

A RANDOMISED CONTROLLED TRIAL OF ORAL  
MISOPROSTOL IN THE INDUCTION OF  
LABOUR AT TERM

CENTRE FOR NEWFOUNDLAND STUDIES

---

**TOTAL OF 10 PAGES ONLY  
MAY BE XEROXED**

(Without Author's Permission)

RORY WINDRIM











National Library  
of Canada

Acquisitions and  
Bibliographic Services

395 Wellington Street  
Ottawa ON K1A 0N4  
Canada

Bibliothèque nationale  
du Canada

Acquisitions et  
services bibliographiques

395, rue Wellington  
Ottawa ON K1A 0N4  
Canada

*Your file Votre référence*

*Our file Notre référence*

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-42461-8

**A Randomised Controlled Trial of Oral Misoprostol in the  
Induction of Labour at Term**

**Rory Windrim, MB., F.R.C.S.C.**

**A Thesis**

**Submitted to the School of Graduate Studies**

**in Partial Fulfilment of the Requirements**

**for the Degree of Master of Science**

**Faculty of Medicine**

**Memorial University, Newfoundland**

**1996 -1998**

**St. John's**

**Newfoundland**

Master of Science, 1996 - 97  
(Clinical Epidemiology)

Memorial University  
St. John's, Newfoundland

Title:

A Randomised Controlled Trial of  
Oral Misoprostol in the Induction  
of Labour at Term

Author:

Rory Windrim, B.A., M.A., B.A.O.,  
B.Ch., M.B., F.R.C.S.C.

Supervisors:

Dr. David Young

Dr. John Harnett

Dr. Patrick Parfrey

Number of Pages:

110

## **Abstract**

Since the completion of the Canadian Multi-centre Post-term Pregnancy Trial, there has been an increase in the number of inductions of labour at term and beyond term. In many centres, the induction of labour rate exceeds 20% of all deliveries.

Concomitant with this increase in induction rates has been an increase in the use of vaginal prostaglandin primarily dinoprostone, to aid in pre-induction cervical ripening and induction of labour. Dinoprostone has been administered by the oral route in the past, but because of unacceptable gastrointestinal side effects, its use has been widely abandoned and replaced by its vaginal administration.

Because of the high costs and limited administration route of dinoprostone, in recent years attention has turned world-wide to the use of another prostaglandin, "misoprostol", in the induction of human labour at term. This medication, initially designed for the treatment of upper gastrointestinal ulcers has been shown to be an effective agent for induction of labour, when administered vaginally.

The purpose of the trial described in this thesis is to evaluate the efficacy and safety of oral administration of misoprostol in induction of labour, when compared to standard methods of induction. Two groups of patients were formed by random assignment. The first are a control group who received standard care at our unit for induction of labour at term. Standard care for these patients would usually include vaginal prostaglandins and/or oxytocin. The second group was the study group. This group received oral misoprostol as the induction of labour agent. The two groups are then compared for both primary and secondary outcome measures. The primary outcome measure is the length of time from commencement of the induction process until

delivery. Secondary outcome measures compared between the two groups include multiple parameters of neonatal and maternal morbidity. Finally we were also interested in the acceptability of oral misoprostol for induction of labour as no other prostaglandin induction agent has been shown to have an acceptable side effect profile when administered orally. We therefore also compared labour and delivery maternal satisfaction scores between the two groups.

This proved to be a negative trial. There were no statistically significant difference in the primary outcome measure (time for induction of labour until delivery) or in any of the secondary outcome measure figures of neonatal or maternal morbidity or maternal satisfaction.

The thesis will be presented in five chapters. The first chapter (Introduction) will provide an overview of why and how induction of labour has been carried out from historical time until the present for the reader new to this area. In the second chapter (Background) a detailed discussion of the role of prostaglandin in the induction of labour will be presented. This background concerning prostaglandin will be narrowed down to a review of the role of a specific prostaglandin (misoprostol) up to the point where this trial started. To conclude this chapter the rational behind the decision to study oral misoprostol use would be presented. In chapter three (Methodology) the exact research question will be specified. The design we chose to attempt to answer this question will also be described. The very important issues of sample size estimation and justification will then be presented prior to a description of the execution of the design in terms of the description of the institution where the study was performed ethics in content, patient recruitment issues etc. In chapter four (Data Analysis) I will present the results of the trial for both primary and secondary outcomes. Levels of statistical significance will also be presented. Finally in chapter five (Discussion and Conclusions) will provide a discussion of the

strength and weaknesses of the study and its implications for practice. Conclusions which may reasonably be drawn from this trial will be presented along with the limitations of these conclusions. Directions for future studies will then be briefly addressed.

Following the body of the text there will be a full set of appendices illustrating the documentation used in the study prior to the bibliography and references.

## **Dedication:**

I dedicate this thesis to my parents, Maura and Austie Windrim.

## **Acknowledgments**

My greatest debt of gratitude is to those pregnant women and their partners, who chose to enroll in this study. The study was completed without any funding, and could not have been carried out without the enthusiastic support of the labour and delivery nursing staff of the Grace Hospital, St. John's, Newfoundland.

I would also like to express my sincere thanks to the Obstetricians and Family Physicians in the Unit, all of whom so freely donated their care, effort and expertise to the conduct of the trial. In particular, Dr. Kelly Bennett shared with me the task of patient recruitment and data retrieval.

Much of the chapter on the history of the induction of labour is modified from "Effective Care in Pregnancy and Childbirth" by Keirse et al.

I would like to thank Esther Denov who has always helped more than she had to, for typing and formatting.

I would also like to thank my Epidemiology supervisors, Dr. John Harnett and Dr. Patrick Parfrey, for their patience and help. My other supervisor, Dr. David Young has been without doubt the best friend, teacher and role-model that any physician could hope to have.

I would especially like to thank my 3 children, David, Catherine and Sara for their wonderful love and patience during the completion of this trial and thesis.

Above all, I would like to thank my wife Trish, without whom I would have nothing.

## **Table of Contents**

Abstract.....	IV
Acknowledgements.....	VII.
List of Tables.....	XII
List of Figures.....	XIII
List of Abbreviations and Symbols Used.....	XIV
List of Appendices.....	XV



## **CHAPTER I : INTRODUCTION**

1.1	Introduction: Induction, Labour, Cervical Ripening.....	1
1.2	Assessment of the Cervix.....	3
1.3	Historical Review of Methods of Labour Induction.....	4

## **CHAPTER II: BACKGROUND**

2.1	Prostaglandins.....	6
2.2	The Present Role of Prostaglandins in the Induction of Labour.	7
2.2.1	Comparisons with Placebo.....	8
2.2.2	Intravenous, Oral and Vaginal Administrations.....	9
2.2.3	Prostaglandins for Cervical Ripening.....	11
2.2.4	Hazards of Prostaglandin Administration.....	12
2.3	The Biochemistry and Pharmacologic Actions of Misoprostol.....	14
2.4	A chronology of the use of Misoprostol in the Induction of Labour.....	16
2.5	Rationale for Studying Oral Misoprostol in the Induction of Labour.....	19

### **CHAPTER III : METHODOLOGY**

3.1	Research Question.....	20
3.2	Outcome Measures.....	23
3.3	Design.....	26
3.4	Subject Specification.....	27
3.5	Description of Experimental Manoeuvre.....	28
3.6	Sample Size.....	31
3.7	Description of Institution Where Study Performed.....	33
3.8	Ethics and Consent.....	34
3.9	Patient Recruitment.....	35
3.10	Randomisation Process.....	37
3.11	Data Handling.....	38

### **CHAPTER V : DATA ANALYSIS**

4.1	Demographic Measures.....	39
4.2	Primary Outcome Measure: Time from commencing induction until delivery.....	41

4.3	Secondary Outcome Measures	
4.3.1	Labour Intervals.....	43
4.3.2	Birth Route.....	46
4.3.3	Maternal Interventions.....	48
4.3.4	Maternal Outcomes.....	50
4.3.5	Neonatal Outcomes.....	52
4.3.6	Post Partum Outcomes.....	54
4.3.7	Dosages.....	56
4.4	Maternal Satisfaction Results.....	57

## **CHAPTER V : DISCUSSION AND CONCLUSIONS**

5.1	Discussion.....	62
5.2	Strengths & Weaknesses.....	66
5.3	Conclusions.....	69
5.4	Future Studies.....	70

<b>APPENDICES.....</b>	<b>71</b>
------------------------	-----------

<b>BIBLIOGRAPHY &amp; REFERENCES.....</b>	<b>82</b>
---	-----------

## List of Tables

Table I	Demographic Data.....		40
Table II	Primary Outcome Measure.....		42
Table III	Labour Intervals. - Unstratified.....		44
Table IV	- Stratified.....		45
Table V	Birth Route.....		47
Table VI	Maternal Intervals.....		49
Table VII	Maternal Outcomes.....		51
Table VIII	Neonatal Outcomes.....		53
Table VIII	Post-partum Outcomes/Costs	a) maternal. ....	55
		b) neonatal.....	55
Table IX	Maternal Satisfaction (LADSI) Results:		
		a) Overall. ....	58
		b) Additional Questions...	59
		c) Choice of Drug Route. ...	60

## **List of Figures**

Figure I	Chemical Structure of Misoprostol Molecule.....	14
Figure II	Sample Size Calculation .....	31

### **List of Abbreviations and Symbols Used**

ACOG	American College of Obstetricians & Gynecology
CI	Confidence Interval
CS	Caesarean Section
EFM	Electronic fetal monitoring
FHR	Fetal Heart Rate
GI	Gastrointestinal
LADSI	Labour & delivery satisfaction index
NRT	Non-reassuring tracing
PG E <sub>1</sub>	Prostaglandin E <sub>1</sub>
PGE <sub>2</sub>	Prostaglandin E <sub>2</sub>
PG F <sub>α</sub>	Prostaglandin F2 alpha
PGF <sub>1α</sub>	Prostaglandin F <sub>1α</sub>
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation

## **APPENDICES**

Appendix I	Bishop Score .....	71
Appendix II	Consent Form .....	72
Appendix III	Distributed guidelines.....	74
Appendix IV/V	Data Sheets .....	75
Appendix VI	Patient Satisfaction Survey.....	77

## **CHAPTER I: INTRODUCTION**

### **1.1 Induction, Labour, Cervical Ripening**

The process whereby labour is begun by medical intervention, prior to its spontaneous occurrence, is known as “induction of labour”. The indications for induction of labour fall into 2 categories; maternal and fetal.<sup>6</sup> Maternal indications for induction of labour include any medical/obstetrical complication where terminating the pregnancy also terminates or lessens the risk to a pregnant woman. The classic example of a maternal indication for induction of labour is that of pre-eclampsia, where marked maternal vaso-constriction occurs through an as yet undefined process, which can produce life threatening secondary changes and it persists until delivery of the fetus and its placenta. Other maternal indications for delivery include: antepartum haemorrhage, uncontrolled diabetes, and chorioamnionitis. Fetal indications for induction of labour include any circumstance where it is felt that delivery of the fetus would provide a healthier environment for its development and growth, than remaining in-utero, the classic example being that of post-dates. Traditionally, post-dates of pregnancy were felt by the majority of obstetrical caregivers to include any pregnancy of 42 weeks duration or longer. Other fetal indications for delivery include ultrasound diagnosed fetal growth restriction, reduced amniotic fluid volume and insufficient blood flow through the umbilical cord.

Since the completion of the Canadian Multi-centre Post-term Pregnancy Trial,<sup>88</sup> many caregivers now recommend consideration of induction of labour one week after the due date (41 weeks gestation). As a result of this, induction of labour has increased in Canada and now accounts for in excess of 20% of deliveries in many centres. In order to be successful, induction of labour must result in adequate uterine contractions and progressive dilatation of the uterine cervix. The total amount of uterine contractility required to achieve cervical dilatation is very



dependent on the state of the cervix. A firm and rigid cervix may require a total quantity of uterine work that is many times greater than that needed when the cervix is softer and more yielding.<sup>106</sup>

The consequences of this for the induction of labour have been known for a long time. Virtually all reports on induction emphasise that the state of the cervix is the most important predictor of success.

Realisation of the importance of the state of the cervix for induction has led to the development of various methods to assess cervical “ripeness” (and their use to predict the outcome of induction) and also the search for methods that decrease cervical resistance prior to induction.

## 1.2 Assessment of the cervix

The cervix is a dynamic structure that undergoes many changes, particularly in late pregnancy.<sup>106</sup> Along with biochemical changes in the proteoglycan matrix and collagen degradation, there is an increase in vascularity, an accumulation of interstitial fluid and migration of white cells and macrophages into the cervical tissue.<sup>106</sup> These changes lead to changes in the biophysical characteristics of the cervix in that they cause a greater compliance and less resistance to dilatation. The increase in compliance is most readily recognised in the differences to palpation between the firm, rigid cervix at the beginning of pregnancy and the soft, oedematous cervix palpated at term.<sup>108</sup> Several cervical scoring systems have been developed in an attempt to establish guidelines for cervical assessment. The best known of these is the score proposed by Bishop (1964),<sup>30</sup> which rates five different qualities (cervical effacement, cervical dilatation, cervical consistency, position of the cervix relative to the axis of the pelvis and descent of the fetal presenting part) on a total score from 0 to 13 (Appendix I) .

### **1.3 Historical Review Of Methods Of Labour Induction Developments Prior**

#### **To The Twentieth Century**

Attempts to induce or augment labour have a long history. Induction of labour was mentioned by Soranos of Ephesus in the second century AD.<sup>45</sup> In the ninth and tenth centuries, Arab physicians described instruments for labour induction.<sup>105</sup> In the sixteenth century, Pare and Guillemeau induced labour in cases of severe uterine haemorrhage.<sup>105</sup> Eucharius Rodion gave a list of substances believed to facilitate labour (in the earliest printed obstetric textbook). These preparations were ingested by women but Rodion also describes packing the genital tract with wool cloth soaked with the extracts of the *Ruta graveolens* and *Aristolochia* sp.<sup>105</sup>

The *medical* history of labour induction really starts in the 18th century, in 1756, when Macauley induced labour before term in order to avoid the hazards of both caesarean section and fetal extraction with the crochet.<sup>56</sup>

#### **Developments during the twentieth century**

An entirely new approach to labour induction was proposed by Benjamin Watson in 1913.<sup>34,105</sup> Watson called this method “medical induction” to distinguish it from surgical intervention and it involved administering castor oil and quinine. The modern era of labour induction began in 1928 with the clinical introduction of purified posterior pituitary extract for medical induction which subsequently became established in 1955, when synthetically prepared oxytocin was made available commercially.<sup>9</sup> At first, highly diluted solutions (“the oxytocin drip”) were used. By 1968, intravenous infusions of escalating doses (“titrated” against uterine contractions) were introduced by Turnbull and Anderson (1968)<sup>105</sup> to reduce the rate of failed

induction after amniotomy.

Since 1968,<sup>99,100</sup> oxytocin has had a rival for labour induction---the prostaglandins. After Karim first reported success with intravenous infusion of prostaglandin  $F_{2\alpha}$ , both this compound and prostaglandin  $E_2$  have been used widely for this purpose. Due to the unique effect of prostaglandins on the uterine cervix, they represent an excellent option for women who, on account of their unfavourable cervix, are poor candidates for induction using oxytocin. Furthermore, because prostaglandins are effective when administered either locally or systemically, local administration has the advantage of requiring much lower doses of prostaglandin and avoids the problem of untoward side effects provoked by intravenous prostaglandin administration. The recent commercial availability of stable preparations of  $PGE_2$ , mainly vaginal tablets and gels, has boosted the clinical use of prostaglandins both for priming the cervix and for inducing labour.

