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Maternal and perinatal outcomes in triplet pregnancy An audit over 12 years at Inkosi Albert Luthuli Central Hospital

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DECLARATION

I, Dr N Parikh, declare that this dissertation is my original work and has not been submitted in any form to another university. Where use was made of the work of others, it has been duly acknowledged in the text.

The research topic entitled

"Maternal and perinatal outcomes in triplet pregnancy
An audit over 12 years at Inkosi Albert Luthuli Central Hospital"

Student _____

Supervisor _____ RAMNARAIN H 5/11/2016

Co supervisor _____

ABSTRACT

Aim: To determine maternal and neonatal outcomes in triplet gestation.

Study Design: Retrospective observational study.

Place and Duration of Study: Obstetric and Gynaecological Department, Inkosi Albert Luthuli Central Hospital, Durban from January 2003 to December 2014.

Patients and Methods: A retrospective analysis of all triplet pregnancies referred from nearby and outlying hospitals that were delivered at IALCH over a 12-year period was done.

Results: Eighty-nine women with triplet pregnancy were studied. Eighty-eight (98.9%) of the women were conceived spontaneously while 1 (1.1%) with the use of ovulation induction. Seventy-seven (86.5%) were booked for antenatal care at the base hospital. Mean duration of gestation was 30.8 weeks. The antenatal complications were preterm delivery in 62%, hypertension in 11%, anaemia in 26 % and preterm premature rupture of membranes in 17% of patients. Nine patients (10%) suffered postpartum haemorrhage. Seventy-five sets of triplets were delivered abdominally. Mean birth weights of the 1st, 2nd and 3rd triplet were 1497, 1499 and 1427 grams respectively. The mean Apgar scores of the 1st, 2nd and 3rd triplet at 1 and 5 minutes after birth were 7.3 and 8.5, 7.2 and 8.4; and 7.0 and 8.3 respectively. Of the 258 infants, 230 (89%) required neonatal intensive care unit admission. Total perinatal mortalities were 36 (13.5%) including 9 cases of intra-uterine demise. One hundred and nine suffered respiratory distress syndrome, 39 had neonatal jaundice and 19 had sepsis.

Conclusion: Triplet pregnancies had a high rate of feto-maternal complications in keeping with other retrospective studies. Risk factors in cases of premature delivery at IALCH included a birth weight of less than 1500 g, gestational age of less than *28* weeks and a maternal age between 25-39 years. Caesarean section was the MOD associated with better neonatal outcomes.

Plagiarism:

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I thank the following regulatory bodies for their permission to conduct this study. The approval letters are attached in the appendix section

1. Biomedical research ethics committee (BREC).
2. KZN, Department of Health.
3. The management of Inkosi Albert Luthuli Central Hospital.
4. Postgraduate Education Office, Nelson R Mandela School of Medicine, University of KwaZulu-Natal.

List of Abbreviations

IALCH	Inkosi Albert Luthuli Central Hospital
NND	neonatal death
SB	stillbirth
MCTA	Monochorioinic triamnoitic
DCTA	Dichorionic triamionitic
TCTA	Trichorionic triamniotic
SD	standard deviation
Hb	haemoglobin
IVH	Intraventricular haemorrhage
TTN	transient tachyponea of the newborn
IUGR	Intrauterine growth restriction
SGA	Small for gestational age
PTL	Preterm labour
PROM	Premature rupture of membranes
CS	caesarean section
VD	vaginal delivery
AST	assisted reproduction technique
LBW	Low birth weight
RPR	rapid plasma reagin
BMI	body mass index
NICU	neonatal intensive care unit
CPAP	continuous positive airway pressure

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CHAPTER ONE:
INTRODUCTION

Incidence

The incidence of multiple gestations has considerably increased over the past three decades(1). This increase is attributed primarily to the growing utilization of ovulation induction, assisted reproductive techniques (ART) and the trend of delayed childbearing in recent decades (2). High order pregnancies pose serious health risks to both mothers and babies and disproportionately contribute to infant and maternal morbidity and mortality rates. Short-term and long-term health issues and conditions result in astronomical costs to both public and private healthcare systems.

Multiple pregnancies account for 3 % of all births(3). There is worldwide variation in the rate of multiple pregnancies, ranging from 6.7 per 1000 deliveries in Japan, to 11 per 1000 deliveries in Europe and North America, to 40 per 1000 deliveries in Nigeria (4). In Italy, the rate of twin pregnancies and higher-order multiple pregnancies has been reported to be 12 per 1,000 and 0.52 per 1,000 respectively (5). The incidence of higher-order multiples pregnancies in the United States has increased from 0.37 per 1,000 live births in 1980 to 1.48 per 1,000 in 2008 (5).
A study in Cameroon found the incidence of triplet deliveries to be 0.13%, which is higher than the 0.06% observed in a study in Belgrade (Serbia) and the 0.09% observed in another study in Saudi Arabia (6).

Risk factors:

The prevalence of spontaneous triplet pregnancy is about 1 in 7000 deliveries, but with the increasing availability of assisted reproductive technologies, the rate of high-order multiple pregnancies has risen dramatically over the last 20 years (7).

The increase in the triplet birth rate has been most marked in women aged 40 years and over, with an increase of over 1000%. Conversely, in women aged 30 to 40 years, the

multiple birth rate increased by 30% with an increase of 13% in women less than 20 years of age (8).

After intrauterine inseminations using husband/partner's semen (IUI-H) in women below 40 years of age, twin pregnancies occurred in 11.9% and triplet pregnancies in 1.3% (9)

There has been a steady reduction in triplet deliveries in Europe over the years from 3.6% in 1997 to 0.8% in 2009 (10). This steady reduction is secondary to new approaches in ART such as singe embryo transfer.

Maternal Outcomes

Non-modifiable Factors

Elliott suggests that there are 4 primary non-modifiable factors that affect outcomes in higher-order multiples: maternal height, parity (previous full-term, non– low birthweight outcome), placentation and number of fetuses (11)**.** Maternal height has also been demonstrated by other investigators to influence multiple-pregnancy outcomes, with women taller than 165 cm (65 inches) giving birth to significantly heavier triplets and women shorter than 157cm (62 inches) significantly more likely to have triplets with ultrasonographic femur length or abdomen circumference measures of 10th percentile, by 28 weeks of gestation(12). Parity, particularly with a previous full-term, non–low birthweight outcome, has been reported to be associated with a better outcome in a subsequent multiple pregnancy(13).

Discordancy in crown-rump length and estimated foetal weight is another factor that influences the rate of foetal growth and length of gestation, with monochorionic placentation more than twice as likely to be associated with birthweight discordancy and significant differences in rates of foetal growth, which in turn has been associated strongly with very early preterm birth(14).

An additional important non-modifiable factor may include maternal age. Older

maternal age may reflect both social and physiologic advantages over their younger counterparts(15). Women who are pregnant with multiples and who are older tend to be of higher socioeconomic status, have more education and social support, and better access to prenatal care and specialized services(16).

Modifiable Factors

The adverse effects of the modifiable factor of smoking in multiple pregnancy has been well-documented by several researchers. (16)

Triplet pregnancies are associated with statistically significantly increased risks of maternal morbidity and obstetric complications, including anaemia, diabetes mellitus, gestation hypertension, eclampsia, abruptio placenta, preterm labour, premature rupture of membrane, and increased caesarean delivery (17)

Pregnancy is generally associated with an increased demand on the iron reserves of the mother. Larger placental mass and added foetuses in triplet pregnancies results in a depletion of iron stores and increased risk of anaemia in the mother. Reported incidence ranges from 13 to 35%(18, 19). Preterm labour, defined as onset of labour prior to 37 completed weeks is the most commonest maternal complication seen with incidence varies between 75-100%(20).

Mode of delivery

Delivery of triplet pregnancies presents a great challenge to obstetricians due to inherent increased perinatal morbidity and mortality risk(10). Majority of these pregnancies are complicated by mal-presentation, prematurity, the need of either abdominal or vaginal operative delivery and the likelihood that one or more new-borns will require immediate specialized care(17). The mode of delivery of triplet pregnancies and outcomes varies between studies.

In a series of 78 triplets, Lipitz et al reported a 78% caesarean section rate(21). The authors were of the view that there is an increased risk of mortality and morbidity in very low birth weight neonates. Furthermore, a vaginally delivered third triplet had a higher incidence of low Apgar scores and respiratory disorders and thus suggests that there is little justification to attempt vaginal delivery in these high risk patients. This varied from a case controlled study of 23 sets of triplets delivered vaginally compared to 23 controls delivered abdominally which found that in selected cases, vaginal delivery of triplets may be safe (22).

