A PROSPECTIVE STUDY OF THE INDUCTION OF LABOUR AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Dr Hatel Laloo

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Masters in Medicine (MMed)

Johannesburg 2018

DECLARATION

I Hatel Laloo declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Masters in Medicine (MMed) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Signature of candidate)

11 day of April 2018 in Johannesburg

PRESENTATIONS ARISING FROM THIS STUDY

1) September 2016- Presentation at Departmental Research day at Chris Hani Baragwanath Academic Hospital
2) March 2017- Perinatal Priorities – Mpekweni, East London

ABSTRACT

Background

Induction of labour implies the artificial initiation of regular uterine contractions before the onset of spontaneous contractions with the purpose of achieving a vaginal delivery.
This study aimed to compare the use of oral misoprostol and vaginal dinoprostone to determine differences in the labour process and the delivery methods. Maternal and fetal outcomes were also compared.

Methods

This is a prospective cross-sectional analytical study using medical record review at the Rahima Moosa Mother and Child Hospital (RMMCH) in Newclare, Johannesburg.
This study included all women undergoing the induction process, who met inclusion criteria from 01 January 2016 to 30 April 2016.

Results

This study included 95 women. Forty-nine women received dinoprostone and 46 women received oral misoprostol. There was minimal heterogeneity between the demographics of the two groups. The differences in the indications for induction were statistically significant (p = 0.001). There was no statistical difference in the time from induction to delivery (p= 0.18), the duration of labour (p=0.10) or in the time from induction to onset of labour (p= 0.37). There was a caesarean section rate of 32.7% in the dinoprostone group and 43.5% in the oral misoprostol group (p=0.30). There was no statistical significance between fetal and maternal outcomes.

Conclusions

This study yielded no difference in the labour process, time to delivery, or maternal and fetal complications between the two groups. Labour was initiated in more patients in the dinoprostone group and dinoprostone resulted in fewer c/s than misoprostol, however this was not statistically significant. There was no difference in neonatal and maternal outcomes.
The use of dinoprostone or misoprostol is therefore equally effective in our setting. A larger study or RCT is recommended to adequately assess neonatal and maternal complication rates.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people

1. Dr S A Bhoora, my supervisor for her continuous support and patience through the process of the MMed
2. Dr P Naidoo for assistance with statistics
3. Dr A Bentley for assistance with statistics and calculations
4. Dr P Mjuleki for assistance with collection of data

TABLE OF CONTENTS

List of Tables

List of Figures

List of abbreviations

ACOG	American College of Obstetricians and Gynecologists
AFI	Amniotic fluid index
APH	Antepartum haemorrhage
BMI	Body mass index
c/s	Caesarean section
CPD	Cephalopelvic disproportion
EUS	Early ultrasound
FSB	Fresh stillbirth
GA	Gestational age
GBS	Group B streptococcus
GDM	Gestational diabetes mellitus
HT	Hypertension
NICU	Neonatal Intensive Care Unit
IOL	Induction of labour
IUGR	Intrauterine growth restriction
kgs	Kilograms
LNMP	Last normal menstrual period
LUS	Late ultrasound
MAS	Meconium aspiration syndrome
MSB	Macerated stillbirth
NICE	The National Institute for Health and Care Excellence
NST	Non- stress test
NVD	Normal vaginal delivery
PCR	Polymerase chain reaction
PG	Prostaglandin
PGE2	Prostaglandin E2
PPH	Postpartum haemorrhage
PROM	Prelabour rupture of membranes
RCT	Randomized control trial
RDS	Respiratory distress syndrome
RMMCH	Rahima Moosa Mother and Child Hospital
RR	Relative risk
SA	South Africa
SOGC	Society of Obstetricians and Gynaecologists of Canada
TTN	Transient tachypnea of the newborn

ug	Micrograms
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Definitions of Medical terms

Body mass index (BMI)	Weight/height^2 (kg/m^2)
Failed induction	Failure to establish labour after two 24 hour cycles of the induction agent
Category 3 trace	Abnormal fetal heart rate tracing which includes: absent baseline fetal heart rate variability with recurrent late deceleration or recurrent variable decelerations or a bradycardia or a sinusoidal pattern
Labour	The onset of regular painful uterine contractions with either a show, spontaneous rupture of membranes and/or cervical changes
Macrosomia	Birth weight more than 4 000g
Obese	BMI of more than 30 kg/m^2
Prolonged pregnancy	Pregnancy extending beyond 294 days or 42 weeks measured from the last normal menstrual period
Randomized control trial (RCT)	A study in which participants are allocated at random to an intervention or treatment modality
Midwife obstetric unit (MOU)	A 24-hour primary health care facility for pregnant women, managed by advanced midwives. Services include antenatal care, intrapartum care, postpartum care, management of emergencies and referral to secondary or tertiary hospitals.

1 INTRODUCTION

"It is not only that we want to bring about an easy labor, without risking injury to the mother or the child; we must go further. We must understand that childbirth is fundamentally a spiritual, as well as a physical, achievement. The birth of a child is the ultimate perfection of human love." Dr. Grantly Dick-Read (1).

Induction of labour (IOL) is a common procedure in obstetric practice (2). Induction of labour implies artificial initiation of regular uterine contractions before the onset of spontaneous contractions with the purpose of achieving a vaginal delivery (3, 4). Induction is thought to be less efficient and has an increased intensity of pain compared to spontaneous labour thus requiring more analgesia and resulting in more assisted deliveries (5). Induction occurs in two stages: cervical ripening followed by induction of uterine contractions (5). This process is also dependent upon the cervical status at the time of induction (5, 6). Induction of labour is indicated where benefits of delivery outweigh the potential harm to both mother and fetus (2, 3, 7).

2 LITERATURE REVIEW

2.1 Prevalence

In the United States of America (USA), IOL accounted for approximately 22% of all deliveries in 2009; more than double of that in 1990 (8). In a cross sectional study involving 83 437 deliveries in 16 countries across Africa between 2004 and 2005, the average rate of IOL was 4.4% (range 1.4%-6.8%) (7). The lower rate of IOL rates in developing countries was thought to be due to lack of familiarity, appropriate medications, monitoring capacity, necessary staff in certain facilities and the lack of operating facilities in primary care centers to perform caesarean sections (c/s) should complications during the induction process occur. Due to these limitations, IOL was not routinely performed (7). In 2012, there was an increase in induction rates to approximately 25% in both developed and developing countries (9). This is due to the rise in medically and obstetrically related inductions, availability of better cervical agents and resources to allow induction (9).

2.2 Physiology of labour

2.2.1 The uterus

During pregnancy, the uterus softens and expands to accommodate the fetus, while the cervix is closed to sustain the pregnancy (3). The uterus is mainly composed of smooth muscle, the myometrium which is pivotal in the role of uterine contractions (10). Myometrial contractions are brought upon by phosphorylation of actin and myosin, which is initiated by oxytocin and prostaglandin (PG) F_2 alpha (10).

2.2.2 The cervix

Khan et al described the inpatient process of cervical ripening and cervical changes as a psychological burden for patients due to prolonged time spent in a hospital setting (11). For successful labour, the cervix has to become a soft and manipulative structure that can efface or shorten (5). Unlike the uterus, the cervix consists of collagen fibers and glycosaminoglycan that decrease in number allowing softening, ripening, dilatation and disarrangement of the collagen fibers of the cervix (3). Interleukin 8 and monocyte chemotactic protein-1 recruit neutrophils and monocytes for cervical ripening (5). These secrete collagenase and elastase

that remodel the cervix (5). Prostaglandins vasodilate cervical capillaries and increase permeability to neutrophils (3, 5). These promote degradation of collagen fibers, therefore promoting cervical softening and effacement (3, 5).

2.2.3 Control pathways

Increases in oxytocin production from the maternal posterior pituitary gland mediate the onset of contractions (3, 10). This increase production commences in the days preceding labour (10). With the onset of labour, there is an increase in oxytocin receptors within the uterus and local oxytocin production in the uterine decidua and fetal membranes (10). All these combined factors bring about the transition from the antenatal to the intrapartum period.

2.3 History

Hippocrates first described IOL with stimulation of the mammary glands and mechanical dilatation of the cervix (12, 13). Induction of labour was initially used to deliver intrauterine fetal deaths (IUFD) as an attempt to expedite delivery in order to reduce the threat to maternal health (14). From the second to the seventeenth century, mechanical methods together with homeopathic medications were commonly used (13). In the early twentieth century, observations were made that the extracts from the posterior pituitary gland caused uterine contractions, but with side effects (13). Theobald described intramuscular, subcutaneous and then intravenous infusion of oxytocin in 1949 (13). Prostaglandins were first described in the 1960s for IOL and most recently misoprostol has been accepted as a safe measure for IOL (13).

2.4 Methods of induction of labour

2.4.1 Mechanical methods

Mechanical methods included uterine bougies, stomach tubes, De Ribe's bag, forced rapid dilatation of the cervix and vaginal c/s (15). In 1942 amniotomy became the method of choice and in 1955 it was used together with other mechanical methods (15). A Cochrane review by Jozwiak et al, on mechanical methods included 9 722 women (16). Methods included laminaria tents, balloon catheters and extra amniotic fluid infusion. Advantages were reduced costs compared to hormonal methods, decrease side effects, decreased hyperstimulation and easier storage (16). Mechanical methods compared to hormonal methods did not decrease the c/s rate or the number of women who delivered within 24 hours (16).

2.4.2 Alternative/ Complementary medicine

Castor oil, seed of the plant *Ricinus Communis*, was used for IOL in the 1930s but was abandoned by 1961 due to its' propensity to produce severe diarrhoea (15). A Cochrane review was inconclusive about the effectiveness but supported the high side effect profile (17). There is also a possibility of castor oil causing teratogenic effects similar to ' fetal hydantoin syndrome'; a syndrome related to the use of epileptic drugs associated with intrauterine growth restriction, cranial and limb deformities (18).

Acupuncture is one of the oldest methods described and is a safe procedure (19). In a double-blinded randomized control trial (RCT) by Modlock et al; 125 women with post term pregnancies were randomized to either acupuncture or "sham" acupuncture (19). "Sham" acupuncture was the use of a needle where the needle retracted and did not penetrate the skin compared to the needle in the acupuncture group that did penetrate the skin (19). This showed no effect of acupuncture on induction (19).

Hypnosis is a relaxation technique, which was commonly used to calm a labouring woman (20). There have been no RCT's describing the benefits or risks of hypnosis and this needs to be studied further (20). It is postulated that hypnosis may delay standard care and should be individualized (20).

Breast stimulation, membrane sweeping and sexual intercourse have also been described. Breast stimulation is thought to trigger the release of oxytocin and membrane sweeping increases PG production (21, 22). Sexual intercourse was thought to have been an alternative method to IOL as semen contains PGs, but this was shown to be ineffective (21, 22).

2.4.3 Pharmacological methods

Vaginal isosorbide mononitrate is a nitric oxide donor, used mainly for patients with angina pectoris (23). Nitric oxide synthase isoforms increase in the cervix preceding labour hence thought that nitric oxide donors could be used as cervical ripening agents (23). Compared to placebo, vaginal isosorbide mononitrate showed no difference in labour outcome, c/s rate or neonatal outcomes (24). It had a high side effect profile causing severe headaches (24).

Hyaluronidase in an injectable form was thought to increase cervical ripening as hyaluronic acid increased the tissue water content (25). This drug when compared to a placebo showed a decrease in c/s rate, decrease use of oxytocin for augmentation and increased cervical favourability after 24 hours with no maternal or neonatal adverse outcomes (25). This method was considered invasive and less invasive methods were preferred (25).

Oxytocin is a hormone produced by the maternal posterior pituitary gland and stimulates uterine contractions during labour (3, 10, 21). Initially oxytocin was used on its own but in 1990 it was to have better effects on labour outcomes as an adjunct to PGs or with amniotomy (15).

Oestrogen, in the form of teratogenic Stilboestrol or Hexoestrol, was first described in 1942 mainly for patients' with an IUFD or for medical termination of pregnancy (21, 24). It was primarily used in these patients, as there was no concern for neonatal outcomes in large doses. When compared to placebo, oestrogen showed no difference in labour or delivery outcomes (24).

Corticosteroids have also been suggested as induction agents but studies remain inconclusive about their effectiveness in inducing labour (26).

Relaxin is a protein hormone produced by the corpus luteum (27). Kelly et al, in a systematic review of four studies including 267 women showed no difference in c/s rate when relaxin was compared to placebo (15.3% vs 14.2%) (27). Further studies are needed to evaluate the full effects of relaxin.

Mifepristone is an oral antiprogestin that has a recognized role in first and second trimester medical termination of pregnancy (28). It has been studied as an inducing agent in the third trimester (28). In a Cochrane systematic review by Hapangama and Neilson, ten trials including 1 108 women, compared mifepristone to placebo (28). Those induced with mifepristone were more likely to achieve labour after 48 hours of induction, had a decrease need for oxytocin augmentation, a decreased rate of c/s but an increased rate of assisted delivery. Different doses ranging from 50mg to 600mg were studied with the lowest effective dose being 200mg for cervical ripening (28). Fetal heart rate changes were observed with mifepristone but no differences in neonatal outcomes (28). Even though mifepristone may be an effective inducing agent, it is costly and not readily available in the government setting in South Africa (SA).

2.5 Maternal characteristics

Induction of labour is indicated where the risks to continue the pregnancy outweigh the benefits (9, 12). Factors that influence the risk: benefit ratio includes gestational age (GA), fetal lung maturity, clinical condition, cervical factors and demographics (9).

2.5.1 Parity

Parity is defined as the number of previous viable pregnancies where viability is specific to a country or institute (3). Nulliparous women were thought to have a higher rate of c/s, however, studies that concluded this included patients with medical conditions and unfavourable cervices, hence a bias (29). In an analytical study by Levine et al, both nulliparous and multiparous women had a increased c/s rate when induced compared to spontaneous labour (29). Nulliparous women were likely to have a prolonged first stage of labour compared to multiparous women who have a prolonged second stage of labour ($p=0.04$). Multiparous women had a higher rate of vaginal delivery than nulliparous women (97% vs 80%,$p < 0.001$) (29). Ivars et al showed that modifying the Bishop's score to include

parity, significantly improved the prediction of success of IOL (30). This implies that parity plays an important role in successful induction (29, 30).