## **CHAPTER II: BACKGROUND**

### **2.1 Prostaglandins**

The development of the prostaglandin method of labour induction has a long history. The oxytocic properties of these substances had been known long before the prostaglandins were identified as such. In 1930, Kurzrock and Lieb, demonstrated the uterotonic effects of fresh human semen *in vitro*.<sup>102</sup> Substances capable of provoking contraction of smooth muscle fibres were found in seminal fluid, by Goldblatt in 1933 and Von Euler 1934.<sup>105</sup> Von Euler named these substances "prostaglandins." Bergstrom and Sjovall isolated the first prostaglandin (PGF<sub>1α</sub>) in 1957<sup>18</sup> and in 1964;<sup>17</sup> the biosynthesis of several uterotonic prostaglandins was achieved. However the obstetric breakthrough resulted from the work of Pickles,<sup>141</sup> who in 1959, had postulated that dysmenorrhoea was caused by the presence in the menstrual fluid of a potent uterotonic substance which he named "menstrual stimulant". Six years later he identified this to be a mixture of prostaglandins E and F. Karim,<sup>100</sup> noting a similarity between "uterine colic" and labour pain, isolated PGE<sub>2</sub> and PGF<sub>2α</sub> in amniotic fluid and showed that the concentration of these substances increased during early labour. In 1968, Karim announced the successful induction of labour at term by constant-dose intravenous infusion of PGF<sub>2α</sub>. In 1969, Embrey suggested that equipotent doses of PGE<sub>2</sub> were equally useful for elective induction of labour.<sup>69</sup>

## **2.2 The Present Role Of Prostaglandins In The Induction Of Labour.**

Prostaglandins are known to play an important role in the physiology of human labour and it is likely that a late step in the complicated series of events preceding the onset of labour is an increase in the endogenous local release of these substances.<sup>2,37,40,53</sup> Most of the early clinical research was conducted with  $\text{PGF}_{2\alpha}$ , because it was thought to have more uterotonic activity and because of the initial “shelf instability” of  $\text{PGE}_2$ .<sup>58,59</sup> Since the early 1970’s, a large number of controlled evaluations of prostaglandins for inducing labour have been conducted, studying issues of efficacy, different vehicles and routes of administration.<sup>77,78,82,84,86,87,90,104</sup> At first, these involved controlled comparisons between intravenous prostaglandins and intravenous oxytocin. Later, with the advent of other routes of prostaglandin administration, the controlled comparisons have been with placebo treatments, with intravenous and buccal oxytocin and between different routes and doses of prostaglandins.

### **2.2.1 Comparisons with Placebo**

Seven studies, all conducted between 1978 and 1984, have compared prostaglandins (administered in various doses, formulations and routes) with placebo treatments that were identical except for the added prostaglandin. The “failure” rate of induction and the proportion of women needing a second induction attempt were statistically significantly lower following prostaglandin administration in all of the trials that provided data on these outcomes.<sup>194</sup>

### 2.2.2 Intravenous, Vaginal and Oral Administration

Early studies of prostaglandins for the induction of labour used the intravenous route of administration.<sup>13,14,2225,87,105,107</sup> Compared with oxytocin they appeared to offer no advantage and were considerably more expensive. They tended to produce bothersome side-effects, mainly vomiting and diarrhoea (which were particularly prominent with  $\text{PGF}_{2\alpha}$ ), but also hypothermia (especially with the use of  $\text{PGE}_2$ ). Finally, they appeared to require an even more careful determination of the infused dose than oxytocin, because of the small margin between doses that would stimulate uterine contractions adequately and those that would cause “hyperstimulation”.

Probably the most widely adopted mode of administration of  $\text{PGE}_2$  (and  $\text{PGG}_{2\alpha}$  in countries where  $\text{PGE}_2$  is not available), has become the vaginal route.<sup>105</sup> Compared with placebo, vaginal prostaglandins have been shown to achieve shorter time to delivery and a higher change of spontaneous vaginal delivery. The proprietary compounds “Prepidil” and “Prostin” are now extremely widespread in their use.

In 1971, Karim and Sharma<sup>99</sup> reported on the oral administration of  $\text{PGE}_2$  for induction. From then on, oral administration of  $\text{PGE}_2$  (in doses increasing from 0.5 to 2 mg) became widely used as an alternative to intravenous infusions of prostaglandins for inducing labour, particularly when combined with amniotomy and in women with a favourable cervix. Thiery and his colleagues (1977),<sup>185</sup> in a randomized controlled comparison involving 50 women, showed that it was not necessary for the prostaglandin tablets to be swallowed: there were no differences detected in any of the outcome measures between the 25 women who received  $\text{PGE}_2$  orally in doses of 0.5 to 3 mg, and the 25 women who were instructed to let the tablets melt away under the tongue.



Because of its gastrointestinal side-effects,  $\text{PGF}_{2\alpha}$ <sup>68</sup> is entirely unsuited for oral administration. However, gastrointestinal side-effects also occur with oral  $\text{PGE}_2$ .<sup>49,61,77,78,82</sup> These side-effects have been reported to affect between 20 and 50 per cent of women, depending on the doses used. In other controlled comparisons, however, the incidence of gastrointestinal side-effects with oral  $\text{PGE}_2$  has been reported to be approximately 10 per cent.<sup>118,146,178</sup>

### 2.2.3 Prostaglandins for Cervical Ripening

A few years after the introduction of prostaglandins for inducing labour in the late 1960s, doses which by themselves were insufficient to induce labour successfully were found to effect a marked softening of the uterine cervix.<sup>38,69,86,171</sup> This phenomenon is not only observed at term; marked cervical softening and changes in the shape of the lower uterine pole are phenomena that are well known to those experienced with prostaglandin-induced terminations of pregnancy in the 2<sup>nd</sup> trimester.<sup>35,64-67,69</sup> In experimental animals it has been shown that this softening results from a direct effect of prostaglandins on the cervix, which need not be mediated by uterine contractility (Liggins 1978),<sup>113</sup> and there is now a substantial body of evidence on the influence of both endogenous and exogenous prostaglandins on biochemical and biophysical characteristics of the cervix.

The occasional need to induce labour in the presence of an unripe cervix requires methods that have not only been shown to increase cervical compliance, but which increase the likelihood of spontaneous vaginal delivery of a healthy baby within a reasonable period of time. Of the various interventions used, only the prostaglandins, which have also been the most extensively studied, have so far approached this goal. Use of prostaglandins in these circumstances decreases the likelihood of “failed induction”, decreases the incidence of labour lasting more than 12 and more than 24 hours, and increases the chances of a spontaneous vaginal delivery.<sup>77,104,135,137</sup>

#### 2.2.4 Hazards of Prostaglandin Administration

The specific hazards attributable to prostaglandins *per se* relate mainly to their effects on the gastrointestinal tract, predominantly nausea, vomiting and diarrhea.<sup>68,82,84,87</sup> The small number of placebo-controlled trials of prostaglandins for induction of labour provides little evidence of these effects.<sup>105,137</sup> Important additional evidence, however, is available from the larger number of trials in which prostaglandins have been compared with oxytocin for the induction of labour.<sup>15,22,87,91,118,147</sup> These effects are minimal when the drugs are administered endo-cervically or extra-amniotically, and maximal when routes of administration (intravenous, oral, and vaginal) are used that lead to high levels of these drugs in either the blood or the gastrointestinal tract.

Pyrexia also results from a direct effect of prostaglandins on thermo-regulating centres in the brain.<sup>38,75,84,99</sup> This is particularly a problem of prostaglandin E<sub>2</sub> administration and may give rise to concern that intrauterine infection has supervened. This concern may be further fuelled by a rise in the leukocyte count, which can also be stimulated by prostaglandin administration. If the membranes are intact and labour has been of relatively short duration however, pyrexia is almost always due to an effect of prostaglandin E<sub>2</sub> rather than to incipient uterine infection.

Important though it is to consider the specific hazards of prostaglandins, it should not be forgotten that they pale into insignificance when considered against the far more worrying complication of uterine hypertonicity and/or polysystole.<sup>39,54,60</sup> In a small number of patients, equal doses of prostaglandins may have a more potent effect on uterine activity than that in the general population. In these patients excessive uterine contraction may lead to fetal hypoxemia with subsequent possible fetal hypoxic brain damage and/or death.<sup>2,3</sup>

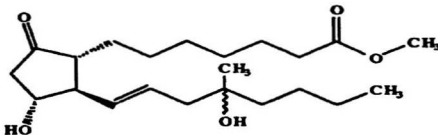
Due to the high costs of these preparations and occasional dissatisfaction with their

effectiveness (in particular with that of Prepidil), investigators have been evaluating other prostaglandins with regard to their effectiveness and safety in the induction of labour.<sup>97</sup> One of these prostaglandins is *misoprostol* which is a prostaglandin E<sub>1</sub> analogue, produced by Searle in its proprietary form as Cytotec<sup>®</sup>.<sup>144</sup> It is used primarily for prophylaxis against non-steroidal anti-inflammatory induced upper gastrointestinal complications.<sup>80,95,98,110,133,144</sup> In 1993, Sanchez-Ramoz<sup>151</sup> demonstrated the effectiveness of misoprostol in a randomized trial versus oxytocin for the induction of labour at term. Since that time, there have been many publications evaluating the use of misoprostol both for induction of labour at term and also for termination of pregnancy. (See section 1.6).

## 2.3 The Biochemistry and Pharmacologic Actions of Misoprostol:

### CHEMISTRY<sup>144</sup>

#### Molecular Structure:



Molecular Formula:  $C_{22}H_{38}O_5$

Molecular Weight 382.5

Chemical Name : (+)methyl(11 $\alpha$ ,13E)16-dihydroxy-16methyl-9-oxoprost-13-en-1-oate

Description: Misoprostol is a novel synthetic prostaglandin E<sub>1</sub> analogue. It is a light yellow, viscous liquid with a musty odour.

Misoprostol is rapidly absorbed following oral administration with peak serum levels occurring in about 30 minutes.<sup>144</sup> It is rapidly de-esterified to misoprostol acid and no intact misoprostol remains in plasma. The de-esterified metabolite which is the primary biologically active material undergoes further metabolism by beta and omega oxidation which takes place in numerous tissues in the body.<sup>144</sup> The elimination, half life subsequently is 1.7 hours. Approximately 60% is excreted by the kidney and 40% through feces.<sup>144</sup> In animal studies, there has been no evidence of embryo-toxicity, feto-toxicity or teratogenicity even at extremely high

doses (10,000 mg/kg). Concerns<sup>11,21,42,46,47,48,74,83</sup> regarding teratogenicity of failed first trimester terminations are presently being prospectively evaluated by the World Health Organization.

In the stomach, the anti-ulcer activity of misoprostol appears to be exerted by histamine receptor activation and the formation of cyclic AMP.<sup>144</sup> The daily recommended dose in adults is 800 µg in 2 or 4 doses. In animal studies, the drug was found to cause uterine contractions and therefore the product monograph advises against its use in pregnancy because of the possibility of causing a miscarriage in early pregnancy or inadvertent induction of labour at term.<sup>144</sup>

Adverse reactions with misoprostol are primarily gastrointestinal with diarrhoea (11.4%) abdominal pain (6.8%) and flatulence (2.9%) found.<sup>144</sup> These side effects were found with the full adult dose of 800 µg O.D.<sup>144</sup> These side effects develop early in the course of treatment, are self limiting and require discontinuation of misoprostol in only 2% of patients. In addition pyrexia, nausea, headache and constipation are found 1-2 % of subjects, similar to that found in subjects taking placebo.<sup>144</sup>

## **2.4 A chronology of the use of misoprostol in the induction of labour**

Intravaginal misoprostol has been shown to terminate first- and second-trimester pregnancies. The earliest studies of misoprostol's use in cervical ripening and labour induction were performed by Bugalho<sup>27-33</sup> and South American investigators,<sup>125,126,127</sup> who reported their experience using intravaginal misoprostol.

By 1994, 16 studies had assessed the effectiveness of misoprostol for cervical ripening and labour induction. Three of these studies were uncontrolled non-comparative studies: one<sup>125</sup> was an open-label dose finding study of 56 term and preterm patients requiring labour induction; another was a review of 149 patients who underwent cervical ripening and labor induction with a single application of 100 µg of misoprostol;<sup>34</sup> and the third assessed the effectiveness and safety of low dose (50 µg) intravaginal misoprostol for cervical ripening and labor induction in 666 pregnant women.<sup>30</sup> Three additional studies evaluated the effectiveness of misoprostol for labor induction in patients with fetal death: a Brazilian study<sup>127</sup> reported the use of oral misoprostol for labor induction in 20 cases of fetal death between 19 and 41 weeks gestation; and two uncontrolled studies<sup>31,32</sup> evaluated the use of misoprostol for termination of pregnancy in cases of fetal death. A seventh study<sup>33</sup> was presented only in abstract form. Another study, which compared patients who received either intravaginal misoprostol or intravenous oxytocin for induction of labor, was not randomized and the groups had unequal allocation (404 women received misoprostol and 52 were induced with oxytocin).

In 1993 Sanchez-Ramos at the University of Florida performed a randomized trial of misoprostol versus oxytocin in 130 patients undergoing induction of labour at term. He found that the interval from induction to vaginal delivery was significantly shorter in the misoprostol group. However, uterine tachysystole also occurred more commonly in the

misoprostol group although this did not achieve a statistical significance. Also in 1993<sup>73</sup> Fletcher et al reported from Jamaica on a double blind randomized trial of 45 women who received either vaginal misoprostol or placebo for induction of labour at term. In this small trial they found that misoprostol was superior to placebo in ripening the cervix and inducing labour. They also found a reduced need for oxytocin and no difference in the two groups in delivery outcomes, neonatal or perinatal complications.

In 1994 Fletcher's group reported<sup>72</sup> on a further small randomized trial of 63 women who received 3 mg of either intravaginal dinoprostone or misoprostol for inducing labour at term. These studies were followed by further randomized trials by Wing et al,<sup>183</sup> and Varaklas et al<sup>173</sup> in 1995. Sanchez-Ramos performed a meta-analysis<sup>150</sup> of the eight randomized clinical trials of intravaginal misoprostol for cervical ripening<sup>41,44,72,73,151,173,183,184</sup> and labor induction. A total of 966 patients (488 treated with misoprostol and 478 controls) were enrolled in these trials. The number of subjects allocated to the misoprostol group in the various trials ranged from 24 to 138, with control groups generally of similar size (21-237). Five of the eight trials were performed in the United States and the remaining three were conducted in Jamaica and Chile. The proportion of nulliparous patients in each group was similar (i.e. 48.7% and 46.2% for misoprostol and control groups, respectively). All patients enrolled in the control groups received PGE<sub>2</sub> or oxytocin, with the exception of one trial in which patients were given placebo. This meta – analysis found vaginal misoprostol to be an effective labour induction agent, when compared to standard induction agents. Although persuasive, there were some problems with this study – primarily those of heterogeneity of included studies and analysis of caesarean section rates.

Firstly in these trials, there was heterogeneity in study design with respect to dosage and schedule of misoprostol administration, use of electronic fetal monitoring (EFM), end points



evaluated, and control drug used. The dose of misoprostol varied from 25 µg every 2 hours to 100 µg as a single dose. The range for cumulative maximum allowable dose was from 50 µg to 600 µg. Continuous EFM and tocodynamometry were performed on all patients in six of eight trials, whereas the other two used electronic monitoring on a selective basis. Oxytocin infusion with or without selective use of PGE<sub>2</sub> gel (0.5 mg intracervically) was used in controls in two studies. In another, 3 mg PGE<sub>2</sub> gel was administered intravaginally to controls. In the remaining four studies, 0.5 mg PGE<sub>2</sub> gel was administered intracervically in controls.

