%)	3 (7.1%)		36 (90%)
PROM	5 (20%)	12 (14.6%)	13 (31%)	598 (11.2%)	5 (12%)
HT Disorders	9 (28%)	39 (47.5%)	13 (31%)	722 (13.1%)	10 (25%)
GDM	5 (20%)	13 (15.9%)	4 (9.5%)	328 (5.97%)	2 (5%)
PPH	1 (4%)	8 (9.8%)	6 (14.3%)		6 (15%)
LBW	69 (96%)	93 (41.3%)	20		
NICU Admission	52 (69.3%)	180 (80%)	24		

It is reported in the literature that preterm labour is the most common adverse outcome in multiple pregnancies, with rates of up to 90%.[1,17,18,27,28] Preterm labour was noted in 60% of our study patients. Postpartum haemorrhage was noted in 4% of triplet pregnancies in our study compared to reports in the literature of 3-9%; postpartum haemorrhage was documented in 14.3% of patients in the Downing et al study, 15 % in the Santema et al cohort and 9.8% in a study from India.[33,37,28] The definitions of preterm labour differ between the various studies between 35 and 37 weeks gestation. The incidence of hypertension in our study was 28% compared to the literature with rates ranging from 13-47%.[23,33,37,38] Anaemia in pregnancy was observed in 20% of patients in our study, whereas

the literature reports rates of 30-40%.[16,33] There was a higher occurrence of gestational diabetes in our study compared to the literature (20% vs 5-14%).[23,33,37,38]

Early determination of chorionicity and amnionicity is essential in multiple pregnancies to facilitate monitoring during pregnancy and delivery, as well as for diagnosis and management of complications such as TTTS.[1,4,5] The majority of patients in our study group attended the antenatal clinic for the first time in the second trimester, making the determination of chorionicity challenging. This may have led to an over diagnosis of monochorionic and dichorionic triplets and as a result influenced the neonatal outcomes. In some patients chorionicity could not be determined antenatally. The literature states that complication rates in patients with monochorionic placentation is increased with fetal death rates of 5.3%.[34] Our study contained 5 monochorionic triplets, one of which was complicated with TTTS and delivered before 28 weeks.

In our group of triplets there were four patients who delivered by normal vaginal delivery (see Table 2); this was not described in the international literature. The caesarean section rate in our study was 84%, compared to rates in the literature of 94 to 100%.[15,23 25, 28]

CHAPTER 5: Strengths, Limitations and Recommendations

There are no studies in South Africa reviewing the outcomes of triplet pregnancies. This study is unique in that it has provided some insights into triplet pregnancies in a South African state hospital context i.e. gestation at delivery, birth weight and NICU admission, which has not previously been interrogated. It has shown some of the differences between triplet conceptions seen internationally and our population at GSH. Given the stark differences in patient demographics and resources available in the first world compared to a developing country like South Africa, it is important to have our own data when counselling patients.

This study was further limited in terms of long-term neonatal follow up, thus precluding neurodevelopmental evaluation in these neonates. Subsequent studies could focus on the long-term neurodevelopmental outcomes seen in triplets, with a review of neurological development at two years and at the start of school. Combining monochorionic and dichorionic triplet data for analysis in subsequent studies may be considered due to the late booking and inaccurate chorionicity.

CHAPTER 6: Conclusion

Triplet pregnancies are rare; however, clinicians caring for obstetric patients should be aware of the risks inherent in triplet pregnancies to the mother, fetus and neonate. A multidisciplinary team, including a neonatologist and fetal medicine specialist, is required in the management of multiple pregnancies.[34] Similar to many pregnancies in South Africa, many of out cohort of triplets were only diagnosed in the second trimester, making chorionicity determination uncertain and possibly influencing the neonatal outcomes. In our study cohort, we found that 60% of patients went into preterm labour and 20% had premature rupture of membranes. Neonates had a 96% chance of low birth weight with an average birth weight of 1.6 kg. Neonates had a 96.3% chance of admission to the NICU and often required a few days in the nursery before discharge. The overall survival rate was shown to be 81% in our setting.

As the number of patients identified at GSH over the five-year period was relatively small, a subsequent multicentre national study may provide a more comprehensive perspective of maternal and neonatal outcomes in a South African setting. Such studies should include an evaluation of neurological development at 2 years of age and again at the start of school. This data would be valuable when counselling patients with triplet pregnancies.

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Appendices

DATA COLLECTION SHEET

File Number:

Triplet series number:

DEMOGRAPHIC INFORMATION					
Maternal Age	< 25 yr	25-35 yr	35-40 yr	> 40 yr	
Parity	Nulliparous	Multiparous			
Gestation at Booking	1st Trimester	2nd Trimester	3rd Trimester		
Conception	Spontaneous	Assisted reproduction			
Chorionicity	Trichorionic	Dichorionic	Monochorionic		
Amnionicity	Triamniotic	Diamniotic	Mono amniotic		
FETAL OUTCOMES					
Gestation at Delivery	<24 weeks	<28 weeks	28-32 weeks	32-36 weeks	>36 weeks
Mode of delivery	Emergency Cesarean Section	Elective Cesarean Section	Vaginal Delivery		
Birth weight **Triplet 1** **Triplet 2** **Triplet 3**	1:	2:	3:		
Low Birth Weight(<2500g)	YES	NO			
Outcome of pregnancy	All surviving	None Surviving	At least 1 surviving	At least 1 died	
Stillbirth	YES	NO			
Congenital Abnormality	YES	NO			
Intrauterine Growth Restriction/ Discordance	YES	NO			

Vascular Anastomosis	YES	NO			
If yes to above: Type	Twin to Twin Transfusion Syndrome	Twin Reversed Arterial Perfusion			
NEONATAL OUTCOMES					
Admission to NICU	YES	NO			
Neonatal death	YES	NO			
If yes to above	Early Neonatal Death	Late neonatal death			
Respiratory Distress	YES	NO			
Necrotising Enterocolitis	YES	NO			
Intraventricular Haemorrhage	YES	NO			
Other e.g. Sepsis	YES	NO			
Duration of hospital stay	<2 days	2-7 days	> 7 days	> 14 days	
Neurodevelopmental delay	YES	NO			
MATERNAL OUTCOMES					
Preterm labour	YES	NO			
Preterm Rupture of Membranes	YES	NO			
Anaemia	YES	NO			
Hyperemesis Gravidarum/ Excessive Vomiting in Pregnancy	YES	NO			
Chronic Hypertension	YES	NO			

Gestational Hypertension including Pre-eclampsia	YES	NO			
Gestational Diabetes	YES	NO			
Antepartum Haemorrhage	YES	NO			
Postpartum Haemorrhage	YES	NO			
Requiring Blood products	YES	NO			
Operative Complications	YES	NO			
Recurrent Hospital Admissions	YES	NO			
Duration of hospital stay	< 2 days	2-5days	>7 days		
Admission to ICU	YES	NO			
Maternal Death	YES	NO			