2.5.2 Obesity

The World Health Organization (WHO) defines overweight as a body mass index (BMI) of greater than 25 kg/m^2 and obesity as a BMI of more than 30 kg/m^2 (31). In SA, 40% of women are obese (32). According to the Saving Mothers report from 2014-2016, obesity was associated with the increased risk of thrombosis, diabetes, macrosomic babies (>4000g), difficult c/s, postpartum haemorrhage (PPH) and post c/s sepsis (33).

A prospective study by Vinturache et al, including 1 996 women, showed that obesity increased the rate of IOL with no difference in induction method; 49% of obese women had IOL (34). These were attributed to obese women having more increased pregnancy-related complications such as pre-eclampsia, macrosomia and diabetes (34). Obese women had a significantly higher c/s rate compared to normal weight women (21.1% vs 11.2%) (34). There was no difference in the duration of labour. Obesity contributed to the increased rates of IOL, poor progress in labour, increased c/s rates, augmentation and increased PPH (34).

This differed in a study by Arrowsmith et al where PPH rates were similar in all BMI categories but agreed that obesity resulted in an increased c/s rate (35).

2.5.3 Indications for induction of labour

2.5.3.1 Post term pregnancy

According to the WHO and The American College of Obstetricians and Gynecologists (ACOG), post term pregnancy is defined as a pregnancy extending beyond 294 days or 42 weeks measured from the last normal menstrual period (8, 36). This is known as Naegele's rule (8, 37). Post term pregnancy is the most common indication for IOL (8, 37, 38). Globally, the prevalence of post term birth is 5 to 10% and varies between countries with some studies stating an incidence of 4 to 22% (39-41). Arrowsmith et al in the United Kingdom (UK) showed that the incidence of post term pregnancy is 22.3% (35). In the United States of America (USA) the incidence of post term pregnancy is approximately 7% (40). Risk factors included advanced maternal age, Caucasian, obesity and primigravidas (41). In

Pakistan the incidence is quoted at 21% (39). Arif et al explained risk factors such as obesity, excess fish consumption and a male fetus contributed to post term pregnancy (39). In New South Wales the incidence of post term pregnancy is 13% (39, 41). Dekker et al attributed this low incidence in New South Wales to patients being induced earlier than 41 weeks gestation (41).

Management of IOL during pregnancy relies on accurate estimation of gestational age (42). Methods for determining GA include the last normal menstrual period (LNMP), clinical assessment of the symphysis-fundal height and ultrasound biometry (42). The use of LNMP for dating the pregnancy may have many faults owing to incorrect recall of dates, irregularity of the menstrual cycle, anovulatory cycles and confusion in whether an atypical light bleed may be menstruation or not (43).

Developed countries have shown a lower incidence of post term pregnancies compared to developing countries (7% vs 10-16%) due to the accessibility of early ultrasound (ultrasound before 23 weeks) and accurate dating (40, 44). A study in Tygerberg, Western Cape South Africa, showed that routine ultrasound between 18-23 weeks GA reduced their incidence of preterm pregnancies from 16.7% to 12%, and post term pregnancies from 10.8% to 8.1% (45). This was also proven by a similar follow up study at Tygerberg Hospital comparing different dating methods (42). This study at Tygerberg Hospital comparing different dating methods showed that only 56% of women were sure of their LNMP and the LNMP was only concordant with ultrasound between 18-23 weeks GA in 35.6% of patients. It also showed that the incidence of preterm and post term pregnancies (4.7% to 1.6%) was significantly decreased in those that had an early ultrasound. Differences in the actual date of delivery and expected date of delivery were largest when the LNMP was used (42). Ultrasound improved the accuracy of the date of delivery from 27% to 42% compared to clinical measurement of the symphysis-fundal height and LNMP. This study concluded that in a low resource setting where patients book late (after 23 weeks), dating with ultrasound is better for estimating GA compared to LNMP and clinical methods (42). A RCT done in Johannesburg also showed a lower rate of IOL in those who had ultrasound between 18-23 weeks (1.6%) versus the control (3.6%) (46).

The concept of inducing post term pregnancies owes to the increased risk of perinatal morbidity and mortality (41). Yudkin proved this finding in an exponential curve of stillbirths (Figure 2.1), which showed that the stillbirth rate is at a low point towards the beginning of the term period and then rises thereafter (41, 47). In a prospective cohort in New York City over a three year period (1987-1989) including 2 454 stillbirths, the incidence of stillbirths increased progressively after 40 weeks gestation (38). The incidence was 2.11 per 1000 live births at 40 weeks and 2.66 per 1000 live births at 43 weeks (38). Other studies have shown the risk of stillbirths at 42 weeks to range from 1.55 to 4.36 per 1000 live births in the 1980s and 1990s (41). A better understanding of IOL led to a reduction in stillbirth rates in the 2000s, 0.6 to 1.17 per 1000 live births (41).

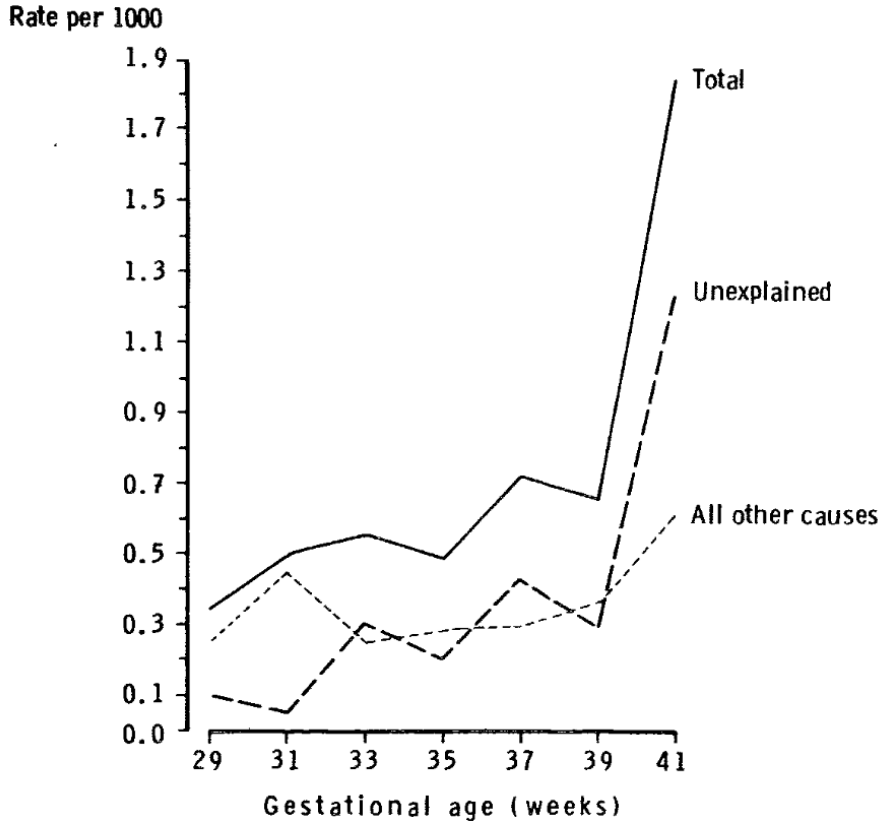


Figure 2.1 Yudkin's curve of stillbirths per 1000 undelivered fetuses for two weekly gestational age

Other fetal complications of post term pregnancy included macrosomia, shoulder dystocia and neurological sequelae (48). Maternal complications include abnormal labour, failed induction, perineal lacerations, sepsis and PPH (48).

Due to these risks and complications, IOL is recommended between 41 and 42 weeks gestational age for healthy women with no associated comorbidities (41, 48). There is currently a RCT underway, the Swedish Post-Term Induction Study (SWEPIS), that aims to establish if IOL at 41 weeks is superior to IOL at 42 weeks (37). This study aims to randomize women across various hospitals in Sweden (with 65 000 deliveries per annum) to either IOL at 41 weeks or expectant management and induction at 42 weeks. According to the protocol of SWEPIS, larger randomized trials are needed for a definitive answer on induction in post term pregnancies since most studies on post-term pregnancies are observational (37). The SWEPIS study will compare neonatal morbidity and mortality in this regard. The study will be completed in August 2018.

Women who decline IOL after 42 weeks should have counseling, twice-weekly fetal non-stress test (NST) monitoring, amniotic fluid index (AFI) measurements or a fetal biophysical profile (2, 4).

2.5.3.2 Prelabour rupture of membranes

Term prelabour rupture of membranes (PROM) occurs in 8 to 10% of pregnant women (49). Spontaneous onset of labour within 12 hours occurs in 79% of women and 95% within 24 hours regardless of cervical favourability (50). Delayed or prolonged labour can occur in those that do not spontaneously labour within 7 days after PROM (50).

Prelabour rupture of membranes is associated with increased maternal and fetal sepsis, umbilical cord compression, and placental abruption; thus, active management is preferred in patients with PROM provided that the benefits of delivery outweigh the risks of prematurity (50-52).

A Cochrane review of 12 trials including 7 000 women showed that active management did not increase the c/s rate or rate of vaginal births, but decreased the rate of chorioamnionitis and endometritis (50). The largest trial used in the Cochrane review was by Hannah et al (52). The Term PROM study, a double-blinded RCT including 5 041 women, compared

expectant to active management. Active management was immediate IOL with oxytocin or prostaglandin E2 (PGE2) gel and expectant management was IOL after 4 days of PROM (52). There was no difference in c/s rate or rate of neonatal sepsis (52). The rates of chorioamnionitis were reduced with oxytocin. Women also preferred a quicker birth time from rupture of membranes (52). The National Institute for Health and Care Excellence (NICE) guidelines recommend IOL 24 hours after PROM due to increased risks of chorioamnionitis (2).

Colonization by Group B streptococcus (GBS), *Streptococcus Agalactiae,* occurs in 10 to 30% of pregnant women (53). GBS is a major cause of neonatal morbidity and mortality. The USA recommends universal screening of GBS between 35 and 37 weeks gestational age with rectovaginal swab specimens and treatment with penicillin (53). This has not yet been implemented in SA as it is not economically viable and there are no studies that address that screening for GBS has any impact on neonatal morbidity and mortality (54). Prolonged rupture of membranes and intra-amniotic infection in women colonized with GBS are among the risk factors of early neonatal GBS infection (53).

A prospective study in Australia included 574 women with PROM and induced only women who were GBS polymerase chain reaction (PCR) positive (55). Those that were PCR negative were managed as outpatients, with 80.6% of these women either going into spontaneous labour or being induced within 72 hours. There were no cases of neonatal GBS infection, maternal chorioamnionitis or postpartum endometritis in mothers who were GBC PCR positive (55). A protocol for GBS screening is yet to be implemented in SA provincial and academic hospitals. There is a study at Chris Hani Baragwanath Academic Hospital in Soweto, Gauteng that is currently in progress to assess the incidence of GBS within the population and neonatal and maternal outcomes.

Commonly used drugs in PROM include oral misoprostol, vaginal dinoprostone and oxytocin (52). A RCT in the United Kingdom (UK), including 758 women with PROM, showed that low dose oral misoprostol has better outcomes than vaginal dinoprostone (56). Misoprostol induction required less use of oxytocin, less need for epidural analgesia and decreased the rate of c/s for poor progress. There were higher rates of uterine hyperstimulation and tachysystole compared to dinoprostone (56, 57). Another study showed that misoprostol, compared to dinoprostone, resulted in more vaginal deliveries within 12 hours and a shorter induction-to-delivery interval (58).

Oral routes of misoprostol were preferred over vaginal routes of dinoprostone due to the following factors (56, 58):

- Easy administration
- Avoided frequent vaginal examinations
- Allowed easy mobilization of the mother
- Lowered the risk of maternal and neonatal sepsis
- Better efficacy than a vaginal drug as the vaginal drugs could be expelled with the draining of amniotic fluid.

2.5.3.3 Hypertension in pregnancy

Hypertension (HT) is one of the leading causes of maternal deaths accounting for 14.77% of maternal deaths in SA (33). Due to this, IOL has been an option for management of patients with gestational hypertension or pre-eclampsia. This is to prevent severe maternal and neonatal complications such as HELLP (Hypertension, Elevated Liver enzymes, Low Platelets) syndrome, placental abruption, maternal death and neonatal asphyxia (59).

A RCT, the Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT), was published in 2009, including 756 patients that compared expectant to active management in hypertensive women at term (59). It showed that IOL decreased poor maternal outcomes and progression of the disease (RR 0.71, $p < 0.0001$). The induction group had a decreased c/s rate, although this was not statistically significant (RR 0.75, $p < 0.085$). There were no differences in neonatal outcomes.

Intrauterine growth restriction (IUGR) is one of the complications of HT in pregnancy and this led to the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT); a RCT comparing expectant to active management in 650 patients with HT and suspected IUGR (60). The trial showed no difference in adverse neonatal outcomes, rates of c/s or assisted delivery. It did support the HYPITAT trial that IOL decreased the progression of gestational HT to pre-eclampsia ($p < 0.005$). Therefore, IOL is supported in IUGR fetuses to possibly decrease the incidence of IUFD (60).

2.5.3.4 Diabetes in pregnancy

Gestational diabetes mellitus (GDM) has been increasing in prevalence with the increase in obesity (61). Gestational diabetes mellitus increases the risk of macrosomia, birth complications, IUFD at term and pre-eclampsia (61, 62). Timing of delivery is crucial in women with GDM due to neonatal morbidity and mortality (62). The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed the higher the glucose levels, the higher the frequency of large for gestational age fetuses, which may lead to macrosomic babies (63). Macrosomia is associated with shoulder dystocia and an increased risk of c/s (64). Infants of mothers who have GDM are also subjected to neonatal hypoglycaemia (63).

The timing of delivery is dependent on the risk of neonatal morbidity and mortality versus the increased risk of stillbirths (62). It is recommended that women with pregestational diabetes be delivered at 39 completed weeks gestational age with confirmation of fetal lung maturity, although this should be individualized (62). Women with GDM controlled on diet and exercise should be delivered between 40 and 41 weeks and if they are on treatment delivery is recommended at 39 completed weeks (62). Inducing labour is beneficial than expectant management in women with GDM and decrease the c/s rate (62).

