THE EFFECT OF MISOPROSTOL ON FETAL HEART RATE PARAMETERS DURING INDUCTION OF LABOUR FROM 38 WEEKS GESTATION

A RETROSPECTIVE AUDIT

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The effect of misoprostol to fetal heart rate parameters during induction of labour from 38 weeks gestation: A Retrospective Audit.

KEY WORDS

Misoprostol

Fetal heart rate

Intrauterine death

Postterm

DISCLAIMER:

I, A.M Feketshane hereby declare that this research project is my original work and has never been submitted to any institution for assessment purposes.

I have acknowledged all sources used and have cited this in the reference section.

Signature: _____   Date: _____

DEDICATION:

This work is dedicated to my late parents, Monwabisi and Nolusapho Feketshane.

My hat off for you guys for the student I have grown to become. I would have done

injustice if I don't mention my brothers Fundile and Zwelandile Feketshane for their

unwavering support during my training period, You truly made every day worth living.

ACKNOWLEDGEMENTS:

My sincere gratitude goes to everyone who made it possible for me to complete this mammoth task.

I wish to thank in particular all the nurses in our antenatal ward F2 who were tirelessly helped me gather the register of all patients who qualified for my study.

I also feel indebted to everyone in the Medical Records and two student interns who put aside their daily duties to assist with my information gathering.

My greatest debt of gratitude goes to my supervisor Professor D.W. Steyn who sacrificed his holiday period and some of his daily duties to offer guidance and input to my progress in order to adhere to the stipulated deadlines. I can confess Prof that I am now a better researcher after this exercise.

ABBREVIATIONS USED

CI   - Confidence Interval

CTG   - Cardiotocograph

e.g.   - for example

FHR   - Fetal Heart Rate

IUD   - Intrauterine Death

ICU   - Intensive Care Unit

mcg   - micrograms

NICE - National Institute for Clinical Excellence

RR   - Relative Risk

SPSS - Statistical Package for Social Science

ABSTRACT

Misoprostol is often used for the purpose of induction of labour. However, its effect on fetal heart rate has not been systematically studied.

Objective

To assess the effect of misoprostol on fetal heart rate parameters during induction of labour from 38 completed weeks in women with previous intrauterine death or postterm pregnancy.

Study design

A retrospective descriptive study of 127 women for a period of 18 months.

Method

Women who underwent induction of labour with misoprostol for either previous intrauterine death or postterm pregnancy at Tygerberg hospital were eligible.

The selected process of induction of labour happened according to the departmental protocol. The primary outcomes were changes in fetal heart rate (variability, accelerations and decelerations) pre-and post-administration of misoprostol. Secondary outcomes were neonatal highcare or intensive care unit (ICU) admissions.

Results

There was no statistical difference in the mean fetal heart rate and baseline variability in relation to time recordings after administration of misoprostol. There were no statistically significant differences in the distribution of accelerations and

decelerations in different time intervals before and after administration. There were more reactive patterns at all time intervals after the administration of misoprostol, but these differences did not quite reach statistical significance. In both study groups no neonatal complications or intensive care admissions were reported.

Conclusion

In the absence of contra indications, 50mcg of oral misoprostol can be given to mothers for induction of labour as no harmful fetal heart tracing abnormalities were found for 45 minutes; however large prospective randomized controlled trials are still needed to confirm effectiveness and evaluate further maternal and neonatal safety issues. Optimal dose and frequency also still need robust interrogation. Based on this thesis it does appear that misoprostol is probably not harmful to the fetus under these circumstances.

ABSTRAK

Misoprostol word dikwels gebruik vir induksie van kraam. Die effek daarvan op fetale hartspoed is egter nie sistematies ondersoek nie.

Doel

Om die effek van misoprostol op fetale hartspoedparameters gedurende die induksie van kraam van 38 voltooide weke in vroue met vorige intra-uteriene dood or oortyd swangerskap te evalueer.

Studei-ontwerp

'n Retrospektiewe beskrywende studie van 127 vroue oor 'n periode van 18 maande.

Metode

Vroue wat induksie van kraam met misoprostol ondergaan het vir of vorige intra-uteriene dood of oortyd swangerskap by Tygerberg Hospitaal is ingesluit.

Die proses van induksie van kraam is volgens departementele protokol uitgevoer. Die primêre uitkomste was veranderinge in fetale hartspoed (variasie, versnellings en verstadigings) pre- en post-toediening van misoprostol. Neonatale hoësorg of intensiewe sorg toelatings was sekondêre uitkomste.

Resultate

Ons het geen statistiese verskille in gemiddelde fetale hartspoed en basislynvariasie in verhouding tot die tyd na toediening van misoprostol gevind nie. Daar was geen statisties betekenisvolle verskille in die verspreiding van versnellings en verstadigings in verskillende tydsintervalle nie. Daar was meer reaktiewe patrone gedurende alle tydsintervalle na die toediening van misoprostol, maar hierdie

verskille was nie statisties betekenisvol nie. In beide studiegroepe was daar geen neonatale komplikasies of intensiewe sorg toelatings nie.

Gevolgtrekking

In die afwesigheid van kontra-indikasies kan 50 mcg misoprostol aan moeders toegedien word vir induksie van kraam aangesien geen skadelike fetale hartsped abnormaliteite gevind is nie. Groot prospektiewe gerandomiseerde gekontroleerde studies word steeds benodig om effektiwiteit te bevestig en om moederlike en fetale veiligheidskwessies verder te evalueer. Optimale dosis en frekwensie benodig ook robuuste ondersoek. Gebaseer op hierdie tesis kom dit voor of misoprostol waarskynlik nie skadelik vir die fetus onder hierdie omstandighede nie.

INTRODUCTION

Induction of labour is a common intervention, performed for medical, obstetric or social indications. (1,2). More than 22% of all gravid women undergo induction of labour in the United States, where the incidence of induction of labour has more than doubled since 1990 to 225 per 1000 live births in 2006. (3) Corresponding figures for South Africa are not available.