Alama et al established a protocol for planned vaginal delivery of triplets (17). The prerequisites are a cephalic presentation of the 1st triplet, electronic monitoring of the 3 foetuses and provided that the delivery be conducted by an experienced obstetrician with a neonatologist present (17). The authors reported an 88% rate of successful vaginal deliveries, concluding that vaginal delivery can be accomplished without an increased maternal or neonatal morbidity and mortality(23).

In another study, conducted locally at Baragwanath Hospital looking at 61 sets of triplet pregnancies that were identified over a 10-year study period(24). All patients except for one, delivered vaginally. The main problem encountered was that most of the vaginal deliveries required manipulation(24). This demonstrated the need for an experienced obstetrician at the time of delivery.

The abdominal route is the current recommended mode of delivery(25). Vaginal delivery was associated with an increased risk of fresh stillbirths (RR 5.7) and neonatal (RR 2.83) and infant (RR 1.61) deaths when compared to caesarean delivery. The increased population-attributable risk of (15.9%) for neonatal and (12.4%) for infant death was avoidable if these triplet foetuses were delivered by caesarean section (26).

Chorionicity

Definitions

Chorionicity refers to the number of placentas that surround the babies in triplet pregnancies.

Categorization of pregnancies based on the number of placenta(1)

- Monochorionic if there is only one placenta
- Dichorionic if there are two placentas
- Trichorionic if there are three placentas

Amnionicity refers to the number of inner membranes (amnions) that surround the babies in triplet pregnancies(1).

Categorization of pregnancies based on the number of amnions:

- Monoamniotic - one amnion (babies sharing amniotic sac)
- Diamniotic - two amnions (one set of twins sharing amniotic sac)
- Triamniotic – three amnions (all separated by amniotic sac)

Perinatal outcome in multiple gestations is affected to a large degree by chorionicity (27). This is also true for triplet pregnancies, as chorionicity has shown to influence mortality rates in triplets (20,21). MCTA triplet pregnancies have a significant higher risk of death (2.6-fold) compared to TCTA triplet pregnancies (27, 28). Recent studies have illustrated that mono or dichorionicity in triplet pregnancies is implicated in adverse perinatal outcomes with a 5.5 fold higher risk of adverse perinatal outcome (29-31).

Khalil, et al (2013) studied 17 sets of triplet pregnancies(32). The majority were dichorionic triamniotic (DCTA) triplet pregnancies (*n*=14), while only three pregnancies were monochorionic triaminotic (MCTA). The overall survival rate was 57%, while the rate of preterm delivery prior to 32 weeks was 58%. The survival rate was 33% and 61% in MCTA and DCTA pregnancies, respectively. Perinatal survival of at least one foetus was 77%. These authors concluded that monochorionic triplet pregnancies are at increased risk of adverse outcomes(32). This is in marked contrast to a study by Zanardini et al (2010) who studied 55 sets of triplet pregnancies(33). The outcome of each pregnancy was assessed in relation to chorionicity. There were 44 sets of TCTA triplet pregnancies and 11 sets of triplet pregnancies with a MC pair or triplet. The neonatal complications of pPROM, IUGR/SGA, RDS and IVH were not significantly higher in

monochorionic pregnancies compared to trichorionic sets. The authors concluded that risk of adverse outcome is not related to chorionicity **().**

Fetal Outcomes

In triplets and higher order gestations, we are faced with increased maternal and fetal risks, in comparison to singleton or twin pregnancies (34). Neonatal complications are due to preterm delivery and LBW (<2500g). According to some recent reports, lengthening of gestational age and birth weight at delivery could primarily influence their outcome (34).

Preterm birth, defined as a birth before 37 weeks, occurs in up to 87.9% - 91 % of triplet pregnancies (35). The risk of extreme preterm birth (<28 weeks) and very preterm birth (28-32 weeks) is increased by 13-fold and almost 20-fold respectively(36). The rate of preterm births before 32 weeks of gestation in triplets is 3.3-fold higher than in twins and 24.1-fold higher than in singletons(2). Only 10 - 13% of the triplets reach a gestational age of more than 35 weeks (37). This exposes the neonate to complications from respiratory distress syndrome, intraventricular haemorrhage, patent ductus arteriosus, sepsis and retinopathy of prematurity. Neonatal respiratory distress syndrome is diagnosed when respiratory distress requiring oxygen therapy is present in the first 24 hours of life(38). This is directly related to prematurity which accounts for up to 78.2% of triplet pregnancies (39).

Retinopathy of prematurity is a developmental disease which occurs mainly in the incompletely vascularized retina of premature infants(40)**.** Prematurity is the most important risk factor. The incidence of retinopathy of prematurity is over 80% in infants less than 1000 g(41). The incidence of intraventricular haemorrhage in preterm infants' ranges from 29-49% of all infants less than 1500 g. The majority of IVH occurs in the first 72 hours of life (42).

In triplet pregnancy the risks of low birth weight are 10–75 fold (43). Birth weight is

closely associated with gestational age, thus the increased incidence of preterm delivery influences the rate of reduced birth weights in triplet neonates(44, 45). 92% of triplets are born with low birth weight(46). The mean birth weight for triplets range 1789 ± 505g (8).

Triplet pregnancies are associated with higher perinatal mortality rates when compared to twin pregnancies (47) and singletons. Perinatal mortality rates range from 121 to 151 per 1000 (29) and are mainly related to the higher incidence of prematurity and its complications.

Incidence of fetal abnormalities have been reported to be in range of 7-10% in multifetal gestation especially for central nervous system and cardiac abnormalities (48). The incidence increases with maternal age as shown below in table 1 (48).

Table 1: Incidence of chromosomal abnormalities in at least one foetus in triplet pregnancies

Maternal age (years)	**Risk in triplets (number and percentages)**
20	1/175 (0.57%)
25	1/150 (0.67%)
30	1/128 (0.78%)
35	1/64 (1.56%)
40	1/22 (4.55%)

Evans and Andriole (48)

African studies of triplet pregnancies

The main highlights of a triplet pregnancy study from Zimbabwe found that there were 105 triplet pregnancies among 286,338 pregnancies with an incidence of 1: 2,727 (39). The mean gestational age at delivery was 32.5 weeks with 81 women (77.1%) delivering before term. Of the 315 babies, 277 (87.9%) weighed less than 2500 g. The overall perinatal mortality rate was 327%. Among the neonates born with a gestation of ≥ 28 weeks, there were fewer perinatal deaths in triplets delivered by caesarean section compared with triplets delivered vaginally ($p < 0.0004$) (49).

In another study from Baragwanath Hospital, 61 triplet pregnancies were identified over a 10-year study period(24). The incidence was 1: 2 789 deliveries. The average maternal age was 29,6 years. Vaginal delivery was the most common mode of delivery with high proportion of manipulation but with good fetal outcome (24).

In another study by Deale and Cronje (1984) performed in hospitals in South Africa and Namibia (50). Information on 367 sets of triplets from 150 out of a possible 452 hospitals was obtained via a questionnaire based study. The incidence of triplets was 0.04% of all deliveries. Forty-five percent of triplets were diagnosed during the first or second stage of labour. The mean birth weights of babies that died in utero or neonatally (within 7 days) were significantly lower than those who survived ($p<0.0001$). Caesarean section was the delivery method for 14% of the infants (50).

In a final African study by Nkwabong and co-workers conducted in Cameroon(6). This retrospective study looked at 43 sets of triplets and identified preterm delivery and pre-eclampsia as most common complications in pregnancy(6). More than 60% of their cohort delivered vaginally whilst 37.2% delivered via caesarean section(6).

There is a great paucity in the literature on triplet pregnancies and such a study is needed looking at the south African population.

CHAPTER 2:
STUDY

Maternal and perinatal outcomes in triplet pregnancy
An audit over 12 years at Inkosi Albert Luthuli Central Hospital

Rationale

The obstetric unit based at Inkosi Albert Luthuli Central Hospital (IALCH) is a specialist hospital based in Durban, KwaZulu-Natal. This unit assesses and manages all high risk obstetric patients including triplet pregnancies referred from nearby and outlying hospitals in KwaZulu-Natal. An audit was essential to evaluate the management practices of triplet pregnancy at this unit. Information gathered from this study would better assist in management of triplet pregnancies in a low resource setting / developing nation.

Aim

Audit the maternal and fetal outcomes in women with triplet pregnancies managed at Inkosi Albert Luthuli Central Hospital's high risk obstetric unit.