Other indications for IOL include(2, 4, 8):

- Oligohydramnios
- Chorioamnionitis
- Intrauterine fetal death (IUFD)
- Fetal malformations incompatible with life

2.5.4 Contraindications to induction of labour

Induction of labour is contraindicated where risks of labour and vaginal delivery outweigh the risks of c/s (9). Patients with a prior lower segment c/s scar are at increased risk of uterine rupture with complications such as PPH, hysterectomy, urinary tract injury and neonatal morbidity and mortality (65). Obstetric haemorrhage is one of the leading causes of maternal mortality in South Africa and accounted for 15.79% of maternal deaths between 2011 and 2013 (33). Of these 7.6% were due to uterine rupture with previous c/s scar and 32.3% due to

bleeding during and after the c/s (33). The risk of uterine rupture increases with PG use and is seen with the use of misoprostol (65, 66).

In a large retrospective cohort study, IOL with PGs in women with a previous c/s scar led to an increased risk of 24.5 per 1000 women of uterine rupture (67). In comparison to elective repeat c/s, IOL with PGs increase the risk of uterine rupture 15 fold (RR 15.6) and this was also found in a population-based study in Norway (66, 67). Patients with a previous c/s scar that desire a trial of labour are high risk and should be monitored vigilantly (66). According to the Society of Obstetricians and Gynaecologists of Canada (SOGC), these women should be in a hospital where theatre facilities are readily available and should an emergency c/s be warranted, this should be achieved within 30 minutes (68). Intrapartum, continuous fetal monitoring is required along side careful examination and monitoring for uterine rupture (68).

Due to this risk of uterine rupture, previous lower segment c/s scar at term is a relative contraindication to IOL (68). Patients with a previous c/s scar in a low resource setting like RMMCH are not induced, as we do not readily have the facilities to monitor these patients or guarantee that an emergency c/s can be performed within 30 minutes.

Other contraindications to IOL include (8, 9, 69):

- Placenta praevia major (due to the increased risk of antepartum haemorrhage and PPH)
- Transverse fetal lie
- Invasive cervical carcinoma
- Cord presentation/prolapse
- Active genital herpes
- Fetal distress

2.6 Labour findings

2.6.1 The role of the Bishop score

Cervical status is a determinant factor in the success of induction (9). The modified Bishop score is a cervical assessment system that determines the likelihood of a vaginal delivery (9). It was originally described in multiparous women (70). Components of the Bishop score include cervical dilatation, effacement, consistency, position and station of the presenting part (70). The higher the Bishop score, the higher the likelihood of spontaneous or induced vaginal delivery (9). A simplified scoring system is currently being studied using three factors: dilatation, station and effacement. It has shown to have a better positive and negative predictive value and positive likelihood ratio compared to the Bishop score using five components (70).

Prior to the introduction of cervical ripening agents, a low Bishop score was associated with failed induction, prolonged labour and increase c/s rate (71). A large study by Johnson et al comprising 7 282 deliveries showed that patients induced with scores less than five had an increase c/s rate (72).

There is controversy about intra- and interobserver differences, as assessing the cervical status is subjective (73). Transvaginal ultrasound is an objective way to assess the cervical status (73). In a prospective study of 340 women, the parameters of transvaginal ultrasound had a 95.5% sensitivity and 84.6% specificity compared to the Bishop score which had a 65.3% sensitivity and 80.8% specificity (73). This was a small study. A larger systematic review by Verhoeven et al that included 5 029 women compared the transvaginal ultrasound to the Bishop score and showed no difference in its ability to predict successful induction (74).

An analysis of the HYPITAT and DIGITAT trial showed no difference in c/s rate or adverse neonatal outcome in women induced with a Bishop score less than six compared to expectant management (75). Hence a Bishop score of less than six indicates an unfavourable cervix and a score of greater than eight increases the probability of a normal vaginal delivery (8, 9). Methods for cervical ripening are therefore needed to induce labour (76).

2.6.2 Dinoprostone

Dinoprostone is a synthetic PGE_2 analogue, used for IOL since the 1960s (77). It is available in cervical gel, vaginal insert or tablet forms and is approved by the Food and Drug administration for cervical ripening in women at or near term (8, 70, 77). It has a half-life of four to seven hours (78). Between 12-28% is absorbed into the circulation (78). Maximum plasma levels are reached within two to three hours and the drug is still detectable six to eight hours after administration (78). Recommendations for the use of the gel form are six hourly with a cumulative dose of 1.5mg /24 hours (8, 78). Side effects of PGs include pyrexia, thermoregulatory effects on the brain, diarrhoea and nausea (12).

Advantages include (78, 79):

- Safety of administration
- Greater bioavailability with a quicker release and absorption
- Predictable clinical response

Disadvantages include (78, 80):

- Frequent vaginal examinations (six hourly)
- Unstable at room temperature, therefore, requires refrigeration
- Unclear evidence regarding intervals of NST monitoring

In a Cochrane review by Thomas et al, 70 RCT's including 11 487 women, compared vaginal dinoprostone to other methods of IOL (77).

- Compared to placebo, dinoprostone resulted in more women delivering within 24 hours (12% vs 0%, RR 0.12). There was marked heterogeneity within the studies and accounting for all of these differences there was no statistical significance in delivery rate between dinoprostone and placebo. There was a decreased c/s rate with dinoprostone of approximately 10%. There were significantly higher rates of uterine hyperstimulation compared to placebo (RR 3.16).
- Low dose vaginal dinoprostone (<3mg) compared to high dose vaginal dinoprostone showed that there was no difference in c/s rate even though low dose vaginal dinoprostone was associated with less uterine hyperstimulation and with less fetal heart rate changes.

2.6.3 Misoprostol

Prostaglandins are a group of cyclopentane derivatives (hydrogel polymers) of arachidonic acid (70). Misoprostol is a synthetic PGE_1 analogue available in tablet forms. Initially misoprostol was used for gastric protection against the effects of non-steroidal anti-inflammatories. In 2002 the Food and Drug Administration approved the use of misoprostol for IOL and cervical ripening (vaginally, orally and sublingually) (8, 70). It imitates the cervical changes of natural PGs by increasing the absorption of water and softening the cervix (70). It also acts directly on the myocytes of the uterus to increase uterine contractility (70).

Misoprostol has a half-life of 20-40 min after oral administration with peak serum concentrations at 30 min and rapid decline by 120 minutes (81). Eighty percent of the drug is excreted by the kidneys (70). Different dosages have been used across the globe ranging from 25ug to 200ug (82).

Advantages include (6, 82):

- Inexpensive
- Easily stored at room temperature
- Non- invasive administration in the oral form
- Few systemic side effects

Disadvantages include (79, 82):

- Diarrhoea and nausea (dose-dependent)
- Pyrexia
- Difficulty in dosing due to the tablet form
- Inability to discontinue misoprostol effects
- Uterine hyperstimulation and tachysystole
- Teratogenic effects

The teratogenic effects of misoprostol include extremities of the fetus (club foot, agenesis of the hands and feet, syndactyly and constriction rings) (82). Mobius sequence was also identified in these fetuses, which is the loss of motor function of the cranial nerves (82). These effects were identified when misoprostol was used in the first trimester for termination of pregnancy (82).

In a Cochrane review by Alfirevic et al, 76 trials including 14 412 women, oral misoprostol was compared to other methods of IOL (82).

- Compared to placebo (1 109 women), misoprostol resulted in more women delivering vaginally within 24 hours (RR 0.16), less use of oxytocin and a decrease in c/s rate.
- Compared to oxytocin alone (1 282 women), misoprostol resulted in a decreased c/s rate (RR 0.88) but had a slower induction time.
- Compared to vaginal dinoprostone (3 859 women), misoprostol resulted in significantly decreased c/s rate (RR 0.88) but no difference in women who achieved vaginal delivery within 24 hours (RR 0.78). There were no differences in rates of hyperstimulation.

2.6.4 Analgesia during labour

" There is no other circumstance in which it is considered acceptable for an individual to experience untreated severe pain that is amenable to safe intervention while the individual is under a physician's care." (83)

The early first stage of labour is more visceral in nature and diffuse as opposed to the late first stage and second stage where the pain is somatic and localized in nature (83). The type of labour influences the need for pain relief: spontaneous or induced labour (84). Non-pharmacological methods include relaxation techniques, distraction techniques, acupuncture, reflexology, aromatherapy, nerve stimulation and sterile water injection (84). Pharmacological methods include nitrous oxide inhalation, opioids and regional anaesthesia (84).

Opioids continue to be used for intrapartum analgesia as they are cost-effective and require no specialized skills (83). Opioids have little effect on maternal pain scores and cause nausea and vomiting (83). Morphine, fentanyl, pethidine and remifentanil are the most commonly used opioids (83). All opioids cross the uteroplacental barrier and cause neonatal respiratory depression (83).

Epidural analgesia is a central nerve blockade technique that blocks pain impulses (85). Advantages include (83, 85):

- Pain relief with motor function spared
- Allows the patient to remain alert
- Continuing pain relief throughout the duration of labour
- Avoids neonatal respiratory depression caused by opioids

Disadvantages include (83, 85):

- Non-uniform spread of anaesthesia
- Hypotension (if significant may cause uteroplacental insufficiency)
- Pyrexia
- Urinary retention
- Post dural puncture headache
- Itchiness, drowsiness, shivering

In a retrospective case series by Antonakou and Papoutsis, epidural analgesia in all women induced was studied (85). The rate of epidural analgesia was 31.2% with a higher assisted delivery rate than c/s rate (23.1% vs 15.1%). The most common indication for c/s was poor progress followed by fetal distress. The c/s rate was not increased by epidural analgesia but by increased birth weight and prolonged second stage of labour. Inducing labour with epidural analgesia had no significant increase in oxytocin use or overall prolonged labour (85). Bannister-Tyrrel et al, in a population based cohort study in Australia, found an epidural rate of 31.5% and epidural analgesia was associated with an increase in c/s rate with a RR of 2.5 (86). Somuah et al in a Cochrane review also concluded that epidurals were associated with a higher rate of assisted delivery (RR 1.42), prolonged second stage of labour (mean difference 13.66 minutes, 95% CI 6.67 to 20.66), increased augmentation with oxytocin (RR 1.19) and increase c/s for fetal distress (RR 1.43) but no overall increase in c/s rate (84).
One study by Ivars et al showed a higher rate of epidural analgesia of 88%. This was a study done in France to compare parity and the Bishop score, however no further elaboration was made on the epidural rate (30).

The RESPITE trial (Remifentanil intravenously administered patient-controlled analgesia (PCA) versus pethidine intramuscular injection for pain relief in labour) by Wilson et al is currently in progress and aims to compare intravenous remifentanil to intramuscular pethidine in a RCT (87). The primary aim is to measure how many women still required an epidural

despite being given remifentanil or pethidine. This study would be useful in an alternative method to epidurals that would be cost-effective and easy to administer (87).

2.7 Delivery methods

2.7.1 Caesarean section rates and normal vaginal delivery rates

Caesarean section increases maternal mortality and morbidity, prolongs postpartum maternal recovery, and increases placental complications in subsequent pregnancies due to the uterine scar (88). It also causes difficulty in establishing breastfeeding, increases neonatal morbidity and mortality, and increases the cost to the health care system (88).

Davey et al included 42 950 births in a cross sectional analysis of c/s following IOL (88). Spontaneous labour occurred in 46.8% of patients and 9.7% of patients were induced. There was an increase in the c/s rate with IOL ($p < 0.001$) (88).

Alfirevic et al showed that misoprostol had a decrease c/s rate compared to dinoprostone (82, 89). However these reviews were based on studies that all used different doses of oral misoprostol ranging from 20ug to 200ug. The most effective dose was shown to be 20ug to 25ug of oral misoprostol as it reduced side effects (82). Alfirevic et al also grouped studies into oral misoprostol doses of less than or more than 50ug. He showed that doses less than 50ug resulted in a decreased c/s rate (89).

A large randomized clinical trial (comprising 695 women) in 2001, done at RMMCH and Liverpool Women's Hospital by Hofmeyr et al, showed no difference in time to achieve vaginal delivery or c/s rates between dinoprostone and misoprostol (90). Rates of maternal and fetal outcomes were also similar. In this study, high doses of oral misoprostol (20ug for the first two or three doses and then 40ug thereafter until adequate uterine contractions were achieved or a maximum period of 12 hours) and high doses of dinoprostone (two milligrams six hourly) were used.

Matonhodze et al performed a similar study to Hofmeyr et al in 2003 (79). The study included 171 women in the three academic hospitals in Johannesburg, SA: RMMCH, Charlotte Maxeke Academic hospital and Chris Hani Baragwanath Academic hospital (79). There was no difference in time to delivery within 24 hours between the two drugs, however there was

an increased c/s rate in the dinoprostone group (24% vs. 14%, RR 0.85). No difference in maternal and fetal outcome between the two groups.

In a study in KwaZulu-Natal (KZN) in 2003 by Moodley et al, 396 women were randomized to receive either misoprostol or dinoprostone (91). This study used 20ug at two hourly intervals of oral misoprostol (until adequate uterine contractions achieved or a maximum of 80ug) and one milligram six hourly of dinoprostone (up to three doses). No difference in delivery rate within 24hours or c/s rate was found. There was an increased number of c/s for fetal distress in the oral misoprostol group. There were no differences in maternal or fetal outcomes between the two groups.

A more recent study in a regional hospital in KZN by Malende et al included 502 women who were induced (92). Inducing agents compared were oral misoprostol and vaginal misoprostol. This study included IUFDs and used vaginal misoprostol with doses ranging from 50-100ug. The overall c/s rate was 40.2%. The overall rate of NVD within 24 hours was 69.7%. They also found that 9.4% of patients required a second cycle of induction and 2.4% a third cycle. Oral misoprostol resulted in more patients requiring another cycle of induction. Neonatal complications were reported in 1.8% of patients; these neonates required neonatal intensive care unit (NICU) admission and there was one reported early neonatal death. There was a delay from the time of booking the c/s to the patient getting to a theatre. There were no adverse maternal outcomes (92).

Some of the above studies were done in a similar setting to our own. Differing results were obtained; this may be the result of different doses used in the studies.