Cervical ripening is the first component of labour induction. If the cervix is not sufficiently dilated, then drugs or mechanical cervical dilators should be used to ripen the cervix before labour is induced. Common medical and obstetric indications include post-term pregnancy, pre-labour rupture of membranes, hypertensive disorders and diabetes mellitus. (2) Various methods of induction of labour have been described. The approach in individual patient depends on the indication for induction of labour, the ripeness of the cervix and whether the membranes have ruptured. Prostaglandins are used to ripen the cervix in women with unfavourable cervical scores where the membranes cannot be ruptured.

Misoprostol is a synthetic prostaglandin analogue which is commonly used for induction of labour in various hospitals in the Western Cape including Tygerberg Hospital. It is cheap and heat stable. It both ripens the cervix and induces labour. Oral use of misoprostol may be convenient, but high doses could cause uterine hyperstimulation and uterine rupture which may be life threatening for both mother and fetus. When used in low doses oral misoprostol is as effective as vaginal dinoprostone, with no increased hyperstimulation. (4)

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If misoprostol is used orally the dose should not exceed 50mcg. This dose can be repeated every four hours for a total of six doses; this is therefore the protocol we follow at Tygerberg hospital.

It is likely that misoprostol will continue to be used for many more years to come and therefore warrants investigation to its effect to fetal heart rate parameters using National Institute for Clinical Excellence Guidelines (NICE) classification. This will be applied to the commonly induced group of women at Tygerberg hospital for example (e.g.) post-term and previous intrauterine deaths who are 38 weeks gestation and above with a live fetus in the index pregnancy.

LITERATURE REVIEW

Using the Medline database, an electronic search was done on the subject of effect of misoprostol on fetal heart rate parameters.

Articles were identified using the keywords "misoprostol" AND "fetal heart rate parameters".

The Med database, Up to date and Cochrane library were also searched.

INTRODUCTION

For a successful induction of labour, adequate uterine contractions and progressive dilatation of the uterine cervix is needed. This realization has therefore led to evolution of various methods used to ripen the cervix (e.g. Prostaglandins) and predict a possible outcome of the induction.

ASSESSMENT OF THE CERVIX

The cervix is a dynamic structure which undergoes many changes more pronounced during the late third trimester. (5) There are biochemical changes in the proteoglycan matrix and collagen degradation. There is a marked increase in vascularity, accumulation of interstitial fluid and migration of white cells into the cervical tissue. (5) These changes lead to alteration in bio-physical characteristics of the cervix in that they cause increased compliance and less resistance to dilatation.

Several cervical scoring systems have been proposed in an attempt to establish guidelines for cervical assessment, so as to predict the chances of a successful

induction. The most widely accepted of these various scores is the one proposed by Bishop in 1964, (6) who suggests assessment of five different characteristics:

(i) Level of descent of the presenting part

(ii) Cervical length

(iii) Cervical dilatation

(iv) Cervical consistency

(v) Position of the cervix relative to the axis of the pelvis.

HISTORICAL PERSPECTIVES

Before 20th century

Early literature records date to the 1500's, with a mixture of juniper berries, cinnamon and castor oil recommended to expedite birth. (7)

The medical history of labour induction really starts in the 18th century. Maculey in 1756 induced labour before term so as to avoid the hazards of both caesarean section and fetal extraction with a crochet. (8)

AFTER 20TH CENTURY

A new approach and the modern era of induction of labour began in 1928 with the introduction of purified posterior pituitary extract which later became established in 1955 when synthetically prepared oxytocin was made available commercially. (9) While the initial oxytocin preparation were crude and unreliable in effect,

development of syntocinon allowed intravenous titration to produce a more predictable and effective method of induction of labour, but by 1968 a rival in the form of prostaglandins had emerged for induction of labour. (10, 11)

This all happened after Karim in 1971 reported success with intravenous F2 alpha and prostaglandins E2 and they now have been widely used for induction of labour ever since.

Prostaglandins represent an excellent option for induction in women who because of unfavourable cervix with intact membranes are poor candidates for induction using oxytocin. To date the commercial availability of stable preparation e.g. Prostaglandins E2 and prostaglandins E1 (tablets) has increased the clinical use of prostaglandins for priming of the cervix and increase chances of vaginal delivery reducing the risk of caesarean section.

PROSTAGLANDINS

Their existence was established through observation by Kurzork and Lieb in 1930, who noticed the ability of human semen to initiate uterine contractions. (12) Von Euler isolated substances from male prostate that were shown to initiate contractions of the uterus and named them prostaglandins. (13) Bergstroom and Sjovall isolated the first prostaglandins (PGF1 alpha in 1957 and in 1964), (14,15) and this led to biosynthesis of several uterotonic prostaglandins.

Prostaglandins consist of 20 carbon fatty acid molecules derived from dietary fatty acid, and consist of a pentane ring attached to 2 adjacent carbons. (16,17,18)

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Prostaglandins are classified into six groups (A to F), based on the structure or substitution of a pentane ring. The sub-script numerical (1,2,3) indicates the number of double bonds in the fatty acid back bone. (16,17,19).

Prostaglandins E1 has a trans double bond between C13 and C14 while prostaglandins E2 has an additional CIS double bond at the C5 C6 position (20,17)

MISOPROSTOL

It is a synthetic prostaglandin related to prostaglandin E1.

