OUTCOMES OF DICHORIONIC TWIN PREGNANCIES IN A SOUTH AFRICAN SETTING

A retrospective review

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Declaration

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Dr Hester Alida Swart

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ABSTRACT

Objective

The aim of this study was to evaluate the perinatal management and outcomes of dichorionic (DC) twin pregnancies in Tygerberg Hospital, a secondary and tertiary referral centre in South Africa (middle-income country).

Method

This retrospective observational study included all DC twin pregnancies seen in the Obstetric Ultrasound Unit between 1 January and 31 December 2011. Primary aims were to review the mode and gestational age at delivery. Secondary aims included a composite of maternal and perinatal outcomes.

Results

266 DC twins were assessed during this period and delivery outcomes were obtained in 227 (85,3%). The mean gestational age at delivery was 35 weeks 1 day (±4 weeks 2 days) and mean birth weight was 2233g (±602g). In 156 of the 213 (73,2%) pregnancies reaching 28 weeks, vaginal delivery was attempted. This resulted in 82 (52,6%) vaginal, 65 (41,7%) emergency caesarean and 9 (5,8%) combined deliveries. In 57 of the 213 (26,8%) pregnancies, a prelabour caesarean delivery was required. This was mainly due to maternal disease (33,3%) and abnormal fetal lie (29.8%).

Hypertensive diseases of pregnancy were the most common maternal complication affecting 70 women (30,3%) and preterm labour or preterm prelabour rupture of membranes were the most common antenatal complication affecting 103 pregnancies (45,4%). Neither the composite maternal adverse outcome (p=0,30) nor the composite early neonatal adverse outcome (p=0,61) was significantly different between the women who experienced labour and the prelabour caesarean delivery group.

Conclusion

DC twin pregnancies were delivered at an earlier gestation and had a higher caesarean rate than reported in other developing countries. Similar to the available literature there was a higher incidence of antenatal maternal and fetal complications compared to singletons. Long intertwin delivery times and a higher rate of combined deliveries were observed in the study population. This could possibly be prevented in limited resource countries with more liberal use of epidural analgesia and active management of the delivery of the second twin during vaginal delivery.

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OPSOMMING

Doelwit

Die doelwit van hierdie studie was om die perinatale hantering en uitkomste van dichorioniese (DC) tweeling swangerskappe in Tygerberg Hospitaal, 'n sekondêre en tersiêre verwysings hospitaal in Suid-Afrika (middel inkomste land) te evalueer.

Metodes

Hierdie retrospektiewe observasie studie was uitgevoer in TBH en het al die DC tweelingswangerskappe ingelsuit wat in die Obstetriese Sonar Eenheid gesien is tussen 1 Januarie en 31 Desember 2011. Die primêre doelwitte was om die metode en swangerskapsduur van verlossing te beskryf. Die sekondêre doelwitte het 'n samestelling van moederlike en perinatale uitkomste ingesluit.

Resultate

266 DC tweelinge is geëvalueer gedurende hierdie periode en verlossings uitkomste is ingesamel by 227 (85.3%). Die mediane gestasie by verlossing was 35 weke 1 dae (±4 weke 2 dae) en gemene geboorte gewig was 2233g (±602g). In 156 van die 213 (73,2%) swangerskappe wat 28 weke gestasie bereik het, is daar prober vir vaginale verlossing. Dit het gelei tot 82 (52,6%) vaginale verlossings, 65 (41,7%) nood keisersnitte en 9 (5,8%) gekombineerde verlossings. 'n Keisersnit is voor die aanvang van kraam uitgevoer in 57 van die 213 (26,8%) gevalle. Dit was hoofsaaklik aangedui vir moederlike siekte (33,3%) en abnormale fetale ligging (24,6%).

Hipertensiewe siektes van swangerskap was die mees algemene moederlike komplikasie en het 70 vroue (30,3%) geaffekteer. Voortydse kraam of voortydse ruptuur van vliese was die mees algemente antenatale komplikasie wat 103 swangerskappe (45,4%) geaffekteer het. Nog die saamgestelde moederlike uitkomste (p=0,30), nog die saamgestelde neonatale uitkomste (p=0,61) was noemenswaardig verskillend tussen die groep vroue wat kraam ervaar het en die groep met 'n keisersnit voor die aanvang van kraam nie.

Gevolgtrekking

DC tweelingswangerskappe is by 'n vroeër gestasie verlos en het meer keisersnitte gehad as wat gerapporteer word in ander ontwikkelende lande. Soorgelyk aan beskikbare literatuur was daar 'n hoër insidensie van antenatale moederlike en fetale komplikasies in vergeleke met enkelswangerskappe. 'n Lang tydperk tussen die verlossings van die twee babas en 'n hoër aantal gekombineerde verlossings is gevind wat moontlik voorkom kan word deur die meer algemene gebruik van epidurale analgesie en aktiewe hantering van die verlossing van die tweede baba tydens vaginale verlossing in lande met beperkte beskikbare bronne.

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List of Abbreviations

AFI: Amniotic fluid index
ANR: Antenatal record
APH: Antepartum haemorrhage
AROM: Artificial rupture of membranes
BMI: Body mass index
BMZ: Betamethasone
BP: Blood pressure
CD: Caesarean delivery
CL: Cervical length
DC: Dichorionic
DM: Diabetes mellitus
EFW: Estimated fetal weight
ELBW: Extremely low birth weight
ENND: Early neonatal death
EUS: Early ultrasound
FGR: Fetal growth restriction
FSB: Fresh stillbirth
GDM: Gestational diabetes mellitus
GHT: Gestational hypertension
HAART: Highly active antiretroviral therapy
Hb: Haemoglobin
HELLP-syndrome: Haemolysis, elevated liver enzymes, low platelet count
HDU: High dependency unit
HGT: Hemo Glucose Test
HIV: Human immunodeficiency virus
ICU: Intensive care unit
IOL: Induction of labour IUFD:
Intra-uterine fetal death
LBW: Low birth weight
LNMP: Last normal menstrual period
LUS: Late ultrasound
MCA: Mid-cerebral artery

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MSB: Macerated stillbirth

MSU: Midstream urine

NICU: Neonatal intensive care unit

PI: Pulsatile index

PPH: Postpartum haemorrhage

PPROM: Preterm prelabour rupture of membranes

PTD: Preterm delivery

PTL: Preterm labour

RPOC: Retained products of conception

RPR: Rapid plasma reagin

TOLAC: Trial of labour after caesarean delivery

UAD: Umbilical artery Doppler

UA-RI: Umbilical artery resistance index

US: Ultrasound

UTI: Urinary tract infection

VBAC: Vaginal birth after caesarean delivery

VD: Vaginal delivery

VLBW: Very low birth weight

WHO: World Health Organization

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List of Definitions

- **Anaemia:** Haemoglobin < 10g/dL
- **Antepartum haemorrhage (APH)**: External bleeding from genital tract in pregnancy > 24 weeks 0 days gestation.
- **Asymptomatic bacteriuria**: No clinical symptoms of urinary tract infection (UTI), urine culture >100 000 colonies/ml of a single organism.
- **Chronic hypertension (CHT):** Pre-gestational hypertension or onset < 20 weeks of gestation.
- **Cystitis:** Acute onset of lower urinary tract symptoms in the presence of a midstream specimen of urine (MSU) with Leucocytes >100 000, Erythrocytes < 1000 and culture positive for one organism.
- **Early neonatal death (ENND):** Demise within the first 7 days of life.
- **Early ultrasound:** performed before 24 week 0 days gestation
- **Extremely low birth weight (ELBW):** A birth weight ≤ 1000g.
- **Small for gestational age (SGA):** Estimated fetal weight < the 10th centile for the gestational age.
- **Fetal growth restriction (FGR):** SGA with abnormal fetal Dopplers
- **Gestational diabetes mellitus (GDM):** Glucose intolerance with onset or first recognition during pregnancy. Fasting Hemo Glucose Test (HGT) ≥ 5.6, mmol/l and/or 2h postprandial HGT ≥ 7.8 mmol/l.
- **Gestational hypertension (GHT):** Onset of hypertension in a previously normotensive pregnant woman who is ≥20 weeks of gestation
- **Gestational proteinuria:** Proteinuria on urine test strip ≥1+ on at least two occasions at least 4 hours apart, but no more than 1 week apart. Alternatively a daily urine protein of ≥300mg in the absence of hypertension measured after 20 weeks gestation.
- **Hypertension:** Systolic blood pressure ≥140mmHg or diastolic blood pressure
  ≥90mmHg in two consecutive measurements at least 4 hours apart.
- **Intensive inpatient fetal surveillance:** The following at minimum: electronic fetal heart rate assessed 4 times daily and ultrasound and Doppler studies done two times per week.
- **Intensive outpatient fetal surveillance:** Increased frequency of electronic fetal heart rate assessment up to two times per week and ultrasound and Doppler assessment up to two times per week
- . **Low birth weight (LBW):** A birth weight ≤ 2500g.

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- **Polyhydramnios:** Deepest pool measured in any quadrant ≥ 8cm or amniotic fluid index (AFI) > 25cm.
- **Postpartum haemorrhage (PPH):** Generally defined as blood loss ≥500 ml within 24 hours after birth, while severe PPH is blood loss ≥1000 ml within 24 hours.
- **Pre-eclampsia:** Onset of hypertension > 20 weeks gestation combined with proteinuria (persistent ≥1+ on urine test strip or ≥300mg/24 hours).
- **Preterm delivery (PTD):** Delivery ≥ 24 weeks 0 days but < 37 weeks 0 days gestation.
- **Preterm labour (PTL):** Onset of true labour ≥ 24 weeks 0 days but < 37 weeks 0 days gestation.
- **Preterm prelabour rupture of membranes (PPROM):** Spontaneous rupture of fetal membranes at least one hour before the onset of labour and < 37 weeks 0 days of gestation.
- **Puerperal sepsis:** Infection of the genital tract occurring at any time between the rupture of membranes or labour and 42 days postpartum in which two or more of the following are present: pelvic pain, fever, abnormal pelvic discharge or delay in the rate of reduction of the size of the uterus (< 2 cm per day in the first 8 days).
- **Pyelonephritis:** Acute onset of fever (oral temperature ≥ 38°), rigors and costovertebral angle tenderness with a MSU showing Leucocytes >100 000, Erythrocytes < 1000 and culture positive for one organism.
- **Threatening miscarriage:** External bleeding from genital tract in pregnancy ≤ 24 weeks 0 days gestation.
- **Threatened preterm labour**: regular uterine contractions without cervical changes.
- **Venous thromboembolism:** Clinical signs suggestive of lower extremity deep vein thrombosis, confirmed by compression duplex ultrasound.
- **Very low birth weight:** A birth weight ≤ 1500g.
- **Wound infection:** Clinical signs of local or systemic infection when wound healing is disrupted and wound tissues are damaged.

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1 Background and Literature Review

1.1. Introduction

The diagnosis of a twin pregnancy is met with awe and excitement but also apprehension by parents and physicians alike. Since the inception of the now invalidated Hellin's Law it has become clear that the birth rate of twins is far from predictable.[1] Data from developing countries regarding rates and management of multifetal pregnancies is scarce and mostly not specific to dichorionic (DC) twins. A secondary analysis by Ganchimeg *et al*. of the World Health Organization (WHO) Multicountry Survey on Mode and Timing of Twin Delivery conducted in 29 low-and middle-income countries was published earlier this year.[2] It provides valuable data on the subject but it has limiting factors such as analysing a small number of deliveries and not specifying the chorionicity. Similar limitations are seen in a retrospective review by Akaba et al. on the outcomes of twin deliveries over 10 years at a Teaching Hospital in Nigeria and other studies.[3-5]

A recent publication on the rates of natural twinning in low-income countries noted it to be 11–15 per thousand births in South-Africa, Namibia, Lesotho and Madagascar.[6] There is a considerable variance in twinning rates seen between countries that could be explained by factors such as maternal age, parity, height and ethnicity.[7,8] A substantial increase in multifetal gestations has been observed in developed countries during the past decade. This is illustrated in a publication from the United States showing that twins account for over 3% of their deliveries with a 76% rise in the rate of twin births from 1980-2009.[9] This rise could be explained by the wide utilization of assisted reproductive technologies and ovulation induction therapies although it has less of an impact in developing countries due to the financial implications.[10-12]

1.2 Maternal outcomes of twin pregnancies

Several review articles highlight the increased maternal morbidity and mortality in twin gestations compared to that of singletons.[13] There is an increased risk of hypertensive disorders of pregnancy with higher rates of gestational hypertension (GHT), pre-eclampsia and eclampsia that presents atypically, at an earlier gestation and with greater severity.[14] They also have higher rates of maternal

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complications like anaemia, gestational diabetes mellitus (GDM), ante- and postpartum haemorrhage and placental abruption.[15]

The higher rates of complications in twins are more pronounced in low-income countries as illustrated in a prospective cross sectional study from Pakistan by Aziz et al. They found higher rates of anaemia, hypertensive disorders of pregnancy and postpartum haemorrhage (PPH) than publications from the developed world.[16]

1.3 Perinatal outcomes of twin pregnancies

The perinatal mortality rate of twins was three times that of singletons in a prospective study conducted in urban Guinea-Bissau.[17] This is mainly due to the preterm delivery (PTD) rate of up to 6 times that of singletons, leading to complications of prematurity and low birth weight (LBW).[18] Perinatal outcomes in twins were compared to singletons by Obiechina *et al* in a publication from a Nigerian tertiary hospital. They found more neonates with a low APGAR score and a higher rate of perinatal death in twins.[19]

Giancotti *et al*. compared pregnancy outcomes of DC and Monochorionic (MC) pregnancies in their publication monitoring 44 cases.[20] Higher rates of adverse pregnancy outcomes were found in MC pregnancies with a PTD rate three times that of DC twins. Similarly, Masheer *et al*., documented poorer perinatal outcomes in MC compared to DC pregnancies in their retrospective cohort study published this year.[21] A review article published in the American Journal of Perinatology concluded that despite the complications unique to MC pregnancies, DC twins have a comparable increased risk of fetal growth restriction (FGR) and poor perinatal outcomes.[22]

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1.4 Timing of delivery of twin pregnancies

In complicated DC twins timing of delivery is a fine balance between the often-conflicting interests of the three individuals involved and is therefore highly individualised. There is also no consensus on the seemingly less complicated issue of optimal timing of delivery of uncomplicated DC twin pregnancies. Delivery at 37 weeks gestation is advocated by Dodd *et al*. in the discussion of their randomised controlled trial conducted across Australia, New Zealand and Italy.[23] They concluded that women with an uncomplicated twin pregnancy had less serious adverse outcomes for the infant if delivered at 37 weeks gestation. This was echoed in a recently published population based cohort study by Wolfe *et al*. that documented the lowest rate of neonatal morbidity with delivery at 37 weeks gestation. They also illustrated a faster acceleration of risk after 37 weeks than compared with that of singletons born past 39 weeks.[24]

In contrast, delivery at 38 weeks gestation is supported in the article by Little *et al*., who weighed the risk of intra-uterine fetal death (IUFD) against the morbidity and mortality of prematurity.[25] A better outcome with this approach was also shown in a prospective cohort study done in Ireland by Breathnach *et al*. They concluded that allowing uncomplicated DC twins to continue to 38 weeks before delivery minimized perinatal morbidity including neonatal intensive care unit (NICU) admissions, hypoxic ischemic encephalopathy, respiratory distress and sepsis.[26] Delivery from 38 weeks onward is also supported by a recent publication by Dias *et al*.[27]

The National Institute for Health and Clinical Excellence (NICE) guidelines recommend delivery of uncomplicated DC twins from 37 weeks 0 days onwards and that continuing beyond 38 weeks 0 days increases the risk of fetal death.[28] This recommendation is further supported by the Cochrane review published this year.[29] In contrast the American College of Obstetricians and Gynaecologists (ACOG) recommends delivery between 38 weeks 0 days and 38 weeks 6 days[30]. Local policy at Tygerberg hospital advises delivery from 38 weeks 0 days onwards.