2.7.2 Time to caesarean section

The interval between decision for emergency c/s to delivery should be no more than 30 minutes (93). In a prospective study by MacKenzie and Cook, deliveries of 415 women were analyzed according to emergency or non-urgent cases. Outcomes were measured by arterial cord blood pH. The mean time from decision to delivery in emergency cases was 42.9 minutes and 71.1 minutes in non-urgent cases (93). The average cord blood pH in the emergency group was 7.20 and 7.24 in the non-urgent cases, which was statistically significant. In most cases, the urgency for the c/s was fetal distress(93). There was no

evidence in this study that a c/s within 30 minutes from decision to delivery would improve neonatal mortality (93).

In 2011, NICE published guidelines that recommended a 30-minute decision to delivery time when there is an immediate life threatening condition to the fetus or mother (94). This could be extended to 75 minutes when there is compromise to either mother or fetus that is not life threatening (94). It is also stated that these guidelines should take into account the team performance for each individual c/s. Limited resources or constraints on the health care personnel may influence this; the healthcare personnel may be occupied with more life threatening cases, therefore, a particular c/s may not be done in the acceptable time frame (94, 95).

2.8 Neonatal outcomes

Neonatal outcomes are measured by NICU admission, the Apgar score at 5 minutes and incidence of neonatal death (82, 90).

Misoprostol showed that more fetuses developed meconium stained liquor when compared to placebo, oxytocin or dinoprostone but overall had no effect on neonatal outcomes (82). When dinoprostone was compared to placebo, there were no differences in neonatal outcome (89).

Neonatal respiratory distress syndrome (RDS) is defined clinically as either an abnormality in respiratory rate, labored breathing or the presence of cyanosis (96). Transient tachypnea of the newborn (TTN) is defined as the acute onset of RDS that improves within a few hours from birth and completely resolves in 24 to 48 hours (96). A retrospective study by Tochie et al in Cameroon found that neonates with Apgar <7 at 1 minute, male gender, birth weight >4000g and prematurity were independent risk factors for RDS (96). Maternal fever and chorioamnionitis were not associated with RDS due to the use of antibiotics and possibly due to the thought that PROM activates an inflammatory cascade that accelerated fetal lung maturity (96). Tochie et al showed that neonatal infections, TTN, hyaline membrane disease and meconium aspiration syndrome (MAS) were the main causes of RDS (96).

Madhi et al, in study in SA between 1997 and 1999, showed a high burden of GBS (3 per 1000 live births) that contributed to RDS and neonatal sepsis (97). Contrary to the study by Tochie et al in Cameroon, Madhi et al showed that PROM was associated with an increase

incidence of RDS and neonatal sepsis (97). Since then, antibiotics have been introduced as routine management for patients with PROM and IOL is advocated if labour does not occur within 24 hours. This could possibly decrease the incidence of RDS and a study at Chris Hani Baragwanath Academic Hospital is currently being conducted to assess the incidence of GBS in neonates.

2.9 Maternal outcomes

The primary concern of IOL is uterine rupture (66). This occurs in 7 per 10 000 women and most commonly in those induced with a previous c/s scar (incidence 20-80 per 10 000) (66). In a population based study over 4 decades in Norway by Al-Zirqi et al, the incidence of uterine rupture in an unscarred uterus was 0.5 per 10 000 (66). Uterine rupture was more likely to occur in patients that were induced or augmented ($P<0.001$). Combination inductions (PGs and oxytocin with or without amniotomy) showed the highest risk of uterine rupture followed by PGs alone. Uterine ruptures in an unscarred uterus have been limited to case reports (98).

Postpartum haemorrhage is defined as blood loss of greater than 500ml at vaginal delivery and greater than 1000ml at c/s (99). There is controversy around this definition as it is difficult to quantify blood loss objectively (99). The definition now includes clinical deterioration as well as clinical shock that may be individualized to each patient (100). Most studies show no increased rate of PPH with IOL (101, 102). Hofmeyr et al also showed that IOL had no significant impact on PPH or maternal adverse events (90). A large secondary analytical study by Levine et al, which included 863 women, showed that PPH was significantly increased in women who were induced compared to spontaneous labour (10% vs 3%, $p=0.001$) thus differing from other studies (29).

Induction of labour has a very low incidence of rupture in an unscarred uterus. Larger studies are needed to establish the risk of PPH with IOL (66, 90).

3 PROBLEM STATEMENT

Induction of labour is a global topic of discussion with the aim of sourcing an agent that is suitable for the patient profile seen in a particular area. In a low resource setting, where there is a lack of beds, high numbers of c/s (compared to the resources available) and lack of staff (compared to the number of patients seen), an "ideal" inducing agent should be sought. This agent should expedite time to delivery and decrease the rate of c/s, thus shortening the length of hospital stay with minimal maternal and fetal adverse outcomes.

The pharmacological agents for IOL used at RMMCH are oral misoprostol and vaginal dinoprostone. Doses used at RMMCH differ from that of other studies. Oral misoprostol is given at 20ug two hourly for 12 doses per cycle over a 24-hour period and dinoprostone one milligram six hourly is used (four doses over a 24 hour period). Patients are given the first cycle of either agent for a 24 hour period followed by a rest period of 24 hours. If spontaneous labour does not occur, a second cycle is given. If spontaneous labour does not occur after the second cycle this is considered a failed IOL and a c/s is planned.

A RCT was conducted with large numbers at RMMCH, 16 years ago (103). Since, there has been a change in patient profiles with an increase in patient numbers as well as a wider spectrum of disease entities. The RCT was also a study done under trial conditions (protocols given within an envelope of which the patient was randomized to) whereas this study is one of real life clinical situations and practice.

This study aims to compare the outcomes of oral misoprostol versus vaginal dinoprostone for IOL in a low resource setting.

4 OBJECTIVES OF THIS STUDY

Primary

1. To assess labour processes and mode of delivery

Secondary

1. To compare patient demographics and characteristics
2. To compare the incidence of maternal and fetal complications

5 METHODS

5.1 Study design

This was a prospective cross-sectional descriptive study. This involved analysis of the clinical history, course of labour, delivery methods and neonatal outcome from patient files.

5.2 Study population

The study included all women who underwent IOL; with singleton live pregnancies, greater than 34 weeks gestational age or more than 2kgs estimated fetal weight.

5.3 Drug selection

Patients were administered either oral misoprostol or vaginal dinoprostone depending on the preference of the attending clinical unit of the patient.

5.4 Setting

Rahima Moosa Mother and Child hospital is a regional academic hospital complex, together with Helen Joseph Academic hospital, situated in Newclare, Johannesburg (Figure 5.1, Region C). Approximately 700 NVDs and 400 c/s deliveries are performed each month and these include both low risk and high risk pregnancies. Rahima Moosa Mother and Child Hospital serves a population of approximately 200 000 people draining from Regions A, B and C (Figure 5.1). The population is urban and mostly low to middle-income, thus most are dependent on state health care services. Rahima Moosa Mother and Child Hospital receives referrals from two midwife obstetric units (MOU's): Discoverers and Diepsloot. As there are no secondary hospitals within the region, all high risk pregnant women are referred to RMMCH.

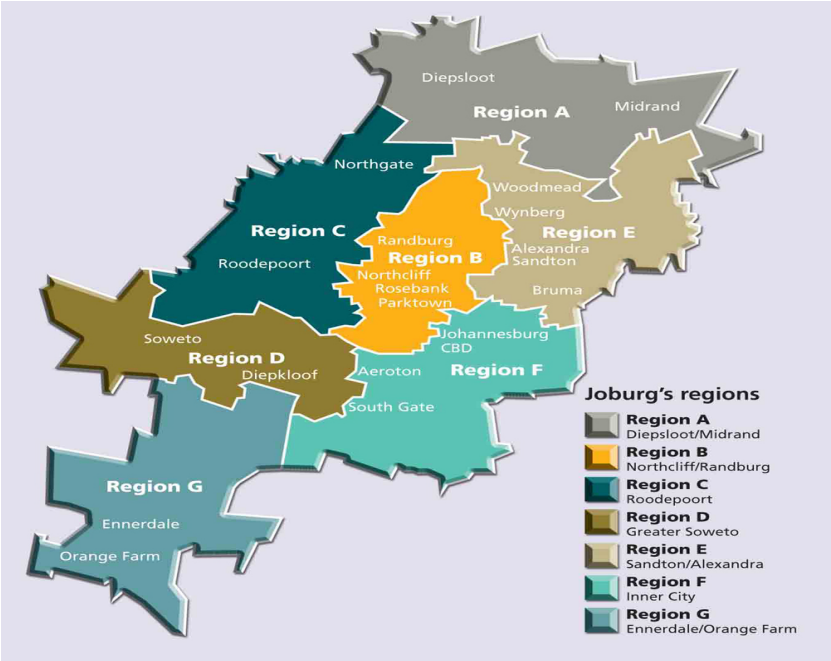


Figure 5.1 Map of the seven regions in Johannesburg

Within the antenatal ward, inductions are conducted in a separate room consisting of 4 beds. This is usually for low risk pregnancies. Inductions also take place in the high care area for high risk patients (severe pre-eclampsia, eclampsia). Patients requiring continuous fetal monitoring are induced in the labour ward area. This ensures that fetal monitoring is performed more frequently and these patients are assessed regularly throughout the induction process.

Rahima Moosa Mother and Child Hospital adhere to protocols regarding IOL, which have been drawn up by the Department of Obstetrics and Gynaecology of the University of the Witwatersrand (104). This serves as a guide within the department.

- If the Bishop score is less than seven, a cervical ripening agent, either oral misoprostol or dinoprostone, is used.
- If the Bishop score is more than seven, amniotomy with oxytocin infusion is used.

An algorithm for the use of misoprostol is drawn up in the protocol book (Appendix A). Dinoprostone is administered six hourly intravaginally at a dose of one milligram. Up to four doses per cycle are given.

5.5 Inclusion Criteria

- Hypertensive disorders of pregnancy (gestational HT, pre-eclampsia, imminent eclampsia)
- Other medical disorders in pregnancy (epilepsy, GDM, overt diabetes mellitus, cardiac diseases, antiphospholipid syndrome, thromboembolic disease)
- Bishop score < seven

5.6 Exclusion Criteria

- All pregnancies <34 weeks gestation or estimated fetal weight <2kgs
- Previous c/s or uterine surgery
- Grand multiparous women (≥ parity of five)
- Multiple pregnancy
- Eclampsia
- Congenital abnormalities of the fetus incompatible with life
- Intrauterine fetal death

5.7 Sample size

All patients that were induced who met inclusion criteria during the period from 01 January 2016 to 30 April 2016 were included in the study. The study intended to include 100 patients, 50 patients in the misoprostol group and 50 patients in the dinoprostone group. During analysis of the results, 5 patients were excluded as both drugs were used in each patient and this would cause a bias. A total 95 patients were included, 46 patients in the misoprostol group and 49 patients in the dinoprostone group.

5.8 Data Collection

Patients in the induction room were reviewed every second morning at 07h00 as the researcher had clinical duties to attend to and this was the time available for data collection. Written informed consent was obtained from those who had met inclusion criteria whilst the patients were in the antenatal ward. Information regarding demographics, antenatal care, comorbidities and choice of induction agent was collected at this point. Post delivery, patients were followed up in the postnatal wards and information regarding their labour and delivery

was collected. If the patients were discharged before the researcher was able to retrieve the remaining information, the files were retrieved from the records department. If no consent was obtained from the patient antenatally, the patient was excluded from the study. Patients were located by using the maternity register that is kept in the labour ward and high care area department.

All data was captured on a data sheet (Appendix B).

5.8.1 Data collection categories

Data were collected under the following categories (Appendix B):

- Maternal demographics
- Indications for IOL
- Labour processes
- Method of delivery
- Fetal complications
- Maternal complications

5.9 Data analysis

Data was captured using Redcap and exported to Microsoft excel. Stata 11 was used for statistical analysis. Continuous data were tested for normality. Where applicable the data are presented as means and standard deviations. Categorical data are presented as proportions and frequencies. The Chi-squared test was used to assess the relationship between categorical variables. A 95% confidence interval was used to analyze all data.

5.10 Ethics

The study received approval from the University of the Witwatersrand's Human Research Ethics Committee, approval number M151126 (Appendix C).

6 RESULTS

There were a total of 4143 deliveries from 01 January 2016 to 30 April 2016. A total number of 200 inductions were conducted during this time of which 107 patients met the inclusion criteria for the study. There were seven patients that were excluded due to missing files or consent was not obtained. There were 50 patients in the misoprostol group and 50 patients in the dinoprostone group. During analysis of the results, five patients were excluded to minimize bias. These five patients required a second cycle of IOL with a different drug to the first. A total of 49 patients were included in the dinoprostone group and 46 patients in the misoprostol group.

6.1 Maternal Characteristics

Table 6.1 Maternal Demographics

Variable		Dinoprostone Median (range) Number (%) n=49	Misoprostol Median(range) Number (%) n= 46	P value
Age		28 (18-41)	28 (18-43)	0.70
BMI		31.3 (23.2-45.7)	33 (23.2-46.7)	0.74
Parity		1 (0-3)	1 (0-3)	0.74
Gravidity		3 (1-6)	2 (1-4)	0.53
Gestational age (GA)		40 (35-43)	38.5 (34-42)	0.04
Method of determination of GA	LNMP	22 (44.9)	26 (56.5)	0.10
	EUS	9 (18.4)	7 (15.2)	
	LUS	18 (36.7)	13 (28.3)	

The maternal characteristics are described in Table 6.1. The mean age of the whole group of patients was 28.49 (n=95) with a standard deviation of 5.73. This was equivalent in both groups separately with no statistical significance. The median BMI for the dinoprostone and misoprostol groups was 31.3 and 33 respectively (p=0.74); 41.1% of patients were obese. Gestational age was determined by three methods: LNMP, early ultrasound (done before 23 weeks) and late ultrasound (done after 23 weeks). It is not routine for every patient to have an ultrasound at the local clinics, as these clinics are not equipped to offer ultrasounds. Majority

of the patients' gestational ages were determined using their LNMP: 44.9% in the dinoprostone group and 56.5% in the misoprostol group. There was no statistical significance when comparing LNMP, EUS or LUS as a method for determination of gestational age between the two groups (p=0.10).