Figure (1) Development of misoprostol from prostaglandin E1 (Collins 1985)

Prostaglandin E1   **Misoprostol**
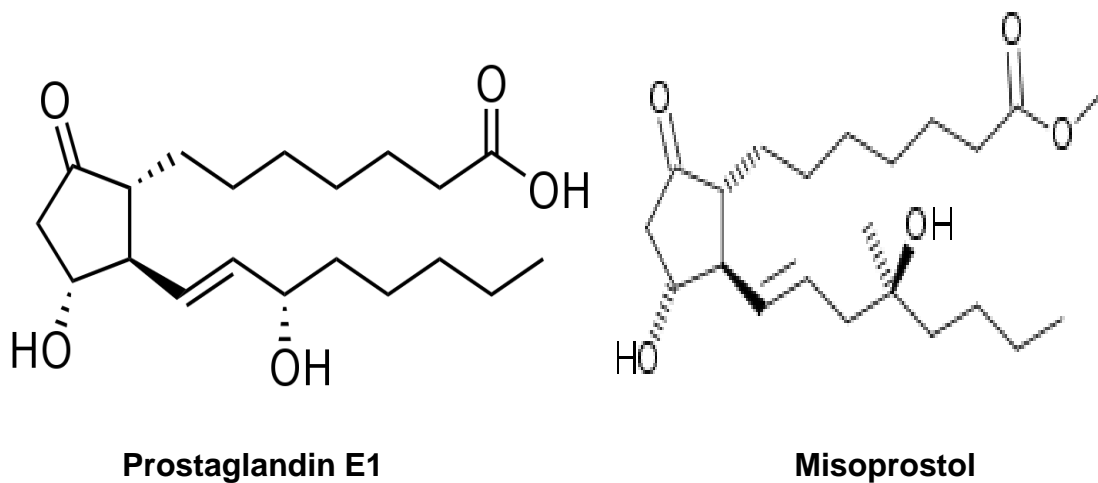
Prostaglandin E1 is an effective inhibitor of gastric acid secretion when administered intravenously. However there are a number of disadvantages when it is used in the treatment of peptic ulcer disease namely the(lack of oral activity, short duration of action and side effects e.g. nausea and vomiting, diarrhoea, trembling). (20)

Misoprostol was then developed to manipulate prostaglandin E1 to produce an orally active compound whilst minimizing side effects.

TOXICITY AND TERATOGENICITY

Pre-clinical trials evaluating the toxicity of misoprostol were performed in rats, mice and dogs in which most clinical sequalae were observed (diarrhoea, emesis, tremor, reduced motor activity). (15) The studies done indicate a safety margin of 500 to 1000 fold between the lethal doses observed in animals and therapeutic doses administered to humans.   Carcinogenic and fertility properties were also studied in rats, mice and rabbits without demonstrable effects attributable to misoprostol. (15) In conclusion misoprostol showed no evidence of embryo toxicity, fetotoxicity or teratogenicity. (15)

MISOPROSTOL FOR INDUCTION OF LABOUR

INTRODUCTION

Misoprostol is licenced for use in the treatment of gastric ulcers. Despite this it has and continues to be used off code in obstetric and gynaecology practice for first and second trimester terminations of pregnancy, (21) and in the third trimester of pregnancy for intrauterine deaths. (22) More recently misoprostol has been used for induction of labour at term in the presence of a viable fetus, with both vaginal (Hofmeyr 2005b) and oral (Alfirevic 2005) routes of administration being used.

SAFETY OF MISOPROSTOL

<u>Misoprostol and uterine rupture</u>

There have been several case reports of uterine rupture and its possible adverse outcomes when used as an induction agent (maternal or fetal death). (23,24,25,26) These were women with scarred and unscarred uteri after administration of either oral or vaginal misoprostol in the presence of a live fetus or intra-uterine death. Doses varied from 25mcg (23,24,26) up to 600mcg in cases of fetal demise. (25) Attempts have since been made to address safety of misoprostol use in a previously scarred uterus with Sciscione (1998) and Wing (1998) initiating randomised controlled trials.

Sciscione compared 50mcg intra-vaginal misoprostol at four hourly intervals with intra-cervical Foleys catheter (women with previous caesarean birth were not excluded). One woman with a scarred uterus suffered rupture following misoprostol but the results are inconclusive as it was not clear as to how many women with scarred uteri were involved.

Wing and colleagues randomised women with a previous caesarean birth where 17 women received 25mcg vaginal misoprostol at six hourly intervals and 21 women received oxytocin. Two women in the misoprostol group were diagnosed with scar disruption and due to the safety concerns of misoprostol in that environment, the trial was terminated prematurely. It is therefore not possible to advise on the safety of misoprostol in women with previous caesarean births until further studies emerge.

Misoprostol and Meconium stained liquor

This concern was raised as to whether the use of misoprostol leads to meconium stained liquor during induction of labour. (27) Postulation by Matonhodze (2002) was that in vitro animal studies indicate the stimulation of ileal smooth muscle by both dinoprostone and misoprostol. However the systematic reviews of both vaginal (Hofmeyr 2005b) and oral (Alfirevic 2005) routes provide re-assurance about the safety of misoprostol with regards to the presence of meconium stained liquor.

COCHRANE REVIEW

Oral misoprostol for induction of labour

Thirteen Randomised controlled trials (Alfirevic 2005) in which oral misoprostol was compared to prostaglandin E2, oxytocin, vaginal misoprostol and placebo, but only four were double blinded placebo controlled.
 One was misoprostol and prostaglandin E2. (28) The last two comparing oral with vaginal misoprostol. (29, 26)

Two trials were identified where oral misoprostol was compared with intravenous oxytocin. Women were allocated as follows, 50mcg at four hourly intervals,(30) and 100mcg four hourly. (31) Meta-analysis results of the two trials showed no difference in two outcomes; caesarean births (188 patients, Relative Risk (RR) 0.97, 95% Confidence Interval (CI) 0.43 – 2.22) and uterine hyperstimulation with fetal heart rate changes (188 patients, RR 0.96, 95% CI 0.25 – 3.66).

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Oral misoprostol versus vaginal prostaglandin E2

Two trials were identified involving 962 women. Women were given vaginal prostaglandin E2 or 50mcg oral misoprostol both six hourly to a maximum of four doses in a 24 hour cycle. (28) Random distribution vaginal prostaglandin E2 or titrated oral misoprostol solution starting at 20mcg increasing to 40mcg if no clinical effect was observed. (32)

Meta-analysis results of the two trials showed no difference in caesarean births (959 patients, RR 0.9, 95% CI 0.70 -1.17),uterine hyperstimulation with associated fetal heart rate changes (929 patients, RR 0.87, 95% CI 0.49 -1.56) and failure to achieve vaginal birth within the first 24 hours of induction of labour (691 patients, RR 1.19, 95% CI 0.94 – 1.51).