Objectives

1. **Primary: Maternal and neonatal outcomes**
    - **a.** Secondary: Maternal characteristics
    1. Incidence of maternal disease in pregnancy: hypertension, diabetes and anaemia
    2. Risk of spontaneous preterm labour and gestational age of onset.
    3. Average gestational age of delivery

4. Mode of delivery and its implications

b.Secondary : Fetal

1. Fetal weights at delivery
2. Fetal outcome based on Apgar score
3. Average fetal NICU admission
4. Neonatal outcome comparing triplet 1, triplet 2 and triplet 3
5. Congenital risk in triplet pregnancies

CHAPTER 3:
METHODOLOGY

Research design

This was a descriptive retrospective chart review of all women with triplet pregnancies managed and delivered at Inkosi Albert Luthuli Central Hospital.

Study population

All women with triplet pregnancies referred to IALCH high risk obstetric unit during the study period extended from the 1st Jan 2003 to 31st December 2014.

Sampling and Data collection

Eligible women were identified from a computer based clinical database at IALCH. Ninety-four medical records were reviewed of women with triplet pregnancies and all relevant data were recorded on to a structured format (Appendix 2).

The following data were collected: maternal age at delivery, mode of conception, type of infertility treatment, parity, chronic diseases, gestational age at the time of delivery, mode of delivery, antepartum and postpartum complications, gestational age at antenatal admission, gestational age at which steroids was administered to enhance fetal lung maturity and length of hospitalization.

The data extracted from neonatal records included: birth weight, Apgar score at 1 and 5 minutes after birth, congenital anomalies, neonatal mortality, neonatal complications, admission to neonatal intensive care unit (NICU) and length of stay in hospital.

Statistical analysis

Data was entered into a computerized datasheet using Microsoft Excel and imported on SPSS (The Statistical Package for Social Sciences; version 23) for analysis. The data was analysed using descriptive statistics with the use of frequency, tables, percentages and cross-tabulation and results are presented as mean± SD, range. Statistical analyses were performed with Chi Square Test and analyses of variance (ANOVA) where appropriate. Significance was set at a p value < 0.05.

Regulatory Approval

The study was approved by the BREC (Biomedical Research Ethics and Committees) (BE 500/14), Postgraduate Education and Research Office, Nelson R Mandela, School of Medicine, Hospital management of the IALCH and the KZN Department of Health (ref no. HRKM155/15).

CHAPTER 4:

DATA ANALYSIS AND FINDINGS

Results

This retrospective chart review of women with triplet pregnancies referred from nearby and outlying hospitals within Kwa Zulu Natal province to Inkosi Albert Luthuli Central Hospital, Durban for assessment and management over a 12-year period extending from 1st January 2003 to 31st December 2014. Data of 94 triplet pregnancies were identified over the study period. On review of these data sheets it was established that only 89 (94.7%) of the 94 medical records met the inclusion criteria with complete documented data. 5(5.3%) patient's records were incomplete with missing clinical information and were subsequently excluded from the analysis. With regard to the method of conception, 88 (98.9%) of the pregnancies were spontaneously conceived whilst 1 conceived (1.1%) with the use of ovulation induction.

Maternal demographics

Our study population was predominantly South African Black women (n=80; 89.9%) which included a small number of South African Indian women (n=5; 5.6%), Whites (n=3; 3.4%) and Coloureds (n=1; 1.1%). Thirty-seven (41.6%) of women gave a positive family history of multiple pregnancy.

The ages of the women ranged from 19 to 42 with a mean age of 30.4 ± 5.5 years. The median age was 29.0 years. The age groups of the women are shown in Table 2. Triplet pregnancy occurred more commonly in the age group 25 – 29 years. The mean (SD) parity was 2 ± 1 (range: 0 – 6) with a median of 2. Triplet pregnancy occurred more frequently in women with parity of two. 12 (13.5%) were primiparous and 77 (86.5%) were multiparous. Table 2 shows the parity of women included in the study. Based on the

body mass index; 13 (17.1%) women were classified as normal, 26 (34.2%) were overweight and 37 (48.7%) obese whilst the remaining 13 (17.1%) were low BMI.

Table 2: Maternal demographics

	Frequency	**Percentage**
Age grouping		
<20	1	1.1 %
20 -24	13	14.6 %
25 – 29	31	34.8 %
30 – 34	20	22.5 %
35 – 39	21	23.6 %
> 40	3	3.4 %
Parity grouping		
0	12	13.5 %
1	21	21.4 %
2	34	34.7%
3	15	15.3 %
>4	7	7.8 %

VARIABLE	MEAN ± SD	MEDIAN	RANGE
Age(years)	30.4 ± 5.5	29	19 – 42
Parity	2 ± 1	2	0 – 6
BMI	31.3 ± 9.0	29.7	39 – 64

Gestational age

Admission to the hospital occurred at a mean gestational age of 28.9 ± 2.9 (range: 21-35) weeks. There was no significant difference between the gestational age at admission and gestational age at delivery (28.9 ± 2.9 vs 30.8 ± 2.8; p=0.1) and all sets of triplets were delivered preterm.

Gestational age at delivery

Forty-two (15.7%) neonates were born < 28 weeks' gestation, 87 (32.6%) neonates between 28 and 31 weeks, 87 (32.6%) neonates between 32 weeks and 33 weeks and 51

(0.7%) neonates between 34 weeks and 36 weeks. Table 3 shows breakdown pregnancies by gestational age grouping.

Table 3: Gestational age grouping at delivery

Gestational age groups	Frequency	Percentage
<28 weeks	14	15.7
28 – 31 weeks	29	32.6
32 – 33 weeks	29	32.6
34 – 36 weeks	17	19.1

Neonatal outcome by gestational age stratified

In this triplet pregnancies series, there were 28 perinatal deaths (21 neonatal deaths and 7 stillbirths) in women who delivered at less than 28 weeks of gestation; 7 perinatal deaths (6 neonatal deaths and 1 stillbirth) in women who delivered between 28 – 31 weeks and 1 perinatal death (1 stillbirth) who delivered between 32 – 33 weeks of gestation as demonstrated in table 4. There was a significance difference between the groups (p=0.001).

Table 4: Neonatal outcome by gestational age stratified

Gestational age	Triplet A			Triplet B			Triplet C		
	Alive	**SB**	**NND**	**Alive**	**SB**	**NND**	**Alive**	**SB**	**NND**
<28 weeks	5	2	7	4	3	7	5	2	7
28 – 31 weeks	25	0	4	28	1	0	27	0	2
32 – 33 weeks	29	0	0	29	0	0	28	1	0
34 – 36 weeks	17	0	0	17	0	0	17	0	0

Classification of birth weight

Forty two (15.7%) neonates were born < 1000 grams' bodyweight, 75 (28.08%) neonates were born < 1500 grams' bodyweight, 147 (55%) neonates were born < 2500 grams' bodyweight and only 3 (1.1%) neonates were born with bodyweight > 2500 grams. Of the 267 babies, 264 (98.8%) infants weighed less than 2500 grams. Classification of bodyweights are shown in Table 5

Table 5: Classification of birth-weight

Birth weight	Frequency	Percentage
< 1000 grams	42	15.7
< 1500 grams	75	28.08
< 2500 grams	147	55
> 2500 grams	3	1.1

Neonatal outcome by birth weight

In neonates born with birthweight < 1000grams, there were 26 perinatal deaths (21 neonatal deaths and 5 stillbirths), In neonates born with birthweight < 1500grams, there were 8 perinatal deaths (6 neonatal deaths and 2 stillbirths) and 2 perinatal deaths (2 stillbirths) in neonates born < 2500 grams. Neonatal outcome based on birthweight shown in table 6.

Table 6: Neonatal outcome by birthweight

Birth weight	Triplet A			Triplet B			Triplet C		
	Alive	SB	NND	Alive	SB	NND	Alive	SB	NND
< 1000 grams	5	1	8	5	3	6	6	1	7
< 1500 grams	21	1	3	24	0	1	22	1	2
< 2500 grams	49	0	0	48	1	0	48	1	0

Steroids

Steroids was given to 75 (84.3%) of the mothers. The mean (SD) gestational age when steroids were started was 28.7 weeks with a median of 28 (range: 20 – 32).

Neonatal course and morbidity

There were 258 (96.6%) neonates born alive which included 27 neonatal deaths. There were a total of 9 (10.1%) stillbirths. Two hundred and thirty one neonates were discharged and sent home. One (0.4%) of the 231 infants had Downs syndrome. Neonatal outcomes are shown in table 7.

The mean birthweight was 1497.7 ± 490.2 grams for the first triplet A and ranged from 540 - 2720 grams, 1499.3 ± 489.9 grams for the triplet B with a range between 410 - 2500 grams. The weight for the triplet C was 1427.9 ± 419.0 grams with a range of 570 –2540 grams. The mean (SD) birthweight was 1475 ± 437 (range: 410-2720) grams. This is shown in table 7. The stillbirth rate was 33 per 1000 live births; The early neonatal death rate was 105 per 1000 live birth rates; The perinatal mortality rate 134 per 1000 live births.