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1.5 Mode of delivery of twin pregnancies

The decision on mode of delivery in twin pregnancies is strongly influenced by the expected perinatal outcome. Other factors that play a role are presentation of the leading[31,32] and second twin[33], gestational age, estimated fetal weight[32] (EFW), concordance in size[31] and previous caesarean delivery (CD).[34]

There is agreement that a trial of labour is advised if both twins are in a vertex position at the onset of labour. If only the presenting twin is cephalic, current evidence supports a trial of labour although more supporting data is needed.[35] Peaceman *et al*. found similar infant morbidity and mortality for both vertex/vertex and vertex/non-vertex presentations when comparing vaginal delivery (VD) and CD.[31] In contrast, an association between a non-vertex second twin and combined delivery was shown in a retrospective study by Persad *et al*.[33] A review article by Cruikshank supports a CD if the presenting twin is breech although this approach still needs more supporting data[35]. The management controversy is clear from a retrospective case-control analysis by Blickstein *et al*. with similar neonatal outcomes in a VD for a presenting twin that is cephalic or breech as long as the EFW is more than 1500g.[32]

There is a widespread belief that CD could lead to a better outcome for a LBW infant although this is not rooted in sound evidence. A review article by Christopher *et al*. advises a trial of labour in late preterm and term infants and that the mode should be individualised at an EFW of less than 1500g based on other factors[36]. Twin discordance in growth, as long as it is not extreme, is also not a contra-indication for a trial of labour, even if the presenting twin is the smaller.[36]

Lastly, data supports a trial of labour after caesarean delivery (TOLAC) for women with twin pregnancies. Similar rates of intrapartum and neonatal death, maternal blood transfusions and uterine rupture are found in publications comparing TOLAC in twins and singletons.[34,38] Despite this data, many still feel that there is only a limited role for TOLAC in women carrying twins.[35]

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Barrett *et al*. recently published a large randomised control trial comparing planned CD and VD for twin pregnancies (DC and MC) between 32 weeks 0 days and 38 weeks 6 days of gestation and with the first twin in the cephalic position. They found no difference in the risk of fetal death serious neonatal morbidity or death between the two groups.[38] There is a trend towards CD for all twin pregnancies in developed countries despite lacking evidence.[39]

There is continuing debate on the preferred mode of delivery, especially in uncomplicated DC twins.

1.6. Conclusion

The literature illustrates a clearly increased incidence of maternal and perinatal morbidity and mortality in twin pregnancies compared to singletons. This increase is more evident in low-income countries. The promotion of general recommendations for managing DC pregnancies is extremely challenging due to the varied confounding factors and comorbidities in this population. There are currently no universal guidelines available on gestational age or mode of delivery that will lead to the optimal outcome in twins despite multiple publications.

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2 Problem statement

It is clear that twin pregnancies are at a significantly higher risk for maternal and perinatal morbidity and mortality compared to singletons. These risks are more pronounced in low-and middle-income countries like South Africa and their prevention can have an important impact on the quality of life of patients and healthcare expenses that are already overextended. The optimization of gestational age and mode of delivery in twins are factors that could have an important influence on preventing poor short and long-term outcomes. Clear guidelines on how to optimize management of twin pregnancies are still not available and conflicting results in the literature makes it even more difficult. Applicable, chorionicity specific data in low and middle-income countries is currently lacking.

Tygerberg Hospital (TBH) is a tertiary hospital and sets the standards and trends followed by referring hospitals in the rest of the Western Cape Province. A firm policy on gestational age and mode of delivery of DC twin pregnancies at TBH will not only be beneficial to the patients managed at this institution, but also to the patients from the broader drainage area. Such a policy will guide individual caregivers and prevent decisions that are not based on best current evidence.

The goal of this study was to evaluate current practices and their outcomes regarding management of DC twins in TBH and compare it to the findings in the literature. The information obtained in this study can assist in the formulation of management guidelines for our setting. It can also serve as a starting point for further research on complicated DC and other types of twins.

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3 Aims and Objectives

The aim of this study was to evaluate the perinatal management and outcomes of DC twin pregnancies in TBH and compare the findings to the current recommendations in the literature.

The *primary outcomes* included

- Gestational age at delivery
- Mode of delivery

The following subgroup analyses were done for deliveries from 28 weeks of gestation *for comparison*

- According to the GA at delivery as follows
  - early preterm: 28 weeks 0 days – 33 weeks 6 days
  - late preterm: 34 weeks 0 days – 36 weeks 6 days
  - term: from 37 weeks onwards
- According to whether a prelabour CD was performed or if the woman experienced labour (whether planned or spontaneous)

The *secondary outcomes* included

- Rates of maternal complications: GHT, pre-eclampsia, eclampsia, abruptio placentae, HELLP (Haemolysis, elevated liver enzymes and low platelets) syndrome, Preterm labour (PTL), Preterm prelabour rupture of membranes (PPROM), GDM, urinary tract infection (UTI), thrombo- embolism, PPH, admissions to High dependency unit (HDU) or Intensive care unit (ICU).
- Rates of perinatal complications: polyhydramnios, fetal growth restriction (FGR), perinatal losses, survival up to discharge
- *Composite maternal adverse outcome* included women who experienced PPH, peripartum hysterectomy, relook laparotomy, blood transfusions, evacuations for RPOC, puerperal infections and HDU or ICU admissions.
- *Composite early neonatal adverse outcome* included neonates who developed any of the following: 5 minute APGAR < 7, FSB, ENND and admission to NICU.

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4 Methods

4.1 Study design

This retrospective record review collected data from all DC pregnancies identified at the TBH Obstetric Ultrasound (US) Unit from 1 January 2011 to 31 December 2011 using the Astraia® database. The neonatal data was collected from the Clinicom Database. Data extraction was performed by the principal investigator. Chorionicity was assigned during the first US evaluation. Dichorionicity was confirmed by the presence of discordant genders, separate placental masses or the presence of a lambda sign. Pregnancies of undetermined chorionicity were excluded from the study. DC pregnancies were routinely seen every four weeks for maternal and fetal evaluations. The surveillance was accordingly intensified if clinical or sonographic abnormalities were detected. The patients with delivery data all delivered at Tygerberg Hospital.

4.2 Setting

TBH is a tertiary level hospital located in Bellville, Cape Town, South Africa that manages complicated referrals from midwife lead obstetric units as well as primary and secondary health care facilities from the Metro East drainage area. With the capacity for 1899 beds, it is the largest hospital in the Western Cape and the second largest hospital in South Africa. It also acts as a teaching hospital in conjunction with the Stellenbosch University's Health Science Faculty.

4.3 Data collection

The data was collected on a data-capturing sheet (Appendix A) by the primary investigator who kept the patient identification log as a separate document in a secure location. This audit contains no deviation from standard clinical practice.

4.4 Data analysis and statistics

STATISTICA version 12 (Stat Soft Inc. 2013) was used to analyse the data. Distributional specific descriptive statistics – frequencies (counts and

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percentages), measures of location (mean and median), spread (standard deviations and percentiles) as well as corresponding 95% confidence intervals were used to describe the data. Categorical data was analysed using the Chi-square test. Where an expected cell value was less than five, the Fischer exact test was used. Continuous data was analysed with Student's T test for parametric and the Mann-Whitney U test for non-parametric data. A p-value of < 0.05 was regarded as significant.

4.5 Ethics approval

The study was approved by the Health Research Ethics Committee of Stellenbosch University (S12/04/112). A waiver of consent was obtained for this anonymous audit as no patient identifying data was used on the data-capturing sheet and the data was collected anonymously using a study code.

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5 Results

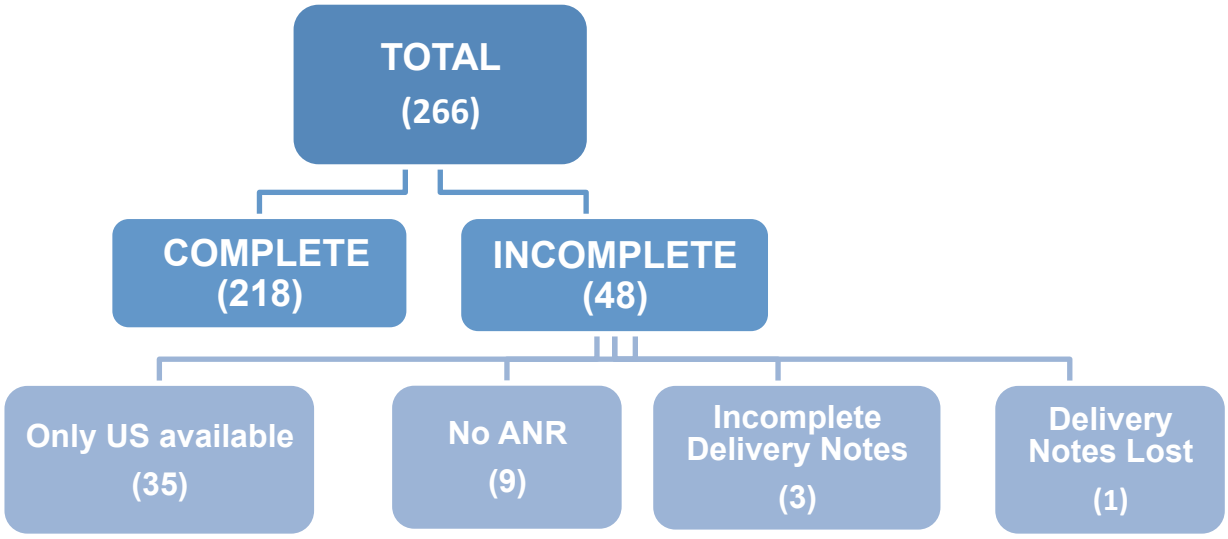
5.1 General results

Data was collected from a total of 266 DC twin pregnancies identified at the TBH Obstetric US Unit from 1 January 2011 to 31 December 2011. 95 twins of unknown chorionicity were seen but excluded from this report even though a substantial proportion of these could actually have been DC twins

Of the 266 in 218 (82%) of the cases all the information could be obtained and in 48 *(*18%) the data was incomplete although these cases were still included in the study. In 35 of the incomplete cases only the US evaluations were available, 9 cases were complete except for missing antenatal records (ANR) while the delivery notes were incomplete in three cases and lost in one (Figure 5.1.1). Overall; US records were available in all; ANR in 222 (83,5%) and delivery records in 227 (85,3%).

The mean gestation at first US was 21 weeks 2 days ± 6 weeks 5 days and in 186/266 (69,9%) women the gestational age was confirmed by US before 24 weeks validating the last normal menstrual period (LNMP) in 49 of these. In 58/266 (21,8%) the gestational age was based only on a late ultrasound (LUS). The twin gestation was detected during the routinely scheduled mid-gestation fetal anomaly US in 189/266 (71,1%).

Figure 5.1.1. Flow diagram of patients included



US: Ultrasound; ANR: Antenatal record

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5.1.1 Baseline characteristics of all women

The characteristics of all the women (with available data) are depicted in Table 5.1.1. The mean age was 29,2y (±6,3y) with 62 (23%) of the women older than 35 and 13 (4,9%) older than 40 years. The median gravidity was 2 (1-7) and parity 1 (0-5) with most women having an inter-pregnancy interval of 4 years. Overall women were overweight with a mean body mass index (BMI) of 30,9kg/m^2 (±7,8kg/m^2) with 112 (42,1%) of them obese with a BMI ≥ 30kg/m^2 and 29 (10,9%) morbidly obese with a BMI ≥ 40kg/m^2. Nearly 20% of the study group had a smoking history and another two of the women (0,9%) admitted to social drug abuse during the pregnancy; one reported using marijuana and one methamphetamine. The prevalence of alcohol use in this group was 2.6% which is lower than expected. This could be due to underreporting which leaves a question regarding accuracy of all the self-reported aspects of the history.

The prevalence of pre-existing morbidities in the studied group were as follows: syphilis disease in 10/234 (4,3%), chronic hypertension (CHT) in 15/234 (6,4%), pre-gestational DM in 2/234 (0,9%), epilepsy in 3/234 (1,3%), asthma in 6/234 (2,6%) and human immunodeficiency virus (HIV) infection in 48/234 (20,5%) with 10/234 (4,3%) of these women on highly active antiretroviral therapy (HAART) before pregnancy.