Oral misoprostol versus oral misoprostol

A meta-analysis showed that women receiving oral misoprostol in doses ranging from 50mcg four hourly to 100mg three hourly and 200mcg six hourly were more likely not to deliver within the first 24 hours. The four trials included 877 patients (RR 1.27, 95% CI 1.09 – 1.47).

If one looks at other outcomes oral misoprostol was associated with fewer caesarean births. This was confirmed in 7 trials that included 1276 patients (RR 0.77, 95% CI 0.61 – 0.97), and no differences were observed in uterine hyperstimulation and route of administration in 6 trials that included 1236 patients (RR 1.1, 95% CI 0.78 – 1.47).

UTERINE HYPERSTIMULATION

This is a well-recognised possible complication after induction of labour with prostaglandins and this can hamper utero placental perfusion which can ultimately present as fetal heart rate abnormalities. Uterine hyperstimulation is well documented and described following misoprostol induction of labour. (33, 34)

It is more pronounced with the use of vaginal misoprostol compared to oxytocin and vaginal prostaglandin E2. (34)

In trying to determine any effect of dose on the occurrence of hyperstimulation, lower dosing regimens defined as 25mcg or less at four hourly or less intervals have been compared with higher dosing regimens. (34)

Women who received lower doses of misoprostol were less prone to experience uterine hyperstimulation with fetal heart rate abnormalities (RR 0.50, 95% CI 0.36 – 0.71). There were also trends towards fewer infants with Apgar scores of <7 at five minutes (RR 0.76, 95% CI 0.40 – 1.45), and fewer neonatal ICU admissions (RR 0.82, 95% CI 0.64 – 1.05).

RATIONALE FOR STUDYING MISOPROSTOL

Although other agents are available in our hospital for pre-labour cervical ripening e.g. vaginal prostaglandin E2 and titrated doses of oxytocin for those with ruptured membranes and have been found to be safe and effective, however there are short-comings with their use.

Vaginal prostaglandin E2 for example is administered six hourly with multiple pelvic examinations by different care providers including high costs of the drug compared to misoprostol tablets.

We therefore assessed the effect of the current oral dosage (50mcg) of misoprostol as an induction agent on the fetal heart rate parameters using the NICE classification. The lack of information on the effect of misoprostol on fetal heart rate parameters further encouraged the study.

MATERIALS AND METHODS

We performed a retrospective descriptive study of all women who underwent induction of labour with misoprostol for either previous intrauterine death or postterm pregnancy at Tygerberg Hospital over an 18 month period. Names of women were identified from the antenatal ward register. We accepted the managing physicians indication for induction of labour as indicated in the patient notes.

The process of induction of labour happened according to a departmental protocol. Once the indication for induction of labour had been confirmed, clinicians ensured that no contra-indication to vaginal delivery existed. A vaginal examination was subsequently done to determine the Bishop score and to ascertain whether cervical ripeness was sufficient to rupture membranes. If not, misoprostol was used to improve the Bishop score to facilitate rupture of membranes at a later stage. The administration of misoprostol took place in the antenatal ward.

A cardiotocograph was performed for 15 minutes prior to the administrationof misoprostol. If the cardiotocograph showed a normal heart rate, variability above 5 beats per minute (BPM) and the absence of decelerations of the fetal heart rate (FHR), the patient took the first dosage of 50 micrograms misoprostol per os. The FHR was then monitored for another 45 minutes. A photostat was made of this record of the first cardiotocograph (approximately 60 minutes).

 All identifications, as well as the note indicating the time of misoprostol administration were removed from photocopies. The photocopy was then cut into five windows of ten minutes each representing the following five periods: The last 10 minutes before taking the dosage, the first ten minutes after taking the medication, minutes ten to 20 after taking the medication, minutes 20 to 30 after taking the

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medication and minutes 30 to 40 after taking the medication. These five copies were then numbered according to a list of computer generated numbers in blocks of 100. This meant that the assessor (Prof DW Steyn) assessed each individual ten minute strip without knowing which patient's record he was looking at or whether the strip was recorded before or after the medication was taken.

Assessment of each ten minute window was done according to the proposal of the National Institute for Clinical Excellence (NICE). In essence, each of the baseline fetal heart rate, fetal heart rate variability and decelerations were identified as reassuring, non-reassuring or abnormal. The presence of accelerations was considered to be reassuring. (See table).

Feature	Baseline (bpm)	Variability (bpm)	Decelerations	Accelerations
Reassuring	110–160	≥ 5	None	Present
Non-reassuring	100–109 161–180	< 5 for >40 to <90 minutes	Early deceleration Variable deceleration Single prolonged deceleration up to 3 minutes	The absence of accelerations with an otherwise normal CTG are of uncertain significance
Abnormal	<100 >180 Sinusoidal pattern ≥ 10 minutes	<5 for ≥ 90 minutes	Atypical variable decelerations Late decelerations Single prolonged Single prolonged deceleration >3 minutes	

Adapted from NICE fetal monitering guidelines, May 2001

The primary outcomes were:

1. Changes in fetal heart rate, fetal heart rate variability, accelerations and decelerations of the fetal heart rate pre- and post administration of misoprostol.

The secondary outcomes were:

1. Neonatal highcare or Intensive Care Unit (ICU) admissions.

The data was analysed using the SPSS software (Statistical Package for Social Science). Discrete data was compared by calculating relative risks with 95% confidence limits, as well as the chi^2 test. Fisher's exact test was used to compare ratios where the expected value in any cell of a two-by-two table was less than five. The means of normally distributed continuous data was compared by analysis of variance, while the medians of continuous data which are not distributed normally, were calculated using the non-parametric Mann Whitney u test. A p-value of < 0.05 was considered to be statistically significant, where applicable.

ETHIC APPROVAL

The project was registered with the Health Research and Ethics Committee (HREC) of the Health Sciences of Stellenbosch University. Ethics Approval with a waiver of consent was obtained **N11/08/248**.