Secondly, with regard to caesarean section rates, none of the individual trials evaluating the effectiveness of misoprostol for cervical ripening and labor induction had sufficient statistical power to detect a significant reduction in the caesarean rate. In the meta-analysis of patients with live fetuses who received intravaginal misoprostol for cervical ripening and labor induction, 168 of 1708 patients (9.8%) were delivered by caesarean. This is however a remarkably low rate, compared to the American average in the same period of 20-25%, considering that many women were high-risk and had an unfavourable cervix. Misoprostol's ability to effect changes in the Bishop score, as well as adequate uterine activity, may have contributed to this low caesarean rate.

All these studies showed misoprostol to be an effective labour induction agent with a very low cost and an acceptable side effect profile. This prompted our group at Memorial University to undertake a randomized trial<sup>130</sup> of 222 patients who were randomized to vaginal misoprostol or standard labour induction methods (dinoprostone and/or oxytocin). This study found a decreased time to vaginal delivery, less time for oxytocin augmentation, a strong trend for less use of epidural analgesia. Median prostaglandin cost per patient with misoprostol was 100th that of the control subjects.

## **2.5 Rationale For Studying Misoprostol Administration In The *Oral* Form In The Induction Of Labour:**

Although the standard agents used in our centre for pre-labour cervical ripening and induction of early labour (i.e.: Prepidil and Prostin) were found to be safe and effective, there were some problems found to be associated with their use. They are administered every 6 hours and many patients require several doses. As a result, patients often had multiple pelvic examinations by different caregivers and frequently spent one or two days in the pre-induction, ripening process. Because of the relatively high costs of these formulations, this was also quite an expensive process. These factors lead our labour and delivery unit at the Grace General Hospital in St. John's, Newfoundland to evaluate the use of an alternative (i.e.: misoprostol) when given vaginally in a randomized clinical trial.<sup>130</sup> The results of this trial showed that when administered vaginally, misoprostol was a safe and inexpensive alternative to standard agents. Unlike vaginal preparations, oral labour induction agents do not require a pelvic examination – thus reducing the number of pelvic exams. Oral administration of prostaglandin could also theoretically reduce chorioamnionitis caused by repeated inoculation of the cervix by lower vaginal organisms. Finally, as misoprostol was developed for oral administration, vaginal absorption has not been well studied. It is possible that oral misoprostol to induce labour might have a more smooth and predictable dose response curve than the vaginal misoprostol studies discussed above. We wished to evaluate whether or not misoprostol when administered orally, (the route for which it was marketed for its gastrointestinal indications), would also be an effective and safe agent when compared to standard care in the induction of labour at term. All prostaglandins administered orally for induction of labour in previous reports had an unacceptable gastrointestinal side effect profile. Thus, if our study were to demonstrate that oral misoprostol was a safe and effective labour induction agent, it would be the first well tolerated *oral* agent described.

## **CHAPTER III: METHODOLOGY**

### **3.1 Research Question:**

The aim of this study was to evaluate the effectiveness, safety and acceptability of a new oral labour inducing agent (misoprostol) versus our standard regimen for labour induction. Our standard regimen for induction of labour at term depends upon the preference of the individual attending physician and on the state of cervical readiness. In general, if the cervix were ready for labour, artificial rupture of membranes supplemented by titration of a dilute intravenous oxytocin infusion is carried out. These patients would not require any prostaglandins and be ineligible to join the study. If the cervix is not ready for labour, then pre-labour cervical ripening with the proprietary dinoprostone agents, Prepidil and Prostin is carried out prior to amniotomy +/- oxytocin stimulation. These patients (i.e. those requiring pre-amniotomy prostaglandins) represent the patients eligible for the study protocol.

We generated two groups in our proposed study. *The standard group* would receive usual care, including one or more of the following: 1) cervical Prepidil; 2) vaginal Prostin or 3) oxytocin. *The study group* would receive oral misoprostol. In order to determine a sample size, it was necessary for us to choose a primary outcome measure. We were primarily interested in oral misoprostol's ability to carry out pre-labour cervical ripening and to induce labour. Once the patient was in established labour, we planned to manage the intrapartum care of the patient, similarly in both groups (i.e. artificial rupture of membranes if necessary, and intravenous oxytocin as indicated). We hypothesised, therefore, that the most important potential difference between the two groups would be the pre-labour cervical ripening and latent phase of the 1st

stage of labour. However, measurement of this phase of the induction process is very subjective and open to bias by unblinded observers. We therefore chose to not measure this as a primary, or secondary outcome and instead measured more absolutely definable phases of labour – for instance length of the 2<sup>nd</sup> stage etc. By choosing the length of time until delivery as our primary outcome measure, we hoped to capture any difference in the latent phase, between the two groups. Patient satisfaction surveys of maternal satisfaction in labour and delivery have shown that the outcome of most importance to the parturient is length of time from induction of labour to delivery (assuming a healthy outcome for both mother and baby). Although other outcome measures such as caesarean section and operative vaginal delivery rates are clearly of great importance, studies to detect differences in these rates would require very large sample sizes. As this was an exploratory study of a novel drug use, we felt that to conduct an initial study of this size, with *duration of labour* as the primary outcome measure was the most appropriate course. We were unable to find in the literature any references on this subject. There are no published data on the clinically significant difference (delta) in time that either patients or caregivers consider important when choosing an induction agent. We therefore chose to poll opinions of members of the medical and nursing staff in the labour and delivery unit at our centre. It was the consensus from these discussions that a difference of four hours (240 min.) between our two groups would be clinically important. In retrospect, we regret that we did not poll patients prior to the study regarding their perspective on the delta, although we did study this with our post care questionnaire. As experience grows with this method of induction, the clinically significant delta as estimated by the patient should be considered in future studies.

Our primary research question therefore became **“when compared with our current standard induction protocol does oral administration of misoprostol for labour induction**

**differ by more than four hours in time to vaginal birth ?”** It was our hypothesis before the study that women prefer to have a labour induction agent administered orally by being handed a tablet to swallow by a nurse rather than by vaginal insertion of a gel by a member of the medical staff. Because we felt that the differences between the two groups would be found in the pre-induction cervical ripening phase of the induction process (without the pain of the active phase of labour), we felt that many women might be prepared to spend an extra four hours in the pre-labour ripening process in order to have their medication administered orally rather than vaginally.

### **3.2 Outcome Measures:**

Our outcome measures were both primary and secondary. As described in section 3.1, our primary outcome measure was the length of time from commencing the induction of labour process until vaginal birth of the neonate. The clinically significant difference chosen as important was four hours (240 min.). This primary outcome specifically addresses the issue of effectiveness but we also wished to prospectively evaluate issues of safety and patient acceptability.

With regard to maternal outcomes, we recorded the following:

- i ) Number of doses of prostaglandins.
- ii) Prostaglandin side-effects.
- iii) Duration of the three stages of labour.
- iv) Route of delivery.
- v) Operative interventions, and their indications.
- vi) Use of narcotic and epidural analgesia.
- vii) Oxytocin augmentation and its duration.
- viii) Blood loss and blood transfusion.
- ix) Perineal trauma.
- x) Post-partum pyrexia.
- xi) Length of stay in hospital.

Risks to the fetus from the use of prostaglandins for the induction of labour consist of

uterine hyperstimulation causing excessive contractions of the uterus with subsequent diminished placental perfusion and umbilical cord flow resulting in possible hypoxic consequences for the fetus. These fetal effects might be suggested by the development of non-reassuring fetal heart rate tracings and/or meconium liquor.<sup>53</sup> Appropriate responses to these findings would be either fetal scalp arterial blood gas sampling or operative delivery for non-reassuring fetal heart rate changes.<sup>5</sup> Data regarding these interventions was prospectively gathered. Immediate postnatal outcomes measures were chosen based on the recent policy statement by the American College of Obstetricians and Gynaecologists concerning the diagnosis of perinatal asphyxia.<sup>3,4</sup> Accordingly in addition to Apgar scores (an assessment of fetal health at 1 and 5 minutes of life), we also carried out umbilical cord arterial blood gas sampling and physical exam for signs of neurologic abnormality and multi-system organ failure on all neonates. As this is currently not a standard of practice at our centre (or in most centres in Canada), all neonates in our study were subjected to a more rigorous evaluation than those outside the study. We also recorded neonatal hypoglycaemia which could represent a long and difficult labour, any neonatal pyrexia, number of days in the neonatal intensive care unit and number of days in hospital.

### **Maternal Satisfaction:**

In recent years there has been increased interest<sup>91,92,109,116,117,134,162,169,176</sup> in maternal satisfaction with the labour and delivery process. We felt that maternal satisfaction was second only to safety in importance as a secondary outcome measure. Our *a priori* assumption was that the patients who had induction of labour by oral misoprostol would have a more acceptable form of induction, as they did not have a vaginal administration or intravenous administration of medication. However, we wished to prospectively evaluate this issue. We were also interested

in the mothers satisfaction with all aspects of her labour, not simply her preferred route of administration of the induction agent.

Accordingly, we asked all entrants in the trial to complete a maternal satisfaction questionnaire (Appendix V). This questionnaire was a modified Labour and Delivery Satisfaction Index (LADSI).<sup>116</sup> This LADSI scale is a validated quality of life tool, one of a number developed in the 1980's. It's use has fallen over the past 5 years, due to the high use of E. Hodnett's labour agency scale.<sup>91</sup>

The questionnaire contains 38 questions concerning various aspects of the birth process. We added an additional four questions to the original LADSI score, specific to this trial, but scored in the same fashion. These additional questions were considered to be exploratory and were not pretested. Clearly, therefore any inferences based on these additional questions need to be viewed with caution. The total LADSI scores for the standard LADSI questionnaire were calculated before consideration of these extra questions. Therefore the additional questions were felt not to affect the interpretation of the standard LADSI score.



### **3.3 Design :**

This question requires a randomized control trial. One group of patients would receive our study intervention (oral misoprostol). The second group, (the standard group), would receive the usual protocol for induction of labour at our centre. In order to blind obstetrical caregivers, it would have been necessary to insert a placebo gel intravaginally in those patients who were receiving oral misoprostol and we did not feel that this was justified. As many of our secondary outcome measures were neonatal, we did however, blind neonatal caregivers as to which induction protocol the neonates mother had received.

### **3.4 Subject Specification:**

The subjects whom we felt were eligible for our study were all those patients admitted to labour and delivery unit of the Grace General Hospital in St. John's for induction of labour at term. Exclusion criteria were as follows:

- 1) contra-indication to vaginal delivery
- 2) non-vertex presentation
- 3) non-reassuring fetal heart rate tracing
- 4) prior uterine surgery
- 5) documented hypersensitivity to misoprostol or other prostaglandins
- 6) history of asthma (which can be exacerbated by prostaglandins).

In order to maximize external validity we did not exclude patients who had other obstetrical problems such as pre-eclampsia, known intrauterine growth restriction, known oligohydramnios, or insulin dependent diabetes. Although we recognize that these obstetrical complications could carry an increased risk of sub-optimal outcomes (for instance, caesarean section), randomization alone would minimize any confounding bias.

### 3.5 Description of Experimental Manoeuvre:

The experimental manoeuvre in this trial was the administration of oral misoprostol for the induction of labour. As there were no reports of the oral administration of misoprostol for induction of labour in the literature, we had to generate a dosing protocol for the administration of oral misoprostol in our labour and delivery suite. In doing so, we were guided by two main considerations: 1) with regard to its use in the prevention of our gastrointestinal ulceration, the recommended<sup>144</sup> dosaging is in 100 - 200 microgram tablets up to a maximum of 800 micrograms/ day; 2) when administered vaginally both in our centre and in other centres, the most commonly administered dose was that of 50 micrograms per vagina every four hours.<sup>130</sup> Our concern was that oral misoprostol might not be as effective an agent as vaginal misoprostol. Therefore, we were concerned that patients receiving 50 micrograms of oral misoprostol every four hours might encounter minimal or no response to this dosage. Accordingly, as part of our oral misoprostol dosage protocol, we allowed an increase of the dose of misoprostol to 100 micrograms orally every four hours following two 50 microgram doses without the desired response. This increase was at the discretion of the attending physician in the event that there was minimal or no clinical response to treatment with 50 micrograms every four hours, as judged by the patient's symptoms and cervical examination. This dose was not to be exceeded.

All study inductions were carried out on an in-patient basis and all patients randomized to receive oral misoprostol were cared for continuously in the labour and delivery suite from randomization until delivery. Continuous electronic fetal heart rate monitoring was carried out for two hours after administration of all prostaglandins and during established labour.

The experimental manoeuvre therefore, was to create two groups of patients. The study group would receive misoprostol 50 micrograms orally every four hours as a minimum dose up

to a maximum dose of oral misoprostol 100 micrograms every four hours. The standard group would receive usual care which in our centre consists of Prepidil 0.5 milligrams intracervically every six hours or dinoprostone 1-2 milligrams intravaginally every six hours or a dilute solution of oxytocin administered intravenously. The choice of the agent to be used in the standard group rested with the individual attending physician caring for that patient based on whichever option the physician felt was optimal for the care of that particular patient.

In both study and control groups, prostaglandins were combined until the patient was contracting regularly and had a Bishop score which allowed artificial rupture of membranes. Once rupture of membranes was carried out, oxytocin augmentation was commenced. subsequently, if there were inadequate cervical change. The decisions with regard to timing of membrane rupture and oxytocin augmentation were made by the attending staff, with no maximum or minimum number of doses of prostaglandin set. Again, as this was an exploratory study, we did not mandate criteria for commencing oxytocin as we felt it safest to allow the attending staff to judge whether or not it was indicated, bearing in mind the many variables present – patients pain, fetal heart rate tracing, etc.

Two possible criticisms of the study design arise at this point. Firstly, heterogeneity in the standard arm could cause difficulty in comparing the two groups. Secondly, the protocol is liberal in the initiation and timing of the two major co-interventions – artificial rupture of membranes and commencement of oxytocin.

Our purpose however was to design a “real life” trial where our new intervention – oral misoprostol - was compared to the best care that could be given to the standard group. In the routine day to day care of non-study patients, practitioners choose the best agent from the heterogenous armamentarium available, which can be tailored to the patients needs. By mirroring

this practice in the standard arm of the trial, we hoped to provide as “strong” a comparison group as possible to our study drug. Thus, patients in the standard arm were not denied the best possible agent for them – complying both with the “first do no harm” ethic and providing the optimal yardstick by which to measure the new agent.

Similarly, we allowed artificial rupture of membranes and/or oxytocin usage when the attending staff felt it optimal for any one patient’s care.

Viewed in this way, we felt that the heterogeneity and freedom of timing in the study design were strengths rather than weaknesses, as two groups could be assembled and compared – i.e. best possible obstetric care using standard induction agents versus best obstetric care using oral misoprostol. As this was a non-blinded study, the risk of bias does arise, when interpreting the results of the study, however we felt that a direct 2 group comparison could be made.

### 3.6 Justification of Sample Size:

As alluded to in section 3.1, we chose as our primary outcome measure the length of time from commencement of induction of labour until vaginal birth, with clinically significant time difference between the two groups of four hours, or 240 minutes. In order to calculate a sample size, we also needed a mean and standard deviation from the time of induction of labour to vaginal birth at our centre. We obtained these figures from the previous trial<sup>100</sup> carried out on vaginal misoprostol at our institution. The mean of time from induction of labour to delivery was 941 minutes and the standard deviation 550 minutes. With regard to type I and type II errors we chose a two-tailed  $\alpha$  of 0.05 and a  $1-\beta$  of 95. This is a smaller type II error than the  $\beta$  of 0.20 usually chosen in similar trials. We chose a smaller than usual type II error in order to reduce the chance of missing a true difference between the two groups.