Table 6.2 Indications for the induction of labour

Indication for induction	Dinoprostone Number of patients (%) n=49	Misoprostol Number of patients (%) n=46	P value
Post term	25 (51)	15 (32.6)	0.03
PROM	0	12 (26.1)	<0.001
HT	9 (18.4)	9 (19.6)	0.44
Medical	8 (16.3)	3 (6.5)	0.07
IUGR	1 (2)	1 (2.2)	0.48
Other	6 (12.3)	6 (13)	0.45

Table 6.2 shows the different indications for which these patients were induced. There was a statistical difference in the indications for induction of labour between the dinoprostone and misoprostol groups ($p<0.001$). This was statistically significant for post term pregnancy and PROM (p 0.03 and $p <0.001$ respectively). The most common indication for induction was post term pregnancy, followed by HT and PROM. Fifty-one percent of patients were induced for post term pregnancy in the dinoprostone group and 32.6% of patients were induced for post term pregnancy in the misoprostol group. Dinoprostone was the drug commonly used for HT and medical disorders. Misoprostol was the drug of choice for patients with PROM. Table 6.3 illustrates the other indications for IOL.

Table 6.3 Other indications for IOL

Indication	Dinoprostone n=6	Misoprostol n=6
Poor obstetric history	4	1
Previous IUFD or stillbirth at term	2	0
Decreased fetal movements at term	0	1
Big baby	0	1
Oligohydramnios	0	1
Chorioamnionitis	0	1
Fetus with supraventricular tachycardia	0	1

6.2 Labour findings

Table 6.4 Findings of the labour process

Variable		Dinoprostone Mean ±SD Median(range) Number (%) n=49	Misoprostol Mean ±SD Median(range) Number (%) n= 46	P value
Total number of doses of each drug		2 (1-7)	7 (3-24)	0.06
Labour initiated		47 (96)	37 (80)	0.03
Time from induction to onset of labour	n	47	37	0.37
	Time (hours)	13 (2-87.5)	14 (6-90)	
Duration of labour		8.9 ± 7.2	12.1 ± 10.4	0.10
Time from induction to delivery (hours)		20.5 (4.5-92)	25 (9-144)	0.18
Analgesia		25	25	0.84

Table 6.4 illustrates the findings of labour related to the induction process. The Bishop score was used to assess cervical favourability prior to induction. The median Bishop score was three in the dinoprostone group and four in the misoprostol group (p=0.46). The first stage of labour was initiated in 96% patients in the dinoprostone group and 80% in the misoprostol

group which was statistically significant (p=0.03). However this did not impact on the duration of labour or the time to delivery in the dinoprostone or misoprostol groups. Augmentation with an oxytocin infusion was used in 31% of patients in the dinoprostone group and 28% in the misoprostol group with no statistical significance (p=0.49).

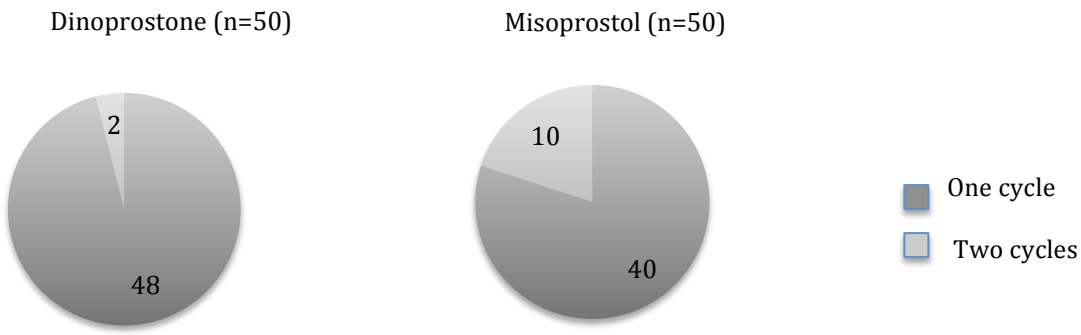


Figure 6.1 Distribution of the number of cycles of induction agents

Figure 6.1 is a representation of the number of cycles patients required in each group. In the dinoprostone group, 4% of patients required a second cycle and 20% in the misoprostol group (p=0.02).

6.3 Delivery Methods

Table 6.5 Mode of delivery

Variable	Dinoprostone Number (%) n=49	Misoprostol Number (%) n=46
Labour initiated	47 (96)	37 (80)
NVD	33 (67.3)	25 (54.3)
Caesarean section	16 (32.7)	20 (43.5)
Assisted delivery	0	1 (2.2)

Table 6.5 shows the mode of delivery within the two induction groups. More patients delivered by NVD in the dinoprostone group as compared to the misoprostol group overall (67.3% and 56.5% respectively). In a subgroup analysis of the patients who actually went into labour in each group, 70.21% of patients delivered NVD in the dinoprostone group and 70.27% patients in the misoprostol group. Of those that went into labour, there was no statistical significance in the rate of NVD between the 2 groups.

Misoprostol had a higher c/s rate overall. In the subgroup analysis, 14 of the 16 c/s (87.5%) in the dinoprostone group were performed on patients in established labour. In the misoprostol group, 11 of the 20 c/s (55%) were performed on patients in established labour. Therefore more c/s were performed in the misoprostol group for failed IOL than the dinoprostone group.

There was no statistical significance in the mode of delivery between the two groups (p=0.19). The one assisted delivery (2.2%) was a vacuum delivery on a patient with a prolonged second stage due to poor maternal effort.

Table 6.6 Indications for Caesarean section

Variable	Dinoprostone Number (%) n=16	Misoprostol Number (%) n=20
Fetal distress	6 (37.5)	7 (35)
Failed IOL	2 (12.5)	6 (30)
CPD	5 (31.3)	3 (15)
Poor progress	2 (12.5)	2 (10)
Other	1 (6.2)	2 (10)

Table 6.6 demonstrates the indications for the c/s in each induction group. The Chi coefficient for the two groups was 2.34 with a p value of 0.51 with no statistical significance. The most common indication for c/s was fetal distress: 37.5% in the dinoprostone group and 35% in the misoprostol group. No patients had developed antepartum haemorrhage or uterine rupture. The time to c/s from the time of booking in the dinoprostone group had a median of 4.25 hours with a range of 0.5 to 17.2 hours. In the misoprostol group, the median time from booking to the c/s taking place was 5.2 hours with a range of 1 to 35 hours. Patients whom the indication for c/s was failed IOL, waited for more than 10 hours for a c/s. In the misoprostol group, one patient waited for 25 hours and the other for 35 hours. The two patients in the dinoprostone group with failed IOL waited 14 and 17 hours respectively for the c/s to take place. Other indications in the dinoprostone group included a c/s for failed augmentation of labour and other indications in the misoprostol group were for a breech presentation and a failed augmentation of labour.

6.4 Neonatal outcomes

Table 6.7 Neonatal outcomes

Variable		Dinoprostone Median(range) Number (%) n=49	Misoprostol Median(range) Number (%) n=46	P value
Neonatal outcome	Alive	49 (100)	46 (100)	1
Apgar at 5 minute		10 (8-10)	10 (9-10)	0.44
Weight (grams)		3160 (2270-4670)	2973 (2085-4565)	0.10
NICU admission		0	2 (4.3)	0.23
Neonatal complication		6 (12.2)	9 (19.6)	0.40
Type of complication	TTN	1 (16.7)	5 (55.6)	0.10
	RDS	3 (50)	1 (11.1)	0.62
	MAS	0	0	
	Other	2 (33.3)	3 (33.3)	0.67

Table 6.7 focuses on the neonatal outcomes. There were no stillbirths in either group. Two neonates required NICU admission in the misoprostol group for congenital pneumonia and respiratory distress syndrome requiring mechanical ventilation. Complications developed in 12.2% of neonates in the dinoprostone group and 19.6% in the misoprostol group although this was not statistically significant (p=0.40). In those neonates who did develop a complication (15 out of 95), 66.67% were respiratory in nature. In the misoprostol group 55.6% of neonates developed TTN and 50% in the dinoprostone group developed RDS. Two neonates in the dinoprostone group developed neonatal jaundice and a persistent hypoglycemia and three neonates in the misoprostol group developed neonatal jaundice, congenital pneumonia and one neonate presented with a supraventricular tachycardia. The diagnosis of the supraventricular tachycardia was made antenatally.

6.5 Maternal outcomes

Table 6.8 Maternal complications intrapartum and postpartum

Variable		Dinoprostone Number (%) n=49	Misoprostol Number (%) n=46	p-value
Maternal complication		7 (14.3)	6 (13)	0.55
Type of complication	Uterine Rupture	0	0	
	PPH	1 (14.3)	0	0.52
	Assisted delivery	0	1 (16.7)	0.48
	Chorioamnionitis	1 (14.3)	2 (33.3)	0.48
	Other	5 (71.4)	3 (50)	0.39

Table 6.8 describes the maternal complications that occurred during labour, delivery and postpartum. The rates of complications were similar between the dinoprostone and misoprostol groups. There were no patients who developed a uterine rupture. The patient who developed a PPH in the dinoprostone group was due to a cervical laceration post NVD. One patient in the dinoprostone group developed a urinary tract infection post operatively, three patients had lower segment tears into the uterine artery during c/s (not significant to cause a PPH) and one patient had a delayed second stage due to inadequate contractions. In the misoprostol group one patient had intraoperative bleeding due to a friable uterus (this was not significant enough to result in a PPH), one patient had retained products of conception post NVD requiring an evacuation of the uterus in theatre and one patient had a lower segment tear intraoperative.

7 DISCUSSION

This study aimed to find the ideal induction agent for a low resource setting. The study showed no statistical significance between dinoprostone and oral misoprostol, however dinoprostone had a lower c/s rate, a shorter duration of labour and required fewer doses to be administered compared to oral misoprostol. This differed to other studies that showed that misoprostol resulted in fewer c/s sections but agreed that misoprostol may have a slower induction time (79, 82, 89).

7.1 Maternal characteristics

There was minimal heterogeneity between the characteristics of the patients' in the dinoprostone and misoprostol groups. The mean maternal age of all the patients collectively in the study (n=95) was 28.49 years and the mean age in each group was 28 years. This was in keeping with other studies where the average age was between 26 -28 years old (29, 35, 79, 91).

The median parity was one in each group. Grand multiparous women were excluded as this is a contraindication to IOL according to the Wits protocol (104). Levine et al showed that regardless of parity, IOL had an increase c/s rate when compared to spontaneous labour (29). Our study had no control group of patients in spontaneous labour to compare the process of IOL as our study compared dinoprostone to misoprostol.

From the 95 patients in our study, 40 patients (41.1%) were obese among the women being induced. This is in keeping with the SA statistics for obese pregnant women (32). Obesity in pregnancy is associated with PPH and macrosomia (34). In our study, only one patient developed a PPH. This patient's BMI was 25.71 and the neonate weighed 2935g. A cervical laceration accounted for the PPH. Of the five patients that had lower segment tears and intraoperative bleeding, four were obese. This blood loss was not classified as a PPH in patient records. Two of the four patients' had macrosomic babies (4670g and 4565g). Measurement of blood loss intraoperative is subjective and there may have been an underestimation of the blood loss during delivery (100). There may be a correlation between maternal obesity, c/s rate, PPH and macrosomia, however this is a small study sample size and a definitive association between these variables cannot be made.

The LNMP was the most common method of determining the gestational age. This may have caused inaccuracy in determining the true gestational age as approximately only 50% of patients remember the date of their LNMP accurately (105). Ultrasound in the first trimester up to 14 weeks gestational age is the most accurate method of determining the gestational age (105).Where a first trimester ultrasound is unavailable, clinical judgement can be of use in dating a pregnancy by combining the LNMP with the size of the uterus or height of fundus in a singleton pregnancy (40). Patients who did have an early ultrasound in our study either had this performed in the private health care sector or were referred to a tertiary institute for a high risk pregnancy. Primary health care centers are not routinely well resourced with trained sonographers or clinicians and ultrasound machines to perform early ultrasounds on patients.

The method of using LNMP to determine gestational age may have led to inaccuracy in dating the pregnancies as post term and thus the higher incidence of post term pregnancy in our study. In our study, 42% of patients were induced for post term pregnancy, thus being the most common indication for IOL. This is higher than the incidence of post term pregnancies in other developed and developing countries: 22.3% in the UK, 21% in Pakistan, 13% in New South Wales and 7% in the USA (35, 39-41). The higher incidence of post term pregnancy in our study is possibly due to dating of GA by LNMP in 50.53% of patients' in our study, as for these patients' LNMP was the only option for dating the pregnancy. Ensuring ultrasound biometry for dating, even in those patients' who book late, would reduce the number of inaccurate post term inductions (42).

In our study there was a higher number of inductions for post term pregnancy in the dinoprostone group (51%) versus the misoprostol group (32.6%). This was due to the method of IOL chosen by the attending clinical units. All patients with PROM were induced only with misoprostol (26.1%) as the Wits protocol favours the use of misoprostol for patients with PROM (104). During the literature analysis, oral misoprostol was shown to be superior to dinoprostone in patients with PROM as oral misoprostol resulted in more vaginal deliveries compared to dinoprostone (52, 56-58, 106). The efficacy of vaginal drugs decreased as these drugs may disembogue with the draining of amniotic fluid and therefore oral misoprostol was more effective than dinoprostone (52, 56-58). Oral misoprostol has also shown to decrease maternal and neonatal sepsis compared to vaginal dinoprostone in patients with PROM (56, 58).

Patients at RMMCH with PROM are induced 24 hours after the rupture of membranes if spontaneous labour does not occur (104). Prelabour rupture of membranes increases the risks of maternal and fetal sepsis, umbilical cord compression and placental abruption (50, 52). Due to these risks, IOL is preferred in comparison to conservative management (52). From the 95 patients, one patient that was induced for PROM developed a chorioamnionitis and had a c/s for fetal distress. Our study had a low incidence of complications from PROM as these patients were actively managed by inducing labour after 24 hours from the rupture of membranes if spontaneous labour did not occur.

Due to the lack of screening for GBS in SA, all patients with PROM for more than 24 hours received antibiotics including penicillin (53, 54, 104). One patient was induced for a suspected chorioamnionitis based on an irritable uterus on clinical examination; there was no malodorous liquor upon delivery and both mother and neonate were healthy with no complications. This could have been a case of a subclinical chorioamnionitis.