RESULTS

We included data from 127 women who were admitted for induction of labour for either postterm pregnancy or a previous intrauterine death over an 18 month period. Seventy-five women had a previous intrauterine death as an indication for induction of labour, while postterm pregnancy was an indication in 52 cases. We analyzed data from the first cardiotocograph recorded immediately before and till forty minutes after the first administration of misoprostol, irrespective of how many courses the individual patients received. There were no deliveries, specifically for fetal distress, during the course of this first administration of misoprostol.

The demographic data of participants are shown in table 1.

	Previous IUD (n = 75)	Postterm (n = 52)	p-value
Age (years)	28.99 ± 5.3	28.31 ± 6.4	0.517
Gestational age at delivery (weeks)	38.03 ± 0.16	41.87 ± 1.10	0.000
Weight (kg)	86.21 ± 17.96	84.73 ± 18.89	0.655
Length (cm)	158.36 ± 7.20	158.96 ± 7.00	0.640
BMI (kg/m^3)	34.01 ± 6.17	33.17 ± 6.70	0.466
RPR positive	0	0	NA
HIV positive	5	8	0.10
Rh-positive	75	50	0.17
Smoker	28	14	0.15
Gravidity	2 (1-5)	2 (1-5)	0.009
Parity	2(1-4)	1(0-4)	0.003
Other complications during previous pregnancy	29 (38.7%)	14 (26.9%)	0.24

Table 1: The demographic data of participants

The nature of the complications during the previous pregnancy is summarized in Table 2.

	Previous IUD (n = 75)	Postterm (n = 52)
Acute Pyelonephritis	0	1
Asthma	2	2
Cardiovascular System	0	1
Diabetes Mellitus	6	0
Epilepsy	1	1
HIV	1	4
Hypertension	14	2
Hypothyroidism	1	1
Preterm Labour	2	1

Table 2: Complications which required attention during previous pregnancies

There were no previous IUD's in women who underwent induction of labour for postterm pregnancy, although two of these women had previous miscarriages. The related conditions at time of the previous IUD are summarized in Table 3.

	Gestational age at time of previous loss					TOTAL
	<28w	28 – 33w	34 - 37	>37 w	Unknown gestation	
Unknown cause	0	6	3	13	4	26
Abruptio placentae	0	5	8	1	0	14
Placental insufficiency	0	7	3	1	3	14
Chorioamnionitis	2	8	1	1	1	13
Congenital abnormalities	0	2	1	0	1	4
Cord prolapse	0	0	1	0	0	1
Other causes	1	2	0	0	0	3

Table 3: Details of the previous IUD's. The right part of the table indicates the gestational age at which the previous loss occurred.

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Twenty-one women underwent caesarean section. (Table 4). While fetal distress occurred more commonly in women with a history of previous IUD, this difference was not statistically significantly different.

	Previous IUD (n = 75)	Postterm (n = 52)
Vaginal delivery	62	44
Caesarean section for cephalo-pelvic disproportion	5	7
Caesarean section for fetal distress	8	1

Table 4: Route of delivery according to indication for induction of labour.

There were no clinically significant problems as far as antenatal fetal assessment was concerned. (Table 5).

	Previous IUD (n = 75)	Postterm (n = 52)	p-value
Umbilical artery Doppler			
• None	12	45	
• Below 75th Centile	6	0	
• 75th – 95th Centile	57	7	0.000
Abnormal SF-growth	0	0	--
Any other antenatal complications	0	0	--
Early ultrasound done	75	37	0.000

Table 5: Antenatal observations and investigations related to fetal well-being.

The perinatal outcome is summarized in Table 6. Seventy percent of babies were male.

	Previous IUD (n = 75)	Postterm (n = 52)	p-value
Birth weight < 2500g	7	8	0.22
Neonatal complications	0	0	--
Neonatal intensive care admission	0	0	--
Mean birth weight (g)	3142.7 ± 468.3	3092.4 ± 535.3	0.58
Gestational age (w)	38.03 ± 0.16	41.87 ± 1.10	0.000

Table 6: The perinatal outcome in the two study groups

The distribution of fetal heart rate characteristics is depicted in table 7.

	Mean / Median	25th Centile	50th Centile	75th Centile
Fetal heart rate (bpm)	134.52 ± 9.02	127.50	133.50	141.00
Accelerations (per 10 min)	2 (0 – 12)	0	2	4
Early Decelerations (per 10 min)	0 (0 – 2)	0	0	0
Variable Decelerations (per 10 min)	0 (0 – 5)	0	0	1
Atypical Variable Decelerations (per 10 min)	0 (0 – 4)	0	0	0
Late Decelerations (per 10 min)	0 (0 – 3)	0	0	0

Table 7: A summary of the major findings of the 635 cardiotocographs included in the study.

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The mean fetal heart rate and the mean fetal heart rate baseline variability for all cardiotocographs are shown in figure 1 and figure 2 respectively.
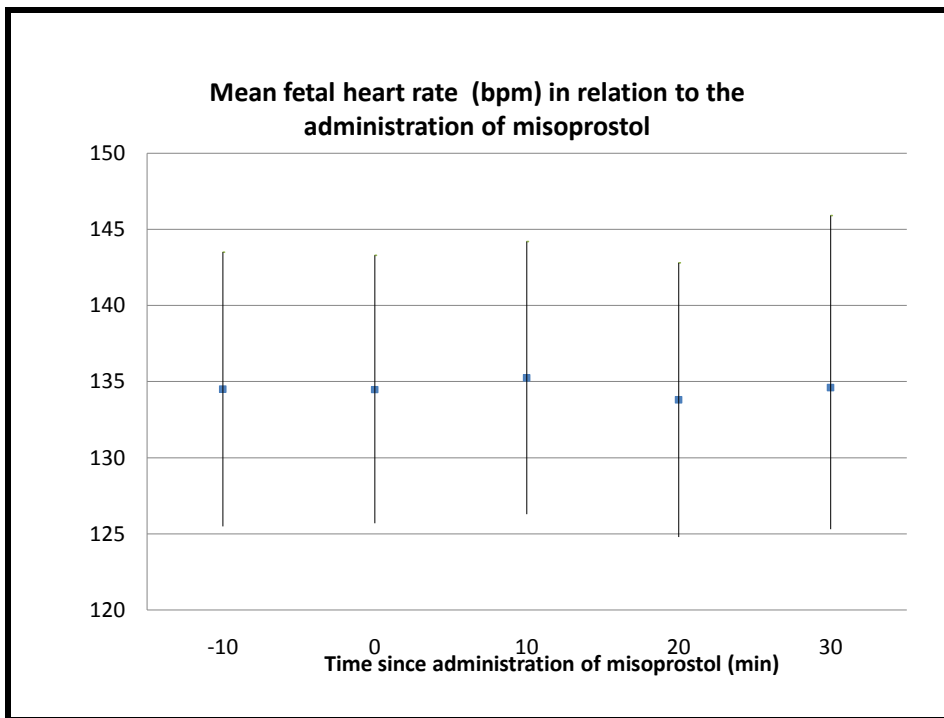