Table 7: Neonatal outcome

	Triplet A	Triplet B	Triplet C
Neonatal outcome			
Alive	76	78	77
Stillbirths	2	4	3
Neonatal deaths	11	7	9
Birthweight			
Mean (SD)	1497.7 ± 490.2g	1499.3 ± 489.9g	1427.9 ± 419.0g
Median	1500g	2000g	2150g
Range	540 – 2720g	410 – 2500g	570 – 2540g

Details of early neonatal deaths

The mean (range) gestational age at delivery was 26 (23-29) weeks. At 1 min, the mean Apgar score was 5 (range: 2-9) and at 5 min the mean Apgar score was 7 (range: 2-10). Twenty two of the 27 infants were < 1000 grams and 5 were < 1500 grams.

Apgar scores

The Apgar score at the 1st minute, ranged from 0 to 10 for all triplets with a mean of 7.2 ± 1.4 while that of the 5th minute ranged from 0 to 10 for all triplets with a mean of 8.4 ± 1.6. The median (range) Apgar score, for liveborns, was 8 (2–10) and 10 (4–10) for 1 and 5 minutes respectively. Apgar scores based on live triplets are shown in table 8.

Table 8: Apgar scores

	Mean ± SD	Median	Range
APGAR SCORE 1MIN			
Triplet A	7.3 ± 1.9	8	1 – 9
Triplet B	7.2 ± 1.7	8	1 – 9
Triplet C	7 ± 5	7.5	2 – 10
APGAR SCORE 5MIN			
Triplet A	8.5 ± 1.5	9	2 – 10
Triplet B	8.4 ± 1.6	9	0 – 10
Triplet C	8.3 ± 1.6	9	0 -10

Neonatal complications

Neonatal complications are shown in Table 9. The commonest neonatal complication was hyaline membrane disease (41%), and this complication also carried the highest mortality rate among the neonates. Other neonatal complications were neonatal jaundice in 14.6 of cases, metabolic acidosis in 1.16%, patent ductus arteriosus in 5.9%, sepsis in 18.4%, hypoglycemia in 0.7%, necrotizing enterocolitis in 3%, intraventricular haemorrhage in 2.6%, congenital pneumonia in 4.1%, and extreme prematurity in 2.6%. Neurological complications were diagnosed in 0.4 % of cases and included hydrocephalus.

In 109 infants the main respiratory pathology was respiratory distress syndrome (RDS); of these, 53 infants received surfactant. The median (range) duration of ventilation was 2 (1–11) days and median duration of CPAP was 2 (1-4) days.

Table 9: Neonatal complications

Neonatal complications	Triple A	Triplet B	Triplet C
Hyaline membrane disease	32	39	38
Neonatal jaundice	14	11	14
Patent ductus arteriosus	7	5	4
Sepsis	19	18	12
IVH			
Grade 1	1	1	
Grade 4	1		1
Grade 3		1	1
Grade 2		1	
Congenital pneumonia	3	3	5
Others			
Seizures	1	1	0
TTN	1	2	2
Hypoglycaemia	1	1	0
Hypothermia	1	0	0
Gangrene (I foot)	1	0	0
Hydrocephalus	1	0	0
Necrotising enterocolitis	1	3	4
Atrial septal defect	0	1	0
Meningitis	0	1	0
Pneumothorax	1	0	0
Disseminated intravascular	0	1	1
clotting	0	0	1
Septic shock	3	1	3
Extreme prematurity	0	2	1
Metabolic acidosis	1	0	1
Cysts			

Infants stay in neonatal intensive care unit

Seventy-nine, seventy three and seventy eight of the triplets A, B and C were admitted to neonatal intensive care unit respectively. The mean (SD) number of days' neonates stayed in NICU was 4.5 ± 5.9 (range: 1- 41) for triplet A compared to 6.9 ± 10.5 (1-73) for triplet B and 5.3 ±7.4 (range: 1- 42) for triplet C. There was no significant difference in the mean duration of hospitalization amongst the triplets (p=0.3).

MATERNAL CHARACTETRISTICS

Maternal hospital stay

The mean length of maternal hospitalization was 24.9 ± 18.3 (range: 1-69). The median number of days of hospitalization was 21.

Booking investigations

The mean (SD) haemoglobin was 10.0 ± 1.4 (range: 7 – 13.5) g/dl with a median of 10.1 g/dl. Sixty (73.2%) were diagnosed as anaemic (Hb < 11 g/dl). Six (6.8%) were rhesus negative and 3.4% were RPR positive.

HIV status

Forty-one (46.1%) of 89 women with triplet pregnancies were HIV infected and 48 (53.9%) were uninfected. CD4 and treatment details were available for 35 (85.4%) of the 41 HIV infected women which is broken down in table 10. The mean (SD) CD4 count was 27.98 ± 185.2 (range: 33-943) cells/mm^3. The median CD4 count was 249cells/mm^3.

Table 10: Treatment of HIV infected women (n=35)

Treatment	Frequency	Percentage
Highly active antiretroviral	17	48.6 %
Dual therapy	13	37.1 %
Fixed dose combination	4	11.4 %
AZT	1	2.9 %

Neonatal outcome based on HIV status in triplet pregnancy

Twenty-one (17.1%) perinatal deaths (20 neonatal deaths and 1 stillbirth) occurred in the 41 HIV infected group compared to 15 (10.4%) perinatal deaths (7 neonatal deaths and 8 stillbirths) in the 48 HIV uninfected group. This was statistically non significant (p=0.105). Breakdown is shown in table 11.

Table 11: Neonatal outcome based on HIV status in triplet pregnancy

HIV STATUS	Triplet A			Triplet B			Triplet C		
	Alive	SB	NND	Alive	SB	NND	Alive	SB	NND
Infected	33	0	8	35	1	5	34	0	7
Uninfected	43	2	3	42	4	2	44	2	2

Mode of delivery

Seventy-five (84.3%) patients delivered by caesarean section. Among these, 81.3% were emergency caesareans and 14 (18.7%) were elective CS. Eleven (12.4%) women had normal vaginal delivery. Three (3.4%) women delivered the first triplet vaginally and the subsequent triplet 2 and triplet 3 by CS because of intrapartum complications. Table 12 shows the indications for CS delivery.

Table 12: Indications for CS delivery

Indications	Frequency	Percentage
Triplet pregnancy	31	41.3 %
Preterm labour	16	21.3 %
Previous CS x2	8	10.6 %
Previous CS x1	11	14.6 %
Premature ROM	8	10.6 %
Antepartum haemorrhage	1	1.3 %

Impact of mode of delivery on neonatal outcome

The neonatal outcomes following different modes of delivery is shown in table 13. There were 16 perinatal deaths (3 stillbirths and 13 neonatal deaths) following CS and 16 perinatal deaths following vaginal delivery (2 stillbirths and 14 neonatal deaths). This was statistically significant ($p<0.0001$). Four perinatal deaths (4 stillbirths) occurred following combined NVD/CS delivery.

Table 13: Neonatal outcome via mode of delivery

Mode of delivery	Triplet A			Triplet B			Triplet C		
	Alive	**SB**	**NND**	**Alive**	**SB**	**NND**	**Alive**	**SB**	**NND**
Caesarean delivery	70	0	5	68	2	5	71	1	3
Vaginal delivery	4	1	6	5	0	6	8	1	2
NVD/CS	2	1	0	1	2	0	2	1	0

Concomitant medical disorders

Table 14 shows the concomitant medical disorders of the study group. Fourteen (15.7%) of the 89 women had concomitant medical disorders. Six (42.9%) had tuberculosis, 4 (28.6%) with chronic hypertension, asthma (n=2; 14.2%), mitral valve regurgitation (n=1; 7.1%) and infertility (n=1; 7.1%).

Table 14: Concomitant medical disorders

Medical disorder	Frequency	Percentage
Chronic hypertension	4	28.6 %
Tuberculosis	6	42.9 %
Asthma	2	7.1 %
Mitral regurgitation	1	7.1 %
Trans Ischaemic attack	1	7.1 %

Antenatal maternal complications

Complications that occurred during these pregnancies included 55 (61.8%) cases of premature labour, 11 (12.4%) cases of pre-eclampsia, 5 (5.6%) cases of gestational hypertension, 23 (25.8%) cases of anaemia, and 15 (16.9%) cases of preterm premature rupture of membranes. The complications observed are shown in Table 15.