Asymptomatic bacteriuria (17,4%) and anaemia (14,6%) was a common finding and a documented blood pressure (BP) of more than 140/90mmHg was documented at booking in 5,1% of the study population.

Table 5.1.1. Baseline characteristics of all women (N % per woman)

Age in years*	29,2 ± 6,3
Gravidity#	2 (1-7)
Parity#	1 (0-5)
Body mass index (kg/m^2)* (n=231)	30,9 ± 7,8
Height (cm)* (n=231)	160,5 ± 12,6
Weight (kg)* (n=231)	80,3 ± 22,2
Time since last delivery (y)#	4 (0-16)
Presentation at booking	**N (%)**
· Rapid plasma reagin positive	10/234 (4,3)
· Human immunodeficiency virus	48/234 (20,5)

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· HAART before pregnancy	10/234 (4,3)
· Haemoglobin < 10g/dl	31/212 (14,6)
· Pre-existing hypertension	15/234 (6,4)
· 1st Blood pressure > 140/90mmHg	11/216 (5,1)
· Pre-existing diabetes mellitus	2/234 (0,9)
· Pre-existing epilepsy	3/234 (1,3)
· Pre-existing asthma	6/234 (2,6)
· Asymptomatic bacteriuria	40/230 (17,4)
· Smoking	45/234 (19,2)
· Alcohol use	6/234 (2,6)
· Social drug abuse	2/234 (0,9)
· Family history twins	88/222 (39,6)
Calculation of GA (n=266)	**N (%)**
· LNMP & Early ultrasound	49 (18,4)
· LNMP & Late ultrasound	22 (8,3)
· Early ultrasound (< 24 weeks)	137 (51,5)
· ---- (> 24 weeks)	58 (21,8)

*Mean ± SD; #Median (Range); HAART: Highly active antiretroviral therapy; LNMP: Last normal menstrual period.

5.1.2 Previous obstetric and perinatal complications

The previous CD (21,8%) rate was high and a previous history of any form of hypertensive disease of pregnancy occurred in just over 10% of the index population [GHT (8,2%); pre-eclampsia (2,4%)]. FGR, fetal anomalies and early neonatal death (ENND) were infrequent findings and 8/206 (3,9%) reported a previous stillbirth.[Table 5.1.2]

Table 5.1.2. Previous obstetric and perinatal complications of all women

Previous obstetric history (N % per woman)	
· Gestational hypertension	17/206 (8,2)
· Pre-eclampsia	5/206 (2,4)
· Abruption	2/206 (1,0)
· Gestational diabetes	4/206 (1,9)
· PTL & PPROM	7/206 (3,4)
· Caesarean delivery	45/206 (21,8)
· Twin pregnancy	3/206 (1,5)
Previous perinatal complications (N% per woman)	
· Fetal growth restriction	1/206 (0,5)
· Major fetal anomaly	2/206 (1,0)
· Stillbirth	8/206 (3,9)
· Early neonatal death	1/206 (0,5)

PTL: Preterm labour; PPROM: Preterm prelabour rupture of membranes.

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5.1.3 Antenatal events: maternal complications

Table 5.1.3 includes the antenatal maternal complications that occurred in the studied group. Hypertensive diseases of pregnancy were the most common maternal complication affecting 70 (30,3%) women with 31 (13,4%) developing GHT and 39 (16,9%) pre-eclampsia. It was complicated by eclampsia and HELLP-syndrome in 1.3% each.
GDM was diagnosed in 14 (6,1%) with 2 needing insulin. Low rates of cystitis (3,0%), pyelonephritis (0,4%) and gestational proteinuria (1,3%) occurred.

Of all the women who had a cervical length measurement before 24 weeks gestation, 3/57 (5,3%) cervices was less than 20mm. Of those pregnancies with a known outcome (n=277), a threatened miscarriage developed in 8 (3,5%) and threatened PTL in 30 (13,2%).

PTL or PPROM were the most common antenatal complications affecting 103 (45,4%) pregnancies with PTL occurring in 77 (33,9%) and PPROM in 26 (11,5%). Tocolysis was given to 38 (16,7%) and antenatal steroids to 77 (33,9%) of the women in the index population. They had a median antenatal hospital stay of 4,5 days with an antepartum haemorrhage (APH) occurring in 10/227 (4,4%), a major placenta praevia in 2/266 (0,8%) and a minor placenta praevia in 1/266 (0,4%).

Table 5.1.3. Antenatal events: maternal complications of all women

Maternal complications	N/N with available data (%)
Gestational hypertension	31/231 (13,4)
Pre-eclampsia (Total)	39/231 (16,9)
Eclampsia	3/231 (1,3)
HELLP Syndrome	3/231 (1,3)
Gestational diabetes	14/231 (6,1)
Gestational proteinuria	3/231 (1,3)
Cystitis	7/231 (3,0)
Pyelonephritis	1/231 (0,4)
Venous thromboembolism	1/231 (0,4)
Cervical length < 20mm (< 24w0d)	3/57 (5,3)
Threatened miscarriage (< 24w0d)	8/227 (3,5)
Threatened PTL	30/227 (13,2)

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PTL	77/227 (33,9)
PPROM	26/227 (11,5)
Tocolysis/Suppression received	38/227 (16,7)
Antenatal steroids received	77/227 (33,9)
Antepartum haemorrhage	10/227 (4,4)
Total antenatal admission days#	4,5 (0-67)
Major placenta praevia	2/266 (0.8)
Minor placenta praevia	1/266 (0.4)

#Median (Range); HELLP Syndrome: Haemolysis, elevated liver enzymes, low platelet count; PTL: Preterm labour; PPROM: Preterm prelabour rupture of membranes.

5.1.4 Antenatal events: fetal complications

Table 5.1.4 depicts the antenatal fetal complications that developed. A single IUFD occurred in eight pregnancies before 24 weeks gestation (between 8 weeks 1 day and 20 weeks 5 days gestation), one of which could be related to maternal methamphetamine use during pregnancy (at 11 weeks 2 days).

FGR after 24 weeks developed in 25 (10,5%) pregnancies and affected 30 (4,2%) fetuses at a median gestation of 30 weeks 4 days (21 weeks 4 days-36 weeks 5 days). Features of placental insufficiency were seen in 31 (13,1%) pregnancies affecting 38 (8,0%) fetuses. This lead to intensified outpatient fetal surveillance in 16 (6,8%) of the woman while intensive inpatient surveillance was needed in 28 (11,8%).

Polyhydramnios was the most common abnormal US finding in 59 (24,9%) of the pregnancies and 80 (16,9%) of the fetuses respectively. Of these pregnancies, 4/59 (6,7%) was associated with an anomalous fetus.

The eight (3,1%) major anomalies diagnosed antenatally (in seven fetuses) were the following: two cases of multicystic dysplastic kidneys, one Tetralogy of Fallot, one unbalanced atrioventricular septal defect, one Vein of Galen malformation, one open spina bifida, one severe ventriculomegaly and one case of an unilateral cleft lip and palate. Minor anomalies were detected on US in 27 (10,2%) women and they were a combination of soft markers (intracardiac echogenic foci, hypoplastic or absent nasal bone, pyelectasis, nuchal oedema, sandal gap and short humerus/femur length) and other minor structural abnormalities namely mild ventriculomegaly, single umbilical artery, brachycephalic head shape, choroid plexus cysts, hyper echoic bowel, megacysterna magna.

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At the last US evaluation 151 (63,7%) of the leading twins were found to be in cephalic position in pregnancies delivering after 24 weeks.

Table 5.1.4. Antenatal events: fetal complications

Fetal complications ≥ 24 weeks	**N % per woman [N % per fetus]**
Polyhydramnios	59/237 (24,9) [80/474 (16,9)]
Single intra-uterine fetal death	9 (3,8) [9 (1,9)]
Small for gestational age	73/237 (30,8) [103 (21,7)]
Fetal growth restriction	25/237 (10,5) [30/714 (4,2)]
Umbilical artery resistance index > P95	31/237 (13,1) [38/474 (8,0)]
Umbilical artery Doppler absent/reversed	11/237 (4,7) [12/474 (2,5)]
Mid-cerebral artery Pulsatile index < P5	16/237 (6,8) [23/474 (4,9)]
Cephalic leading twin at last ultrasound	151/237 (63,7)
Final fetal opinion ≥ 24 weeks	
Intensified outpatient fetal surveillance	16/237 (6,8)
Intensified inpatient fetal surveillance	28/237 (11,8)
Fetal anomalies (all fetuses)	
Major fetal anomaly	7/266 (2,6)
Minor fetal anomaly	27/266 (10,2)

P95: 95th centile; P5: 5th centile

5.1.5 Delivery outcomes of all women

Table 5.1.5 summarizes the delivery outcomes of all the pregnancies included in the study. The median gestational age at delivery for the index population was 35 weeks 1 day (± 4 weeks 2 days). Labour occurred spontaneously in 137 (60,4%) of the women, an induction of labour (IOL) was performed in 33 (14,5%) and a prelabour CD was performed in 57 (25,1%). [Figure 5.1.2].

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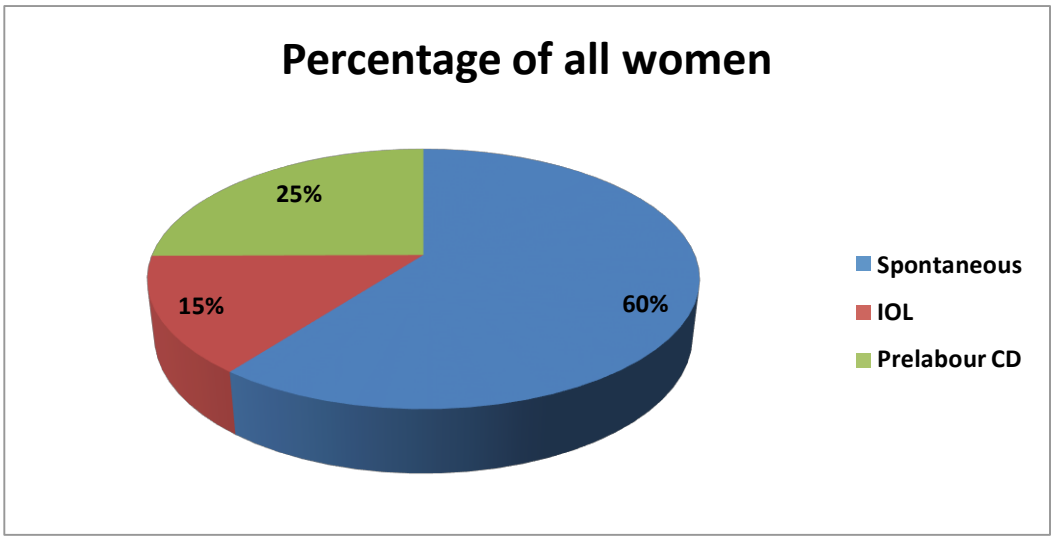
Figure 5.1.2. Onset of labour of all women



*IOL: Induction of labour; CD: Caesarean delivery

There were 7 (3,1%) spontaneous miscarriages at < 24 weeks. One case was complicated by several minor fetal anomalies and the patient miscarried subsequent to the insertion of a cervical cerclage for a short cervical length. There were also 5 (2,2%) spontaneous PTL between 24 weeks 0 days and 27 weeks 6 days gestation. PTL occurred spontaneously in 81 (35,7%) women in total. In 49 (21,6%) labour occurred spontaneously at term.

Of the 33 women who needed an IOL, two were less than 28 weeks 0 days pregnant. One induction was for complex ventriculomegaly at 23 weeks and the other for severe pre-eclampsia at 25 weeks gestation.

The 31 inductions after 28 weeks were indicated for the following: hypertensive disorders in pregnancy in 15 (48,4%), maternal medical conditions in 2 (6,5%), FGR in 4 (12,9%), PPROM in 2 (6,5%), routine delivery after 38 weeks in 4 (12,9%) and for an unknown indication in 4 (12,9%). The inductions were performed by rupturing of the membranes in 12 (38,7%), Prostaglandin E2 (PGE2) gel insertion in 10 (32,3%), oxytocin infusion in 5 (16,1%), bulb catheter placement in one (3,2%) and in 3 cases the method was not specified.