Diabetic patients were induced with dinoprostone: 16.3% in the dinoprostone group and 2.2% in the misoprostol group. This was due to the diabetic unit at RMMCH using dinoprostone as their induction agent of choice due to preference of the Head of unit. There is insufficient evidence on which induction agent is superior in diabetic patients.

7.2. Labour findings

In this study, the median Bishop score was three in the dinoprostone group and four in the misoprostol group with no statistical significance. Patients with a ‘ score of greater than seven are augmented with oxytocin and not a cervical ripening agent (104). This is in keeping with studies showing that the higher the Bishop score, the higher the likelihood of a NVD (9). Most studies excluded women with a Bishop score of greater than six and some greater than eight, which was dependent upon the institution protocol (79, 90, 91). The range of medians in these studies was between four and five. In our study, the median Bishop score was lower than that of the studies in the literature. This may be due to lower parity. The possibility of pregnancies labeled as “post term” (which may not have been the case due to dating with LNMP in most of our patients) may have contributed to the lower bishop scores in our study. This was not clinically significant as the Bishop score was still classified as being unfavourable. However, as in the Tygerberg study, even ultrasounds beyond 23 weeks have been shown to be more accurate in dating the pregnancy compared to LNMP and clinical

methods, hence this policy should be adopted in our institute (42). This may reduce the number of inductions for post term pregnancy.

Labour was successfully initiated in 96% of women in the dinoprostone group and 80% in the misoprostol group. This was statistically significant (p=0.03). This correlates to the number of failed inductions of 4% in the dinoprostone group and 13% in the misoprostol group in our study. This difference in patients in whom labour was successfully initiated may seem to be due to the fact that the dinoprostone group had a higher number of inductions for post term pregnancy; however there was no difference in the bishop score between the two groups. Thus a definitive reason for the higher number of patients in whom labour was initiated in the dinoprostone group cannot be determined. Many studies focused on c/s rate and failure to achieve vaginal delivery within 24 hours rather than if labour was successfully initiated, or the incidence of failed induction (79, 82, 90). One study by Moodley et al, showed a rate of failed induction of 5.7% in the dinoprostone group and 6% in the misoprostol group, however failed IOL was defined as not having achieved labour within 24 hours from the time of induction (91). In our study failed IOL is defined as not achieving established labour after administration of two cycles of an inducing agent. The second cycle of induction meant that after the first cycle of 24 hours, the patient would rest for 24 hours and then start another cycle of the same inducing agent for a repeated 24 hours.

At RMMCH in this study, labour was more frequently initiated with dinoprostone than misoprostol. Despite this finding being statistically significant, there was no impact in the time from induction to the onset of labour, the overall duration of labour or the time from induction to delivery. This was in keeping with literature around the globe (77, 82). Our study differed to that of Alfirevic et al that showed women induced with misoprostol were more likely to achieve vaginal delivery within 24 hours compared to dinoprostone; however, there was marked heterogeneity between the studies compared by Alfirevic et al (82, 89).

Fifty percent of patients in the dinoprostone group and 50% of patients in the misoprostol group received analgesia, at least in one form. Overall, 10% of patients who received analgesia received an epidural with the remainder 90% receiving an opioid in the form of pethidine 100mg intramuscularly six hourly. In order to counteract the nausea and vomiting, metoclopramide is given concurrently. The literature describes a rate of epidural analgesia of approximately 31-32% (84-86). These are quoted rates in first world countries. One study by Davey et al showed that 52% of women who were induced or had labour that was augmented

received an epidural compared to 18% of those who had spontaneous labour (88). In a local study by Matonhodze et al at RMMCH, analgesia rates ranged from 26-37% in patients' that were induced and thus have improved over the last 15 years in our study.

Since January 2016, the Anaesthetic Department at RMMCH provides a 24 hour epidural service. A higher rate of epidural analgesia is expected and further studies would be able to ascertain this to compare rates after the implementation of a 24-hour service. In a study in Nigeria by Enabor et al, 51 % of patients believed that inducing labour would inflict more pain (107). Most women in labour should be receiving analgesia and this leaves room for improvement at RMMCH, as only 50% of labouring women receive any form of analgesia (83). The low rate of women receiving analgesia may be attributed to patient, staff and resources. Patients' do not request analgesia and midwives may not administer analgesia due to the high patient load. The lack of skills of the health care workers administering epidural analgesia, the lack of monitoring equipment and drugs all contribute to a low rate of administration of analgesia.

In our study, 2% of patients required a second cycle of induction in the dinoprostone group and 13% in the misoprostol group. Most studies reviewed in the literature did not mention the number of cycles required (77, 79, 82, 90, 91). It is therefore difficult to measure our study against international centres. One study by Malende et al in KZN showed that 15% of patients induced with oral misoprostol required a second cycle of IOL, in keeping with the findings of our study (92).

7.3 Delivery methods

In our study more patients delivered vaginally in the dinoprostone group than the misoprostol group even though this was not statistically significant. Dinoprostone had a c/s rate of 32.3% and misoprostol had a c/s rate of 43.5%. Studies by Alfirevic et al and Matonhodze et al both showed an increase in c/s rate with dinoprostone (79, 89). This may be due to the higher doses of dinoprostone used in these studies. The SOGC guideline showed that misoprostol was more effective than dinoprostone in achieving vaginal delivery (4). Moodley et al showed no difference in c/s rate between misoprostol and dinoprostone (91). The same doses used in our study were also used by Moodley et al, hence the congruency in results. However, in the subgroup analysis of those patients in whom labour was initiated, there was no difference in

the NVD rate between the dinoprostone and misoprostol group (70.21% and 70.27% respectively). More c/s were performed for failed IOL in the misoprostol group.

Despite no statistical significance in the c/s rate between dinoprostone and misoprostol in our study, this has marked clinical significance. The difference in the c/s rate between dinoprostone and misoprostol was 10.8%. This increase in number of c/s in the misoprostol group means that these patients had a longer hospital stay, thus increasing costs and had exposure to an invasive surgical procedure that is associated with an increase in morbidity and mortality (88). At RMMCH, a patient who has an uncomplicated c/s stays in hospital for two days post c/s and is monitored by a doctor each day. A patient, who delivers vaginally and has no complications, is discharged six hours post delivery. Some patients are discharged the next day, during daylight hours, as it is not safe to discharge patients at night due to lack of transport facilities. The midwives monitor, discharge these patients and alert the doctor on call shoul complications arise. Therefore an increase in c/s rate in the misoprostol group increased the burden of patients to the doctors, nursing staff and hospital system in an already patient overloaded environment.

The most common indication for c/s in the dinoprostone and misoprostol groups was fetal distress (37.5% and 35% respectively). Dinoprostone had a decreased c/s rate for failed IOL compared to misoprostol (12.5% and 30% respectively). All doses of misoprostol were given two hourly, and the mixture prepared in a dark bottle to maintain thermal stability at room temperature. However if the bottles were not thoroughly mixed before administration, the patient would simply be consuming water or not receive the recommended 20ug dose. This may have attributed to incorrect administration and thus an increased rate of failed IOL in the oral misoprostol group. The ACOG stated that uterine tachysystole with or without fetal heart rate changes occurs more frequently in women induced with misoprostol compared to dinoprostone (8). In our study uterine hyperstimulation is not discussed as this is not routinely documented in patient files and therefore could not be analyzed. Cardiotocographic traces were misplaced from patient files and these were not analyzed. The researcher was not present at each delivery to assess these aspects. Bernardes et al showed that fetal distress was the commonest indication for c/s in patients' induced, but this was a subgroup analysis of the HYPITAT and DIGITAT trials, therefore these patients were already compromised due to medical conditions and these maternal comorbidities were the actual cause of the fetal distress (75).

Two large systematic reviews also showed that oral misoprostol reduced the likelihood of c/s (76, 82). In studies done in SA, Matonhodze et al and Hofmeyr et al showed an increased rate of fetal distress in the dinoprostone group compared to the misoprostol group (79, 90). Moodley et al showed similar rates of fetal distress in both groups with no statistical significance (91). Malende et al showed that fetal distress was the most common indication for c/s after IOL, followed by cephalopelvic disproportion and failed IOL (92).

In comparison, our study differed in that dinoprostone and misoprostol had similar rates of c/s for fetal distress. This may be attributed to the small study sample size. Misoprostol resulted in a larger number of patients requiring a c/s for failed IOL. Patients with failed IOL waited a long time for c/s (up to 35 hours). Therefore misoprostol contributed to a longer hospital stay and increased costs were incurred due to this.

7.4 Neonatal outcomes

Fetuses with congenital abnormalities and intrauterine fetal deaths were excluded in our study, as this would skew data on neonatal outcomes.

Most studies showed no difference in neonatal outcomes between dinoprostone and misoprostol (79, 82, 90, 91). These studies mainly commented on mortality, NICU admission, Apgar at five minutes and MAS. Moodley et al showed that MAS occurred in 8.2% of neonates in the dinoprostone group and 10.9% in the misoprostol group, but this was not statistically significant (91).

In our study the neonatal complications were respiratory in nature, RDS and TTN, rather than MAS. This could be due to the small study sample size and the overall rare occurrence of these complications. The higher incidence of RDS and TTN may be attributed to 26% of patients induced for PROM in keeping with the study by Madhi et al (97). Congenital pneumonia was diagnosed in two neonates, but whether this was due to GBS or another organism is unknown. Our study showed no significant difference in neonatal outcomes.

7.5 Maternal outcomes

Maternal complication rates were similar in the dinoprostone and misoprostol groups in this study: 14.3% in the dinoprostone group and 13% in the misoprostol group. In keeping with literature, there were no cases of uterine rupture as the incidence of uterine rupture in an unscarred uterus is low: 0.5 per 10 000 deliveries (98). Of the 13 patients who developed complications, one patient had a PPH. This was a patient, in the dinoprostone group, who sustained a cervical laceration intrapartum. This patient was induced for gestational diabetes mellitus and delivered a 2935g neonate. The laceration most likely occurred from the patient prematurely bearing down, as it was noted in the patient's file that the patient was restless, uncooperative and bearing down when she was in the first stage of labour. Lower segment tears at c/s occurred in three patients in the dinoprostone group and one patient in the oral misoprostol group. The blood loss from these tears were not classified as a PPH as the patients were haemodynamically stable, but there could be a margin of error as the estimated blood loss is a subjective measure.

Levine et al showed an increase in PPH among women who had IOL compared to spontaneous labour (29). Matonhodze et al showed no cases of uterine rupture and similar rates of PPH to our study, which was also in keeping with the findings of other studies (79, 90-92).

In our study, despite no statistical significance in maternal complication rates, the sample size was too small to comment adequately on maternal complication rates.

8 LIMITATIONS

- The study sample size was small to adequately comment on neonatal and maternal complications, especially that of MAS and uterine rupture.
- There was a selection bias of the drugs used in our study. The choice of the drug depended on the individual unit the patient was admitted to. The diabetic unit preferred the use of dinoprostone; therefore all diabetic patients were induced with dinoprostone only.
- There may have been interobserver differences in determining the Bishop score as patients are assessed by health care workers of different levels of experience: intern doctors, medical officers, registrars in training and specialist consultants. However this was unlikely to have significantly influenced the study.

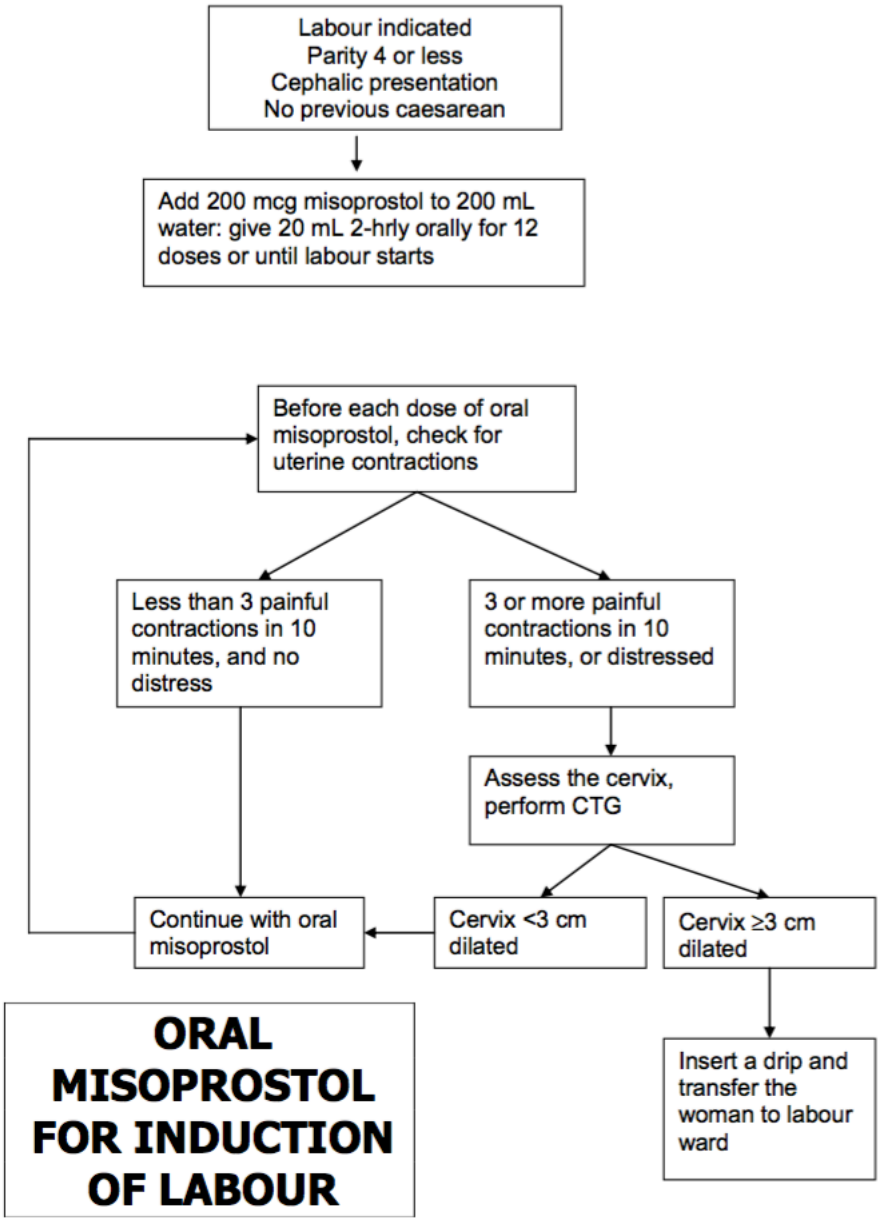
9 CONCLUSION

Since the advent of IOL, many methods have been studied in women with different antenatal disorders in an attempt to reduce maternal and neonatal morbidity and mortality.