Table 15: Maternal complications antepartum

Antenatal complication	Frequency	Percentage
Preterm labour	55	61.8 %
Anaemia	23	25.8 %
Pre-eclampsia	11	12.4 %
Gestational hypertension	5	5.6 %
PPROM	15	16.9%
Others		
Antepartum haemorrhage	1	1.1 %
Pyelonephritis	2	2.24 %
Vitamin B12 deficiency	1	1.1 %
Upper respiratory tract infection	3	3.4 %
IUGR	2	2.2 %
Rhesus negative	2	2.2 %
Varicella zoster	1	1.1 %
Urinary tract infection	2	2.2%

Postpartum maternal complications

Postpartum haemorrhage occurred in 9 patients with all 9 patients required blood transfusion. Only one required surgical intervention. Puerperal anaemia was documented in 4 women. Table 16 shows breakdown of maternal postpartum complication.

Table 16: Postpartum maternal complications

Postpartum complication	Frequency	Percentage
Postpartum haemorrhage	9	10.1 %
Anaemia	4	4.49 %
Wound sepsis	3	3.37 %
Pre-eclampsia	1	1.12%
Others		
Postpartum cardiomyopathy	1	1.12 %
Depression / psychosis	2	2.24 %
Deep vein thrombosis	1	1.12 %

Chorionicity

Amongst the 89 sets of triplets, 78 pregnancies had clear ultrasound findings of chorionicity. Amongst these 78 sets of triplets, 33 (42.3%) had dichorionic placentae, 27 (34.6%) had trichorionic placentae and 18 (23.16%) had monochorionic placenta. All had triamniotic pregnancy.

Table 17: Types of chorionicity (n=78)

Chorionicity	Frequency	Percentage
Monochorionic Triamniotic	18	23.1 %
Dichorionic Triamniotic	33	42.3 %
Trichorionic Triamniotic	27	34.6 %

Neonatal outcome based on chorionicity

On the basis of chorionicity, there were 8 perinatal deaths (6 neonatal deaths and 2 stillbirths) in the MCTA group, 10 perinatal deaths (8 neonatal deaths and 2 stillbirths) in DCTA group and 11 perinatal deaths (8 neonatal deaths and 3 stillbirths) in the TCTA group. Table 18 shows breakdown.

Table 18: Neonatal outcome based on chorionicity

CHORIONICITY	Triplet A			Triplet B			Triplet C		
	Alive	SB	NND	Alive	SB	NND	Alive	SB	NND
MCTA	16	0	2	14	2	2	16	0	2
DCTA	30	0	3	29	2	2	30	0	3
TCTA	22	1	4	24	1	2	24	1	2

Congenital anomalies

Congenital anomalies occurred in 4 (1.5%) neonates in 3 (3.4%) different pregnancies and included one case each of:

1. double outlet right ventricle/mal-position of great vessels /patent ductus arteriosus, dysmorphism (low set ears/webbed neck/club feet /chromosomes (46xx). The outcome was a LNND
2. pelvic ureteric junction obstruction
3. Downs syndrome in triplet A and B of same pregnancy. Triplet A demised post delivery whilst Triplet B demised at the age of three from a pneumonia.

Chapter 5:
Discussion, limitations, conclusions and recommendations

Discussion

In this study, we report the outcome, including maternal and neonatal mortality and neonatal morbidity, for a 12 year cohort of 267 triplets born from 89 mothers at a single large tertiary hospital in South Africa. There were no maternal deaths. The ages of our patients ranged from 19 to 42 with a mean (SD) of 30.8 ± *5*.5 years. The majority (34.8%) of triplet pregnancies occurred in the 25-29 age group compared to other studies having a majority of 40.2 – 40.5% in the 30-34 age group(16, 17).The majority of the patients were between parity 0 – 6 with 86.5% of women were multiparous with 13.5% being primigravidae. In contrast, a study reported that most (81.8%) of triplet pregnancies occurred in primigravidae (51), which is supported by other studies showing 51-53% triplets occur in primigravidas (16, 17).

Optimal gestational age for delivery has not been established by randomized trials and most evidence comes from retrospective cases. The mean gestational age at delivery in this study (30.8 weeks) which was less than that reported in other studies which varied between 31.7 and 33 weeks(6, 52, 53). This disparity in the gestational age at delivery between this study and other studies was due to the fact that majority of triplet pregnancies in our study population had preterm labour and delivered preterm with a range of 24 -35 weeks. A large epidemiologic analysis found that only 16% remain undelivered at 36 weeks of gestation(54). In our institute, we have a policy delivering triplet pregnancies via CS before 35 weeks. Delivery between 34-35 weeks is associated with least fetal risk (16).

Our study presents similar results with the literature in terms of maternal complications of postpartum haemorrhage, anaemia and hypertensive disorders especially pre-eclampsia. In our study, anaemia (73.2%) was the most common antenatal complication. This varied from other studies showing incidence 38%- 58%(47, 53). This discrepancy

could be due to a higher prevalence of nutritional iron deficiency in our population. Preterm labour (61.8%) was the second most commonest complication seen with a lower incidence then other reports (47, 53, 55). Tocolytic agents were used in our study, but no improvements could be seen in the mean gestational age at delivery, birthweight or the outcome of the newborns. Other antenatal complication in this study were 11 (12.4%) cases of pre-eclampsia, 5 (5.6%) cases of gestational hypertension and 15 (16.9%) cases of preterm premature rupture of membranes. The mean antenatal hospital stay of our mothers was 24.9 ± 18.3 (range 1-69) days, which is very similar to other reports where the average antenatal stay was approximately 11–42 days (2, 45, 56).

In this study, there were 36/267 (13.5%) perinatal deaths, 28 perinatal deaths in women who delivered at less than 28 weeks of gestation; 7 perinatal deaths in women who delivered between 28 – 31 weeks and 1 perinatal death who delivered between 32 – 33 weeks of gestation.

Gestational age represents the main factor affecting birth weight, which correlates with morbidity and survival rates(16, 57, 58). The prevalence of low birth weight and preterm deliveries was high among our triplet births. Both low birth weight and prematurity are known risk factors for adverse health, cognitive and behavioural outcomes later in life(59). It is important to note that only 10 - 13% of the triplets reach a GA of more than 35 weeks (37).

According to birthweight, 26 perinatal deaths occurred in neonates < 1000grams, 8 perinatal deaths with birthweight < 1500grams and 2 perinatal deaths in neonates born < 2500 grams. These findings are consistent with other studies(60). Our perinatal mortality rate of 134 per 1000 live births was higher compared to reported rates of 41-121 per 1000 live births (11, 53, 61). This discrepancy can be explained by a higher number of our triplet pregnancies delivering preterm with 48.3% delivering prior to 31 weeks. The overall survival of triplets in our study was 86.5%. According to Joseph et al (2002) in triplet pregnancies, the risk of stillbirth increases from 5% at 28 to 33 weeks to 16% at 34 to 36 weeks. In our study, the figures were 3.4% and 0% respectively(62). Although previous studies have reported a higher neonatal morbidity and mortality in the third born triplet(42), we found no difference in outcome according to the birth order, which was

probably due to the policy of delivering all triplet pregnancies by caesarean section at IALCH.

Among the 267 neonates in our audit, neonatal complications included hyaline membrane disease in 109 babies (41%), hyperbilirubinemia in 39 (14.6%), sepsis in 49 (18.4%), PDA/atrial septal defect in 16 (26) and NEC in 8 (2.9%) and IVH in 7 (2.6%). Our findings are in keeping with other studies and differ mainly in the incidence of sepsis of 5 %(29) while Al-Shukri et al (2014) reported similar hyaline membrane disease in 46%, hyperbilirubinemia in 43%, sepsis in 33%, PDA/atrial septal defect in 5 9% and NEC in 4%(56). With regard to congenital anomalies, we observed 4 cases (1.5%) in 3 different pregnancies.

Most of our patients conceived spontaneously (98.9%) which is comparable with 94.62 % by Katke and Thakre (2015), 89.75 % by Erdemoglu et al (2005) and 99.1% by Panwala et al (1971)(63-65). In the US, 43.5 % of triplet and higher order multiple births were generated by ART, 38.5% were attributed to ovulation-inducing drugs without ART, and 18% occurred spontaneously(66). Our results vary from other studies that show only 8.8% to 13.6% conceive spontaneously vs 86.4% -91% conceived by ART (51, 53). Assisted Reproductive Technologies are not available to our study population due to low resource availability and astronomical costs involved.

The mean parity before delivery was 2 ± 1.0 and ranged from 0 to 6 with only 13.5% occurring in primigravida. Based on the body mass index (BMI), 13 (17.1%) women were of normal weight, 26 (34.2%) women were overweight and 37 (48.7%) women were obese.

Although hospitalization of triplets is not routine and in patient bed rest has not shown to reduce risk of preterm birth(67). At our unit, we generally admit our triplets at 28 weeks. The main reasons for admission include socioeconomic factors in that patients are referred from health care centres in rural areas which have poor transport facilities and infrastructure as well as a lack of neonatal services.