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Table 5.1.5. Delivery outcomes of all women [N/N with available data (%)]

Gestational age at delivery *	35w1d (± 4w2d)
Onset of labour:	**(n=227)**
Spontaneous · <24w0d · 24w0 – 27w6d · 28w0d – 33w6d · 34w0d – 36w6d · ≥37w0d	137 (60,4) 7 (3,1) 5 (2,2) 29 (12,8) 47 (20,7) 49 (21,6)
Induction of labour · <28w · 28w0d – 33w6d · 34w0d – 36w6d · ≥37w0d	33 (14,5) 2 (0,9) 0 12 (5,3) 19 (8,4)
No labour (prelabour caesarean delivery) · <28w · 28w0d – 33w6d · 34w0d – 36w6d · ≥37w0d	57 (25,1) 0 14 (6,2) 16 (7,0) 27 (11,9)
Vaginal delivery attempted	170 (74,9)
Vaginal delivery (both twins)	94 (41,4)
· Assisted delivery	11 (4,8)
· Delivery interval > 10min	62 (27,3)
· Successful attempted vaginal delivery	94/170 (55,3)
Combined delivery	9 (4,0)
Caesarean delivery (both twins)	124 (54,6)
· Intrapartum caesarean delivery	677 (29,5)
Induction of labour indications > 28w	**(n=31)**
· Hypertensive disorders	15 (48,4)
· Maternal medical conditions	2 (6,5)
· Fetal growth restriction	4 (12,9)
· PPROM	2 (6,5)
· Routine after 38 weeks	4 (12,9)
· Unknown	4 (12,9)
Mode of IOL > 28w	**(n=31)**
· Artificial rupture of membranes	12 (38,7)
· PGE2 gel insertion	10 (32,3)
· Oxytocinon infusion	5 (16,1)
· Bulb catheter placement	1 (3,2)
· Method not specified	3 (9,7)

*Mean ± SD; IOL: Induction of labour; PGE2: Prostaglandin E2; PPROM: Preterm prelabour rupture of membranes

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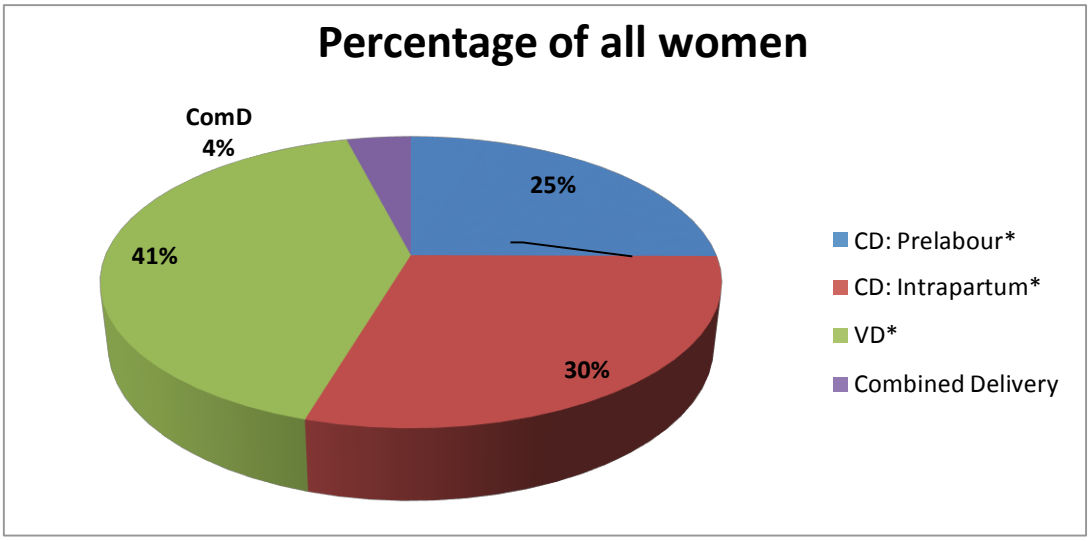
Figure 5.1.3 illustrates the different modes of delivery of the index population. A VD was attempted in 170 (74,9%) and achieved successfully for both twins in 94 (41,4%). An intrapartum CD for both twins was performed in 67 (29,5%) and a combined delivery occurred in 9 (4,0%) of the women. Four of the combined deliveries were indicated for a compound presentation in a transverse lie for the second twin; three for pathological fetal heart rate tracings; one due to a prolonged second stage of over four hours and one for a cord presentation of the second twin. The median intertwin delivery interval in those whom had a combined delivery was 1h30min (00h36min-4h25min). The intertwin delivery interval was more than 10 minutes in 53 (34,0%), and more than 30 minutes in 25 (16,0%) of all the women who experienced labour.

A CD (including prelabour and intrapartum) for both twins was performed in 124 (54,6%) of the index population. A prelabour CD were performed for 57 women: 14 (24,6%) of them were between 28 weeks 0 days and 33 weeks 6 days, 16 (28,1%) between 34 weeks 0 days and 36 weeks 6 days and 27 (47,4%) were at term gestation.

Figure 5.1.3. Mode of delivery of all women



*Both twins, ComD: Combined delivery; VD: Vaginal delivery; CD: Caesarean delivery

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5.1.6 Postpartum events of all women

The median total postpartum hospital stay for the mothers was 5 days (1-67 days). The most common postpartum events encountered were HDU admission in 6,7% if the women (with no ICU admissions in this study population) and blood transfusions in 11 (4,9%). The composite maternal adverse outcome for all the women was 23/225 (10,2%). [Table 5.1.6]

Table 5.1.6. Postpartum events of all women [N/N with available data (%)]

	N % per woman (n=225)
Total postpartum admission days[#](n=225)	5 (1-67)
Postpartum haemorrhage	7 (3,1)
Blood transfusion	11 (4,9)
High dependency unit admission	15 (6,7)
Composite maternal adverse outcome	23 (10,2)

Median (Range)

5.1.7 Early neonatal outcomes of all fetuses

Table 5.1.7 depicts the early neonatal outcomes for the pregnancies included in the study. The mean birth weight was 2233g (±602g) for all live born babies.

Live births occurred in 423 (93,6%) of the cases and 16 (3,6%) had a 5 minute APGAR of less than 7. A Fresh stillbirth (FSB) was delivered in 20 (4,4%) of the cases with 19 of them occurring before 28 completed weeks of gestation. In one case the fetus demised at 35 weeks 6 days gestation. The mother was diagnosed with severe FGR at 32 weeks gestation with abnormal umbilical artery Doppler's (UAD) and middle cerebral artery (MCA) Doppler's. She subsequently developed GHT at 34 weeks and missed her follow up visit. She went into spontaneous labour at 35 weeks 6 days and delivered a 2300g FSB and a healthy co-twin.

There were 6 cases of a single fetal demise resulting in a macerated stillbirth (MSB) of those women with a known outcome. Three of them were

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known to have demised before 28 weeks at 20, 25 and 27 weeks respectively.

In three cases, the demise occurred after 28 weeks gestation. The first mother was diagnosed with GDM at 26 weeks that was well controlled with correct diet only. FGR was diagnosed at 33 weeks and at the subsequent review at 35 weeks there was a normal Doppler assessment. She presented in spontaneous labour at 37 weeks 3 days with the leading twin in breech presentation. An emergency CD was done and a MSB of 1710g delivered. In the second case the mother developed GHT but had a normal assessment at 37 weeks and was booked for an elective CD the next week. The surgery could not be performed due to limited theatre time and her surgery was rescheduled. She subsequently presented in spontaneous labour at 39 weeks 3 days and a 2380g MSB was delivered with a CD. The third case was known with FGR in one twin since 25 weeks gestation. She presented in spontaneous labour at 29 weeks 2 days and delivered a 840g MSB.

An ENND occurred in 6 (1,3%) and admission to NICU in 7 (1,6%) of all the babies. The median hospital stay was 7 days (0-169 days) and 413 (91,4%) survived up to discharge. The composite early neonatal outcome was 29 (6,4%).

Table 5.1.7. Early neonatal outcomes of all babies with available data (%)

Birth weight (g)* † (n=423)	2233 ± 602
* Extremely low birth weight <1000g†	13 (3,1)
* Very low birth weight <1500g†	48 (11,4)
* Low birth weight<2500g†	284 (67,0)
Live born	423 (93,6)
5 minute APGAR < 7†	16 (3,6)
Fresh stillbirths	20 (4,4)
· <28w	19 (4,2)
· 28w0d – 33w6d	0
· 34w0d – 36w6d	1 (0,2)
· ≥37w0d	0
Macerated stillbirths (presumed GA at demise)	6
· <28w	3
· 28w0d – 33w6d	1

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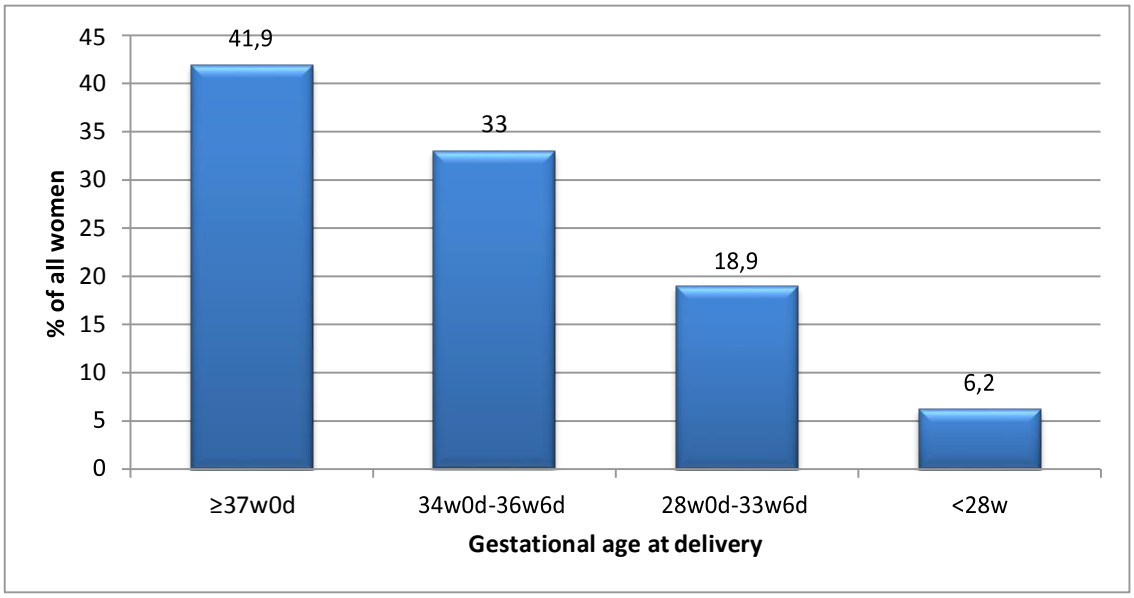
· 34w0d – 36w6d · ≥37w0d	2 0
Early neonatal death	6 (1,3)
Admission Neonatal intensive care unit	7(1,6)
Hospital stay (days)#	7 (0-169)
Surviving to discharge	413 (91,4)
Composite Neonatal Adverse Outcome	29 (6,4)

* Mean ± SD; # Median (Range); † Live born only; GA: Gestational age.

5.2 Results according to the gestational age at delivery

The first subgroup analysis of this study was to evaluate the gestational age at delivery (from 28 weeks onwards) and how it related to antenatal events and pregnancy outcomes. The 3 subgroups were the early preterm group (between 28 weeks 0 days and 33 weeks 6 days), late preterm group (between 34 weeks 0 days to 36 weeks 6 days) and term group (from 37 weeks 0 days onwards). Figure 5.2.1 illustrates the distribution of the gestational age at delivery of the 227 pregnancies where it was known. It was less than 28 weeks 0 days in 14 (6,2%), early preterm deliveries occurred in 43 (18,9%), late preterm deliveries in 75 (33,0%) and term deliveries in 95 (41,9%). The total preterm delivery rate for the pregnancies delivering after 28 weeks was 55,4%.

Figure 5.2.1. Gestational age at delivery of all women



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In summary, the main determinants for early PTD were pre-eclampsia, spontaneous PTL or PPROM and fetal compromise. The main determinants for late PTD were similar, but to a lesser degree. The early preterm group was significantly more likely to be induced compared to the term group but this association did not reach significance compared with the late preterm group. The only other findings reaching statistical significance were more maternal postpartum admission days and longer neonatal hospital stay in the early preterm compared to the term group.

5.2.1 Baseline characteristics according to the gestational age at delivery

Compared to the term group, the early preterm group had significantly more women with previous PTL and PPROM (7,1% vs. 1,1%; p=0,03) with a trend towards more positive syphilis screening test, HIV positive results, GHT and stillbirths. Conversely the term group had a trend towards higher parity, more obesity and lower incidences of previous pre-eclampsia, PTL and PPROM although none of these trends were statistically significant when compared to the early and late preterm group.

The median gestational age of delivery was 31 weeks 0 days for the early preterm group, 35 weeks 4 days for the late preterm group and 38 weeks 0 days for the term group. The mean birth weight was 1516g (± 330g) for the early preterm group, 2189g (± 387g) for the late preterm group and 2623g (± 475g) for the term group. [Table 5.2.1]

Table 5.2.1. Baseline characteristics and pre-existing morbidities according to the gestational age at delivery

	Delivery GA 28w0- 33w6 ***Early preterm***	**Delivery GA 34w0 - 36w6** ***Late preterm***	**Delivery GA ≥ 37w0** ***Term***	**Early preterm vs. Term (p)**	**Late preterm vs. Term (p)**
Patients	**43/227 (18,9)**	**75/227 (33,0)**	**95/227 (41,9)**		
Age(y)	28,8 ± 6,1	29,5 ± 6,3	28,5 ± 6,3	NS	NS
Gravidity#	2 (1-5)	2 (1-7)	3 (1-6)	NS	NS
Parity#	1 (0-4)	1 (0-4)	1 (0-5)	NS	NS
GA at delivery#	31w5 (28w5-33w6)	35w4 (34w0-36w6)	38w0 (37w0-40w2)	0,05	0,05

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Birth weight(g)*	1516 ± 330	2189 ± 387	2623 ± 475	0,05	0,05
Pre-existing morbidities	**N % per woman**	**N % per woman**	**N % per woman**		
BMI > 30kg/m^2	20/43 (46,5)	32/73 (43,8)	50/93 (53,8)	NS	NS
Hypertension	0/42 (0)	5/74 (6,8)	3/94 (3,2)	NS	NS -
Diabetes mellitus	1/42 (2,4)	0/74 (0)	1/94 (1,1)	NS	NS -
HIV positive	10/42 (23,8)	14/74 (18,9)	17/94 (18,0)	NS	NS -
HIV on HAART	1/42 (2,4)	2/74 (2,7)	6/94 (6,4)	NS	NS
RPR positive	4/42 (9,5)	3/74 (4,1)	2/94 (2,1)	0,07	NS
Smoking	5 /42 (11,9)	18/74 (24,3)	16/94 (17,0)	NS	NS
Previous obstetric history					
GHT	6/42 (14,3)	5/73 (6,8)	6/95 (6,3)	NS	NS
Pre-eclampsia	1/42 (2,4)	2/73 (2,7)	1/95 (1,1)	NS	NS
PTL&PPROM	3 /42 (7,1)	3/73 (4,1)	1/95 (1,1)	0,03	NS
Previous CD	6 /42 (14,3)	14/73 (19,2)	18/95 (18,9)	NS -	NS
Stillbirth	4 /42 (9,5)	1/73 (1,4)	2/95 (2,1)	0,07	NS

*Mean ± SD; #Median (Range); GA: Gestational age; BMI: Body mass index; HIV: Human immunodeficiency virus; HAART: Highly active antiretroviral therapy; RPR: Rapid plasma reagin; GHT: Gestational hypertension; PTL: Preterm labour; PPROM: Preterm prelabour rupture of membranes; CD: Caesarean delivery; NS: Non-significant.