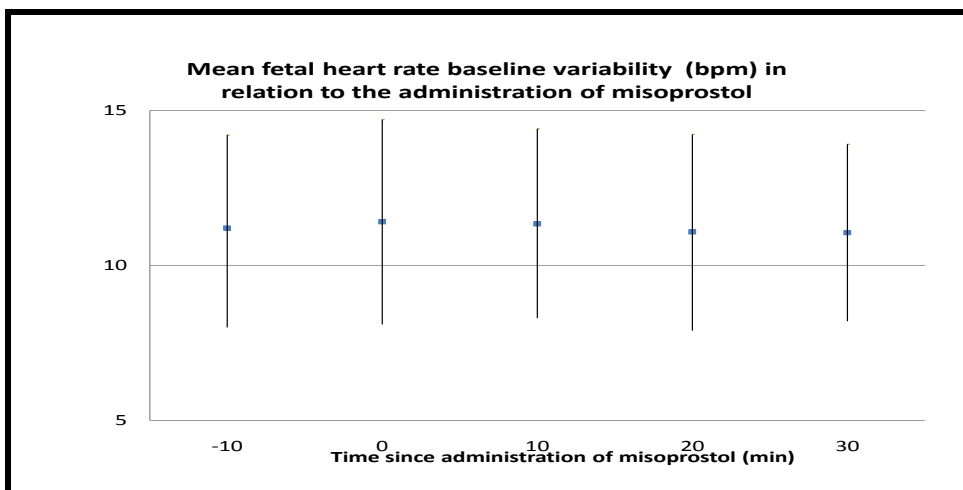Figure 1: The mean fetal heart rate for all recordings.

Figure 2: The mean fetal heart rate baseline variability for all recordings.

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The distribution of accelerations and decelerations in the different time intervals is shown in table 8. There were no statistically significant differences between any of the related groups.

	-10	0	10	20	30
Accelerations (per 10 min)	2 (0;3.75)	2 (1;4)	2 (1;4)	2 (0;4)	2 (1;4)
Early Decelerations (per 10 min)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)
Variable Decelerations (per 10 min)	0 (0;1)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)
Atypical Variable Decelerations (per 10 min)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)
Late Decelerations (per 10 min)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)
Variability (bpm)	11.2 ± 3.2	11.4 ±3.2	11.3 ±3.0	11.1 ±3.1	11.1 ±3.0

Table 8:   Changes in accelerations and decelerations of the fetal heart rate in relation to the timing of the administration of misoprostol (median (25th centile;75th centile).

Table 9 contains data about the distribution of fetal heart rate and fetal heart rate variability at the different time intervals for each of the two groups. There were no statistically significant differences between the values of any time interval compared with any other time interval for any of the two groups.

	INDICATION FOR INDUCTION OF LABOUR									
	Previous IUD					Postterm pregnancy				
TIMING	-10	0	10	20	30	-10	0	10	20	30
FHR (bpm)	135.13 ± 9.12	133.76 ± 9.09	134.19 ± 8.98	133.19 ± 9.44	134.41 ± 9.98	133.5 ± 8.9	135.54 ± 8.59	136.69 ± 8.84	134.67 ± 8.30	134.86 ± 8.35
• 25th Centile	127.50	127.25	127.00	127.50	127.50	127.50	129.00	131.00	127.50	127.50
• 75th Centile	141.00	141.00	141.00	137.25	141.00	139.00	143.50	141.00	141.00	139.00
Baseline Variability (bpm)	11.26 ±3.40	11.37 ± 2.82	11.51 ± 2.80	11.19 ± 3.56	11.19 ± 2.95	11.12 ± 2.94	11.47 ± 3.75	11.12 ± 3.32	10.92 ± 2.49	10.86 ± 3.06
• 25th Centile	8.00	10.00	10.00	8.00	9.50	8.00	10.00	8.00	10.00	8.00
• 75th Centile	14.00	14.00	12.00	13.00	12.00	12.00	14.00	12.00	12.00	12.00

Table 9:   The distribution of fetal heart rate and fetal heart rate variability at the different time intervals depending on the indication for the induction of labour. (Mean ± standard deviation).

INDICATION FOR INDUCTION OF LABOUR										
	Previous IUD					Postterm pregnancy				
TIMING	-10	0	10	20	30	-10	0	10	20	30
Accelerations (per 10 min)	2(0; 4)	2(1; 4)	2(1; 4)	2(0; 4)	2(1; 4)	1(0; 3)	2(0; 4)	2(0; 4)	2(0; 3)	2(1; 5)
Early Decelerations (per 10 min)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)
Variable Decelerations (per 10 min)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)	0(0; 1)
Atypical Variable Decelerations (per 10 min)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)
Late Decelerations (per 10 min)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)	0(0; 0)

Table 10: The distribution of accelerations and decelerations of the fetal heart at the different time intervals depending on the indication for the induction of labour. (Median (25th centile;75th centile).