This study attempted to compare the outcomes of vaginal dinoprostone and oral misoprostol at RMMCH. Labour was initiated in more patients in the dinoprostone group and dinoprostone resulted in fewer c/s than misoprostol, however this was not statistically significant. There was no difference in neonatal and maternal outcomes.

The use of dinoprostone or misoprostol is therefore equally effective in our setting. A larger study or RCT is recommended to adequately assess neonatal and maternal complication rates.

Appendix A: Algorithm for misoprostol administration



Appendix B: Data Sheet

Confidential

DATA SHEET

Study ID	_____
Age	_____
Weight at time of induction (KG)	_____
Height	_____
BMI	_____
Parity	_____
Gravidity	_____
Gestational age	_____
Gestational Age Determination	◯ Dates ◯ Early U/S < 14 weeks ◯ Late U/S > 14 weeks ◯ First palpation
Indication of IOL	☐ post term/post dates ☐ PROM ☐ Hypertensive disorders ☐ Medical disorders(DM/Epilepsy/ Chronic renal failure/ cardiac disease) ☐ Intrauterine growth restriction ☐ fetal malformations ☐ other
Bishop's score	_____
NST before commencing induction	◯ Reassuring ◯ Suspicious ◯ Abnormal
Number of cycles of IOL	◯ 1 ◯ 2
First cycle	◯ Prandin ◯ Misoprostol
Second cycle	◯ Prandin ◯ Misoprostol
Total number of doses of oral misoprostol	_____
Total number of doses of Prandin	_____
Time of prandin dose 1	_____
Time of prandin dose 2	_____
Time of prandin dose 3	_____
Time of prandin dose 4	_____
Failed induction	◯ Yes ◯ No
Date at first dose of induction agent	_____

Time at first dose of induction agent _____

Did labour occur?
- ◯ Yes
- ◯ No

Time at onset of labour _____

Date of delivery _____

Time at delivery _____

Use of syntocinon
- ◯ Yes
- ◯ No

Delivery outcome
- ◯ NVD
- ◯ C/S

Indication for C/S
- ☐ Fetal distress
- ☐ Failed induction
- ☐ CPD
- ☐ Poor progress
- ☐ APH
- ☐ Uterine dehiscence
- ☐ Chorioamnionitis
- ☐ Other

Define Other _____

Time from booking to C/S taking place (hrs:min) _____

Analgesia used
- ◯ Yes
- ◯ No

Type of analgesia used
- ◯ Pethidine
- ◯ Phenergan
- ◯ Aterax
- ◯ Morphine
- ◯ Epidural

Time analgesia given dose 1 _____

Time analgesia dose 2 _____

Time analgesia dose 3 _____

Fetal complications
- ◯ Yes
- ◯ No

Type of fetal complication
- ◯ TTN
- ◯ RDS
- ◯ MAS (meconium aspiration syndrome)
- ◯ Other

Define other _____

Neonatal outcome
- ◯ Alive
- ◯ FSB
- ◯ MSB

Neonatal ICU admission
- ◯ Yes
- ◯ No

Weight (grams) _____

Apgar at 5 min _____

Maternal complication
- ◯ Yes
- ◯ No

Type of maternal Complication
- ◯ Uterine rupture
- ◯ Post partum haemorrhage
- ◯ Instrumental delivery
- ◯ Uterine hyperstimulation
- ◯ Chorioamnionitis
- ◯ Other

Define other _____

Other information

Comments

_____

Appendix C: Ethics approval

R14/49 Dr Hatel Laloo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151126

NAME: (Principal Investigator)	Dr Hatel Laloo
DEPARTMENT:	Obstetrics and Gynaecology Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	A Prospective Study of the Induction of Labour at Rahima Moosa Mother and Child Hospital
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (21/12/2015)
SUPERVISOR:	Dr Shastra Bhoora
APPROVED BY:	Professor A Dhai, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: Turnitin report

Turnitinfinalsubmission.docx

ORIGINALITY REPORT

5%	1%	5%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Anesthetic and Obstetric Management of High-Risk Pregnancy, 2004. Publication	1%
2	Anim-Somuah, Millicent, Rebecca MD Smyth, Leanne Jones, and Millicent Anim-Somuah. "Epidural versus non-epidural or no analgesia in labour", Cochrane Database of Systematic Reviews Reviews, 2011. Publication	1%
3	Alfirevic, Zarko, Nasreen Aflaifel, Andrew Weeks, and Andrew Weeks. "Oral misoprostol for induction of labour", Cochrane Database of Systematic Reviews, 2014. Publication	<1%
4	"POSTER PRESENTATIONS", BJOG An International Journal of Obstetrics & Gynaecology, 09/2008 Publication	<1%
5	Wing, D.A.. "Titrated oral misoprostol was as effective as dinoprostone for induction of	<1%

Reviews, 2012.
Publication

39	talkbirth.me Internet Source	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

REFERENCES

1. Dick-Read G. 1953 [Available from: http://birthwithoutfearblog.com/2010/11/29/birth-without-fears-favorite-quotes] Accessed 10 February 2017.
2. National Institute for Clinical Excellence. Inducing labour. NICE guideline. 2008;CG70.
3. Cronje H, Grobler C. Obstetrics in Southern Africa. 2nd ed. Pretoria: Van Schaik Publishers; 2003. p. 245-50.
4. Leduc D, Biringer A, Lee L, Dy J, Clinical Practice Obstetrics C, Special C. Induction of labour. J Obstet Gynaecol Can. 2013;35(9):840-57. [http://dx.doi.org/10.1016/S1701-2163(15)30842-2]
5. Blickstein I. Induction of labour. J Matern Fetal Neonatal Med. 2009;22 Suppl 2:31-7. [http://dx.doi.org/10.1080/14767050902860567]
6. Deshmukh VL, Yelikar KA, Waso V. Comparative study of efficacy and safety of oral versus vaginal misoprostol for induction or labour. J Obstet Gynaecol India. 2013;63(5):321-4. [http://dx.doi.org/10.1007/s13224-012-0337-3]
7. Vogel JP, Souza JP, Gulmezoglu AM. Patterns and Outcomes of Induction of Labour in Africa and Asia: a secondary analysis of the WHO Global Survey on Maternal and Neonatal Health. PLoS One. 2013;8(6):e65612. [http://dx.doi.org/10.1371/journal.pone.0065612]
8. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin No.107. Obstet Gynecol. 2009;114:386-97.
9. Wing D. Induction of labor 2017 [Available from: http://www.uptodate.com/home/index.html] Accessed 24 February 2017.
10. Dewhurst K. Dewhurst's Textbook of Obstetrics and Gynaecology. In: Edmonds K, editor. 8th ed. Oxford, UK: Wiley-Blackwell; 2012.
11. Khan RA, Khan ZE, Ashraf O. Concurrent versus sequential methods for labor induction at term. Int J Gynaecol Obstet. 2007;96(2):94-7. [http://dx.doi.org/10.1016/j.ijgo.2006.10.002]
12. Kambhampati K, Reddy M, Quadri I, Suneetha B, Ramya V. Comparative study of oral and vaginal misoprostol for induction of labour, maternal and Foetal outcome. Journal of clinical and diagnostic research. 2013;7(12):2866-9.
13. Sanchez-Ramos L, Kaunitz A. Induction of labor 2009. [http://dx.doi.org/10.3843/GLOWM.10130] Accessed 17 February 2017.

14. Sreegouri S. Labor induction: history, physiological background, different methods of labor induction 2012 [Available from: http://srsree.blogspot.com/2012/03/labor-induction-history-physiological.html] Accessed 24 February 2017.
15. Nabi HA, Aflaifel NB, Weeks AD. A hundred years of induction of labour methods. European journal of obstetrics, gynecology,and reproductive biology. 2014;179:236-9. [http://dx.doi.org/10.1016/j.ejogrb.2014.03.045]
16. Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Boulvain M. Mechanical methods for induction of labour. The Cochrane database of systematic reviews. 2012(3):CD001233. [http://dx.doi.org/10.1002/14651858.CD001233.pub2]
17. Kelly AJ, Kavanagh J, Thomas J. Castor oil, bath and/or enema for cervical priming and induction of labour. The Cochrane database of systematic reviews. 2001(2):CD003099. [http://dx.doi.org/10.1002/14651858.CD003099]
18. Lippert TH, Mueck AO. Labour induction with alternative drugs? Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2002;22(4):343. [http://dx.doi.org/10.1080/01443610220141218]
19. Modlock J, Nielsen BB, Uldbjerg N. Acupuncture for the induction of labour: a double-blind randomised controlled study. BJOG. 2010;117(10):1255-61. [http://dx.doi.org/10.1111/j.1471-0528.2010.02647.x]
20. Nishi D, Shirakawa MN, Ota E, Hanada N, Mori R. Hypnosis for induction of labour. The Cochrane database of systematic reviews. 2014(8):CD010852. [http://dx.doi.org/10.1002/14651858.CD010852.pub2]
21. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Medley N, Dias S, et al. Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2016;20(65):1-584. [http://dx.doi.org/10.3310/hta20650]
22. Lim CE, Ng RW, Xu K. Non-hormonal methods for induction of labour. Curr Opin Obstet Gynecol. 2013;25(6):441-7. [http://dx.doi.org/10.1097/GCO.0000000000000027]
23. Collingham JP, Fuh KC, Caughey AB, Pullen KM, Lyell DJ, El-Sayed YY. Oral misoprostol and vaginal isosorbide mononitrate for labor induction: a randomized controlled trial. Obstet Gynecol. 2010;116(1):121-6. [http://dx.doi.org/10.1097/AOG.0b013e3181e408f2]
24. Dowswell T, Kelly AJ, Livio S, Norman JE, Alfirevic Z. Different methods for the induction of labour in outpatient settings. The Cochrane database of systematic reviews. 2010(8):CD007701. [http://dx.doi.org/10.1002/14651858.CD007701.pub2]

25. Kavanagh J, Kelly AJ, Thomas J. Hyaluronidase for cervical ripening and induction of labour. The Cochrane database of systematic reviews. 2006(2):CD003097. [http://dx.doi.org/10.1002/14651858.CD003097.pub2]
26. Kavanagh J, Kelly AJ, Thomas J. Corticosteroids for cervical ripening and induction of labour. The Cochrane database of systematic reviews. 2006(2):CD003100. [http://dx.doi.org/10.1002/14651858.CD003100.pub2]
27. Kelly AJ, Kavanagh J, Thomas J. Relaxin for cervical ripening and induction of labour. The Cochrane database of systematic reviews. 2001(2):CD003103. [http://dx.doi.org/10.1002/14651858.CD003103]
28. Hapangama D, Neilson JP. Mifepristone for induction of labour. The Cochrane database of systematic reviews. 2009(3):CD002865. [http://dx.doi.org/10.1002/14651858.CD002865.pub2]
29. Levine LD, Hirshberg A, Srinivas SK. Term induction of labor and risk of cesarean delivery by parity. J Matern Fetal Neonatal Med. 2014;27(12):1232-6. [http://dx.doi.org/10.3109/14767058.2013.864274]
30. Ivars J, Garabedian C, Devos P, Therby D, Carlier S, Deruelle P, et al. Simplified Bishop score including parity predicts successful induction of labor. European journal of obstetrics, gynecology, and reproductive biology. 2016;203:309-14. [http://dx.doi.org/10.1016/j.ejogrb.2016.06.007]
31. World Health Organization. Obesity: preventing and managing the global epidemic: World Health Organization; 2000.
32. The heart and stroke foundation South Africa 2016 [Available from: http://www.heartfoundation.co.za/media-releases/national-obesity-week-south-africa's-weighty-problem] Accessed 12 March 2017.
33. Pattinson R. Saving Mothers 2014-2016: The Seventh Report of the National Committee for Confidential Enquiries into Maternal Deaths in South Africa. Pretoria: Government Printer. 2018. [https://www.sasog.co.za/Content/Docs/Saving_Mothers.pdf] Accessed 10 April 2018.
34. Vinturache A, Moledina N, McDonald S, Slater D, Tough S. Pre-pregnancy Body Mass Index (BMI) and delivery outcomes in a Canadian population. BMC pregnancy and childbirth. 2014;14:422. [http://dx.doi.org/10.1186/s12884-014-0422-y]
35. Arrowsmith S, Wray S, Quenby S. Maternal obesity and labour complications following induction of labour in prolonged pregnancy. BJOG. 2011;118(5):578-88. [http://dx.doi.org/10.1111/j.1471-0528.2010.02889.x]

36. World Health Organization. WHO recommendations for induction of labour: Geneva: World Health Organization; 2011.
37. Elden H, Hagberg H, Wessberg A, Sengpiel V, Herbst A, Bullarbo M, et al. Study protocol of SWEPIS a Swedish multicentre register based randomised controlled trial to compare induction of labour at 41 completed gestational weeks versus expectant management and induction at 42 completed gestational weeks. BMC pregnancy and childbirth. 2016;16:49. [http://dx.doi.org/10.1186/s12884-016-0836-9]
38. Feldman GB. Prospective risk of stillbirth. Obstet Gynecol. 1992;79(4):547-53.
39. Arif A, Khan N, Zeb L. Mode of delivery and fetal outcome in patients with pro-longed pregnancy undergoing elective induction at 41 & 41+ weeks. J Postgrad Med Inst. 2015;29(4):227-30.
40. Galal M, Symonds I, Murray H, Petraglia F, Smith R. Postterm pregnancy. Facts Views Vis Obgyn. 2012;4(3):175-87.
41. Dekker RL. Labour induction for late-term or post-term pregnancy. Women Birth. 2016;29(4):394-8. [http://dx.doi.org/10.1016/j.wombi.2016.01.007]
42. Geerts L, Poggenpoel E, Theron G. A comparison of pregnancy dating methods commonly used in South Africa: a prospective study. S Afr Med J. 2013;103(8):552-6. [http://dx.doi.org/10.7196/samj.6751]
43. Savitz DA, Terry JW, Jr., Dole N, Thorp JM, Jr., Siega-Riz AM, Herring AH. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. Am J Obstet Gynecol. 2002;187(6):1660-6.
44. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. The Cochrane database of systematic reviews. 2015(7):CD007058. [http://dx.doi.org/10.1002/14651858.CD007058.pub3]
45. Geerts L, Theron AM, Grove D, Theron GB, Odendaal HJ. A community-based obstetric ultrasound service. Int J Gynaecol Obstet. 2004;84(1):23-31.
46. van Dyk B, Motto JA, Buchmann EJ. Routine second-trimester ultrasound for low risk pregnancies in a South African community. Int J Gynaecol Obstet. 2007;98(3):257-8. [http://dx.doi.org/10.1016/j.ijgo.2007.03.034]
47. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. Lancet. 1987;1(8543):1192-4.
48. Norwitz E. Postterm pregnancy 2016 [Available from: http://www.uptodate.com/home/index.html] Accessed 20 March 2017.
49. Fankhauser C, Burklin IF, Hodel M, Origlia Ikhilor P. [Prelabour Rupture of Membranes at Term: In- or Outpatient Management? A Survey in Birth Institutions in

the German-Speaking Part of Switzerland]. Z Geburtshilfe Neonatol. 2016;220(5):207-14. [http://dx.doi.org/10.1055/s-0042-111016]