The mean antenatal hospital stay was 24.9 ± 18.3 (range 1-69) days, which is very similar to other reports where the average antenatal stay was approximately 11–42 days (2, 45, 56).

Adequate antenatal care has been found to be superior in improving prematurity and adverse pregnancy outcomes in triplets. The importance of early booking in the antenatal clinic cannot be over emphasized. It exposes the patient to some preventive measures shown to reduce maternal complications thereby reducing both maternal and neonatal morbidity and mortality. More than 75% of the patients in this study were enrolled for antenatal care but, the gestational age at booking for antenatal care was unknown. Early diagnosis of triplet pregnancy allows for the initiation of measures to improve outcome. The diagnosis of triplet pregnancy was made at a mean gestational age of 25.7 ±5.0 weeks ranging from 11 – 35 weeks in this study. This is late compared to studies showing 18.6 weeks(39) and 15 weeks (68). This difference is attributed to several factors seen in developing countries. This includes late presentation to antenatal care services, women staying in rural areas, lack of adequate transportation and poor resources at peripheral clinics.

In this study,based on the chorionicity, there was no difference in gestation at delivery between the groups (p=0.5). The number of TCTA were significantly greater in number compared to DCTA and MCTA (p=0.01) but the perinatal deaths were greater in TCTA. In addition, there was no significant difference in complications among the groups. This differs from study by Fennessy et al (2015) studied 53 sets of triplets, 25 sets were conceived by ART and 28 were conceived spontaneously. these authors found TCTA delivered at a later gestation than monochorionic or dichorionic triplets and that trichorionic triplets were significantly less likely to die compared to monochorionic (MC) or dichorionic (DC) triplets (p = .025)(69).

There is no consensus on the optimal mode of delivery of triplet pregnancies and results are conflicting with studies suggesting vaginal route associated increased risk of stillbirth RR5.7 and neonatal death 2.83(26). In our audit, 84.3 % of the patients delivered by CS. Of the 14 (15.7%) attempts at vaginal delivery, 3 patients required emergency CS after

the vaginal delivery of the triplet A due to foetal distress. There were 16 perinatal deaths following CS, 16 perinatal deaths following vaginal delivery and 4 perinatal deaths following combined CS/ NVD delivery.

Our study provides conclusive evidence that babies delivered via CS had better outcomes than NVD with PMR in CS group 69.5 per 1000 live births compared to 551 per 1000 live births in NVD group ($p<0.001$). This differs with a case controlled study that showed vaginal delivery to be safe (22). Similar findings of 88.8% CS and 11.2% vaginal delivery in a series of 44 triplets has been reported(51).

Neonates of triplet gestation constitute a significant proportion of NICU admissions(70). In our study about 86.1% of newborns required intensive care. The main neonatal morbidity was marked by respiratory problems, occurring in approximately 40.1% of our triplets. In our audit, in 109 neonates the main respiratory diagnosis was respiratory distress syndrome (RDS); of these, 53 infants received surfactant. The median (range) duration of ventilation was 2 (1–11) days and median duration of CPAP was 2 (1-4) days. Triplet pregnancy is a high risk pregnancy. In 21 (17.1%) of our patients the problem of triplet pregnancy was further compounded by being HIV positive. We observed worse perinatal outcome in women with triple pregnancy infected with the HIV virus. Twenty-one (17.1%) perinatal deaths (20 neonatal deaths and 1 stillbirth) occurred in HIV infected group compared to 15 (6.9%) perinatal deaths (7 neonatal deaths and 8 stillbirths) in HIV uninfected group ($p<0.001$).

Although our study sample was small, our findings are consistent with the literature in confirming that triplet pregnancies carry a greater risk of prematurity and neonatal morbidity and mortality.

Limitations

The patients in the study were referred at different gestational ages from different hospital. This means that they had received variable care before the referral, which makes it difficult to correlate the maternal and neonatal outcome with the care provided.

The true prevalence of triplet pregnancies in the population could not be calculated as IALCH is a referral center for only high risk pregnancies.

A limitation in this study was the late diagnosis of triplet pregnancies making the diagnosis of chorionicity unreliable.

Another limitation to this study was the retrospective design and small sample size. It was comparable to other studies in the literature. The retrospective nature of this study made finding some data of the pregnancy management (e.g. duration of tocolysis and steroids use) difficult.

Neonates weighing less than 1500 grams, who may be expected to have the highest mortality and morbidity, were followed up at regional hospitals. This is a potential limiting factor in our study in addition to the lack of complete follow-up data on long term outcomes of triplets in general.

Conclusion

Triplet pregnancies had a high rate of feto-maternal complications in keeping with other retrospective studies. Risk factors in cases of premature delivery at IALCH included a birth weight of less than 1500 g, gestational age of less than *28* weeks and a maternal age between 25-39 years. The management of triplet pregnancies at our center was comparable to other studies. I have generated a manuscript from this thesis included in appendix 1 for European Journal of Obstetrics & Gynecology and Reproductive Biology (ref: EJOGRB-16-15283).

Recommendations

Early diagnosis allows for essential and optimal antenatal care designed for triplet pregnancies that would improve both maternal outcome and reduce foetal mortality and morbidity. Every effort should be made to prolong the gestational period to improve foetal survival rates. Furthermore, women carrying triple pregnancies should be referred to tertiary centers with expertise diagnosis from nearby and outlying health facilities.

In our audit, it was not possible to perform meaningful comparisons within the cohort because of small number of studied sample especially of triplets conceived by ART.

A detailed study on chorionicity in triplet pregnancies should be undertaken to establish the fetal outcome based on chorionicity.

CHAPTER 6:

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APPENDIX 1

Manuscript

PERINATAL OUTCOME OF TRIPLETS BASED ON GESTATIONAL AGE AT DELIVERY AND MODE OF DELIVERY

Parikh N[1], Budhram S[2], Ramnarain H[3]

ABSTRACT

Objective

Triplet pregnancies are associated with a higher risk of perinatal mortality and morbidity when compared to singleton or twin pregnancies. There has been no recent data on triplets from African studies. This study sought to analyse the perinatal outcome of triplets based on gestational age at delivery (GAD) and mode of delivery (MOD).

Study Design

A retrospective analysis of all triplet pregnancies that were delivered at IALCH over a 12-year period was done.

Results

89 triplet pregnancies delivering 267 neonates were included in the analysis.

The mean birth-weight was 1497.7 ± 490.2 grams for the first triplet A and ranged from 540 - 2720 grams, 1499.3 ± 489.9 grams for the triplet B with a range between 410 - 2500

grams. The weight for the triplet C was 1427.9 ± 419.0 grams with a range of 570 –2540 grams. The mean (SD) birth-weight was 1475 ± 437 (range: 410-2720) grams. These differences were not statistically significant in between groups (p=0.6).

The mean (range) GAD was 30.8 ± 2.8 weeks. The median (range) Apgar score, for live-born neonates was 8 (2–10) and 9 (4–10) for 1 and 5 minutes respectively.

Two hundred and fifty-eight (96.6%) neonates were born alive with 27 neonatal deaths recorded. The stillbirth rate was 33 per 1000 live births. The early neonatal death rate was 105 per 1000 live births and the perinatal mortality rate was 134 per 1000 live births. The mean (range) GAD for pregnancies resulting in neonatal deaths was 26 (23-29) weeks. Seventy-five (84.3%) patients delivered by caesarean section whilst eleven (12.4%) women had a vaginal delivery. The commonest neonatal complication was hyaline membrane disease (41%), and this complication also accounted for the highest number of mortalities among the neonates.

Conclusion

In conclusion, triplet pregnancies in our cohort had a high rate of neonatal complications. Poor neonatal outcomes were mostly related to a birth weight of less than 1500g and a gestational age at delivery of less than 28 weeks. Caesarean section was found to be associated with better neonatal outcomes.

Keywords

Triplet pregnancy; premature delivery; vaginal delivery; caesarean section; multifetal

PERINATAL OUTCOME OF TRIPLETS BASED ON GESTATIONAL AGE AT DELIVERY AND MODE OF DELIVERY

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INTRODUCTION

The incidence of multiple gestations has increased considerably over the past three decades. This increase is primarily attributed to the growing utilization of ovulation induction, assisted reproductive techniques and the trend, in recent decades, of delayed childbearing (1).

In triplet and higher order gestations, we are confronted with increased maternal and foetal risks in comparison to singleton or twin pregnancies (2). Neonatal complications are mostly due to preterm birth (PTB) and low birth weight (LBW) (<2500g). Recent reports suggest that delaying delivery, aimed at increasing the gestational age and birthweight, may influence the outcomes of these pregnancies (2).