If such a difference were missed, the risk would be that this new technique might be incorrectly offered to the large population of induction patients and many women could subsequently suffer longer labours as a consequence. Sample size for our study was calculated by the following calculation:<sup>101</sup>

#### **Sample size calculation**

Sample size for t-test comparison of 2 means<sup>45</sup> is as follows :

$$\begin{aligned}
 N &= \frac{2 (Z\alpha + Z\beta)^2 \sigma^2}{\Delta^2} \\
 \Rightarrow 2N &= \frac{4 (Z\alpha + Z\beta)^2 \sigma^2}{\Delta^2} \\
 &\quad \text{If } \alpha = 0.05, \text{ (two sided), then } Z_\alpha = 1.96, \\
 &\quad \beta = 0.05, \text{ then } Z_\beta = 1.645, \\
 &\quad \Delta = 240, \\
 &\quad \sigma = 550 \text{ (standard deviation from previous study).} \\
 \Rightarrow 2N &= \frac{4(1.96 + 1.645)^2 550^2}{240^2} \\
 \Rightarrow 2N &= 273
 \end{aligned}$$

Therefore the sample size for the study was 273 subjects.

As earlier experience with misoprostol studies in our centre had found a zero “drop out” rate, we chose not to increase the sample size to allow for dropouts. This decision was justified by the zero drop out rate found in this study.

### **3.7 Description of Institution Where Study Performed:**

This study was performed in the labour and delivery suite of the Salvation Army Grace General Hospital, St. John's Newfoundland between February 28, 1995 and September 10, 1995. This centre is the provincial perinatal unit with a regional perinatal mortality rate of less than 10/1000 and a maternal mortality rate of  $< 10/100,000$ . The Grace Hospital is the provincial referral centre for complicated pregnancies and offers a tertiary level neonatal intensive care unit. Annually, there are about 7,000 births/year in the province with approximately 2800 at our centre. Our facility offers a full epidural service and is a teaching hospital with undergraduate medical and nursing students in addition to post-graduate residents in obstetrics and gynaecology. The patient population is predominantly (>95%) Caucasian of European ethnic origin. During the day care is provided by the attending physician, and at night time an "on-call" obstetrician remains in the facility continuously until care is reassumed by the patient's attending physician the following morning. The caesarean section rate for women undergoing induction of labour in our centre averages 15%. Overall caesarean section rate is approximately 18 - 20%, commensurate with similar centres across Canada.



### **3.8 Ethics and Consent:**

This research proposal received the approval of the Human Investigation Committee of the Salvation Army Grace General Hospital, St. John's and the of the Faculty of Medicine, Memorial University, Newfoundland.

All potential subjects were counselled fully by an obstetrics resident and/or attending obstetrician prior to signing the consent form (see appendix II). All patients were given a patient information sheet, to keep. These efforts supported informed choice.

### **3.9 Patient Recruitment:**

Candidates for the study were initially approached regarding enrollment at one of three different venues. The first venue would be in the offices of the attending physician when the decision was made to schedule the patient for induction of labour. At this time, the attending physician would explain the study to the patient and explore the risks and benefits of enrolling. The second venue was at our Fetal Assessment Unit, where the majority of patients whose pregnancies of 41 weeks or longer are seen for an ultrasound evaluation of fetal health, known as the biophysical profile. Since many patients are scheduled for induction of labour following this biophysical profile, they were approached and counselled at this time regarding enrollment in the study. Any patients who expressed an interest were given an information sheet (see appendix X) in order to consider the issue further before they came through the labour and delivery suite for the induction process. The third venue where patients were approached was the labour and delivery suite. Patients were occasionally seen for induction of labour without having been evaluated in the Fetal Assessment Unit or having had the trial discussed with them by their attending physician. At this point, the initial offer for information regarding the study to the patient was made by the nursing staff, with subsequent counselling by the resident or attending medical staff.

Regardless of venue of initial counselling, all patients were seen again in the labour and delivery suite. They then had a repeat, detailed counselling discussion with either an obstetrical resident or an attending physician regarding all the risks and benefits implicit in enrolling in the trial, both in the study and in control groups. Patients were then given time to consider the issues and discuss it privately with their partners. The counsellor reattended to answer any further questions present before the consent form was signed. The voluntary nature of

enrollment in, and continuation within the trial were underlined to the patient both in the consent form and verbally. No effort was made to coerce patients to enter the trial and any patient who expressed any misgivings about enrollment was not enrolled. It was made as clear as possible to trial candidates that a decision not to enroll would in no way negatively impact on care.

### **3.10 Randomization Process:**

Randomization was achieved with the use of random number tables blocked in fours, generated by a computer program. Numbered cards were then marked either “Oral Misoprostol” or “Standard” and placed in numbered opaque envelopes, by an administrative assistant not involved in patient care. Randomization was carried out within two different strata:

1) patients with intact membranes at induction of labour.

2) patients whose membranes had spontaneously ruptured prior to enrolling in the trial.

Two sets of sequentially numbered envelopes were left in the labour and delivery suite.

When an eligible patient had been seen and counselled fully and signed her consent to enroll in the trial, a pelvic examination was carried out in order to provide a blinded baseline assessment of cervical ripeness. This ripeness is evaluated as a Bishops Score (table I) and represents as objective an assessment of cervical preparedness as possible. Following this evaluation, the next envelope in sequence was opened and group assignment made. Once the envelope had been opened, the patient's name was written beside the number of the envelope and on the sheet of paper accompanying the envelopes. This list of recruited patients and their corresponding open envelope was checked twice daily by the principal investigator. By strict adherence to this process, we were able to ensure that no envelopes were opened out of sequence, that no envelopes were lost and that no envelopes were skipped. Meticulous care was paid to this entire process since in the past, criticism<sup>156</sup> has been levelled at the “sealed envelope” form of randomization, as being prone to caregiver interference and randomization bias.

### **3.11 Data Handling:**

Data were recorded on the sheets shown in appendices III and V. This process was carried out in two stages, firstly, prior to leaving the hospital, the patient was given the LADSI questionnaire described in section 3.2 and asked to complete and return the same. She was also given the opportunity to comment on her care with the investigator. Subsequently primary and secondary outcome data were abstracted from the maternal and neonatal charts. The raw data were then transferred to a computer database. At no time did the principal investigator have access to the pooled data. Subsequent data storage and analysis was carried out with the aid of the "Statistix" 4.1 computer software package (Analytical Software, Tallahassee, Florida) .

## **CHAPTER IV:     RESULTS**

Data were analysed on an “intent to treat” basis by parametric (Student’s t) and non parametric (chi-square, Fisher exact, Mann-Whitney U) statistics as appropriate, using “Statistix 4.1” (Analytical Software, Tallahassee, Florida). The primary outcome measure was considered significant if  $P < 0.05$  (as per sample size calculation). In view of multiple significance testing, other analyses were be considered exploratory and significant only if  $P < 0.001$ , a conservative approach.

### **Results:**

None of 275 randomized subjects withdrew or were lost to follow up.

#### **4.1     Demographic Analysis**

Maternal pre-induction and neonatal demographic data are presented in Table I. As would be expected from randomization, no statistically significant differences were seen between the two groups. However, there are 2 apparent imbalances which occurred by random chance. Firstly, “oligohydramnios” was the induction indication in 9 standard patients, but only 1 study patient. Because oligohydramnios may result in an increased incidence of non-reassuring fetal heart rate tracing, this imbalance could have slightly increased the risk of caesarean section in “standard” group patients. This possibility would have been off set by the other imbalance which arose by random chance --- there were 16 more patients with a poor Bishop Score ( $<6$ ) in the study group, than in the standard group. Neither of these demographic parameters were statistically significant different between the 2 groups and are not indicative of failure in the randomization process.

**TABLE I**                      **Demographic Data**

	<b>Misoprostol</b>  <b>N = 137</b>	<b>Control</b>  <b>N = 138</b>
<b>Pre-induction</b> Nulliparous	86	94
Induction Indications		
Post term	81	74
PROM	26	30
Hypertension	8	14
Oligohydramnios	1	9
Other	21	11
Maternal Age in years	27.3 (5.1)	26.8 (4.6)
Gestation in days	282.9 (10.1)	284.2 (8.6)
Gravidity	1.8 (1.0)	1.6(0.9)
Parity	0.5 (0.7)	0.4 (0.7)
Bishop score     median	5 (3,7)	6 (4,7)
Bishop score     <6	82	64
<b>Neonatal</b> Birth weight in grams	3581 (528)	3539(485)

Data given as number, mean (standard deviation SD) or median (interquartile range) as appropriate.

#### **4.2 Primary Outcome Measure: Time from commencing induction until delivery.**

Data for mean vaginal birth intervals are presented in Table II. No statistically significant difference between the two groups was found in the primary outcome measure. Mean time from induction to vaginal birth in the study group was 926 minutes, and in the standard group was 909 minutes, a difference of only 17 minutes (PO.81).

An analysis of the primary outcome with non-parametric statistics, allows inclusion of birth interval data from caesarean patients. A caesarean birth is a failure to deliver vaginally (time to vaginal birth is infinite), and therefore is ranked longer than any vaginal birth. Rank order methodology makes no assumption regarding normal distribution, is statistically conservative, and uses medians as the measure of central tendency. By employing this analysis, the two groups could be compared without excluding caesarean sections from the data. The median time to vaginal birth was 882 minutes for control subjects and 958 minutes with oral misoprostol ( $P=0.16$ , Mann-Whitney U). Again no statistically significant difference was found between the two groups.



**TABLE II**                      **Primary Outcome Measure**

	Misoprostol N=116	Control N=125	P
Induction to birth	926 (521)	909 (585)	0.81

Data given in minutes as mean (SD)

P by Student's t test.

### **4.3 Secondary Outcome Measures:**

#### **4.3.1 Labour Intervals:**

There were no significant differences between the two groups in the other relevant peripartum intervals when analysed overall, irrespective of membrane status, table III.

Analysis was also carried out according to stratification by membrane status. In participants who were stratified as membranes ruptured, the interval to vaginal birth was a mean of  $734 \pm 468$  minutes with oral misoprostol versus  $557 \pm 312$  minutes ( $P=0.13$ ). Durations of membrane rupture were  $2149 \pm 908$  minutes and  $1952 \pm 651$  minutes ( $P=0.11$ ). In subjects who were stratified as membranes intact, the interval to vaginal birth was a mean of  $974 \pm 524$  minutes with oral misoprostol versus  $1002 \pm 606$  minutes ( $P=0.73$ ). Duration of ruptured membrane status were  $296 \pm 278$  minutes and  $330 \pm 266$  minutes ( $P=0.40$ ). Again, there were no statistically significant differences in delivery times between the groups when analysed according to membrane status stratification.

**TABLE III      Labour Intervals Unstratified**

	Misoprostol N=116	Control N=125	P
Induction to full dilation	859 (487)	844 (549)	0.83
Membrane rupture duration	664 (877)	667 (761)	0.97
First stage	348 (247)	352 (218)	0.89
Second stage	63 (68)	75 (79)	0.22
Third stage	10 (10)	11 (9)	0.86

Data given in minutes as mean (SD)

P by Student's t test.

**TABLE IV                      Labour Intervals****A “Ruptured Membranes”**

	<b>Oral Misoprostol</b>	<b>Control</b>	<b>P</b>
<b>Induction to Vaginal Birth</b>	<b>734(468)</b>	<b>557(312)</b>	<b>0.13</b>
<b>Duration of Membrane Rupture</b>	<b>2149(908)</b>	<b>1952(651)</b>	<b>0.11</b>

Data expressed in minutes as mean and standard deviation

P by students t test

**B “Intact Membranes”**

	<b>Oral Misoprostol</b>	<b>Control</b>	<b>P</b>
<b>Induction to Vaginal Birth</b>	<b>974(524)</b>	<b>1002(606)</b>	<b>0.73</b>
<b>Duration of Membrane Rupture</b>	<b>296(278)</b>	<b>330(266)</b>	<b>0.40</b>

Data expressed in minutes as mean and standard deviation

P by students t test

#### 4.3.2 Birth route:

There was no difference in birth route (table V), (chi-square = 3.51, three degrees of freedom,  $P=0.18$ ). With oral misoprostol there were 93 spontaneous deliveries, 13 vacuum, ten forceps assisted, and 21 caesarean births. With control protocol, there were 103 spontaneous, nine vacuum, 13 forceps assisted and 13 caesarean births. There was no statistically significant difference in caesarean births [relative risk (RR)=1.63, 95% confidence interval (CI)= 0.85 to 3.12] between the two groups. However, the fact that there were 61% more caesarean sections in the misoprostol group, than in the control group deserves further assessment of its clinical significance. This issue is addressed in the discussion, Chapter 4. Non-reassuring fetal status was the indication for nine caesareans with oral misoprostol and six control participants (RR=1.51, CI= 0.55 to 4.13). In subjects who were stratified as membranes ruptured, three caesareans were done in the study group and four in the control group (RR=0.87, CI=0.21 to 3.52). With membranes intact, there were 18 caesareans with misoprostol versus nine with control protocol (RR=1.95, CI=0.91 to 4.14). The numbers involved in this sub-analysis post stratification are too small to allow inferences to be made.

**TABLE V**      **Birth Route**

	Misoprostol	Control	Relative Risk	Confidence Interval	
	N = 137	N = 138		5%	95%
Spontaneous delivery	93	103	0.9	0.62	2.2
Vacuum delivery	13	9	1.44	.82	3.2
Forceps Delivery	10	13	0.76	0.6	2.1
Caesarean Section	20	13	1.63	.85	3.12

### 4.3.3 Maternal Interventions:

Table VI summarizes the data concerning peripartum maternal interventions. There was a difference in oxytocin use, but this was undoubtedly influenced by the fact that vaginal PGs were considered contraindicated with membranes ruptured. Use of oxytocin was less ( $RR=0.38$ ,  $CI=0.24$  to  $0.63$ ) with oral misoprostol induction when membranes were ruptured, but not with intact membranes ( $RR=0.78$ ,  $CI=0.55$  to  $1.10$ ).

**TABLE VI** **Maternal Intervention – without stratification**

	Misoprostol N=137	Control N=138	Relative Risk	Confidence Interval	
Intrapartum Frequency				5%	95%
Oxytocin used	46	75	0.62	0.47	0.82
Epidural	68	74	0.93	0.74	1.16
No analgesia	15	15	1.01	0.51	1.98
Meconium	20	25	0.81	0.47	1.38
Scalp pH done	4	5	0.81	0.22	2.94
NRT*	22	13	1.70	0.90	3.24

\* Non-reassuring fetal heart rate tracing.



#### **4.3.4 Maternal Outcomes:**

Oral misoprostol use was not associated with increased perineal trauma, table VII. No subject in either group received pharmacologic or caesarean intervention for uterine hyperstimulation. Manual removal of the placenta after vaginal birth was carried out on two patients in each group. A single oral misoprostol recipient was given a blood transfusion subsequent to a caesarean incision extension into the broad ligament. With regard to gastrointestinal symptoms, emesis was reported in four participants in the control group and one with oral misoprostol ( $P=0.37$ , Fisher exact test). No patient in either group developed diarrhoea.

**TABLE VII**      **Maternal Outcomes**

	Misoprostol N=137	Control N=138	Relative Risk	Confidence Interval	
				5%	95%
Episiotomy	34	40	0.86	0.58	1.27
Laceration	59	75	0.85	0.67	1.09
Third / fourth degree Laceration	3	5	0.60	0.15	2.48
Intact perineum	29	23	1.27	0.78	2.08

#### **4.3.5 Neonatal Outcomes:**

Neonatal outcomes were similar (Table VIII). Umbilical cord blood acid base analysis was performed in 216 participants (78%). There was no difference in mean cord blood pH, mean base deficit or median 5 minute Apgar score between the two groups. The frequency of cord blood pH less than 7.15 (11 in study group versus seven in control) was not different (RR=1.49, CI= 0.60 to 3.69). One neonate in either group had 5 minute Apgar score less than seven. No neonate developed respiratory distress syndrome or meconium aspiration.