The number of recordings with at least one acceleration per recording in the group who had been induced for previous IUD was 76.8%. The corresponding figure for the postterm group was 70.3%. (p = 0.09). The distribution in relation to the timing of the misoprostol is shown in figure 3.
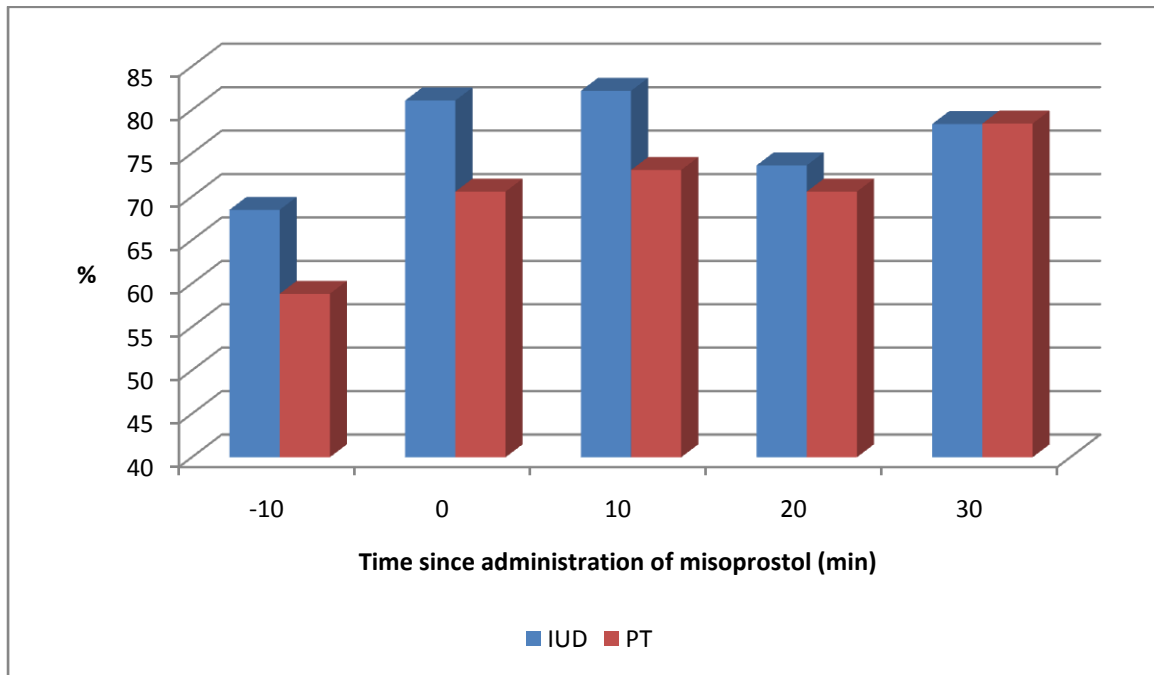

Figure 3: The percentage of recordings with at least one acceleration per recording in relation to the timing since administration of misoprostol in the two study groups.

The occurrence of reactive patterns (recordings with at least two accelerations) is illustrated in figure 4. There were more reactive patterns at all time intervals after the administration of misoprostol (figure 4) but these differences did not quite reach statistical significance. (Chi^2 for linear trend; p = 0.09).
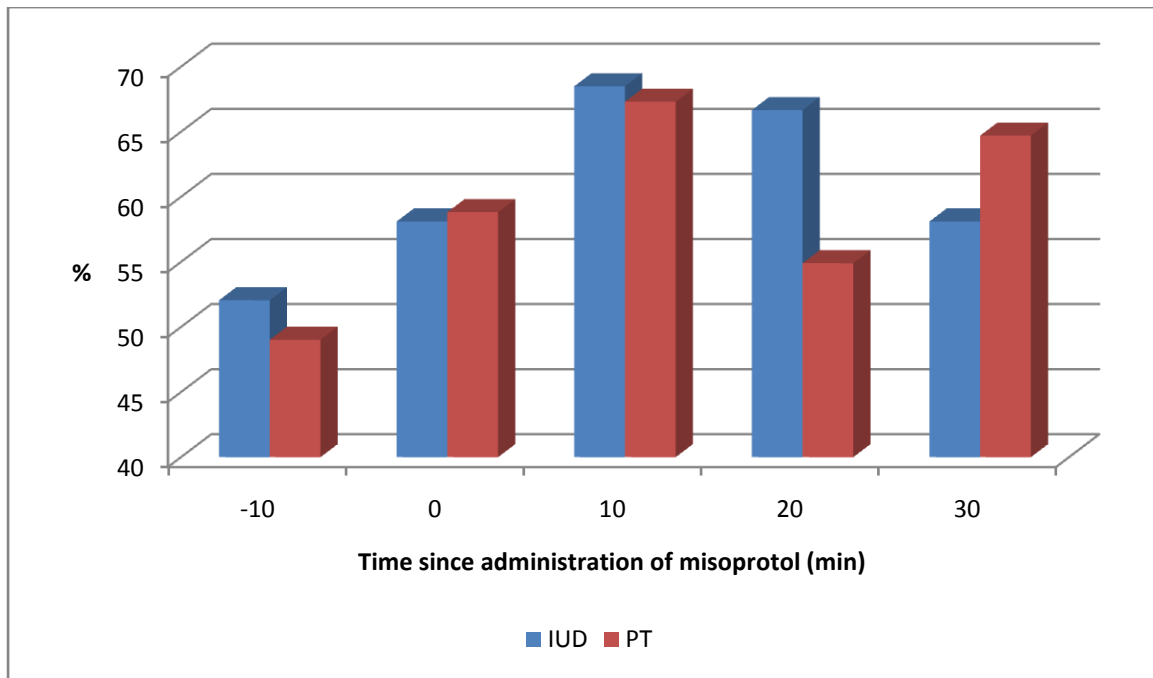
Figure 4: The percentage of reactive patterns in each group related to the time of the administration of misoprostol.

DISCUSSION

Prostaglandins are highly efficacious cervical ripening agents that are useful clinically as adjuvants to labour induction. Notwithstanding the beneficial use of these agents, they are however associated with potential for uterine hyperstimulation and fetal heart rate abnormalities. We did a retrospective study to determine the effect of 50mcg misoprostol given orally on fetal heart rate, fetal heart rate variability, accelerations and decelerations in the first 40 minutes after administration. We did not reassess the effect of misoprostol in subsequent doses.