PTB, defined as a birth before 37 weeks of gestational age, occurs in up to 87.9% - 91 % of triplet pregnancies (3). The risk of extreme PTB (<28 weeks) and very PTB (28-32 weeks) is increased by 13-fold and almost 20-fold respectively (4). This exposes the neonate to complications from respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), patent ductus arteriosus (PDA), sepsis and retinopathy of prematurity.

In triplet pregnancies the risks of LBW are 10–75 fold (5). Birth weight is closely

associated with gestational age, thus the increased incidence of PTB influences the rate of LBW in triplet neonates (6, 7). 92% of triplets are born with LBW (8). The mean birth weight for a newborn triplet is 1789 ± 505g (9).

Delivery of triplet pregnancies presents a major challenge to obstetricians due to the inherent risks of increased perinatal morbidity and mortality. The vast majority of these pregnancies are complicated by mal-presentation, prematurity, the need of either abdominal or operative vaginal delivery and the likelihood that one or more neonates will require immediate specialized care. The mode of delivery (MOD) and outcomes of triplet pregnancies vary in the literature.

There have been no recent African studies published regarding triplet pregnancies and neonatal outcomes. This study thus sought to analyse triplet pregnancies over a 12-year period, specifically looking at the perinatal outcomes in relation to the gestational age at delivery (GAD) and the MOD.

MATERIAL AND METHODS

This was a descriptive, retrospective chart review of all triplet pregnancies that were delivered at Inkosi Albert Luthuli Central Hospital (IALCH) from 1st January 2003 to 31st December 2014. IALCH is a quaternary hospital located in Durban, Kwazulu Natal, South Africa and serves as a referral hospital for all health facilities in and around the province. All patient records were accessible on the hospital's electronic patient database. The following data were collected from the maternal records: maternal age at

delivery, mode of conception, parity, gestational age at which corticosteroids were administered to enhance foetal lung maturity, GAD and MOD. The data extracted from the neonatal records included: birth weight, Apgar scores at 1 and 5 minutes after birth, neonatal mortality, neonatal complications, admission to neonatal intensive care unit (NICU) and length of hospital stay.

Statistical analysis

Data was analysed using SPSS (Statistical Package for Social Sciences; version 23). The data was analysed using descriptive statistics with the use of frequency, tables, percentages and cross-tabulation and results are presented as mean± SD, range. Statistical analyses were performed with Chi Square Test and analyses of variance (ANOVA) where appropriate. Significance was set at a p value < 0.05.

RESULTS

94 triplet pregnancies were identified over the study period. On review of the records it was established that only 89 (94.7%) of the 94 pregnancies could be included in the study as the other 5 medical records had insufficient data due to incomplete medical records. A total of 89 triplet pregnancies delivering 267 neonates were therefore included in the analysis.

The neonatal outcomes based on birth-weight, GAD and triplet order at birth are illustrated in tables 1 and 2 respectively.

The mean birth-weight was 1497.7 ± 490.2 grams for the first triplet A and ranged from 540 - 2720 grams, 1499.3 ± 489.9 grams for the triplet B with a range between 410 - 2500 grams. The weight for the triplet C was 1427.9 ± 419.0 grams with a range of 570 –2540 grams. The mean (SD) birth-weight was 1475 ± 437 (range: 410-2720) grams. These differences were not statistically significant in between groups (p=0.6).

The mean (range) GAD was 30.8 ± 2.8 weeks. The median (range) Apgar score, for live-born neonates was 8 (2–10) and 9 (4–10) for 1 and 5 minutes respectively. Table 3 details this information.

Two hundred and fifty-eight (96.6%) neonates were born alive with 27 neonatal deaths recorded. There were a total of 9 (10.1%) stillbirths with a stillbirth rate was 33 per 1000 live births. The early neonatal death rate was 105 per 1000 live births and the perinatal mortality rate was 134 per 1000 live births. The mean (range) GAD for pregnancies resulting in neonatal deaths was 26 (23-29) weeks. The mean Apgar score at 1 minute was 5 (range: 2-9) and at 5 minutes was 7 (range: 2-10). Twenty-two of the 27 neonates had a birthweight less than 1000grams and 5 were between 1000grams and 1499grams.

Seventy-five (84.3%) patients delivered by caesarean section. Among these, 81.3% were emergency caesarean sections (CS) and 14 (18.7%) were elective CS. Eleven (12.4%) women had a vaginal delivery. Three (3.4%) women delivered the first twin vaginally and the subsequent triplet 2 and triplet 3 by CS because of intrapartum complications. Table 4 shows neonatal outcomes based on MOD.

Seventy-nine, 73 and 78 of the triplets A, B and C were admitted to NICU respectively. The mean (SD) number of days that neonates stayed in NICU was 4.5 ± 5.9 (range: 1-41) for triplet A versus 6.9 ± 10.5 (1-73) for triplet B versus 5.3 ±7.4 (range: 1- 42) for triplet C. There was no significant difference in the mean duration of hospitalization amongst the triplets (p=0.3).

The commonest neonatal complication was hyaline membrane disease (41%), and this complication also accounted for the highest number of mortalities among the neonates. Other neonatal complications are shown in figure 1. In 109 neonates, the main respiratory pathology was respiratory distress syndrome (RDS), of these, 53 neonates received surfactant. The median (range) duration of ventilation was 2 (1–11) days and median duration of CPAP was 2 (1-4) days. Two hundred and thirty-one neonates were discharged home. One (0.4%) of the 231 infants had Down syndrome.

DISCUSSION

Foetuses and neonates of triplet pregnancies are at a higher risk of mortality and morbidity when compared to singleton and twin pregnancies. A proposed gestational age for delivery, to optimize neonatal outcomes, has not been established with most evidence coming from retrospective cases and a lack of randomised controlled trials. The mean GAD in our study (30.8 weeks) was less than that reported in other studies, which varied between 31.7 and 33 weeks(10-12). This disparity may be due to the fact

that the majority of triplet pregnancies in our study population had spontaneous preterm labour and delivered preterm with a gestational age range of 24 -35 weeks.

Gestational age represents the main factor affecting birth weight, which correlates with morbidity and survival rate(13-15). The prevalence of LBW and PTB was high in our cohort with all the pregnancies ending preterm. Both LBW and prematurity are known risk factors for adverse health, cognitive and behavioural outcomes later in life(16).

Our perinatal mortality rate of 134 per 1000 live births was higher compared to reported rates of 41-121 per 1000 live births (12, 17, 18). This discrepancy may be explained by a higher number of our triplet pregnancies delivering preterm with 48.3% delivering prior to 31 weeks. The overall survival of triplets in our study was 86.5%.

There is no consensus on the optimal MOD of triplet pregnancies and results are conflicting with studies suggesting that vaginal route may be associated with an increased risk of stillbirth (RR5.7) and neonatal death (RR 2.83)(19). In our audit, 84.3 % of the patients delivered by CS. Of the 14 (15.7%) attempts at vaginal delivery, 3 patients required emergency CS after the vaginal delivery of the triplet A due to foetal distress. There were 16 perinatal deaths following CS, 16 perinatal deaths following vaginal delivery and 4 perinatal deaths following a combination of CS and vaginal delivery.

Our study provides conclusive evidence that babies delivered by CS have better outcomes than those delivered vaginally with a PMR in the CS group of 69.5 per 1000 live births compared to 551 per 1000 live births in the vaginal delivery group ($p<0.001$).

This differs with a case controlled study that showed vaginal delivery to be safer (20). Similar findings of an 88.8% CS rate and an 11.2% vaginal delivery rate have been reported in a series of 44 triplets (21).

Although previous studies have reported higher rates of neonatal morbidity and mortality in the third born triplet(22), we found no difference in outcome according to the birth order of the triplets.

Neonates of triplet gestations constitute a significant proportion of NICU admissions(23). In our study about 86.1% of neonates required intensive care. The neonatal morbidity was mainly due to respiratory problems, occurring in approximately 40.1% of our triplets, hyperbilirubinemia in 14.6% and sepsis in 18.4%. Our findings are in keeping with other studies and differ mainly in the incidence of sepsis, reported at 5% elsewhere (24).

CONCLUSION

Triplet pregnancies, in our cohort, had a high rate of neonatal complications in keeping with other retrospective studies. In our cohort, poor neonatal outcomes were mostly related to a birth weight of less than 1500 g and a GAD of less than 28 weeks. Caesarean section was the MOD associated with better neonatal outcomes. Outcomes at our center were comparable to those in other studies.

ACKNOWLEDGEMENTS

I would like to acknowledge the support provided by my supervisors Dr S Budram and Dr H Ramnarain during this research project. I would like to thank the staff at Inkosi Albert Luthuli Hospital.