While there was no mother whose neonate met the ACOG criteria for birth asphyxia, one control group neonate did develop neonatal seizures. This mother was an insulin dependent diabetic whose labor was induced at 38 weeks gestation with vaginal dinoprostone. When a non-reassuring FHR tracing developed, preparations were made for a caesarean, but the cervix became fully dilated and a vacuum assisted delivery was performed. This infant had Apgar scores of 4 at 1 minute, and 9 at 5 minutes, a cord artery pH of 6.90 and a base deficit of 19. The neonate developed seizures requiring therapy and at 9 months postnatal follow up has moderate developmental delay.

**TABLE VIII Neonatal Outcomes**

	Misoprostol N=137		Control N=138		P
	Median	Quartile	Median	Quartile	
Apgar 1 min	9	(8,9)	9	(9,10)	0.87
Apgar 5 min	9	(9,10)	9	(9,10)	0.54
Apgar 1 min < 7	N 21		N 15		0.27
Apgar 5 min < 7*	1		1		1.00
	Mean	SD	Mean	SD	
Cord pH	7.28	(0.10)	7.28	(0.10)	0.86
Base deficit	4.9	(3.5)	5.2	(3.8)	0.38
ACOG Criteria for	N		N		
Apgar 5 min 3	0		0		
Cord pH < 7.00	3		2		1.00
Base deficit > 16	2		3		0.68

Quartiles are 25 and 75 per cent.

Cord blood acid base data are from 111 and 105 neonates respectively.

P for median by Mann-Whitney U, and for mean by Student's t test.

P for categorical data by chi-square, except as \* indicated by Fisher exact test.

#### 4.3.6 Post-partum Outcomes/Costs : (tables IX a and b)

There were no differences between the 2 groups with respect to the number of days in hospital for mother or baby. The only difference in health care costs between the 2 groups, therefore, is drug cost. As misoprostol's cost per dose is 0.01 that of dinoprostone,<sup>130</sup> the difference potentially does have significant cost saving implications if its use becomes widespread.

There were no differences in maternal or neonatal fever rates between the 2 groups. Crude measures of neonatal well-being post delivery, (hypothermia and hypoglycaemia) were also equal in both groups.

Of interest, is that the mean number of pelvic exams was the same in the study and standard groups. This higher than expected number of pelvic exams in the oral misoprostol group may have been caused by caregivers unfamiliarity with this new induction protocol, (ie frequent pelvic exams prior to decision regarding the number of doses of oral misoprostol).

**Table IX : Post - partum Outcomes/Costs**

<b>A Maternal</b>	<b>Oral misoprostol</b>	<b>Standard</b>	<b>P</b>
Hospitalization (mean # days)	3.9	4.1	NS
mean number of Days temp. >38.5°C	0	0	NS
Total number vaginal examinations (mean)	5	5	NS

<b>B Neonatal</b>	<b>Oral misoprostol</b>	<b>Standard</b>	<b>P</b>
Hospitalization (mean # of days)	4.0	4.1	NS
mean number of days temp. >38°C	0	0	NS
mean # days temp <36.5°C	0	0	0
Dextrostick <5MMol	75	75	NS

#### **4.3.7 Prostaglandin Dosages:**

Oral misoprostol was used a median of three doses and maximum of eight doses. Fifty-nine study group subjects received a 100 µg oral misoprostol dose at least once, with a median two, and maximum six doses. In the control group 94 patients received dinoprostone, 11 received vaginal misoprostol and 33 received intravenous oxytocin only. The maximum number of vaginal PG doses was six with a median of two. Induction interval, birth route, and neonatal outcomes for participants who received vaginal misoprostol in the control group were not different from other subjects in their assigned group.

#### **4.4 Maternal Satisfaction Results:**

Of the 275 patients in the study, 189 questionnaires were returned for analysis. This response rate (70%) is typical of questionnaires of this kind, and is sufficient to allow analysis. Of the 189 respondents; 5 patients were excluded, as 4 or more questions had not been answered (by convention questionnaires with 10% or more unfinished questions are not included in the analysis). In a further 5 patients, 3 or less questions were unanswered. In these patients; as per convention,<sup>91</sup> the mean score for that patient's questionnaire was substituted for any unanswered question.

All questionnaires were then reviewed and cumulative score obtained. This total score represents the overall measure of satisfaction with the birth process. For positive statements, the maximum score is 10. For negative statements, the score is inverted, so that a patient who totally disagreed (score 1) with a negative statement had a score of 10 ascribed for that statement. The most satisfied a patient could be with the study therefore is a total score of 380 (38 statements, 10 marks per statements).

Table Xa contains the total scores and means from all returned questionnaires. There was no statistically significant difference between the total score means in the two groups, demonstrating comparable satisfaction with the labor process group regardless of the method of induction.



**TABLE X a**                      **Total LADSI Scores From Satisfaction Questionnaires**

<b>Group</b>	<b># Patients</b>	<b>Total</b>	<b>Mean</b>	<b>Variance</b>	<b>Standard Deviation</b>
<b>Standard</b>	85	28143	331.1	3281.2	57.3
<b>Misoprostol</b>	99	34326	346.7	1212.9	34.8
<b>Difference</b>			-15.6 NS		

#### 4.4 B Additional Study LADSI Questions

Table Xb displays the perceived incidence of gastrointestinal side effects between the 2 groups.

**Xb**      Mean Scores for additional questions

	Standard	Study	Significance
<b>Question # 39</b>	7.3	8.3	NS
<b>Question # 40</b>	5.1	6.4	NS
<b>Question # 41</b>	7.3	8.6	NS

The answers to 39 and 40 indicate that there were no differences in the perceived incidences of gastrointestinal side effects between the two groups. This is the first documentation of the use of an oral prostaglandin to induce labour which is well tolerated.

However the following points should be noted: firstly, this is a relatively small study, with only 137 patients receiving oral misoprostol. Secondly, this part of the questionnaire was not pre-tested or validated. Thirdly, a dichotomous choice – regarding presence or absence of gastrointestinal symptoms may diminish the reporting of minor GI symptoms. A graded set of symptoms choices should be provided in future studies.

#### 4.4 C : Choice of Drug Route

Question : I would prefer oral rather than vaginal administration (Agree 10 – Disagree 1).

Table Xc demonstrates patients preferences with regard to route of induction agent respondents clearly prefer induction by an oral agent in both groups.

**Xc**                      **Choice of Drug Route**

Q 41	Standard	Study	Total
1	6	4	10
5	3	3	6
6	4	0	4
7	0	1	1
8	2	1	3
9	3	4	7
10	16	29	45
<b>Total</b>	<b>34</b>	<b>42</b>	<b>76</b>

In both groups, patients would clearly rank oral over vaginal drug administration. This question leads in to question 42, regarding the extra number of hours that patients would be prepared to spend in the induction process, in order to receive an oral rather than 2 vaginal doses.

When asked (question 42): how many extra hours would they be prepared to spend in the induction process, in order to have oral treatment, all patients responded “zero”. Although this question was worded carefully in order to underline that TOTAL induction to delivery time was the issue, it is possible that some patients felt that the question concerned painful labor time. If this were the case, it may partially explain the unanimity among patients that they would not wish to spend any extra time in the induction process.

Had the choice been presented on a continuous scale, it is possible that some, if not most, patients would have indicated 1 or 2 hours of induction time as a reasonable “price” to pay for oral drug administration. This question, therefore, was not well designed in the study and the issue remains open, to be elucidated by further research.

## **CHAPTER V: DISCUSSION AND CONCLUSIONS:**

### **5.1 Discussion:**

Since the report of Sanchez-Ramos et al in 1993,<sup>151</sup> there has been increasing interest in vaginal misoprostol as a method for labor induction, probably because it is so inexpensive. His RCT has been followed by several others (including the one from our centre) all of which have supported vaginal misoprostol as cost effective. No investigator has found a significant increase in substantive adverse neonatal outcomes, although an increase in uterine tachysystole has been observed.<sup>150</sup> Pharmacokinetic data on low dose vaginal misoprostol use at term are lacking.<sup>144</sup>

As discussed in the rationale behind this trial, there are no other reports using oral misoprostol for term labor induction with living fetuses. However after completion of this trial, but before its publication, Ngai et al<sup>151</sup> in Hong Kong reported a double blind RCT with a single 200 µg oral misoprostol dose versus placebo for cervical priming, in pre-labor rupture of membranes at term. Twelve hours later an intravenous oxytocin induction protocol was begun, if the participant was not in progressive labor. Thirty-nine subjects received oral misoprostol, with 41 receiving placebo. The Bishop score was significantly improved with misoprostol ( $P<0.05$ ). Thirty-four women given misoprostol went into labor without oxytocin, compared to 20 of those given placebo ( $P<0.001$ ). Interval to onset of uterine activity and delivery were both shorter with misoprostol ( $P<0.01$ ). There were three caesareans in each group. Neonatal outcomes and gastrointestinal tolerance were comparable. The authors concluded that a single 200 µg misoprostol oral dose was effective for cervical priming, and may be effective for labor induction.

The oral misoprostol protocol and its purpose in our study are different from that of the

Hong Kong investigators. Our median cumulative dose per subject for labor is similar to their single dose. It is reassuring that they did not find a significant problem with excessive uterine activity.

The Hong Kong study of oral misoprostol for pre-induction of labour and the study reported in this thesis along with the trials previously discussed in section 1.6 contribute to an evolving body of evidence that misoprostol is an effective agent in the induction of labour at term in human pregnancy.

As both oral misoprostol and standard methods were equally effective, this was a negative trial, where the only difference found between the groups was in the use of oxytocin – less oxytocin was used in the PROM patients who were randomised to oral misoprostol than standard methods. This difference is explained by the fact that vaginal prostaglandins were not offered to PROM patients in our centre at the time of this trial – thus skewing the numbers in favour of the oral misoprostol group. However, the most important consideration in the assessment of any new intervention is safety. Before oral misoprostol can be adopted for widespread use, its safety for both the fetus/neonate and mother must be demonstrated. Because no neonate in our study was assessed an Apgar score at 5 minutes of 3 or less, none met the ACOG criteria for birth asphyxia. The new-born of most concern was described previously,<sup>4,5</sup> and was born to a control group participant induced with vaginal dinoprostone. The frequencies of other commonly reported worrisome neonatal short term outcomes (Apgar score at 5 minutes of 6 or less, and cord blood pH less than 7.15), or other indicators of possible compromise of intrapartum fetal well-being, (non-reassuring FHR monitoring, frequency of fetal scalp pH sampling, and meconium stained amniotic fluid) were not increased. There were also no differences in length of stay in hospital or neonatal pyrexia etc. while in hospital. However, it

must be pointed out that neonatal asphyxia is an uncommon event and that this study was not designed with the power to demonstrate a difference in neonatal asphyxia between the 2 groups. Such a study would require a larger sample size than the 237 cases reported in this thesis.

The second major consideration with regard to safety is that of the mother's safety. Again, no statistically significant difference was found in perineal trauma, peripartum intervention, or routes of delivery. The most significant risk of any induction agent, uterine hyperstimulation, is shared by both neonate and mother. If uterine hyperstimulation with concern for fetal status subsequent to oral misoprostol occurred, operative delivery or intravenous tocolytic therapy with an agent such as ritodrine would be necessary. Lavage or removal of tablet remnant, an option in vaginal PG use, is not possible. No subject in either group was treated with tocolytic agents or caesarean for uterine hyperstimulation.

One of the most important and interesting aspects of this trial is the issue of caesarean section rates in the two groups while the frequencies of caesarean birth overall ( $RR=1.63$ ,  $CI=0.85$  to  $3.12$ ) or for non-reassuring fetal status ( $RR=1.51$ ,  $CI=0.55$  to  $4.13$ ), were not different, the difference in the caesarean section rates in the 2 groups (67% higher in the oral misoprostol group) is of great interest to the clinician. This trend towards a higher caesarean section rate in the oral misoprostol group is particularly strong in the intact membranes stratum, and almost achieves statistical significance. In fact, a further 5 caesarean sections in the oral misoprostol group would have caused a statistically significant difference.

The trend towards such an important outcome as an increased caesarean rate with oral misoprostol's use is disturbing, particularly in light of the lower caesarean section rates seen with its vaginal use, when compared to standard methods. Clearly, if its use does increase the risk of

caesarean section, oral misoprostol could not be considered for routine use in labour induction. When considering this issue, however, the following should be considered: firstly, a statistically significant difference was not found between the two groups. Secondly, the caesarean section rate was a secondary outcome – one of 30 others – and as such is subject to the risks of multiple comparisons between groups. This risk is exacerbated by sub-analysis according to stratification (total of 60 comparisons between groups).

In order to resolve this issue of caesarean section risk with oral misoprostol, it would have been necessary to design the trial with a difference in caesarean sections as the primary outcome measure. In order to detect an increase of 5% in the caesarean section rate, such a study would have required a sample size of 1106 per arm. However, it must be borne in mind that this trial represents the first study of the use of this drug for labour induction. It would appear inappropriate to subject 1106 patients to an intervention, with absolutely no evidence as to whether or not it is effective. Hence it was felt that the design described in this thesis was the most appropriate in the exploratory evaluation of this novel technique. Clearly, however, the completion of a small exploratory randomised trial should not be sufficient to allow widespread acceptance of a new intervention, particularly in the vital area of human labour and delivery. This theoretical biological risk (i.e. misoprostol induced uterine hyperstimulation, subsequent fetal asphyxia and/or caesarean section) is, in the author's opinion, the most important unresolved question with regard to misoprostol's use for labour induction, whether administered orally or vaginally.



## 5.2 Strengths and Weaknesses:

Consideration of the strengths of a study involves two principle areas. Firstly, is the question an important one, and secondly how well is the question answered? With regard to the clinical importance of this study, the following points may be made. The induction rate is growing in Canada, resulting in the exposure of many healthy women and their fetus/neonates to induction agents. However, all of the presently available agents are expensive and none are free of side effects. Furthermore in an occasional patient, all the presently available agents will fail to induce labour. There is, therefore, the need to continue the search for an optimal labour induction regime and to continue to provide information on all the agents in the induction armamentarium. Any potential side effects, or risks, to this young healthy population must be fully exposed. As misoprostol has been shown to be an effective induction agent, therefore, any research on it's application is important. This perception of its clinical importance is widespread. A med-line search at the time of rewriting this thesis (August 1998) reveals that there have been 32 randomized trials of standard prostaglandins versus misoprostol in the 1997 to 1998 period alone. During the same time period, there have been no reports of trials comparing standard prostaglandins to any other agents.

The second area in discussion of a studies' strength centres around how well the question is answered. This study complies well with the principles for conducting and reporting a randomised trial of a new intervention. The study population and the venue for the trial are carefully described. All patients who entered were randomised. All subjects who entered were cared for according to randomisation and they were reported on fully at completion. All relevant outcomes were prospectively evaluated and reported.

Uniquely, among studies of the labour induction, we reported on patients' satisfaction with their birth experience. We designed a trial with the power to detect the delta which our centre considered to be important, and defended that delta in the text. We avoided misinterpretation of the data by setting a very low p-value for secondary outcome analysis; avoiding over comparison between groups and setting a  $\beta$  of 5. Finally, we attempted not to overstate the case in favour of oral misoprostol and pointed to the need for further research, before it could be recommended for general use.