50. Dare MR, Middleton P, Crowther CA, Flenady VJ, Varatharaju B. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). The Cochrane database of systematic reviews. 2006(1):CD005302. [http://dx.doi.org/10.1002/14651858.CD005302.pub2]

51. Jha N, Sagili H, Jayalakshmi D, Lakshminarayanan S. Comparison of efficacy and safety of sublingual misoprostol with intracervical dinoprostone gel for cervical ripening in prelabour rupture of membranes after 34 weeks of gestation. Archives of gynecology and obstetrics. 2015;291(1):39-44. [http://dx.doi.org/10.1007/s00404-014-3383-5]

52. Hannah ME, Ohlsson A, Farine D, Hewson SA, Hodnett ED, Myhr TL, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. N Engl J Med. 1996;334(16):1005-10. [http://dx.doi.org/10.1056/NEJM199604183341601]

53. Practice CoO. Prevention of Early-onset Group B Streptococcal Disease in Newborns: Committee Opinion Number 485. Obstetric Anesthesia Digest. 2012;32(2):84-5.

54. No G-tG. The prevention of early-onset neonatal Group B Streptococcal disease. London: RCOG. 2012.

55. Chan WS, Chua SC, Gidding HF, Ramjan D, Wong MY, Olma T, et al. Rapid identification of group B streptococcus carriage by PCR to assist in the management of women with prelabour rupture of membranes in term pregnancy. The Australian & New Zealand journal of obstetrics & gynaecology. 2014;54(2):138-45. [http://dx.doi.org/10.1111/ajo.12145]

56. Bricker L, Peden H, Tomlinson AJ, Al-Hussaini TK, Idama T, Candelier C, et al. Titrated low-dose vaginal and/or oral misoprostol to induce labour for prelabour membrane rupture: a randomised trial. BJOG. 2008;115(12):1503-11. [http://dx.doi.org/10.1111/j.1471-0528.2008.01890.x]

57. Zhang Y, Wang J, Yu Y, Xie C, Xiao M, Ren L. Misoprostol versus prostaglandin E2 gel for labor induction in premature rupture of membranes after 34 weeks of pregnancy. Int J Gynaecol Obstet. 2015;130(3):214-8. [http://dx.doi.org/10.1016/j.ijgo.2015.04.031]

58. Nagpal MB, Raghunandan C, Saili A. Oral misoprostol versus intracervical prostaglandin E2 gel for active management of premature rupture of membranes at

term. Int J Gynaecol Obstet. 2009;106(1):23-6. [http://dx.doi.org/10.1016/j.ijgo.2009.03.014]

59. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009;374(9694):979-88. [http://dx.doi.org/10.1016/S0140-6736(09)60736-4]

60. Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). Bmj. 2010;341:c7087. [http://dx.doi.org/10.1136/bmj.c7087]

61. American Diabetes A. 13. Management of Diabetes in Pregnancy. Diabetes Care. 2017;40(Suppl 1):S114-S9. [http://dx.doi.org/10.2337/dc17-S016]

62. Caughey AB, Valent AM. When to Deliver Women with Diabetes in Pregnancy? Am J Perinatol. 2016;33(13):1250-4. [http://dx.doi.org/10.1055/s-0036-1585589]

63. Group HSCR. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG. 2010;117(5):575-84. [http://dx.doi.org/10.1111/j.1471-0528.2009.02486.x]

64. American College of Obstetricians Gynecologists. Gestational diabetes. ACOG practice bulletin no. 180. Obstet Gynecol. 2017;130(1):e17-31.

65. Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean section. The Cochrane database of systematic reviews. 2013(3):CD009792. [http://dx.doi.org/10.1002/14651858.CD009792.pub2]

66. Al-Zirqi I, Stray-Pedersen B, Forsen L, Daltveit AK, Vangen S. Uterine rupture: trends over 40 years. BJOG. 2016;123(5):780-7. [http://dx.doi.org/10.1111/1471-0528.13394]

67. Lydon-Rochelle M, Holt VL, Easterling TR, Martin DP. Risk of uterine rupture during labor among women with a prior cesarean delivery. N Engl J Med. 2001;345(1):3-8. [http://dx.doi.org/10.1056/NEJM200107053450101]

68. Martel MJ, MacKinnon CJ, Clinical Practice Obstetrics Committee SoO, Gynaecologists of C. Guidelines for vaginal birth after previous Caesarean birth. J Obstet Gynaecol Can. 2005;27(2):164-88.

69. Gebhardt S, Arends E. Standardised Maternal Guideline for induction of liabour with misoprostol: guideline. South African Journal of Obstetrics and Gynaecology. 2008;14(1):43-8.

70. Stephenson ML, Wing DA. A novel misoprostol delivery system for induction of labor: clinical utility and patient considerations. Drug Des Devel Ther. 2015;9:2321-7. [http://dx.doi.org/10.2147/DDDT.S64227]
71. Arulkumaran S, Gibb DM, TambyRaja RL, Heng SH, Ratnam SS. Failed induction of labour. The Australian & New Zealand journal of obstetrics & gynaecology. 1985;25(3):190-3.
72. Johnson DP, Davis NR, Brown AJ. Risk of cesarean delivery after induction at term in nulliparous women with an unfavorable cervix. Am J Obstet Gynecol. 2003;188(6):1565-9; discussion 9-72.
73. Keepanasseril A, Suri V, Bagga R, Aggarwal N. A new objective scoring system for the prediction of successful induction of labour. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2012;32(2):145-7. [http://dx.doi.org/10.3109/01443615.2011.637142]
74. Verhoeven CJ, Opmeer BC, Oei SG, Latour V, van der Post JA, Mol BW. Transvaginal sonographic assessment of cervical length and wedging for predicting outcome of labor induction at term: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2013;42(5):500-8. [http://dx.doi.org/10.1002/uog.12467]
75. Bernardes TP, Broekhuijsen K, Koopmans CM, Boers KE, van Wyk L, Tajik P, et al. Caesarean section rates and adverse neonatal outcomes after induction of labour versus expectant management in women with an unripe cervix: a secondary analysis of the HYPITAT and DIGITAT trials. BJOG. 2016;123(9):1501-8. [http://dx.doi.org/10.1111/1471-0528.14028]
76. Chen W, Xue J, Peprah MK, Wen SW, Walker M, Gao Y, et al. A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labour. BJOG. 2016;123(3):346-54. [http://dx.doi.org/10.1111/1471-0528.13456]
77. Thomas J, Fairclough A, Kavanagh J, Kelly AJ. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. The Cochrane database of systematic reviews. 2014(6):CD003101. [http://dx.doi.org/10.1002/14651858.CD003101.pub3]
78. Bygdeman M. Pharmacokinetics of prostaglandins. Best Pract Res Clin Obstet Gynaecol. 2003;17(5):707-16.
79. Matonhodze BB, Hofmeyr GJ, Levin J. Labour induction at term--a randomised trial comparing Foley catheter plus titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone. S Afr Med J. 2003;93(5):375-9.

80. Calder AA, Loughney AD, Weir CJ, Barber JW. Induction of labour in nulliparous and multiparous women: a UK, multicentre, open-label study of intravaginal misoprostol in comparison with dinoprostone. BJOG. 2008;115(10):1279-88. [http://dx.doi.org/10.1111/j.1471-0528.2008.01829.x]
81. Rouzi AA, Alsibiani S, Mansouri N, Alsinani N, Darhouse K. Randomized clinical trial between hourly titrated oral misoprostol and vaginal dinoprostone for induction of labor. Am J Obstet Gynecol. 2014;210(1):56 e1-6. [http://dx.doi.org/10.1016/j.ajog.2013.08.033]
82. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. The Cochrane database of systematic reviews. 2014(6):CD001338. [http://dx.doi.org/10.1002/14651858.CD001338.pub3]
83. American College of Obstetricians and Gynecologists. Obstetric analgesia and anesthesia. ACOG Practice Bulletin No. 177. Obstet Gynecol. 2017;129:e73-89.
84. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. The Cochrane database of systematic reviews. 2011(12):CD000331. [http://dx.doi.org/10.1002/14651858.CD000331.pub3]
85. Antonakou A, Papoutsis D. The Effect of Epidural Analgesia on the Delivery Outcome of Induced Labour: A Retrospective Case Series. Obstet Gynecol Int. 2016;2016:5740534. [http://dx.doi.org/10.1155/2016/5740534]
86. Bannister-Tyrrell M, Ford JB, Morris JM, Roberts CL. Epidural analgesia in labour and risk of caesarean delivery. Paediatr Perinat Epidemiol. 2014;28(5):400-11. [http://dx.doi.org/10.1111/ppe.12139]
87. Wilson M, MacArthur C, Gao Smith F, Homer L, Handley K, Daniels J, et al. The RESPITE trial: remifentanil intravenously administered patient-controlled analgesia (PCA) versus pethidine intramuscular injection for pain relief in labour: study protocol for a randomised controlled trial. Trials. 2016;17(1):591. [http://dx.doi.org/10.1186/s13063-016-1708-3]
88. Davey MA, King J. Caesarean section following induction of labour in uncomplicated first births- a population-based cross-sectional analysis of 42,950 births. BMC pregnancy and childbirth. 2016;16:92. [http://dx.doi.org/10.1186/s12884-016-0869-0]
89. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. Bmj. 2015;350:h217. [http://dx.doi.org/10.1136/bmj.h217]

90. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG. 2001;108(9):952-9.
91. Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term--a comparative study. S Afr Med J. 2003;93(5):371-4.
92. Malende B, Moodley J, Kambaran S. Induction of labour at a regional hospital in KwaZulu-Natal, South Africa: research. South African Journal of Obstetrics and Gynaecology. 2014;20(1):22-6.
93. MacKenzie IZ, Cooke I. What is a reasonable time from decision-to-delivery by caesarean section? Evidence from 415 deliveries. BJOG. 2002;109(5):498-504.
94. National Institute for Clinical Excellence. Caesarean section. NICE guideline. 2011;CG132.
95. Griffiths M. What is the acceptable decision-to-delivery interval for an emergency caesarean section? BJOG. 2016;123(3):476. [http://dx.doi.org/10.1111/1471-0528.13718]
96. Tochie JN, Choukem SP, Langmia RN, Barla E, Koki-Ndombo P. Neonatal respiratory distress in a reference neonatal unit in Cameroon: an analysis of prevalence, predictors, etiologies and outcomes. Pan Afr Med J. 2016;24:152. [http://dx.doi.org/10.11604/pamj.2016.24.152.7066]
97. Madhi SA, Radebe K, Crewe-Brown H, Frasch CE, Arakere G, Mokhachane M, et al. High burden of invasive Streptococcus agalactiae disease in South African infants. Ann Trop Paediatr. 2003;23(1):15-23. [http://dx.doi.org/10.1179/000349803125002814]
98. Gibbins KJ, Weber T, Holmgren CM, Porter TF, Varner MW, Manuck TA. Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. Am J Obstet Gynecol. 2015;213(3):382 e1-6. [http://dx.doi.org/10.1016/j.ajog.2015.05.048]
99. Belfort M. Overview of postpartum haemorrhage 2017 [Available from: http://www.uptodate.com/home/index.html] Accessed 04 April 2017.
100. Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124(5):e106-e49. [http://dx.doi.org/10.1111/1471-0528.14178]
101. Kelly AJ, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. The Cochrane database of systematic reviews. 2001(2):CD003101. [http://dx.doi.org/10.1002/14651858.CD003101]
102. Ayaz H, Black M, Madhuvrata P, Shetty A. Maternal and neonatal outcomes following additional doses of vaginal prostaglandin E2 for induction of labour: a

retrospective cohort study. European journal of obstetrics, gynecology, and reproductive biology. 2013;170(2):364-7. [http://dx.doi.org/10.1016/j.ejogrb.2013.07.021]

103. Hofmeyr GJ, Matonhodze BB, Alfirevic Z, Campbell E, de Jager M, Nikodem C. Titrated oral misoprostol solution--a new method of labour induction. S Afr Med J. 2001;91(9):775-6.

104. Buchmann EJ, Edridge WW, Guidozzi F, Frank K. Wits Obstetrics 2017. Bera E, editor: Department of Obstetrics and Gynaecology, University of the Witwatersrand; 2017.

105. American College of Obstetricians and Gynecologists. Methods for Estimating the Due Date. Committee Opinion No. 700. Obstet Gynecol. 2017;129:150-4.

106. Hannah ME, Hodnett ED, Willan A, Foster GA, Di Cecco R, Helewa M. Prelabor rupture of the membranes at term: expectant management at home or in hospital? The TermPROM Study Group. Obstet Gynecol. 2000;96(4):533-8.

107. Enabor OO, Olayemi OO, Bello FA, Adedokun BO. Cervical ripening and induction of labour-awareness, knowledge and perception of antenatal attendees in Ibadan, Nigeria. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2012;32(7):652-6. [http://dx.doi.org/10.3109/01443615.2012.657271]