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Table 1. Foetal and neonatal outcomes based on birth weight and triplet order at birth

Birth weight in grams	**Number (n)**	**Percentage %**	**Triplet A**			**Triplet B**			**Triplet C**		
			Alive	SB	NND	Alive	SB	NND	Alive	SB	NND
0-999	42	15.7	5	1	8	5	3	6	6	1	7

1000-1499	75	28.1	21	1	3	24	0	1	22	1	2
1500-2499	147	55.1	49	0	0	48	1	0	48	1	0
≥ 2500	3	1.1	1	0	0	1	0	0	1	0	0

SB: Stillborn NND: Neonatal death

Table 2. Foetal and neonatal outcome based on gestational age and triplet order at delivery

SB: stillborn NND: neonatal death

Gestational age at delivery (weeks)	**Triplet A**			**Triplet B**			**Triplet C**		
	Alive (n)	**SB (n)**	**NND (n)**	**Alive (n)**	**SB (n)**	**NND (n)**	**Alive (n)**	**SB (n)**	**NND (n)**
< 28	5	2	7	4	3	7	5	2	7
28 –31	25	0	4	28	1	0	27	0	2
32 –33	29	0	0	29	0	0	28	1	0
34 –36	17	0	0	17	0	0	17	0	0

Table 3. Apgar scores of live born neonates based on triplet order at birth

Apgar score at 1 minute			
	Mean ± SD	Median	Range
Triplet A	7.3 ± 1.9	8	1 – 9

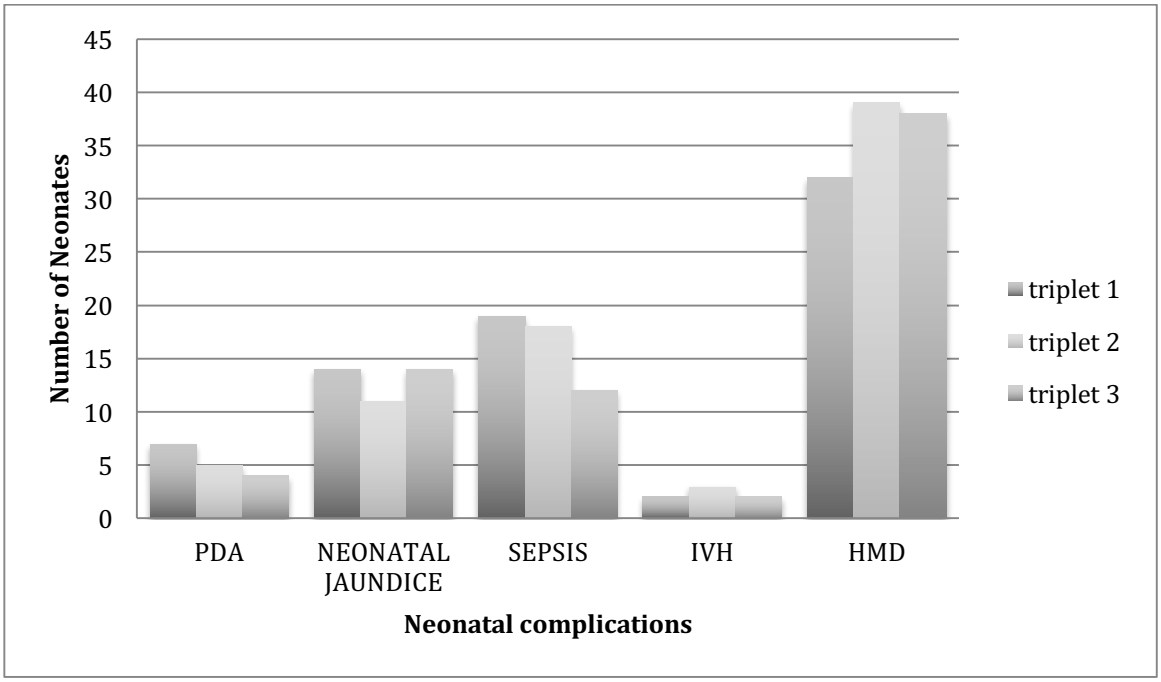
Triplet B	7.2 ± 1.7	8	3 – 9
Triplet C	7 ± 5	7.5	2 – 10
Apgar score a 5 minutes			
Triplet A	8.5 ± 1.5	9	2 – 10
Triplet B	8.4 ± 1.6	9	4 – 10
Triplet C	8.3 ± 1.6	9	5 -10

Table 4. Foetal and neonatal outcomes based on triplet order at birth and mode of delivery

Mode of delivery	**Triplet A**			**Triplet B**			**Triplet C**		
	Alive	**SB**	**NND**	**Alive**	**SB**	**NND**	**Alive**	**SB**	**NND**
Caesarean section	70	0	5	73	2	5	71	1	3
Vaginal delivery	4	1	6	5	0	6	4	1	2
Combination (Caesarean Section and vaginal delivery)	2	1	0	0	2	0	2	1	0

SB: Stillborn NND: Neonatal death

Figure 1: Prevalence of neonatal complications



PDA: Patent ductus arteriosus HMD: Hyaline Membrane Disease
IVH: Intraventricular Haemorrhage

APPENDIX 2:

Data sheet

- Study No.
- Age (yrs)
- Parity
- Race
- Geographical
- Height (cm)
- Weight (kg)
- BMI (weight/h^2)
- Antenatal Care (yes=1; no=2)
- Rhesus (positive =1; negative =2)
- RPR (positive =1; negative =2)
- HIV (positive =1; negative =2)
- Treatment
- HB

- Screening GDM
- Family or personal history of multiple pregnancy (yes =1; no =2) [ ]
- Method of conception (tick)

  1. Spontaneous

  2. Fertility drugs (Assisted Reproduction Technique)

  3. In vitro fertilization

If method of conception is with use of fertility drugs, state infertility treatment

(list)…….

- Medical disorders

  (list)……

- Gestational age at diagnosis (weeks) [ ]
- Gestational age first US [ ]
- Ultrasound features:

  ……

  ……

- Gestational age at admission (weeks) [ ]

[ ]

- Number of admissions
- Hospitalization duration
- Antepartum maternal complications (list)

……

……

……

- Antepartum management of complications

……

……

……

- Steroids given (yes=1; no=2)
- Gestational age steroids given
- Reason:……
- Tocolysis
- Drug administer: ……..

- Mode of delivery (tick)

Caesarean section

Elective

Emergency

If emergency state indication

Normal vaginal delivery

Assisted vaginal delivery

- Maternal postpartum complications (list)

……

……

- Maternal outcome (alive=1; demised=2)

Triplet pregnancy and neonatal outcome

	Triplet A	Triplet B	Triplet C
Birthweight (grams)			
Sex			
Live birth			
Stillbirth			
Abortion			
Neonatal death			
Apgar score 1 min			
Apgar score 5 min			
Neonatal complications			
Malformations (type)			
NICU (Yes=1; No=2)			
If yes length of stay (days)			

- Triplet complications

……

……

APPENDIX 3:

BREC APPROVAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

07 July 2015

Dr Nitish Parikh
School of Clinical Medicine (Obstetrics and Gynaecology)
drnuparikh@yahoo.com

PROTOCOL: Maternal and Perinatal outcomes in triple pregnancy, an audit over 12 years at Inkosi Albert Luthuli Central Hospital
Degree: MMed: Student Number: 211560847.
BREC reference number: BE500/14

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 26 November 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 02 July 2015 to queries raised on 10 June 2015 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from **07 July 2015.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **11 August 2015**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc: Supervisor - Dr H Ramnarain: Ramnarain@ukzn.ac.za

Biomedical Research Ethics Committee
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APPENDIX 4:

DEPT OF HEALTH APPROVAL

health
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Health Research & Knowledge Management sub-component
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Reference : HRKM155/15
NHRD Ref.: KZ_2015RP52_138
Enquiries : Ms G Khumalo
Telephone : 033 – 395 3189

Dear Dr N U Parikh

Subject: Approval of a Research Proposal

1. The research proposal titled **'Maternal and perinatal outcomes in triplet pregnancy: An audit over 12 years at Inkosi Albert Luthuli Central Hospital'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 01/07/2015

APPENDIX 5:

IALCH APPROVAL

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
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Reference: BE: 500/14
Enquiries: Medical Management

18 May 2015

Dr N Parikh
Department of Obstetrics and Gynaecology
IALCH

Dear Dr Parikh

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Maternal and Perinatal outcomes in triple pregnancy, an audit over 12 years at Inkosi Albert Luthuli Central Hosptial.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

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Dr M Letebele
Medical Manager