With regard to weaknesses of the study, these primarily concern the following areas. Firstly, as this was the first ever use of this agent, we felt that blinding was inappropriate. This is of importance, as obstetrical care with respect to the co-interventions of oxytocin and artificial rupture of membranes, was not rigidly mandated in either arm. A biased caregiver, therefore could offer these co-interventions more aggressively in his/her favoured arm, thereby confounding the results. As all caregivers were asked to give the optimal obstetric care to any and all patients, we hoped to minimise this risk. Clearly however, further studies should be fully blinded. In such future studies a more didactically defined "standard care" protocol, with less heterogeneity of standard options would also be helpful. A double-blinded trial of oral misoprostol versus vaginal prostin gel with standardised rupture of membranes and oxytocin administration in both arms would be an example of such a study.

Apart from the weaknesses of unblinding and standard group heterogeneity, the other leading weaknesses of the study are as follows. Firstly, non-participants were not documented, or described. Neonatal umbilical cord pH and patient questionnaires were not obtained in all cases. The delta was subjectively chosen, with no consumer input.

The sample size is insufficient to form conclusions regarding maternal risks – specifically caesarean section risk or fetal risks specifically uterine hyperstimulation induced hypoxic asphyxia.

### **5.3 Conclusions:**

In this 273 patient randomized controlled clinical trial no significant differences in effectiveness or safety were found between oral misoprostol and standard labour induction agents. Oral misoprostol was very well tolerated orally. Responding parturients indicated their preference for an oral rather than vaginal route of administration of induction medications. More studies are needed to confirm effectiveness, and to evaluate further the issues of maternal side effects and neonatal safety. Optimal dosage and frequency of administration also need to be resolved. However, based on the study reported in this thesis, it does appear that oral misoprostol may be an effective and safe induction agent, and may be the first effective induction agent that is well tolerated orally because of its minimal gastrointestinal side effects.

## **5.4 Future Studies**

Since the completion of the data analysis for this trial there have been further studies demonstrating again the effectiveness of misoprostol in the induction of labour at term. The question of whether or not there is enough evidence for the widespread use of misoprostol for induction of labour at term as cited by clinical trial protocols remains controversial. If oral misoprostol is to become widespread in its use in routine clinical induction of labour, this will result from one of three developments. Firstly, as evidence accumulates, there might simply be a generalized consensus that this medication represents a reasonable option for the induction of labour at term. Secondly, a large meta-analysis and overview of all the randomized trials performed to date might provide evidence to justify a change in accepted practice. The third possibility is that of a large multi-centre trial. Ideally this trial would be a double-blinded randomized controlled trial, with sufficient power to look not only at length of time from induction of labour to delivery, but also to evaluate substantive and meaningful outcomes, such as frequency of caesarean sections and neonatal asphyxia.

Criteria	Points Award			
	0	1	2	3
Cervical Dilatation (cm)	0	1 - 2	3 - 4	5 - 6
Cervical effacement (%)	0 - 30	40 - 40	60 - 70	≤ 80
Cervical consistency	Firm	medium	Soft	
Cervical position	Posterior	central	anterior	
Station (in relation to the spines)	3 cm above	2 cm above	1 - 0 cm above	1 - 2 cm below

## **Appendix II**

**Consent Title:**           **Randomized Trial Comparing Oral Misoprostol Versus  
Standard Protocol for Labour Induction**

**Investigators:**       **Drs. Rory Windrim, David Young and William Mundle**

You are being asked to participate in a research study. Participation in the study is entirely voluntary. You may freely decide not to participate or to withdraw from the study at any time without affecting your normal treatment. Confidentiality of information concerning participants will be maintained by the investigators. The investigators will be available should you have any problems or questions regarding this study.

### **Description and Background Information:**

I understand I have been scheduled for induction of labour. I am aware that standard treatment usually involves the intravenous administration of a substance called oxytocin plus cervical/vaginal application of prostaglandin-containing cream for cervical ripening if necessary. I know that the procedure usually involves an artificial rupture of membranes of “breaking of my water”.

Prostaglandins, although primarily used as cervical ripening agents, also stimulate labour. These medication can be administered orally or vaginally.

This trial will attempt to decide if administration of misoprostol orally - a prostaglandin not widely used for induction of labour, but often used for gastrointestinal disorders - will safely decrease the time required from start of drug administration to delivery.

### Study Design:

If I choose to enter this study, I will be randomized (chosen as if by flipping a coin) into one of two groups. One group will receive the standard treatment as described above while the other group will receive misoprostol orally. There would be no additional examinations or blood tests, other than those needed for standard labour induction. After delivery, my chart will be reviewed by the investigators for information regarding my delivery and baby. I understand that I will remain under the care of my physician who will manage my labour/delivery as deemed necessary.

### Alternative Treatments:

The alternative should I choose not to enter the study, would be induction via the standard method employing oxytocin (see above).

### Voluntary Participation:

I have discussed the information provided with my physician and he/she has answered any questions about my care/treatment that I have.

### Confidentiality/Access to Medical Records:

I understand that records concerning my labour, delivery and hospital stay will be reviewed and I give my permission for this. No records bearing my name will be provided to anyone other than the investigators in this study. I will not be identified in any publications in any manner.

Patient Signature \_\_\_\_\_ Date \_\_\_\_\_

Investigator Signature \_\_\_\_\_ Date \_\_\_\_\_



### **Appendix III**

#### **ORAL CYTOTEC STUDY**

##### **Guidelines:**

1. Eligible patients are those booked for induction with no contraindication (e.g. previous caesarean section, severe IUGR, etc).
2. All eligible patients to be counselled by attending physician and/or resident prior to signing consent. If no one is available please call Dr. Windrim to counsel the patient.
3. After enrolling patient should be assigned to PROM or intact membrane group.
4. Bishop Score should be performed prior to opening envelope.
5. Please slug all forms with the addressograph, except the questionnaire, which should be given to the patient.
6. Medications should be judged at the time of administration and not pre-ordered, so that there is an individual order for each Cytotec, etc. given.
7. PO Cytotec is to be given every four (4) hours as needed. The first two dosages should be 50 µg misoprostol. If there is no change in the cervix, or no labour, this may be increased to 100 µg for subsequent doses at the order of the attending physician. Under no circumstances should dosing higher than 100 µg misoprostol q4h be used.
8. If there are any questions please call Dr. Windrim:

**Office - \_\_\_\_\_**

**Pager - \_\_\_\_\_**

**Home - \_\_\_\_\_**

### Appendix IV

Group			
Chart #			
Age			
Gravida, Para			
Gestation (days)			
Bishop – Position			
- Consistence			
- Effacement			
- Dilation			
- Station			
# Doses of Narcotic			
Epidural			
PG # of Doses			
Mg. PG			
Mg. Misoprostol			
Oxytocin # minutes			
Indication for Induction			
Type of Delivery:	SVD Vacuum Forceps LSCS		
Indication for OR:	NRT	FTP	None
Episiotomy:	Nil	Lat.	Midline
Lacerations			
Manual Removal of Placenta			
Blood Loss:	Normal	or	
Scalp pH			
Side Effects:	Nausea	Vomiting	Diarrhoea

Questionnaire Sent \_\_\_Yes \_\_\_No

**Appendix V**

NAME	
GRACE #	
# days Mom	
# days Baby	
# days temp > 38.5 Mom	
# days temp > 38.5 Baby	
# days temp < 36.5	
Dextrostick	
# Pelvic exams	

## Appendix VI

### POST- PARTUM MISOPROSTOL STUDY SATISFACTION SURVEY

Please rate the following statements on the basis of strongly agree = 10 and strongly disagree = 1

- |    |  |   |   |   |   |   |   |   |   |   |    |
|----|--|---|---|---|---|---|---|---|---|---|----|
| 1. | I was very satisfied with the care we received during labour and delivery.                     | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 2. | Sufficient attention was paid to the safety of mother and baby during labour and delivery.     | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 3. | The staff gave us all the care and attention they could during labour and delivery.            | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 4. | Some unnecessary interventions were carried out on mother or baby during labour and delivery.  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 5. | Our wishes were always respected during labour and delivery.                                   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 6. | I feel happy about this labour and delivery experience.  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 7. | I felt in control of what happened during labour and delivery.                                 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 8. | I felt some mistakes were made in the care received from the staff during labour and delivery. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

- |     |   |                      |
|-----|---|----------------------|
| 9.  | If the staff had been more capable during labour and delivery I would have been happier with the care received. | 1 2 3 4 5 6 7 8 9 10 |
| 10. | I would be feeling better now if the staff had been more considerate during labour and delivery.                | 1 2 3 4 5 6 7 8 9 10 |
| 11. | The nurse gave us all the care and attention I wanted during labour and delivery.                               | 1 2 3 4 5 6 7 8 9 10 |
| 12. | The doctor gave all the attention needed during labour and delivery.  | 1 2 3 4 5 6 7 8 9 10 |
| 13. | I would have liked the staff to have responded to me differently during labour and delivery.                    | 1 2 3 4 5 6 7 8 9 10 |
| 14. | Sufficient attention was paid to comfort during labour and delivery.  | 1 2 3 4 5 6 7 8 9 10 |
| 15. | I would have liked the management of labour and delivery to have been done differently.                         | 1 2 3 4 5 6 7 8 9 10 |
| 16. | There was too much equipment used during labour and delivery.   | 1 2 3 4 5 6 7 8 9 10 |
| 17. | The staff were sometimes rude to me during labour and delivery.   | 1 2 3 4 5 6 7 8 9 10 |

- |     |  |   |   |   |   |   |   |   |   |   |    |
|-----|--|---|---|---|---|---|---|---|---|---|----|
| 18. | There were too many staff or students involved in the labour and delivery.       | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 19. | Staff treated me as if this was just one more delivery.                          | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 20. | The staff helped me to feel like this was a very special event.                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 21. | The appropriate amount of equipment was used to monitor the labour and delivery. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 22. | There were occasions when no one explained to me what was going on.              | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 23. | There were unnecessary restrictions on mothers walking around during labour.     | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 24. | The most comfortable position was used for the actual delivery.                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 25. | The things done to the baby immediately after birth were all necessary.          | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 26. | I held the baby as soon as I wanted.   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 27. | They tried to delivery the placenta too quickly.                                 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

- |     |  |                      |
|-----|--|----------------------|
| 28. | I was given all the information needed about progress in labour.         | 1 2 3 4 5 6 7 8 9 10 |
| 29. | The nurse was with me as much as I wanted.                               | 1 2 3 4 5 6 7 8 9 10 |
| 30. | I saw the doctor as often as I wanted.                                   | 1 2 3 4 5 6 7 8 9 10 |
| 31. | I was satisfied with the way pain was relieved during delivery.          | 1 2 3 4 5 6 7 8 9 10 |
| 32. | I was dissatisfied with the way pain was relieved during delivery.       | 1 2 3 4 5 6 7 8 9 10 |
| 33. | There were too many vaginal examinations.                                | 1 2 3 4 5 6 7 8 9 10 |
| 34. | Our birth plans were ignored.  | 1 2 3 4 5 6 7 8 9 10 |
| 35. | Recovery time in labour and delivery .                                   | 1 2 3 4 5 6 7 8 9 10 |
| 36. | The nurse made the labour and delivery a better experience.              | 1 2 3 4 5 6 7 8 9 10 |
| 37. | I wish all doctors were as good as ours.                                 | 1 2 3 4 5 6 7 8 9 10 |
| 38. | The doctor made the labour and delivery a better experience.             | 1 2 3 4 5 6 7 8 9 10 |
| 39. | I did not experience diarrhoea during my induction, labour and delivery. | 1 2 3 4 5 6 7 8 9 10 |

40. I did not experience stomach cramps during my induction, labour and delivery. 1 2 3 4 5 6 7 8 9 10
41. I would prefer an oral to vaginal medication to "ripen" my cervix. 1 2 3 4 5 6 7 8 9 10
42. I would be prepared to spend an extra \_\_\_\_ hours between beginning the ripening process and delivery, in order to have the medications orally instead of vaginally. Choose number of hours: 0 6 12 18 24



### **Bibliography and References**

- 1) Aburel E. Le declenchement du travail par injection intra-amniotique. Rev Medicochir Iasi (Roumanie), 20:310-320, 1939.
- 2) American College of Obstetricians and Gynecologists. Prostaglandin E<sub>2</sub> gel for cervical ripening. ACOG Committee Opinion No. 123. Washington, DC: American College of Obstetricians and Gynecologists, 1993.
- 3) American College of Obstetricians and Gynecologists OG Committee Opinion. Fetal distress and birth asphyxia; Washington DC. ACOG Committee Opinion No 137; 1994.
- 4) American College of Obstetricians and Gynecologists. Utility of umbilical cord blood acid-base assessment; Washington, DC, ACOG Committee Opinion No 138; 1994.
- 5) American College of Obstetricians and Gynecologists Bulletin. Fetal heart rate patterns: Monitoring, interpretation, and management. Washington, DC: ACOG Bulletin No 207;1995.
- 6) American College of Obstetricians and Gynecologists. Induction and augmentation of labor. ACOG Technical Bulletin No. 217. Washington, DC: American College of Obstetricians and Gynecologists, 1995.

- 7) Agrawal NM. Epidemiology and prevention of non-steroidal anti-inflammatory drug effects in the gastrointestinal tract. *Br J of Rheumatology* 34 Suppl : 5-10, 1995.
- 8) Anonymous. Misoprostol and legal medical abortion. *Lancet* 338(8777):1241-2, 1991.
- 9) Bainbridge MN, Nixon WCW, Schild HO, Smyth CN. Synthetic oxytocin. *Br Med J*, 1:1133-1135, 1956.
- 10) Baird DT, Norman JE, Thong KJ, Glasier AF. Misoprostol, mifepristone, and abortion. *Lancet* 339(8788):313, 1992.
- 11) Barbosa RM, Arilha M. The Brazilian experience with Cytotec; *Studies in Family Planning* 24(4):236-40, 1993.
- 12) Bardhan KD, Bjarnason I, Scott DL, Griffin WM, Fenn GC, Shield MJ, Morant SV. The prevention and healing of acute non-steroidal anti-inflammatory drug-associated gastroduodenal mucosal damage by misoprostol. *Br J of Rheum* 32(11):990-5, 1993.
- 13) Beard RJ, Harrison R, Kiriakidis. A clinical and biochemical assessment of the use of oral prostaglandin E<sub>2</sub> compared with intravenous oxytocin for labor induction in multiparous patients. *Eur J Obstet Gynecol Reprod Biol* 5:203-7; 1975.

- 14) Beazley JM, Gillespie A. Double-blind trial of prostaglandin E<sub>2</sub> and oxytocin in induction of labour. *Lancet* 1:152-155; 1971.
- 15) Bernstein EP. Prostaglandin E<sub>2</sub> for cervical ripening and labour induction: A multicenter placebo-controlled trial. *Can Med Assoc J.* 145:1249-54;1991.
- 16) Bergmann JF, Naudin R, Simoneau G, Caulin C, Segrestaa Jm. Protection with misoprostol of gastric mucosa lesions induced by aspirin. Measurements for the difference in transgastric potential. (French) *Therapie* 47(2):124-5. 1992.
- 17) Bergstrom S, Danielsson H, Samuelsson B. The enzymatic formation of PGE<sub>2</sub> from arachidonic acid. *Biochim Biophys Acta*, 90:207-210, 1964
- 18) Bergstrom S, Sjoval J The isolation of prostaglandin. *Acta Chem Scand*, 11: 1086, 1957.
- 19) Bernstein EP, Prostaglandin E<sub>2</sub> for cervical ripening and labour induction : A multicenter placebo-controlled trial. *Can Med Assoc J*, 145:1249-54, 1991.
- 20) Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol* 24:266-268, 1964.
- 21) Bond, GR, Van Zee A. Overdosage of misoprostol in pregnancy. *Am J Obstet & Gynecol* ; 71 (2) : 561-2,1994.