5.2.2 Antenatal events: maternal complications according to the gestational age at delivery

Compared to the term group, the early preterm group had a significantly higher incidence of pre-eclampsia (25,6% vs. 9,5%; p=0,02), PTL (65,1% vs. 7,4%; p=<0,01), PPROM (23,2% vs. 0%; p<0,01) and APH (9,3% vs. 0%; p<0,01). Similarly this group had a significantly higher chance of receiving tocolysis (41,9% vs. 9,5%; p<0,01) and antenatal steroids (79,0% vs. 15,8%; p<0,01) when compared to the term group. Although there was a trend towards a higher incidence of short cervices in the early preterm group this did not reach statistically significance. This pattern of events were also seen in the late preterm group when compared to the term group with a higher incidence of pre-eclampsia (24,7% vs. 9,5%; p<0,01), PTL (50,7% vs. 7,4%; p<0,01), PPROM (17,8% vs. 0%; p<0,01) and APH (6,8% vs. 0%; p<0,01). [Table 5.2.2]

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Table 5.2.2: Maternal complications according to the gestational age at delivery [N (%)/women]

	Delivery GA 28w0- 33w6 *Early preterm*	Delivery GA 34w0 - 36w6 *Late preterm*	Delivery GA ≥ 37w0 *Term*	Early preterm vs. Term (p)	Late preterm vs. Term (p)
Patients	**43/227 (18,9)**	**75/227 (33,0)**	**95/227 (41,9)**	-	-
Asymptomatic bacteriuria	6/42 (14,3)	10/73 (13,7)	20/95 (21,1)	NS	NS
GHT	4/43 (9,3)	11/73 (15,0)	13/95 (13,7)	NS	NS
Pre-eclampsia	11/43 (25,6)	18/73 (24,7)	9/95 (9,5)	0,02	<0,01
CL < 20mm at < 28w0d	3/43 (7,0)	1/73 (1,4)	4/95 (4,2)	NS	NS
Threatened m/c	2/43 (4,7)	1/73 (1,4)	0/95 (0)	NS	NS
Threatened PTL	2/43 (4,7)	12/73 (16,4)	12/95 (12,6)	NS	NS
PTL	28/43 (65,1)	37/73 (50,7)	7/95 (7,4)	<0,01	<0,01
PPROM	10/43 (23,2)	13/73 (17,8)	0/95 (0)	<0,01	<0,01
Tocolysis	18/43 (41,9)	8 /73 (11,0)	9/95 (9,5)	<0,01	NS
APH	4/43 (9,3)	5/73 (6,8)	0/95 (0)	<0,01	0,01

GA: Gestational age; GHT: Gestational hypertension; CL: Cervical length; PTL: Preterm labour; PPROM: Preterm prelabour rupture of membranes; BMZ: Betamethasone; APH: Antepartum haemorrhage; NS: Non-significant.

5.2.3 Antenatal events: fetal complications according to the gestational age at delivery

Compared to the group delivering at term, the early preterm group had a higher incidence of FGR (20,9% vs. 3,2%; p<0,01); more placental insufficiency with UAD being absent or reversed (11,6% vs. 0%; p<0,01); more middle cerebral artery pulsatile index (MCA PI) < P5 (16,3% vs. 1,1%; p<0,01) and a higher incidence of inpatient fetal surveillance (16,3% vs. 5,3%; p=0,04). The women in the early preterm group were also significantly less likely to be induced than the term group (0% vs. 20%; p<0,01). The higher incidence of polyhydramnios in the early preterm group did not reach significance.

This trend towards more signs of placental insufficiency was also noted in the late preterm group compared to the term group with more FGR (16,0% vs. 3,2%;

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p<0,01); more UAD being absent or reversed (6,7% vs. 0%; p=0,02); more MCA PI < P5 (9,3% vs. 1,1%; p=0,01) and a higher incidence of inpatient fetal surveillance (16,0% vs. 5,3%; p=0,02). The trend towards a higher incidence of induction in the term group was only significant when compared to the early preterm group. [Table 5.2.3]

Table 5.2.3: Fetal complications according to the gestational age at delivery

	Delivery GA 28w0d-33w6d *Early preterm*	**Delivery GA 34w0d-33w6d *Late preterm***	**Delivery GA ≥ 37w0 *Term***	**Early preterm vs. Term(p)**	**Late preterm vs. Term (p)**
Fetal Complications	**N (%) per women; [N (%) per fetus]**	**N (%) per women; [N (%) per fetus]**	**N (%)/women; [N (%)/ fetus]**		
Patients	**43/227 (18,9)**	**75/227 (33,0)**	**95/227 (41,9)**	NS	NS
Single IUFD	3/43 (6,9) [3/86 (3,5)]	1/74 (1,4) [1/148 (0,07)]	4/95 (4,2) [4/190 (2,1)]	NS	NS
Major fetal anomaly	1/43 (2,3)	4/75 (5,3)	1/95 (1,1)	NS	NS
Minor fetal anomaly	5/43 (11,6)	9/75 (12,0)	9/95 (9,5)	NS	NS
Polyhydramnios	13/43 (30,2) [18/86 (20,9)]	18/75 (24) [24/150 (16,0)]	24/95 (25,3) [32/190 (16,8)]	NS	NS
SGA	18 (41,9) [25 (29,1)]	33 (44,0) [46 (30,1)]	21 (22,1) [30 (15,8)]	0,02 [0,01]	<0,01 [<0,01]
FGR	9 (20,9) [11 (12,8)]	12 (16,0) [14 (9,3)]	3 (3,2) [3 (1,6)]	<0,01 <0,01	<0,01 <0,01
UA RI > P95	8/43 (18,6) [11/86 (12,8)]	12 (16,0) [13 (8,7)]	9 (9,5) [11 (5,8)]	NS; 0,05	NS, NS
UAD absent/reversed	5/43 (11,6) [5/86 (5,8)]	5 (6,7) [5 (3,3)]	0	<0,01; <0,01	0,02; 0,02
MCA < P5	7/43 (16,3) [10/86 (11,6)]	7/75 (9,3) [9/150 (6,0)]	1/95 (1,1) [2/190 (1,1)]	<0,01; <0,01	0,01; 0,01
Outpatient fetal surveillance	5/43 (11,6)	5/75 (6,7)	4/95 (4,2)	NS	NS
Inpatient fetal surveillance	7/43 (16,3)	12/75 (16,0)	5/95 (5,3)	0,04	0,02
Spontaneous labour	29/43 (67,4)	47/75 (62,7)	49/95 (51,6)	NS	NS
IOL >28w0d	0/43 (0)	12/75 (16,0)	19/95 (20,0)	<0,01	NS

Median (Range); GA: Gestational age; IUFD: Intra-uterine fetal death; FGR: Fetal growth restriction; GA: Gestational age; UA-RI: Umbilical artery resistance index; UAD: Umbilical artery Doppler; MCA: Mid-cerebral artery; IOL: Induction of labour; NS: Non-significant.

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5.2.4 Delivery outcomes according to the gestational age at delivery

There was no significant difference in the mode of delivery between the three groups. There was a trend towards more combined deliveries in the term group, but this was not statistically significant. The late preterm group had a trend towards more intrapartum CD, but this also did not reach significance. The total postpartum admission days were statistically more in the early preterm compared to the term group [7 days (2-38) vs. 4 (1-34); p=0,05]. Despite a higher trend in composite maternal outcome score in the late preterm group, it did not reach significance. [Table 5.2.4]

Table 5.2.4: Delivery outcomes according to the gestational age at delivery

	Delivery GA 28w0d-33w6d ***Early preterm***	**Delivery GA 34w0d-33w6d** ***Late preterm***	**Delivery GA ≥ 37w0** ***Term***	**Early preterm vs. Term(p)**	**Late preterm vs. Term (p)**
Delivery outcomes	**N (%) per women**	**N (%) per women**	**N (%)/ women**		
Patients	**43/227 (18,9)**	**75/227 (33,0)**	**95/227 (41,9)**		
Vaginal delivery (both twins)	17/43 (39,5)	28/75 (37,3)	37/95 (38,9)	NS	NS
Successful VD in labouring women	17/29 (58,6)	28/59 (47,5)	37/68 (54,4)	NS	NS
Combined delivery	1/43 (2,3)	2/75 (2,7)	6/95 (6,3)	NS	NS
Caesarean Delivery	25/43 (58,1)	45/75 (60,0)	52/95 (54,7)	NS	NS
Prelabour CD	14/43 (32,6)	16/75 (21,3)	27/95 (28,4)	NS	NS
Intrapartum CD	11/43 (25,6)	29/75 (38,7)	25/95 (26,3)	NS	NS
PPH	1/43 (2,3)	4/75 (5,3)	2/95 (2,1)	NS	NS
Blood transfusion	2/43 (4,7)	5 /75(6,7)	3/95 (3,2)	NS	NS
Composite maternal adverse outcome	3/43 (7,0)	10/75 (13,3)	5/95 (5,3)	NS	0,06
Antenatal admissions (mean per patient)	23/43 (0,54)	31/75 (0,42)	37/95 (0,39)	NS	NS
Total antenatal admission days#	4 (0-32)	4,5 (0-67)	4 (0-29)	NS	NS
Total postpartum admission days# (mother)	7 (2-38)	5 (2-67)	4 (1-34)	0,05	NS

Median (Range); GA: Gestational age; VD: Vaginal delivery; CD: Caesarean delivery; PPH: Postpartum haemorrhage; NS: Non-significant.

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5.2.5 Early neonatal outcomes according to the gestational age at delivery

The rate of live born babies was similar in all three groups with a trend towards better outcomes in the term group when compared to the early preterm group. The early preterm group had the lowest incidence of live born babies and the highest incidence of 5 min APGARs < 7 but the only significant difference when compared to the term group was the prolonged neonatal hospital stay [median 14 days (1-169) vs. 1 day (0-11) p=0,05]. Strikingly the late preterm group had the highest incidence of ENND but this was not statistically significant. The difference in the composite early neonatal outcome score between the three groups also did not reach statistical significance. [Table 5.2.5]

Table 5.2.5: Early neonatal outcomes according to the gestational age at delivery

	Delivery GA 28w0d-33w6d ***Early preterm***	**Delivery GA 34w0d-33w6d** ***Late preterm***	**Delivery GA ≥ 37w0** ***Term***	**Early preterm vs. Term(p)**	**Late preterm vs. Term (p)**
Neonatal outcome	**N (% per fetus)**	**N (% per fetus)**	**N (% per fetus)**	NS	NS
Live born	83/86 (96,5)	148/150 (98,7)	183/190 (97,3)	NS	NS
5min APGAR < 7†	3/86 (3,5)	5/150 (3,3)	4/190 (2,1)	NS	NS
Fresh stillbirth	0/86	1/150 (0,7)	0/190	NS	NS
Macerated stillbirth	3/86 (3,5)	1/150 (0,7)	5/190 (2,7)	NS	NS
ENND	0	3/150 (2,0)	1/190 (0,5)	NS	NS
Neonatal hospital stay (days)#	14 (1-169)	3 (0-165)	1 (0-11)	0,05	NS
Composite early neonatal adverse outcome	6/86 (7,0)	9/150 (6,0)	5/190 (2,7)	NS	NS

Median (Range) †Live born only; GA: Gestational age; ENND: Early neonatal death; NS: Non-significant.

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5.3 Results according to the mode of delivery

The second subgroup analysis of this study was to evaluate the mode of delivery (from 28 weeks onwards) and how it related to antenatal events and pregnancy outcomes. The two subgroups were a labour group that included women who experienced labour (whether spontaneous or induced) and a prelabour CD group. The prelabour CD group includes all women with an indicated CD and four women in whom the CD was performed for failed IOL. In 156 (73,2%) of the 213 women whose pregnancies were known to reach 28 weeks gestation, the conditions were deemed favourable for an attempted VD while in 57 (26,8%) a prelabour CD was done.

In summary, the labour group had a higher incidence of GHT and PTL than the prelabour CD group but a lower incidence of previous CD, pre-eclampsia and Doppler evidence of placental insufficiency in comparison. Thus, the main determinants for a prelabour CD were previous CD, current pre-eclampsia or placental insufficiency and lack of spontaneous PTL.

5.3.1 Baseline characteristics according to the mode of delivery

Women in the labour group were more likely to be on HAART, smokers, have a positive syphilis screening test and a previous history of PTL and PPROM although none of these finding were statistically significant. In contrast, women in the prelabour CD group were more likely to be older, have a higher BMI, have pre-existing CHT and DM and a previous history of pre-eclampsia. The only statistically significant difference between the two groups were the increased incidence of a previous CD in the prelabour CD group ($p<0,01$). [Table 5.3.1]

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Table 5.3.1. Baseline characteristics according to the mode of delivery

	Labour group ≥ 28w0	Prelabour CD ≥ 28w0	p Value
Patients	**156/213 (73,2)**	**57/213 (26,8)**	
Age in years#	28,7 ± 6,3	29,9 ± 6,2	NS
Gravidity#	2 (1-7)	2 (1-5)	NS
Parity#	1 (0-5)	1 (0-4)	NS
Pre-existing morbidities	**N % / woman**	**N % / woman**	
Body mass index > 30kg/m^2	69/152 (45,4)	33/53 (62,3)	NS
Hypertension	7/153 (4,6)	4/56 (7,1)	NS
Diabetes mellitus	1/153 (0,7)	1/56 (1,8)	NS
Human immunodeficiency virus positive	30/154 (19,5)	11/56 (19,6)	NS
HIV on HAART	19/154 (12,3)	5/56 (8,9)	NS
Rapid plasma reagin positive	9/154 (5,8)	0/56 (0)	0,06
Smoking	31/153 (20,3)	8/56 (14,3)	NS
Previous obstetric history			
Gestational hypertension	12/153 (7,8)	5/56 (8,9)	NS
Pre-eclampsia	2/153 (1,3)	2/56 (3,6)	NS
PTL & PPROM	5/153 (3,3)	1/56 (1,8)	NS
Caesarean delivery	22/153 (14,4)	17/56 (30,3)	<0,01
Stillbirth	5/153 (3,3)	3/56 (5,4)	NS

Median (Range); CD: Caesarean delivery; HAART: Highly active antiretroviral therapy; NS: Non-significant.