It was more difficult to assess the ten minute windows of the cardiotocographs (CTG's) than we anticipated. Determining fetal heart rate was often difficult over such a short period. The investigator could not compare the ten minute window with the two windows immediately prior to or immediately after index ten minutes because of the randomization process. We therefore determined the highest and lowest fetal heart rate, as well as the average fetal heart rate for each ten minute window. The eventual analyses were the same irrespective of which rates were used.

Assessment of the variability was also at times limited to only two minutes, especially when several accelerations were present. It was not difficult to calculate accelerations once the baseline was established. The classification of decelerations depended on the presence of decelerations and also whether they were recorded. Some decelerations classified as variable may have been late or early where possible contractions were not monitored. It is of interest to note that where abnormalities occurred in a single ten minute window, they invariably recovered in the following two ten minute window, as was observed after the randomization was unblinded.

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We found no statistical significant difference of mean fetal heart rate and baseline variability in relation to time recordings after administrating of misoprostol (Table 9). There were no statistically significant differences in the distribution of accelerations and decelerations in different time intervals (table 8).

Previous reports are consistent with the index study except that the vaginal route of lower dosing misoprostol regimen (defined as 25mcg or less at 4 hourly intervals) was used. These women were likely to experience uterine hyperstimulation, both with (RR 0.50, 95% CI 0.36-0.71) and without (RR 0.61, 95% CI 0.49-0.76) fetal heart changes, with trends towards fewer infants with Apgar scores of less than seven at five minutes (RR 0.76, 95% CI 0.40-1.45), and fewer neonatal intensive care unit admissions (RR 0.82, 95% CI 0.64-1.05). (34)

There were more reactive patterns at all time intervals after the administration of misoprostol (figure 4) but these differences did not quite reach statistical significance. The percentage of reactive patterns, compared with the ten minute prior to the dosage was highest in the windows starting 10 and 20 minutes later respectively. This is in keeping with studies that concentrated on pharmacokinetic properties after oral and vaginal misoprostol administration. Following oral administration misoprostol is rapidly absorbed; the plasma level increases and peaks at about 30 minutes then declines by 120 minutes and remains low thereafter. (35)The mean onset of effect after oral route was 7.8 minutes, with maximal effect after a mean of 25.5 minutes. The mean onset of uterine activity was seen after 20.9 minutes, with a maximal effect after 46.3 minutes. (35)

In both study groups, no neonatal complications or neonatal intensive care admissions were reported (table 6). Serious side effects (e.g. fetal hypoxia) are

usually secondary to hyperstimulation of the uterus. The majority of studies which compare labour induction with misoprostol and dinoprostone or oxytocin show greater incidents of uterine hyperstimulation with misoprostol. However in studies using lower doses 50 mcg oral misoprostol 4 hourly or 25mcg vaginal misoprostol 4 hourly, hyper stimulation rate are similar to those women induced with dinoprostone. (4). There were no cases of hyperstimulation as assessed by CTG's or as reported in the patient files.

The mean birth weights were 3142.7g in the previous IUD group and 3092.4g in the post term groups in spite of significant difference in gestational age at birth. The reason for this difference is unclear. This difference is probably not of clinical importance, considering the good perinatal outcome in both groups. However, it may be that current clinical and other methods used to determine efficiency of placental function is not adequate. Even if this was the case, the lack of serious adverse outcomes is reassuring.

In total from both groups, 16.5% delivered by caesarian section. Fetal distress occurred commonly in women with a history of previous IUD but this difference was not statistically significant (10% in the previous IUD group and 1.9 % in the post-term group). In the literature 44 trials included in meta-analysis provided data for 5735 subjects who participated in trials that assessed the impact of misoprostol on caesarian section rate. In 26 of 44 trails (59.1%) caesarian section rate was lower for patients randomized to receive misoprostol. This data provides strong support for the conclusion that misoprostol reduces caesarean rate amongst women who undergo induction of labour compared to women receiving alternative induction agents (36). It will be impossible though to draw any conclusions from the index study as only one

induction agent (misoprostol) was used. Nonetheless the caesarean section rate was significantly lower than the rate of our service which is currently 41%.

It was also of interest to note that as many as 14.1% of the total inductions were not justified as they were not necessarily repeatable causes (e.g. 13 chorioamnionitis, 4 congenital abnormalities and 1 cord prolapse), see (Table 2). This affords us an opportunity to heighten awareness amongst colleagues about strict academic criteria that have to be followed before induction of labour, as this practice might lead to avoidable iatrogenic maternal and fetal morbidity. Complications would include uterine hyperstimulation, failed induction of labour and cord prolapse. (36). All of the above mentioned adverse outcomes would then ultimately lead to an increase in the caesarean section rate and there may be challenges in anterpartum and intrapartum care in subsequent pregnancies due to lower segment morbidly adherent placenta implantations. (37)

The demographic data of the participants (Table 1) showed no statistical difference; however it would be interesting to assess the link between smoking, high BMI, previous or current diabetes and hypertension or preeclampsia with misoprostol use. The index study lacks statistical power to assess such parameters and therefore large prospective randomized control trials are still needed.

STRENGHTH AND WEAKNESSES OF THE INDEX STUDY

The index study confirms the absence of fetal heart tracing abnormalities when using low dose (first 50mcg) oral misoprostol; however we do not know the effect that could be caused by administration of subsequent doses. It was also difficult to determine the study size because we were not comparing different methods of induction. This was for a period of eighteen months at Tygerberg Hospital in patients with normal umbilical artery Doppler studies and found to be safe from a practical point of view. However we do not know what would have happened to patients with compromised umbilical artery Doppler e.g. pre-eclampsia, more large prospective randomized control trials are still needed.

CONCLUSION

1. In the absence of contra indications, 50mcg of oral misoprostol can be given to mothers for induction of labour as no harmful fetal heart tracing abnormalities were found for 45 minutes, however large prospective randomized control trials are still needed to confirm effectiveness and evaluate further maternal and neonatal safety issues. Optimal dose and frequency also still need robust interrogation.

2. Based on this thesis it does appear that misoprostol is probably not harmful to the fetus when it is given in dosages of 50mcg orally.

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