- 22) Bremme K, Bygdeman M. Induction of labor by oxytocin or prostaglandin E<sub>1</sub>. Acta Obstet Gynecol Scand, 11-21, 1980.
- 23) Bremond A, Dominici J, Magnin P. L'induction artificielle du travail. Etude comparee de trois methodes a propos de 334 observations. Rev Franc Gynecol, 73: 673-676, 1978.
- 24) Brindeau A. La pratique de l'Art des Accouchements, Vol. IV. Paris: Vigot, pp 36-40, 1926.
- 25) Brindley BA, Sokol RJ. Induction and augmentation of labor: Basis and methods for current practice. Obstet Gynecol Survey 43:730-43;1988.
- 26) Briner W, House J. Synthetic prostaglandin E<sub>1</sub> misoprostol as a treatment for tinnitus. Archives of Otolaryngology & Head & Neck Surg 119(6):652-4, 1993.
- 27) Bugalho A, Bique C, Almeida L, Bergstrom S. Pregnancy interruption by vaginal misoprostol. Gynecol & Obstet Invest; 36(4):226-9, 1993.
- 28) Bugalho A, Bique C, Almeida L, Bergstrom S. Application of vaginal misoprostol before cervical dilation to facilitate first-trimester pregnancy interruption. Obstet & Gynecol. (Pt 1)729-31; 1994.

- 29) Bugalho A, Bique C, Machungo F, Faundes A. Low-dose vaginal misoprostol for induction of labor with a live fetus. *Int J Gynaecol Obstet.* 49:149-55; 1995.
- 30) Bugalho A, Bique C, Machungo F, Bergstrom S. Vaginal misoprostol as an alternative to oxytocin for induction of labour in women with late fetal death. *Acta Obstet et Gynecol Scandinavica.* 74(3):194-8.1995.
- 31) Bugalho A, Bique C, Machungo F, Faaundes A. Induction of labour with intravaginal misoprostol in intrauterine fetal death. *Am J Obstet & Gynecol* 171(2)538-41,1994.
- 32) Bugalho A, Bique C, Machungo F, Bergstrom S. A comparative study of vaginal misoprosol and intravenous oxytocin for induction of labour. *Gynecol Obstet Invest.* 39:252-6; 1995.
- 33) Bugnon A, Paniagua AE, Postiglione G, Lardizaba JL. Induction of labor with misoprostol. (Spanish) *Ginecologia y Obstetricia de Mexico.* 62:407-14, 1994.
- 34) Bugnon A, Paniagua AE, Postiglione G, Lardizaba JL. Induction of labor with misoprostol. (Spanish) *Ginecologia y Obstetricia de Mexico.* 62:407-14, 1994.
- 35) Bygdeman M. Treatment in miscarriage and abortion. Widened use of drugs has many advantages. (Swedish) *Lakartidningen* 91(14):1396-7, 1994.

- 36) Bygdeman M, Swahn ML, Gemzell-Danielsson K, Gottlieb C. The use of progesterone antagonists in combination with prostaglandin for termination of pregnancy. Human Reprod. Suppl 1:121-5, 1994.
- 37) Calder AA. The management of the unripe cervix. In: Human Parturition. Keirse MJNC, Anderson ABM, Bennebroek Gravenhorst J (eds). The Hague: Leiden University Press, 201-217; 1979.
- 38) Caldeyro-Bancia R, Heller H. Oxytocin. New York: Pergamon Press. 1961.
- 39) Campbell JM, Induction of Labour using prostaglandin E<sub>2</sub> pessaries. Clin Exp Obst Gyn 1984.
- 40) Campos GA, Guzman S, Rodriguez JG, Voto LS, Margulies M. Misoprostol -- Un analogo de la PGE<sub>1</sub> para la induccion de parto a termino: Estudio comparativo y randomizado con oxitocina.(analog for induction of labor at term: comparative and randomized study with oxytocin. (Spanish) Revista Chilena de Obstet y Gincolo. 59(3):190-6; 1994.
- 41) Castilla EE, Orioli IM. Teratogenicity of misoprostol: data from the Latin-American Collaborative Study of Congenital Malformations (ECLAMC). Am J of Med Genet; 51(2):161-2, 1994.

- 42) Chalmers I, Keirse MJN. Evaluating elective delivery. In : Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford University Press, 981-987; 1989.
- 43) Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E<sub>2</sub> gel (Prepidil Gel): Randomized comparison. Am J Obstet Gynecol 173:1137-42; 1995.
- 44) Chifrani T. A Short History of Obstetrics and Gynecology. Springfield, Ill: Thomas; 1960.
- 45) Coelho HL, Teixeira AC, Santos AP, Forte EB, Morais SM, La Vecchia C, Tognoni G, Herxheimer A. Misoprostol and illegal abortion in Fortaleza, Brazil. Lancet. 341(8855):1261-3, 1993.
- 46) Coelho HL, Teixeira AC, Cruz M de F, Gonzaga SL, Arrais PS, Luchini L, La Vecchia C, Tognoni G. Misoprostol: the experience of women in Fortaleza, Brazil. Contraception. 49(2):101-10, 1994.
- 47) Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. Lancet. 341(8855):1258-61, 1993.

- 48) Craft I. Amniotomy and oral prostaglandin E<sub>2</sub> titration for induction of labor. *BMJ*;2:191-4;1972.
- 49) Creinin MD. Methotrexate and misoprostol for abortion at 57-63 days gestation. *Contraception*. 50(6) :511-5, 1994.
- 50) Creinin MD, Darney PD. Methotrexate and misoprostol for early abortion. *Contraception*; 48(4):339-48, 1993.
- 51) Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs. misoprostol alone for early abortion. A randomized controlled trial. *JAMA*. 272(15):1190-5, 1994.
- 52) Cunningham FG, MacDonald PC, Grant NF, Leveno KJ, Gilstrap LC. Williams Obstetrics 19<sup>th</sup> Edition. ISBN 0-8385-9634-7, 1997.
- 53) Curtis P, Evans S, Resnick J. Uterine hyperstimulation: The need for standard terminology. *J Reprod Med* 1978; 32:91-5.
- 54) Delmas PD. Non-steroidal anti-inflammatory drugs and renal function. *Br J of Rheumatology*. 34 Suppl 1:25-8, 1995.
- 55) Denman T. Principles of Midwifery on Puerperal Medicine. London: E Cox, 1785.



- 56) Doube A, Davies J, Notarianni L, Holgate K, Fenn GC. Effect of misoprostol on concentrations of prostaglandins in synovial fluid. *Annals of the Rheumatic Diseases*. 50(11):797-9, 1991.
- 57) Eastman NJ. The induction of labor. *Am J Obstet Gynecol*, 35:721-730, 1938.
- 58) Edwards D, Aitken RE, Begg AF, MacKay PM, Marchant RM. Predilatation of the cervix before suction curettage for therapeutic abortion in early pregnancy. *Austral & NZ J of Obstet & Gynaecol*. 34(1):103-4. 1994.
- 59) Egarter CH, Husselein PW, Rayburn WF. Uterine hyperstimulation after low dose prostaglandin E<sub>2</sub> therapy: tocolytic treatment in 181 cases. *Am J Obstet Gynecol*; 163: 794-6; 1990.
- 60) Elder MG. Uterine action after induction of labour with oral prostaglandin E<sub>2</sub> tablets compared with intravenous oxytocin. *Br J of Obstet and Gynecol*. 82(8), 674-81, 1975.
- 61) el-Refaey H, Calder L, Wheatley DN, Templeton A. Cervical priming with prostaglandin E<sub>1</sub> analogues, misoprostol and gemeprost erratum appears in *Lancet*. 343(8907):1207-9; 1994.

- 62) el-Refaey H, Hinshaw K, Templeton A. The abortifacient effect of misoprostol in the second trimester. A randomized comparison with gemeprost in patients pre-treated with mifepristone (RU486). *Human Reprod*; 8(10):1744-6; 1993.
- 63) el-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU486) and oral or vaginal misoprostol. *N Eng J Med*; 332(15):983-7, 1995.
- 64) el-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure . Comment in: *Br J Obstet Gynaecol* 1995.
- 65) el-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception*. 49(2): 111-4, 1994.
- 66) el-Rafaey H, Templeton A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. *Human Reprod*; 10(2):475-8, 1995.
- 67) Embrey MP. *The Prostaglandins in Human Reproduction*. Edinburgh: Churchill Livingstone; 1975.

- 68) Embrey MP. The effect of prostaglandins on the human pregnant uterus. *J Obstet Gynaecol Br Commnwith*. 86: 783-789. 1969.
- 69) Fenn GC, Robinson GC. Misoprostol—a logical therapeutic approach to gastroduodenal mucosal injury induced by non-steroidal anti-inflammatory drugs? *J of Clin Pharmacy & Therapeutics*. 16(6):385-409, 1991.
- 70) Ferris LE, Basinski AS. Medical abortion: what does the research tell us? *CMA J.*, 154(2) :165-70; 1996.
- 71) Fletcher HM, Mitchell S, Frederick J, Simeon D, Brown D. Intravaginal misoprostol versus dinoprostone as cervical ripening and labour-inducing agents. *Obstet Gynecol* ; 83:244-7; 1994.
- 72) Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. *Br J Obstet Gynaecol*; 100:641-4; 1993.
- 73) Fonseca W, Alencar AJ, Pereira RM, Misago C. Congenital malformation of the scalp and cranium after failed first trimester abortion attempt with misoprostol.. *Clinical Dysmorphology*. 2 (1) :76-80,1993.
- 74) Fortier-Bealieu M, Heron F, Noblet C, Cardot F, Manchon N, Moore N, Bourreile J. Misoprostol-associated fever in cirrhotic patient. *Lancet* . 340, 1992.

- 75) Fossaluzza V, Di Benedetto P, Zampa A, De Vita S. Misoprostol-induced urinary incontinence. *J of Internal Med.* 230(5):463-4, 1991.
- 76) Freedman EA, Sachtleben MR. Oral prostaglandin E<sub>2</sub> for induction of labor at term. *Obstet Gynecol*, 43:178-85; 1974.
- 77) Friedman EA, Sachtleben MR, Green W. Oral prostaglandin E<sub>2</sub> for induction of labor at term. II. Comparison of two low-dosage regimens. *Am J Obstet Gynecol*, 123:671-674; 1975.
- 78) Fullerton T, Sica DA, Blum RA. Evaluation of the renal protective effect of misoprostol in elderly, osteo arthritic patients at risk for nonsteroidal anti-inflammatory drug-induced renal dysfunction. *J of Clinical Pharma.* 33(12):1225-32, 1993.
- 79) Garris RE, Kirkwood CF, Misoprostol: A prostaglandin E<sub>1</sub> analogue. *Clinical Pharmacy*; 8:627-44; 1989.
- 80) Gazarian M, Berkovitch M, Koren G, Silverman ED, Laxer RM; Experience with misoprostol therapy for NSAID gastrophathy in children. *Annals of the Rheumatic Dis.* 54(4):277-80, 1995.

- 81) Gemzell Danielsson K, Swahn ML, Bygdeman M. Effect of antiprogesterin, hCg and a prostaglandin analogue on human uterine contractility. *Contraception*. 47(3):295-301, 1993.
- 82) Golbus MS, Creasy RK. Uterine priming with oral prostaglandin E<sub>2</sub> prior to elective induction with oxytocin. *Prostaglandins*, 14:577-581; 1977.
- 83) Gonzalez CH, Vargas FR, Perez AB, Kim CA, Brunoni D, Marques-Dias MJ, Leone CR, Correa Neto J, Llerena Junior JC, de Almeida JC. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. *Am J of Med Genet*; 47(1):59-64; 1993.
- 84) Gordon-Wright AP, Elder MG. Prostaglandin E<sub>2</sub> tablets used intravaginally for the induction of labour. *Br J Obstet Gynaecol*, 86: 32-36; 1979.
- 85) Graham DY, White RH, Moreland LW, Schubert TT, Katz R. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDS. Misoprostol Study Group. *Annals of Internal Med*. 119(4):257-62, 1993.
- 86) Graves G, Baskett T, Gray JH, Luther ER. The effect of vaginal administration of various doses of prostaglandin E<sub>2</sub> gel on cervical ripening and induction of labor. *Am J Obstet Gynecol*;151:178-81;1985.

- 87) Haeri AD, Scher J, Davey DA, Leader M. Comparison of oral prostaglandin E<sub>2</sub> and intravenous oxytocin for induction of labor. S Afr Med J, 50:516-18; 1976.
- 88) Hannah ME, Hannah WJ, Hellmann, Hewson S, Milner R, Willan A. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. The Canadian Multicentre Post-term Pregnancy Trial Group. N Engl J Med; 326(24): 1587-92; 1992.
- 89) Hausknecht RV. Methotrexate and misoprostol to terminate early pregnancy. N Engl J Med ; 333:537-40; 1995.
- 90) Henshaw RC, Cooper K, el-Refaey H, Smith NC, Templeton AA. Medical management of miscarriage: non-surgical uterine evacuation of incomplete and inevitable spontaneous abortion. BMJ. 306(6882):894-5, 1993.
- 91) Hodnett E, Simmons-Tropea D. The Labour Agency Scale: Psychometric properties of an instrument measuring control childbirth. Research in Nursing and Health; 10(5), 301-310; 1987.
- 92) Hodnett ED, Osborn RW. A randomized trial of the effects of monitrice support during labor. Mother's views two to four weeks postpartum; 16(4), 177-183; 1989.

- 93) Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E<sub>2</sub> for termination of second-trimester pregnancy. *N Engl J Med*; 331:290-3; 1994.
- 94) Jallad NS, Cattani A, Weidler DJ. Efficacy of misoprostol in controlling indomethacin induced fecal blood loss in arthritic patients. *Internat J of Clinical Pharmacol, Ther & Toxicol*. 1993.
- 95) Jaszewski R, Graham DY, Stromatt SC. Treatment of nonsteroidal anti-inflammatory drug-induced gastric ulcers with misoprostol. A double-blind multicentre study. *Digestive Dis & Sc*. 37(12):1820-4, 1992.
- 96) Johnson JS, Karboski JA, Williams GO. Profuse diarrhea after misoprostol use in a patient with a history of Crohn. *Annals of Pharmacotherapy*; 1993.
- 97) Jonsson B, Haglund U. Cost-effectiveness of misoprostol in Sweden. *Internat J of Technol Assess in Health Care*. 8(2):234-44; 1992.
- 98) Karim A. Antiulcer prostaglandin misoprostol: single and multiple dose pharmacokinetic profile. *Prostaglandins*; 33 (Suppl): 40-50; 1987.
- 99) Karim SMM, Sharma SC. Oral administration of prostaglandins for the induction of labour. *Br Med J*, 1:260-2; 1971.

- 100) Karim SMM, Trussell RR, Patel RC, Hillier K. Response of pregnant human uterus to PGE<sub>2α</sub> induction of labour. Br Med J, 4:621-623, 1968.
- 101) Kastenbaum, M, Hoel, D, Bowman, K. Sample size requirements. Biometrika 57,2, p.421.
- 102) Keirse MJNC. Endogenous prostaglandins in human parturition. In: Human Parturition. Keirse MJNC, Anderson ABM, Bennebroek Gravenhorst J (eds). The Hague: Leiden University Press, 101-142, 1979.
- 103) Keirse MJNC, Thiery M, Parewijck W, Mitchell MD. Chronic stimulation of uterine prostaglandin synthase during cervical ripening before the onset of labor. Prostaglandins, 15: 671-682, 1983.
- 104) Keirse MJNC. Prostaglandins in preinduction cervical ripening: Meta analysis of worldwide clinical experience. J. Reprod Med (suppl)38:89-98;1993.
- 105) Keirse MJNC, Chalmers I. Methods for inducing labour. In: Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford University Press; 1057-79; 1989.