5.3.2 Antenatal events: maternal complications according to the mode of delivery

In the labour group there were significantly more women who developed GHT (16,8% vs. 3,6%; p=0,01), PTL (43,9% vs. 7,1%; p<0,01) and receive tocolysis (21,9% vs. 1,8%; p<0,01) with only a trend towards more admissions and PPROM. In the prelabour CD group there were significantly more pre-eclampsia (32,1% vs. 12,9%; p<0,01) and a trend towards more antenatal admission days. [Table 5.3.2]

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Table 5.3.2. Maternal complications according to the mode of delivery

	Labour group ≥ 28w0	Prelabour CD ≥ 28w0	
Maternal complications	**N % / woman**	**N % / woman**	**P Value**
Patients	**156/213 (73,2)**	**57/213 (26,8)**	
Asymptomatic Bacteriuria	24/155 (15,4)	12/56(21,4)	NS
Gestational Hypertension	26/155 (16,8)	2/56 (3,6)	0,01
Pre-eclampsia	20/155 (12,9)	18/56 (32,1)	<0,01
Cervical length < 20mm at < 28w0d	8/155 (5,2)	0/55 (0)	NS
Threatened Miscarriage	2/155 (1,3)	1/56 (1,8)	NS
Threatened preterm labour	19/155 (12,3)	7/56 (12,5)	NS
Preterm labour	68/155 (43,9)	4/56 (7,1)	<0,01
PPROM	21/155 (13,5)	3/56 (5,4)	NS
Tocolysis/Suppression	34/155 (21,9)	1/56 (1,8)	<0,01
Antenatal Betamethasone	49/155 (31,6)	21/56 (37,5)	NS
Antepartum haemorrhage	6/155 (3,9)	3/56 (5,4)	NS
Antenatal admissions (mean per patient)	73/156 (0,47)	18/56 (0,32)	0,06
Total antenatal admissions days[#]	4 (0-32)	5 (3-67)	NS

Median (Range); CD: Caesarean delivery; PPROM: Preterm prelabour rupture of membranes; NS: Non-significant.

5.3.3 Antenatal events: fetal complications according to the mode of delivery

A single IUFD occurred in 9 (5,8%) pregnancies affecting 9 (2,9%) of the fetuses in the labour group and in 1 (1,8%) pregnancy affecting 1 (0,9%) of the fetuses in the prelabour CD group. A major fetal anomaly was diagnosed in 3 (1,9%) of the women in the labour group and in 3 (5,3%) of the prelabour CD group. Polyhydramnios was found on US in 36 (23,1%) of women and 49 (15,7%) of fetuses in the labour group and in 19 (33,3 %) of women and 25 (21,9%) of fetuses in the prelabour CD group. Thus, there was a trend towards more polyhydramnios and all fetal anomalies in the prelabour CD group. [Table 5.3.3]

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Table 5.3.3. Comparison of fetal complications according to the planned mode of delivery

	Labour group ≥ 28w0	**Prelabour CD ≥ 28w0**	
	N (%) / women) [N (%) / fetus]	**N (%) / women) [N (%) / fetus]**	**P value**
Patients	**156/213 (73,2)**	**57/213 (26,8)**	
Single fetal demise	9 (5,8) [9 (2,9)]	1 (1,8) [1 (0,9)]	NS
Major fetal anomaly	3 (1,9)	3 (5,3)	NS
Minor fetal anomaly	13 (8,3)	10 (17,5)	0,06
Polyhydramnios	36 (23,1) [49 (15,7)]	19 (33,3 [25 (21,9)]	NS
Small-for-gestational age	54 (34,6) [79 (25,3)]	19 (33,3) [24 (21,1)]	-
Gestation of diagnosis of SGA[#]	31w3 ± 4w0	31w4 ± 2w5	
Fetal growth restriction	13 (8,3) [14 (4,5)]	11 (19,3) [14 (12,3)]	0,03 [0,01]
UA RI > P95	16 (10,3) [19 (6,1)]	13 (22,8) [16 (14,0)]	0,02; <0,01
UAD absent/reversed	1 (0,6) [1 (0,3)]	9 (15,8) [9 (7,9)]	<0,01 <0,01
Middle cerebral artery PI < P5	6 (3,9) [8 (2,6)]	9 (15,8) [13 (11,4)]	<0,01; <0,01
Outpatient fetal surveillance	7 (4,5)	7 (12,3)	0,05
Inpatient fetal surveillance	14 (9,0)	10 (17,5)	NS

Median (Range); CD: Caesarean delivery; UA-RI: Umbilical artery resistance index; UAD: umbilical artery Doppler; PI: Pulsatile index; P5: 5th percentile; NS: Non-significant.

In the labour group FGR affected 13 (8,3%) pregnancies and 14 (4,5%) fetuses while in the prelabour CD group it affected 11 (19,3%) pregnancies and 14 (12,3%) fetuses. There was significantly more evidence of placental insufficiency with more fetuses with UAD RI > P95 (14,0% vs. 6,1%; p=0,01), UAD absent/reversed (7,9% vs. 0,3%; p<0,01), and MCI PI <P5 (11,4% vs. 2,6%; p<0,01) in the prelabour CD group.

5.3.4 Delivery outcomes according to the mode of delivery

The mean age of delivery was 35 weeks 6 days for the labour group and 36 weeks 0 days for the prelabour CD. No significant differences were observed although there were trends towards more PPH but shorter postpartum hospital stay in the

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labour group. There were also trends towards more blood transfusions and a higher composite maternal outcome score in the prelabour CD group. [Table 5.3.4]

Table 5.3.4: Delivery outcomes according to the mode of delivery

Delivery outcomes	**Labour group ≥ 28w0 (A)**	**Prelabour CD ≥ 28w0 (B)**	**p-value**
Patients	**156/213 (73,2)**	**57/213 (26,8)**	
Gestational age at delivery#	35w6 ± 2w4d	36w0 ± 2w5d	NS
Caesarean delivery	74/156 (47,4)	57/57 (100)	NS
Postpartum events			
Postpartum haemorrhage	6/156 (3,8)	1/56 (1,8)	NS
Blood transfusion	5/156 (3,2)	5/56 (8,9)	NS
Total postpartum admission days#	4 (1-38)	5 (3-67)	NS
Composite maternal adverse outcome	13/156 (8,3)	8/56 (14,3)	NS

Median (Range); CD: Caesarean delivery; NS: Non-significant

The mode of delivery for the labour group was a VD for both twins in 82 (52,6%) and 74 (47,4%) had an intrapartum emergency CD. The intrapartum CD can further be subdivided into the 65 (41,7%) intrapartum CD for both and 9 (5,7%) combined delivery with a CD for the second twin.

Figure 5.3.1 illustrates the indications for the intrapartum CD. The most common indication was an abnormal lie of the presenting twin (52,3%). An intrapartum CD was performed on 6 women who declined vaginal birth after Caesarean section (VBAC) despite qualifying for it according to our guidelines. They all presented in spontaneous labour with four in PTL and two at term gestation.

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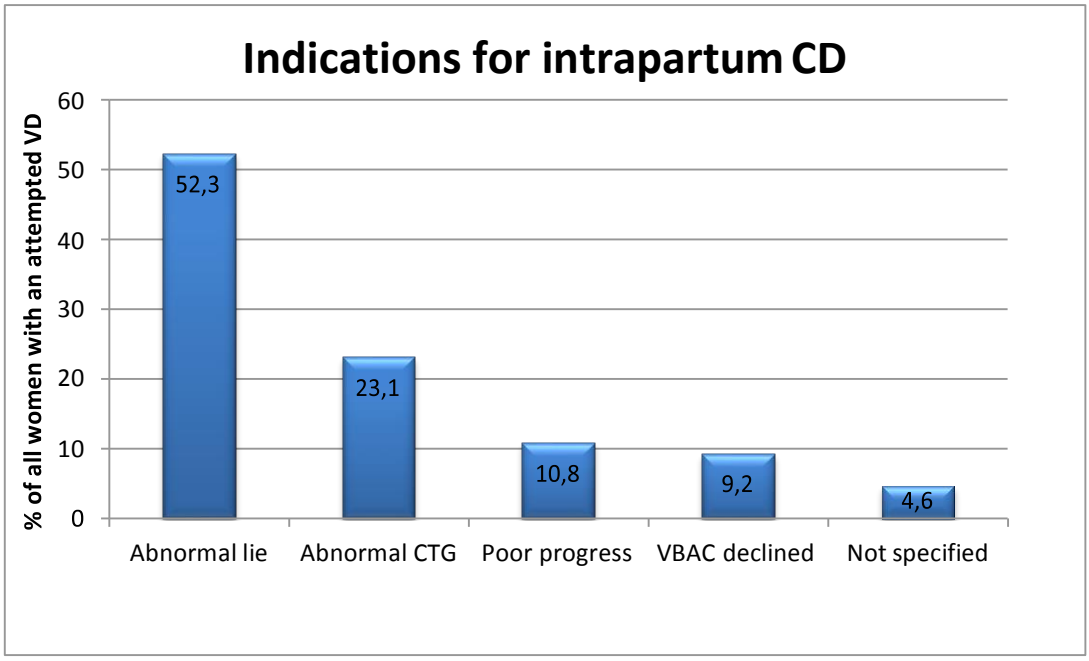
Figure 5.3.1. Indications for intrapartum CD (excluding combined deliveries) in the labour group



*CD: Caesarean Delivery; VBAC: Vaginal birth after Caesarean section

During labour the action line was reached in 16 (10,3%), augmentation was administered in 24 (15,4%), epidural analgesia performed in 2 (1,3%) and 8 (5,1%) women involving 9 fetuses had an assisted VD.

In the labour group the mean delivery interval was 18,3 ± 33,1min (19,8 ± 17,2min when both twins delivered vaginally, 1,7 ± 1,4min when both delivered by emergency CD and 106,7 ± 74,2min when only twin 2 was delivered abdominally). In 53/156 (34,0%) there were an inter-delivery interval of more than 10min and in 25/156 (16,0)% more than 30min. This interval affected the APGAR score of Twin B in the labour group and was significantly shorter in neonates with a 5 minute APGAR score ≥ 7 (15,1 ± 28,5min vs. 40,6 ± 55,9min, p=0,02). [Fig 5.3.2]

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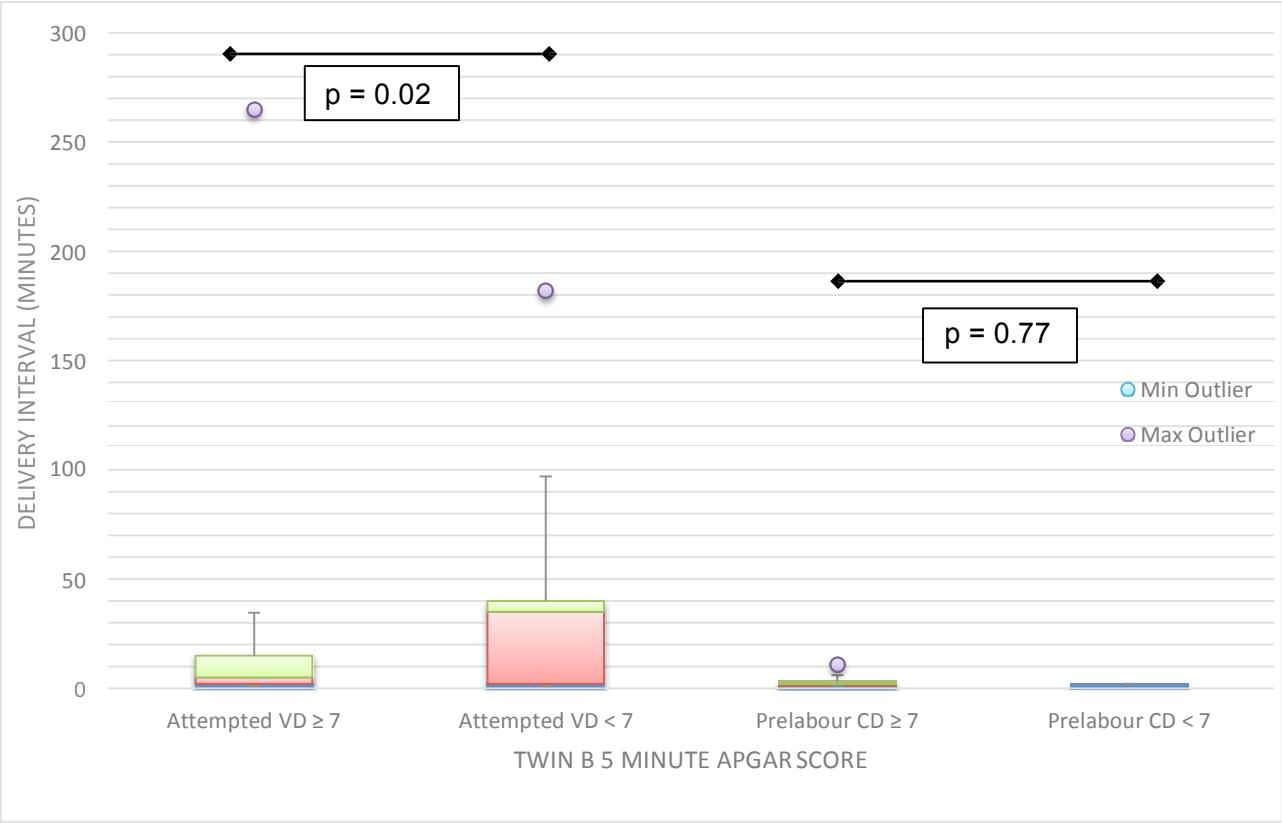
Figure 5.3.2: Intertwin delivery interval according to 5-minute APGAR score in Twin B delivering after 28 weeks



Complications in the labour group included a grade I-II perineal tear in 13 (8,3), PPH in 4 (2,6%), atonic uterus in 2 (1,3%), one grade III-IV perineal tear, one retained placenta, one puerperal sepsis related to post placental insertion of an intra-uterine contraceptive device and one diagnosis of pyelonephritis. One woman underwent a caesarean hysterectomy after a CD complicated by an atonic uterus. She went into spontaneous PTL at 34 weeks 5 days and a CD was performed for poor progress. After the hysterectomy she was admitted to a HDU and received a massive blood transfusion but she eventually made a full recovery.