- 106) Keirse MJNC, van Oppen ACC. Preparing the cervix for induction of labour. In : Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford University Press; 988-1056; 1989.
- 107) Keirse MJNC, von Oppen ACA. A comparison of prostaglandins and oxytocin for inducing labour. In : Chalmers I, Enkin M, Keirse MJNC, eds. Effective care in pregnancy and childbirth. Oxford University Press; 1080 - 1111, 1989.
- 108) Kerigan AT. Methotrexate and misoprostol used in abortions. Comment in: CMA J, 1994.
- 109) Kitzinger S. Some Mothers' Experience of Induced Labour. London: Nat'l Childbirth Trust, 1975.
- 110) Koch M, Capurso L, Dezi A, Ferrario F, Scarpignato C. Prevention of NSAID-induced gastroduodenal mucosal injury: meta analysis of clinical trials with misoprostol and H2-receptor antagonists. Digestive Diseases; 13 Suppl 1:62-74, 1995.
- 111) Lanza FI, Kochman RI, Geis GS, Rack EM, Deysach LG. A double-blind placebo-controlled, 6-day evaluation of two doses of misoprostol in gastroduodenal mucosal protection against damage from aspirin and effect on bowel habits. Am J of Gastroent. 86(12):1743-8, 1991.

- 112) Leatt P, Schneck R. Work environments of different types on nursing sub-units. *J of Advanced Nursing*; 7: 581-594; 1982.
- 113) Liggins GC. Controlled trial of induction of labor by vaginal suppositories containing prostaglandin E<sub>2</sub> Prostaglandins, 18:167-72; 1979.
- 114) Lim JM, Soh EB, Raman S. Intravaginal misoprostol for termination of mid-trimester pregnancy. *Austr & NZ J of Obstet & Gynecol*; 35(1):54-5; 1995.
- 115) Liu B, Sun J, Tao W. The pathological investigations on termination of early pregnancy with mifepristone. *Chinese J of Obstet Gynaecol*; 30(1):7-9, 1995.
- 116) Lomas J, Dore S, Enkin M, Mitchell A. The labor and delivery satisfaction index : The development and evaluation of a soft outcome measure. *Birth*. 14(3):125-9, 1987.
- 117) Lumley J. Assessing satisfaction with childbirth. *Birth*, 12:141-5;1985.
- 118) Lykkesfeldt G, Osler M. A comparison of three methods for inducing labor: oral prostaglandin E<sub>1</sub> buccal desaminoxycotin, intravenous oxytocin. *Acta Obstet Gynecol Scand*, 58: 321-5; 1979.
- 119) Lykkesfeldt G, Osler M. Induction of labor with oral prostaglandin E<sub>2</sub> and buccal demoxycotin without amniotomy. *Acta Obstet Gynecol Scand*, 60:429-30; 1981.

- 120) Macer I, Buchanan D, Yonekura ML. Induction of labor with prostaglandin E<sub>2</sub> vaginal suppositories. *Obstet Gynecol*; 63:664-8;1984
- 121) MacKenzie IZ, Bradley S, Embrey MP. A simpler approach to labor induction using lipid-based prostaglandin E<sub>2</sub> vaginal suppository. *Am J Obstet Gynecol*, 141:158-162; 1981.
- 122) MacWalter RS, Lindsay GH. A policy for minimizing NSAID induced peptic ulcer. *Scottish Med J*. 37(1):3-4, 1992.
- 123) Macrow P, Elstein M. Managing miscarriage medically. *BMJ*. 306(6882):876. 1993.
- 124) Marcisz C, Jondeerko G, Gina R, Szkliniarz J. Effect of misoprostol, a synthetic equivalent of prostaglandin E<sub>1</sub> on broncho dilation in bronchial spasm. *Polski Tygodnik Lekarski*. 47(34-35):733-4, 1992.
- 125) Margulies M, Veto LS, Caruzzi P, Uranga Imaz F. Induction del habajo de parto con un analogo de la PGE<sub>1</sub>: Un estudio abierto. no comparativo, de hallazgo de dosis. *Prensa Med Arg*; 78:9-13;1991.
- 126) Margulies M, Campos Perez G, Voto LS. Misoprostol to induce labour. *Lancet*. 339(8784):64, 1992.

- 127) Mariani-Neto C, Leao EJ, Baretto EM, Kenj G, De Aquino MM. Use of misoprostol for labor induction in stillbirth. *Rev Paul Med*, 105:325-54;1987.
- 128) McKinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. *Human Reprod.* 8(9):1502-5, 1993.
- 129) Mundle WR, Young DC. Misoprostol versus standard therapy for medical termination of pregnancy. *Int J Gynaecol Obstet; Suppl 2* -46:20, 1994.
- 130) Mundle WR, Young DC. Vaginal misoprostol for induction of labor: randomized controlled trial. *Obstet Gynecol*; 88:521-5; 1996.
- 131) Ngai SW, To WK, Lao T, Ho PK. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. *Obstet Gynecol*; 87: 923-6.; 1996
- 132) Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet*; 338(8777):1233-6, 1991.
- 133) Numo R. Prevention of NSAID-induced ulcers by the co-administration of misoprostol: implications in clinical practice. *Scand J of Rheum. Suppl.* 92:25-9, 1992.

- 134) Oakley A. Social consequences of obstetric technology: the importance of measuring "soft" outcomes. *Birth* 10:99-108,1983.
- 135) Owen J, Winkler CL, Harris J, Hauth JC, Smith MC. A randomized, double-blind trial of prostaglandin E<sub>2</sub> gel for cervical ripening and meta-analysis. *Am J Obstet Gynecol*, 165: 991-6,1991.
- 136) Paller MS, Manivel JC. Prostaglandins protect kidneys against ischemic and toxic injury by a cellular effect. *Kidney Internat*. 42(6):1345-54, 1992.
- 137) Pearce DJ. Pre-induction priming of the uterine cervix with oral prostaglandin E<sub>2</sub> and a placebo. *Prostaglandins*, 14:571-576; 1977.
- 138) Pentecost AF. The effect of buccal "Pitocin" on the unripe cervix. *Curr Med Res Opin*, 1:482-484; 1973.
- 139) Peplow PV. RU486 combined with PGE<sub>1</sub> analog in voluntary termination of early pregnancy-- a comparison of recent findings with gemeprost or misoprostol. *Contraception*. 50(1):69-75, 1994.
- 140) Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elkik F, Leclerc P, Ulmann A, Baulieu EE. Early termination of pregnancy with mifepristone (RU486) and the orally active prostaglandin misoprostol. *N Eng J of Med*. 328(21):1509-13, 1993.

- 141) Pickles VR. A plain-muscle stimulant in the menstruum. *Nature*, 180: 1198-1199, 1959.
- 142) Platz-Christensen JJ, Neilsen S, Hamberg L. Is misoprostol the drug of choice for induced cervical ripening in early pregnancy termination? *Acta Obstet et Gynecol Scandinavica*. 74(10):809-12; 1995.
- 143) Playford RJ, Batten JJ, Freeman TC, Beardshall K, Vesey DA, Fenn GC, Baron JH, Calam J. Gastric output of pancreatic secretory trypsin inhibitor is increased by misoprostol. *Gut*. 32(11):1396-400, 1991.
- 144) Product monograph for Cytotec. Searle Canada Inc. 1992.
- 145) Ramos, LS, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: A meta-analysis. *Am J Obstet Gynecol*; Vol 89 (4); 633-642, 1997.
- 146) Ratnam SS, Khew KS, Chen C, Lim TC. Oral prostaglandin E<sub>2</sub> in induction of labor. *Austral NZ J Obstet Gynaecol*, 14: 26-30; 1974.
- 147) Read MD, Martin RH. A comparison between intravenous oxytocin and oral prostaglandin E<sub>2</sub> for the induction of labour in parous patients. *Curr Med Res Opin*, 2:236-239; 1974.

- 148) Rocha J. Brazil investigates drug's possible link with birth defects. Comment in BMJ, 310 (6972): 128; BMJ 1994 Sept , 309(6957) : 757-8, 1995.
- 149) Rosenfeld A. The difficult issue of second-trimester abortion. N Eng J Med, 331(5): 324-5, 1994.
- 150) Sanchez-Ramos L, Kaunitz AM, Weats RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction : A meta analysis. Obstet & Gynecol ; 89(4):633-642;1997.
- 151) Sanchez-Ramos L, Kaunitz AM, Del Valle GO, Delke I, Schroeder PA, Briones DK. Labor induction with the prostaglandin E<sub>1</sub> methyl analogue misoprostol versus oxytocin: A randomized trial. Obstet Gynecol; 81:332-6, 1993.
- 152) Sang GW, Weng LJ, Shao QX. Termination of early pregnancy by two regimens of mifepristone with misoprostol: a multicentre clinical trial. (Chinese) Chung-Hua Fu Chan Ko Tsa Chih (Chinese J of Obstet & Gynecol) 29(12): 735-8, 763, 1994.
- 153) Sang GW, Weng LJ, Shao QX, Du MK, Wu XZ, Lu YL. Termination of early pregnancy by two regimens of mifepristone with misoprostol and mifepristone with PG05--a multicentre randomized clinical trial in China. Contraception. 50(6):501-10, 1994.

- 154) Schonhofar PS. Brazil: misuse of misoprostol as an abortifacient may induce malformations . Lancet. 337(8756): 1534-5, 1991.
- 155) Schuler L, Ashton PW, Sanseverino MT. Teratogenicity of misoprostol. Lancet.339(8790):437, 1992.
- 156) Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in Obstetrics and Gynecology Journals. JAMA;272:125-8;1994.
- 157) Senior J, Marshall K, Sangha R, Baxter G, Clayton J. In vitro characterization of prostanoid EP–receptors in the non-pregnant human myometrium. Br J of Pharmacol. 102(3):747-53, 1991.
- 158) Shearer MH. The difficulty of defining and measuring satisfaction with perinatal care. Birth; 10:17;1983.
- 159) Shield MJ. Novel applications of misoprostol. Pharmacol & Therapeutics. 65(1):125-47, 1995 .
- 160) Stamps P, Piedmond E, Nurses and work satisfaction: An index for measurement. Ann Arbor, Michigan: Health Administration Press Perspectives. 1986.



- 161) Speert H. *Obstetrics and Gynecology in America. A History.* Chicago: College of Obstetricians and Gynecologists, 181-182. 1980.
- 162) Stewart P. Patient's attitudes to induction of labour. *Br Med J.* 2:749-752; 1979.
- 163) Thiery M, Amy JJ. Induction of labour with prostaglandins. In: *Prostaglandins and Reproduction.* Karim SMM (ed). Lancaster. MTP Press 149-228; 1975.
- 164) Thiery M, Baines CJ, Keirse MJNC. The development of methods of inducing labour. In Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth.* Oxford University Press; 969-80; 1989.
- 165) Thiery M, Benijts G, Martens G, Yo Le Sian A, Amy JJ, Derom R. A comparison of buccal (oromucosal) and oral prostaglandin E<sub>2</sub> for the elective induction of labor. *Prostaglandins*, 14:371-9; 1977.
- 166) Thiery M, DeCoster Jm, Parewijck W, Noah ML, Derom R, Van Kets H. Endocervical prostaglandin E<sub>2</sub> for preinduction cervical softening. *Prostaglandins*, 27:429-39, 1984.
- 167) Thong KJ, Baird DT. Induction of abortion with mifepristone and misoprostol in early pregnancy. *Br J Obstet Gynaecol*; 99(12):1004 -7; 1992.

- 168) Thiery M, DeCoster Jm, Parewijck W, Noah ML, Derom R, Van Kets H, Defoort P, Aertsens W, Debruyne G, De Geest K, Vanderkerckhove F. Endocervical prostaglandin  $E_2$  for preinduction cervical softening. *Prostaglandins*; 27:429-39; 1984.
- 169) Thong KJ, Dewar MH, Baird DT. What do women want during medical abortion? *Contraception*; 46(5):435-42; 1992.
- 170) Ulmann A, Silvestre L. RU486: the French experience. *Human Reprod*; 9 Suppl 1:126-30. 1994
- 171) Ulmsten U, Ekman C, Belfrage P, Bygdeman M, Nyberg C. Intracervical versus intravaginal  $PGE_2$  for induction of labor at term in patients with an unfavorable cervix. *Arch Gynecol*;236:243-8;1985.
- 172) Ulmsten U, Wingerup L, Belfrage P, Erkman G, Wiqvist N. Intracervical application of prostaglandin gel for induction of term labor. *Obstet Gynecol*, 59:336-9; 1982.
- 173) Varaklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin  $E_2$  gel for induction of labor at term. *Obstet Gynecol* ; 86:541-4. 1995.

- 174) van Look PF, von Hertzen H. Misoprostol and birth defects. Comment on: BMJ 1994.
- 175) Viegas OAC, Adaikan PG, Singh K, Arulkumaran S, Kottegoda SR, Ratnam GS.  
Intrauterine response to nipple stimulation in late pregnancy. *Gynecol Obstet Invest*,  
22: 128-133, 1986.
- 176) Ware JE, Davies-Avery A, Stewart AL. The measurement and meaning of patient  
satisfaction. *Health Med Care Services, Rev* 1978;1:2-15.
- 177) Webster D, Penney GC, Templeton A, A comparison of 600 and 200 mg mifepristone  
prior to second trimester abortion with the prostaglandin misoprostol.  
*BMJ of Obstet & Gynecol*; 103(7): 706-9; 1996.
- 178) Westergaard JG, Lange AP, Pedersen GT, Secher NJ. Oral oxytocics for induction of  
labour. A randomized study of prostaglandin E<sub>2</sub> tablets and demoxytocin resorbibles.  
*Acta Obstetrica et Gynecologica. Scaniairca*. 62(2): 103-10, 1983.
- 179) Widomski DL, Walsh RE, Baron DA, Hidvegi Mi, Fretland DJ, Collins PW, Gaginella  
TS. Effects of the prostaglandin analogue misoprostol on inflammatory mediator release  
by human monocytes. *Agents & Actions*. 34(1-2):30-1, 1991.

- 180) Wiebe ER. Methotrexate and misoprostol used in abortions. Comments in: CMAJ; 1994.
- 181) Wilkie ME, Beer JC, Newman D, Raferty M, Marsh FP. Evidence that the risks of misoprostol outweigh its benefits in stable cyclosporin-treated renal allograft recipients. Transplant. 54(3):565-7, 1992.
- 182) Windrim R. A retrospective comparison of misoprostol versus intra-amniotic Prostaglandin  $F_{2\alpha}$  in the management of 2<sup>nd</sup> trimester genetic termination of pregnancy. 20<sup>th</sup> Annual Ontario and Quebec Perinatal Investigators Meeting, Kingston, Ontario. 1996.
- 183) Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin  $E_2$  gel for preinduction cervical ripening and labor induction. Am J Obstet Gynecol 172:1804-10, 1995.
- 184) Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: An effective agent for cervical ripening and labor induction. Am J Obstet Gynecol : 172:1811-6, 1995.

- 185) Wingerup L, Andersson KE, Ulmsten U. Ripening of the uterine cervix and induction of labour at term with prostaglandin E<sub>2</sub> in viscous gel. *Acta Obstet Gynecol Scand*, 57:403-406; 1978.
- 186) Xu MF, Jin YC, Cen HX. Histopathology appearance of intrauterine residue after medical abortion by mifepristone and prostaglandin analogue. *Chung-Hua Fu Chan Ko Tsa Chih (Chinese J of Obstet & Gynecol)* 29(12):739-41. 763. 1994.
- 187) Zahradnik HP. Misuse of misoprostol in abortion induction. (German) *Deutsche Medizinische Wochenschrift*. 117(45):1735-6, 1992.
- 188) Zastowny TR, Roghmann KM, Hengst A. Satisfaction with medical care; replications and theoretic reevaluation. *Health Med Care Services Rev*; 1:2-15;1983.