The indications for the prelabour CD are illustrated in Figure 5.3.3 with the majority of them (84.2%) indicated for the following: hypertensive disorders of pregnancy (33,3%), abnormal lie of the presenting twin (24,6%), previous CD and not deemed favourable for VBAC (14,0%) and fetal compromise (12,3%).

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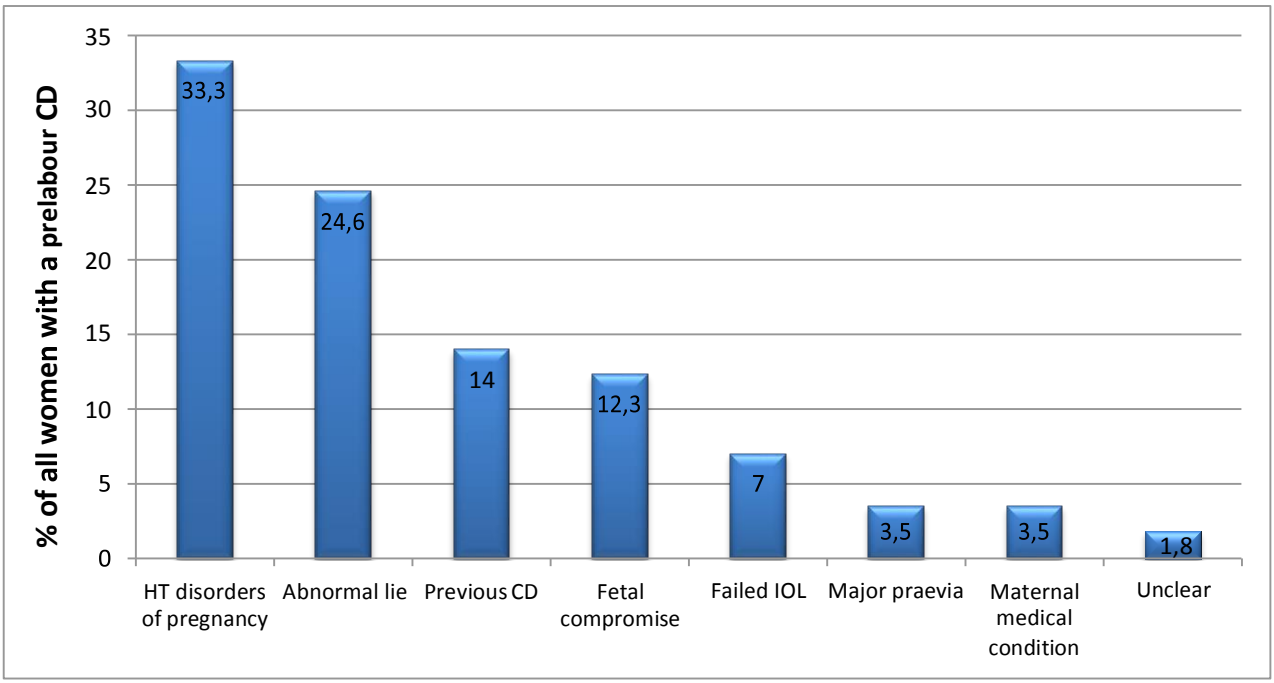
Figure 5.3.3 Indications for prelabour CD



*CD: Caesarean delivery; HT: Hypertension; IOL: Induction oflabour

Complications in the prelabour CD group included one PPH (1,8%) and one subtotal hysterectomy (1,8%) after a CD at 28 weeks 1 day for a suspected abruption but with an intraoperative diagnosis of placenta accreta. This mother had an uneventful recovery in the HDU. The total maternal hospital stay was longer in the prelabour CD group, but there was no statistical significant difference in either maternal or neonatal outcome score.

5.3.5 Early neonatal outcomes according to the mode of delivery

No significant differences were seen between the two groups although there was a trend towards more APGAR scores below 7 at 5 minutes, longer neonatal hospital stay and higher composite neonatal outcome score in the labour group. [Table 5.3.5]

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Table 5.3.5 Early neonatal outcomes according to the mode of delivery

	Labour group ≥ 28w0 (A)	**Prelabour CD ≥ 28w0 (B)**	**p-value**
Neonatal outcome	**N (% per fetus) n=312**	**N (% per fetus) n=112**	
Birth weight (g)*	2228 ± 563	2293 ± 659	NS
Live born	303 (97,1)	111 (99,1)	NS
5 min APGAR < 7†	9 (2,9)	3 (2,7)	NS
Fresh stillbirth	1 (0,3)	0	NS
Macerated stillbirth	8 (2,6)	10 (8,8)	NS
Early neonatal death	3 (1,0)	1 (0,9)	NS
Neonatal hospital stay (days)#	7,5 (0-165)	7,0 (0-165)	NS
Composite early neonatal adverse outcome	15 (4,8)	5 (4,5)	NS

*Mean ± SD; # Median (Range); †: Live born only; CD: Caesarean delivery; NS: Non-significant

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6. Discussion

In the index study, the mean gestational age at delivery was 35 weeks 1 days ± 4 weeks 2 days, with a mean live born birth weight of 2233 ± 602g. A total PTD rate of 55% was observed with 42% of the women delivering after 37 weeks and 10% still undelivered by 39 weeks. The main determinants of early PTDs were pre-eclampsia, spontaneous PTL or PPROM and fetal compromise. The determinants for late PTDs were similar but to a lesser degree.
Labour was experienced by 75% of the women (including the 15% who were induced) with 41% delivering both twins vaginally and a combined delivery performed in 4%. A Prelabour CD was performed in 25% of women (all after 28 weeks) with the main determinants of a prelabour CD being previous CD, current pre-eclampsia or placental insufficiency and lack of spontaneous PTL. An adverse outcome was experienced by 10% of the women and 6% of the fetuses. A fetal loss rate of 6%, a live birth rate of 94% and a neonatal survival discharge rate of 91% was observed.

The timing of the delivery, whether spontaneous or planned, is an important consideration in the management of twin pregnancies. The PTD rate in the index population was 55%, which is higher than in other developing countries. This is illustrated in a retrospective study of twin deliveries managed over ten years in a tertiary hospital in Abuja, Nigeria that found a PTD rate of 39,7%[3]. A similar rate of 41% was documented in a observational study done at a teaching hospital in Enugu, Nigeria.[4] Our findings are more in keeping with the developed world, where a large cross-sectional study from the United States over 17 years found that PTD, whether spontaneous or induced labour, occurred in 55% of twin pregnancies.[40] The rate of term deliveries in the index study was 42% which is similar to the 46% found in the developed world.[41]

An important concept in twin pregnancies is the optimal length of gestation, which may be shorter in twins compared to singleton pregnancies. By utilising the concept of the prospective risk for fetal death, Khan *et al*., noted that in multiple gestations the prospective risk was equivalent at 37-38 weeks to that of post term singletons.[42] The exact gestation with the best outcome in uncomplicated DC twins is still not clear. It seems that the lower gestational age limit is between 37 weeks 0 days[23] and 38 weeks

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0 days[26] and the upper gestational age limit starts from 38 weeks 0 days onwards[28] with the odds of neonatal death increasing considerably after 40 weeks gestation.[43] In the index study it seems that the best fetal and neonatal outcomes were observed in those delivered after 37 weeks of gestation.

The mean gestational age at delivery of 35 weeks 1 days in the index study is shorter than the 37 weeks 6 days illustrated in the recently sanctioned WHO cross sectional study on the outcomes of twin pregnancies in 21 low- and middle-income countries.[2] Even in comparison to the developed world the twins in the index study were delivered at an earlier average gestation as illustrated by the study from the United Kingdom by Blondel *et al*.[44] Most of the PTDs in the index study were unavoidable with 65% occurring spontaneously despite attempts to suppress labour in most cases. Furthermore, the 35% elective/iatrogenic PTDs were mainly indicated for maternal disease and fetal compromise and thus also unavoidable. A mere 2,3% of all the women in the index population were routinely induced at 38 weeks. This low rate could be explained by the fact that a policy of delivery of uncomplicated DC pregnancies at 38 weeks of gestation was only introduced into our hospital at the time of the index study.

The mean birth weight for all live births in the index population was 2233 ± 602g with a LBW in 67%.Over a third of these infants had LBW due to iatrogenic PTD. This LBW rate is significantly higher than the 50,9% noted in the United States, the 49,9% in Canada and the 50,4% in England-Wales.[44]

The majority of our patients (55%) had a CD of which 26% occurred before the onset of labour. These figures are much higher than the recent cross sectional study in 21 low and middle income countries by Ganchimeg *et al*. showing a 39% CD rate in twins with 17% of the CD performed before the onset of labour.[2] The results of the index study are more in keeping with the increasing CD trend seen worldwide, especially in the developed world. This is illustrated in a UK population database review by Steer *et al*., that shows an increase in the CD rate from 22,5% in 1988 to 60,0% in 2000 with more than half of them being performed electively.[45]

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In their study, Fox *et al*. noted that even the patients at the highest risk for CD have a nearly 50% likelihood for a successful VD.[46]. Their finding of a successful VD in 52,6% of the patients that attempted VD, further supports its safety. Spontaneous onset of labour occurred preterm and before the final assessment of preferred mode of delivery in almost half of the cases in the index study. The successful VD rate could have been significantly higher if there had been an opportunity to select cases more accurately at an earlier gestation.

Many institutions are considering the practice of routine CD for all twin pregnancies for the proposed benefit in neonatal outcome as alluded to in the study by Ganchimeg *et al*.[2] In the index study there was no apparent benefit seen in the neonatal outcomes of the prelabour CD group (4,5% vs. 4,8%). There was a trend towards more maternal morbidity in this group (14% vs. 8%) when compared to those women who experienced labour. Similarly no benefit in planned CD was found by the recently published large randomised trial of planned CD or VD in twin pregnancies by Barrett *et al*.[38] They found only one day difference in the mean gestational age at delivery between the planned VD and planned CD group. This is similar to the index population with no significant difference between the labour group and the indicated CD group (p=0,88) after 28 weeks 0 days of gestation.

Combined vaginal abdominal delivery is viewed as the mode of delivery with the least desirable outcome[35] and its rates vary widely. An increasing trend was noted by Sullivan *et al*., with a rate of 17% in a small retrospective series that was attributed to the decline in obstetric skills and experience.[47] In the index study, 6% of the labour group had a combined delivery which is similar to the 4% found in the study by Akaba *et al*. at a tertiary hospital in Nigeria.[3] Persad *et al*. analysing data of deliveries over 20 years at a maternity hospital in the province of Nova Scotia, Canada found the rate of combined deliveries to be a comparable 4,3%.[33] Nevertheless the combined delivery rate in the index study is higher than reported in a large 10 year review of consecutive twin pregnancies after 32 weeks gestation in a tertiary centre that noted a rate of only 2,2%.[48] This low incidence was speculated to be due to the liberal use of epidural analgesia which was clearly not the practice in the index study.
Consistent with the general obstetric population in the region, the study cohort comprised of a high-risk group of women with a high incidence of hypertension (6%),

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smoking (19%) and HIV (21%). Their increasing age (23% older than 35y) and BMI (42% obese) are both factors that are associated with multiple gestations. Not surprisingly, this led to a high rate of maternal and fetal complications.

The most common maternal antenatal complication noted was hypertensive disorders. A review on hypertensive disorders indicated that twin pregnancies are at increased risk compared to singletons with a relative risk of GHT, pre-eclampsia and eclampsia of 1,2-2,7; 2,8-4,4 and 3,4-5,1 respectively.[49] These significantly higher rates for both GHT and pre-eclampsia in women carrying twins (13% vs. 5-6% in singletons) were also reported in a large prospective study by Sibai *et al*.[50] The index study also illustrated this trend with an incidence of all hypertensive disorders of pregnancy of 30% and 17% specifically developing pre-eclampsia. These figures are considerably higher than an international study done in Thailand where 18,4% of twin pregnancies developed GHT[51] as well as a study from Nigeria where 14,5% developed severe hypertension.[4] The incidence of severe early onset pre-eclampsia of 5% in the index study was lower than the 12,7% reported in the study by Sibai *et al*[50] although the baseline risk of the twin pregnancies in their study was not clear as 61% were multiparous and the previous obstetric outcomes were not given. Of the women developing pre-eclampsia in the index study, 36% required an indicated PTD.

Of the live born infants, two thirds were LBW. This was mainly due to prematurity although a significant number of term live born infants were also SGA (16%). In the index population, 31% of the fetuses were identified as being SGA prenatally (affecting both twins in 13%) which is a much higher rate than the 18% reported from France.[52] Doppler evidence of placental insufficiency was found in 13% of this SGA group, with 24 of these 38 fetuses reaching 34 weeks gestation.

In twins, the median adjusted birth weight beyond 24 weeks is known to be progressively lower than in singletons. The pathophysiological implications of this remain unclear[53,54] but may well lead to potential adverse effects into adulthood similar to those seen in singletons with primary uteroplacental insufficiency.

In 25% of the group of woman delivering after 24 weeks gestation, polyhydramnios was diagnosed on antenatal ultrasound. Although a common finding in twins, this incidence is considerably higher than the 18% reported by Hernandez *et al*., in their retrospective cohort study on DC pregnancies.[55] They also found an associated fetal

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anomaly in 4% of these pregnancies, while the index study found this association in 4/59 (7%). Furthermore, polyhydramnios is a well-documented risk factor for PTL which was a common occurrence in the index study.[56]

The delivery interval between the two babies was more than 10 minutes in 34% of the index population, including the combined deliveries. A statistically significant association was also noted between an intertwin delivery time of more than 20 minutes and an APGAR score of <7 for twin B for those women whom experienced labour. The retrospective study of Leung *et al*., looked at the effect of twin-to-twin delivery interval on the umbilical cord blood gas of the second twin. They clearly noted the increased risk of fetal distress and acidosis when the delivery interval exceeds 30 minutes as occurred in 16% of their patients who experienced labour.[57] The association between a longer intertwin delivery time and poorer outcome for the second twin is illustrated by many other researchers.[58,59] In contrast the results by Rydhstrőm *et al*. support the notion that the interdelivery interval does not influence perinatal mortality of the second twin as long as modern management of the delivery occurs.

These high standards of intrapartum care can often not be met in low to middle income countries due to staff shortages, patient overload and lack of expertise. This is illustrated by the fact that only 1,3% of the women who experienced labour in the index study received epidural analgesia despite a recently published Cochrane review concluding that it provides better pain relief in labour than non-epidural analgesia.[61] There are concerns that epidural analgesia may increase the likelihood of CD[62] although a recent publication by Wong *et al*., did not find this to be the case. In fact they found that it provided better analgesia and resulted in a shorter duration of labour than systemic analgesia.[63] Furthermore, the use of epidural analgesia is associated with a reduced risk for combined delivery.[48] The practise of more liberal use of epidural analgesia and the active management of delivery of the second twin might be advantageous in our setting.

Strengths and limitations of the study

The study has several limitations. The possibility of bias in the inclusion criteria of the study is acknowledged. It is possible that woman who received antenatal ultrasounds received better antenatal care and thus developed fewer complications. A high-risk

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obstetric population also has an increased chance of receiving an antenatal ultrasound.

During the study period, 95 twins of unknown chorionicity were seen but excluded from this report even though a substantial proportion of these could actually have been DC twins. Outcome data were missing I5% of the cohort. The effect on the study results is difficult to determine since missing data may have resulted from uncomplicated DC twins in patients from rural areas being further managed at their local health facility, but could also have been due to unplanned emergency deliveries at their local institutions before their next assessment.

This study benefitted from the detailed review of all cases and thus gives an almost complete representation of dichorionic pregnancies outcomes in a South African setting. This is the first study to the investigators knowledge that addressed the lack of detailed data on twins specified for their chorionicity in low to middle income setting. The comprehensive review of the delivery outcomes specifically the mode and gestational age of delivery might aid in the future planning of more research as well as aiding in the setting of institutional guidelines. Although specific placental histopathological confirmation of chorionicity was not obtained in this study, no uncertain chronicity twin pregnancy was enrolled in this review.

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7. Conclusion

DC twin pregnancies were delivered at an earlier gestation and had a higher CD rate than reported in other developing countries. Similar to the available literature there was a higher incidence of antenatal maternal and fetal complications compared to singletons. Due to the high preterm birth rate (due to complication or spontaneous preterm labour) as well as that most women delivered before 38w gestation it was not possible to define the management of uncomplicated DC twin delivery time and mode. Additionally the only aspect that could be noted to have a significant impact on the outcomes of this DC twinsets were the longer intertwin delivery time and higher rate of combined deliveries were observed in the study population. This could possibly be prevented in limited resource countries with more liberal use of epidural analgesia and active management of the delivery of the second twin during vaginal delivery.

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8. Appendices

Appendix A – Data Collecting Sheet

DCDA Twins

				Number -		Date -	
BASELINE							
1	Age *(y)*	xx					[.....]
2	G	P	T1	T2	E		[...../...../...../...../.....]
3	Weight *(kg)*	xxx					[.....]
4	Height *(cm)*	xxx					[.....]
PRE-EXISTING Hx							
5	Medical	0.Nil, 1. CHT, 2. DM, 3. Epilepsy, 4. Asthma, 5. HAART, 6.Thyroid Dysfx, 7. Other					[.....]
	Medication	_____					
6	Surg. *(C/S)*	0.Nil, 1. Multiple C/S, 2. Single C/S LUS,3. Single C/S Other,4. Single C/S Unknown					[.....]
7	Surg. *(Other)*	0.Nil, 1.Uterine , 2.Cervical, 3.Ectopic, 4. Other					[.....]
8	Familial	0.No twins, 1.Twins					[.....]
9	Social *(Current)*	0.Nil, 1. Tabacco, 2. Alcohol, 3. Tik (MA), 4. Other social drugs					[.....]
PAST OBSTETRIC Hx							
10	Time since del.*(y)*	0<1, 1=1 2=2 etc					[.....]
11	Prev. earliest del. *(wks)*	xxw					[.....]
12	Mom Compl	0. Nil, 1.GHT, 2.PreE, 3. Abruptio, 4. GDM, 5. PTL, 6. PPROM, 7. Other					[.....]
13	Fetal Compl	0. Nil, 1. Twins, 2. Anomalies, 3.SGA, 4. SB, 5. NND, 6.Other					[.....]
		Anomaly	_____				
ANTENATAL							
General Care							
14	Booking date	yyyy/mm/dd					[...../...../.....]
15	LNM date (sure)	yyyy/mm/dd					[...../...../.....]
16	1st SFH *(cm)*	xx					[.....]
17	Date of 1st SFH	yyyy/mm/dd	yyyy/mm/dd				[...../...../.....]
18	Booking SBP *(mmHg)*	xxx					[.....]
19	Booking DBP *(mmHg)*	xxx					[.....]
20	Syph. screen	0.Negative, 1.Rx, 2.Not Rx					[.....]
21	Sensitisation	0.None, 1.Rh, 2.Other					[.....]
22	Hb (g/dl)	xx.x					[.....]
23	HIV	0. Negative, 2. PMTCT, 3. HAART					[.....]
24	HIV 32wks re	0.No, 1. Neg, 3. Positive					[.....]
25	HIV: CD4	xxx					[.....]
26	ASB	0.Negative, 1.Rx, 2.Not Rx, 3. Not done					[.....]
U/S General							
27	Date of **very first scan(FS)**	yyyy/mm/dd					[...../...../.....]
28	Gest at **FS** *(wks)*	xxwxd					[.....]
29	Calc of GA	1. LNMP+EUS, 2. LNMP+LUS, 3. EUS, 4. LUS (Acc), 5. LUS (Not Acc)					[.....]
30	Ind for FS	1. Routine, 2. Increase SFG, 3. Risk Factor, 4. Complication 5. Other					[.....]
31	Date of first **formal** scan			yyyy/mm/dd			[...../...../.....]
32	Gest. at first formal scan *(wks)*			xxwxd			[.....]

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33	Ind for TBH	1. Routine, 2. Fetal abn, 3. Growth abn, 4. SF abn, 5. Maternal, 6. Other	[.....]
34	DP ever **[A]** *(mm)*	xxx	[.....]
35	GA at DP**[A]** *(wks)*	xxwxd	[.....]
36	DP ever **[B]** *(mm)*	xxx	[.....]
37	GA at DP**[B]** *(wks)*	xxwxd	[.....]
38	**Anomalies**	0. None, 1. Minor, 2. Major	[.....]
39	**UA**-RI **[A]** Worst *(value)*	x.xx	[.....]
40	UA-RI [A] Worst *(code)*	1. <50, 50-75, 75-95, Absent	[.....]
41	GA at W-UAD-RI**[A]** *(wks)*	xxw	[.....]
42	**UA**-RI **[B]** Worst *(value)*	x.xx	[.....]
43	**UA**-RI **[B]** Worst *(code)*	1. <50, 2. 50-75, 3. 75-95, 4. Absent	[.....]
44	GA at W-UAD-RI**[B]** (wks)	xxw	[.....]
45	GA first Cx Lx **< 20mm** *(wks)*	xxw	[.....]
46	**Cx Length** shortest *(mm)*	xx	[.....]
47	GA at Shortest CxL *(wks)*	xxw	[.....]

LAST US

48	Date	yyyy/mm/dd	[...../...../.....]
49	GA *(wks)*	xxwxd	[.....]
50	Leading twin	1. Ceph, 2. Breech, 3. Other	[.....]
51	**Growth**	1. Both N, 2. One IUGR, 3. Both IUGR	[.....]
52	First Gest IUGR noted *(wks)*		[.....]
53	**Placenta**	1. High, 2. Low then N, 3. Minor Praevia, 4. Major Praevia	[.....]
54	EFW **[A]** *(gr)*	xxxx	[.....]
55	EFW **[B]** *(gr)*	xxxx	[.....]
56	DP **[A]** *(mm)*	xxx	[.....]
57	DP **[B]** *(mm)*	xxx	[.....]
58	UA RI **[A]** (val	x.xx	[.....]
59	UA RI **[A]** (co	1. <75, 2. 75-95, 3. >95, 4.AEDF, 5.REDF	[.....]
60	UA RI **[B]** (val	x.xx	[.....]
61	UA RI **[B]** (co	1. <75, 2. 75-95, 3. >95, 4.AEDF, 5.REDF	[.....]
62	MCA PI **[A]** value	x.xx	[.....]
63	MCA PI **[A]**	1. normal, 2. abnormal	[.....]
64	MCA PI **[B]** value	x.xx	[.....]
65	MCA PI **[B]**	1. normal, 2. abnormal	[.....]
66	Final opinion	0. Healthy, 1.Fetal compromise (non-significant), 2.Fetal Com. (significant warrant	[.....]

Complications: maternal

67	HDP	0.Nil, 1. GHT, 2. EOPE(-compl), 3. EOPE (+compl), 4. LOPE (-compl), 5. LOPE (+com	[.....]

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68	G-Urinary	0. Nil, 1. GPU, 2. Cystitis, 3. PN	[.....]
69	DM	0. Nil, 1. GDM on diet, 2. GDM on oral meds, 3. GDM on insulin	[.....]
70	Other	0. Nil, 1.VTE, 2.Severe anemia, 3.Abruptio, 4.Other	[.....]
Complications: Fetal			
71	TPTL @ Gest *(wks)*	xxwxd	[.....]
72	PTL @ Gest *(wks)*	xxwxd	[.....]
73	PPROM @ Gest *(wks)*	xxwxd	[.....]
74	Thr MC @ Gest *(wks)* *[< 24w]*	xxwxd	[.....]
75	APH @ Gest *(wks)* *[≥ 24w]*	xxwxd	[.....]
76	Single IUFD @ Gest *(wks)*	xxwxd	[.....]
Complications: Adm. Antenatal			
77	Total No of Admissions	xx	[.....]
78	Total No of In-pt days	xx	[.....]
79	Indications	1. PPROM, 2. PTL (incl. TPTL), 3. APH, 4. Uro infections,5. Medical work-up	[.....]
80	BMZ dosages*(nr)*	xx	[.....]
81	Supression	0.No, 1.Yes	[.....]
INTRAPARTUM			
82	Date of delivery	yyyy/mm/dd	[...../...../.....]
83	Gestation at delivery *(wks)*	xxwxd	[.....]
84	Mode of delivery	1. NVD, 2. C/S, 3. Combined	[.....]
			[.....]
Labour			
85	Onset	1. Spontaneous, 2. Elective IOL, 3. Elective CS, 4. Termination	[.....]
86	Ind. elective (	1.Routine 38w, 2.Mat. disease, 3.Fetal, 4.Prev CS, 5. Praevia, 6. Other	[.....]
87	IOL	1.Miso, 2.Prepidil, 3.Oxytocinon, 4.AROM, 5.Bulb Catheter	[.....]
88	Action line reached	1. Yes, 2. No, 3. No notes	
	Action taken		
89	Aug. stage 1	1. Yes, 2. No, 3. No notes	[.....]
90	Epidural	1. Yes, 2. No, 3. No notes	
91	Order*(at ons*	1. CC, 2.CB ,3.BC, 4. BB, 5. CT, 6. BT, 7. TC, 8. CT, 9. TT	[.....]
92	Time of delivery A *(h/min)*	xxhxx	[.....]
93	Time of delivery B *(h/min)*	xxhxx	[.....]
94	Delivery interval >10min	0. No, 1. Yes xxx	[.....]
	VAGINAL		
95	Assisted del. **A**	0. None, 1. Vacuum, 2. Forceps	[.....]
96	Assisted del. **B**	0. None, 1. Vacuum, 2. Forceps	[.....]
97	Complications	0. Nil, 1. Perineal tear I-II, 2. Perineal tear III-IV, 3.Ret Plac, 4.Atonic uterus, 5.Cervical Tear, 6.PPH, 7.Shoulder distocia, 8.Other	[.....]

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CAESAREAN

98	For twin	1. Both, 2. Twin B	[.....]
99	Ind. for c/s	0. Nil, 1.Failed IOL, 2.FD, 3.Prol. labour, 4.CPD, 5. Abruptio, 6.Breech leading twin,	[.....]
100	Complications	0. Nil, 1. Surgical (GI or GU), 2. PPH, 3. Blynch (Comp Sutures), 4.Hysterectomy, 5.	[.....]

POSTNATAL

Neonatal

			A	B	
	Baby Folder Number				
101	**Baby A**: BW(g)	xxxx			[.....]
102	Apgars (1/5/10 min)	x/x/x			[..../..../....]
103	Sex	1.M, 2.F			[.....]
104	Demise	0. Nil, 1. FSB, 2. MSB, 3. ENND, 4. Other			[.....]
105	Admission	0. Nil, 1. NNICU, 2. GW			[.....]
106	Indication	0.Healthy Lodger, 1. WT, 2.HGT Mx, 3.Sepsis, 4.Jaundice, 5. Feeding, 6.Resp, 7. Otl			[.....]
107	Date of D/C	yyyy/mm/dd			[...../...../.....]
108	**Baby B**: BW(g)	xxxx			[.....]
109	Apgars (1/5/10 min)	x/x/x			[..../..../....]
110	Sex	1.M, 2.F			[.....]
111	Demise	0. Nil, 1. FSB, 2. MSB, 3. ENND, 4. Other			[.....]
112	Admission	0. Nil, 1. NNICU, 2. GW			[.....]
113	Indication	0.Healthy Lodger, 1. WT, 2.HGT Mx, 3.Sepsis, 4.Jaundice, 5. Feeding, 6.Resp, 7. Otl			[.....]
114	Date of D/C	yyyy/mm/dd			[...../...../.....]

Maternal

115	Total Days Hosp (days)	xxx	[.....]
116	PP-general	0. Nil, 1. Blood T/F, 2. Evac for RPOC, 3. VTE, 4. Anaesthesia, 5. Relook lap, 6. Othe	[.....]
117	PP-infection	0. Nil, 1.Wound inf., 2.Endometritis, 3.Mastitis, 4.UTI, 5.Other	[.....]
118	Admitted	0. Nil, 1. General Ward, 2. HDU, 3.ICU	[.....]
119	Re-adm in TBH	0. Nil, 1. BP, 2. HGT, 3. Anemia (TF), 3. Wound-inf, 4. Puer.sepsis, 5. VTE 6. Other	[.....]

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