A MASKED RANDOMIZED COMPARISON OF ORAL AND VAGINAL ADMINISTRATION OF MISOPROSTOL FOR LABOUR INDUCTION

KELLY ANGELA BENNETT

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by

Kelly Angela Bennett

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

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ABSTRACT

Objective: To test the null hypothesis that administering misoprostol orally or vaginally will result in no difference in time to vaginal birth, and to determine whether different frequencies of tachysystole and hyperstimulation are associated with route of administration.

Methods: Two hundred six women after 37 completed weeks' gestation who presented with an indication for induction were randomly assigned to receive misoprostol (50 μg) orally or vaginally every 4 hours as needed to induce labour. Placebo use and allocation concealment accomplished blinding until data analysis was completed. Sample size was calculated to allow a two-tailed α of .05 and power (1-β) of 80%. All fetal heart rate and uterine activity graphs were classified according to Curtis' criteria before the induction groups were unmasked.

Results: Analysis involved 104 women in the oral group and 102 in the vaginal group. The mean time (± standard deviation) to vaginal birth with oral misoprostol was 1072 (± 593) minutes compared with 846 (± 385) minutes with the vaginal protocol ($P = .004$). There were no significant differences in cesarean rate, epidural use or neonatal outcomes. More frequent tachysystole for 20 minutes ($P < .01$) and hyperstimulation ($P < .04$) were observed with vaginal misoprostol. No neonatal asphyxia occurred in either group.

Conclusion: Misoprostol effectively induces labour, given orally or vaginally. There is a shorter interval to vaginal birth with vaginal application; however, the more frequent occurrence of fetal heart graph abnormalities in this group suggests that, until the optimal dosing interval for vaginal use is determined, the preferred route of misoprostol administration might be oral.

DEDICATION

For my parents.

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Chapter 1

INTRODUCTION

Induction of Labour

Induction of labour is the initiation of cervical ripening and uterine contractions before their spontaneous onset. Induction is often indicated for a variety of obstetrical, medical or fetal complications of pregnancy. Various mechanical and pharmacological methods are currently used to induce labour; however, no single method or agent has been suitable for all clinical situations. All available methods of induction of labour have associated medical risks; therefore, the decision to induce labour should only be made when the risk of continuing a pregnancy outweighs the risk of induction.

For certain clinical conditions such as severe preeclampsia, the decision to induce labour is straightforward. For other conditions, the point at which the risk of continuing pregnancy outweighs the risks associated with induction is not clear. Furthermore, the risk-to-benefit ratio may be influenced by the methods used to induce labour, and by the methods used to assess fetal well-being when expectant management is chosen. Induction requires continuous electronic fetal and uterine contraction monitoring, which often reduces a woman's mobility and comfort.

Ideally, induction agents should mimic spontaneous labour while avoiding excessive uterine activity. However, because the mechanisms that control the initiation of parturition are

not well understood, such goals are difficult to achieve. The major concerns associated with induction are ineffective labour and excessive uterine activity. Both problems may lead to an increased risk of cesarean delivery. Excessive uterine activity is defined as contractions of abnormally high intensity or frequency that lead to impaired uteroplacental circulation and consequently, decreased fetal oxygenation. When contractions of abnormally high intensity or frequency occur, insufficient recovery time resulting in fetal heart rate abnormalities could necessitate operative delivery or lead to fetal asphyxia.

Cervical Ripening for Labour Induction

In 1964, Bishop[1] described a pelvic scoring system that predicted vaginal delivery in multiparous women. The five components of the score were: position, consistency, effacement and dilatation of the cervix and station of the fetal vertex. A maximum score of thirteen described a ripe cervix. Bishop noted that with a score of nine or more the risk of failed induction was minimal. Bishop scores of 0-3 indicated a high likelihood of failed induction. This served as the basis for the concept of ripening the cervix for women whose score is unfavourable, before attempting induction with oxytocin.

Since the discovery of prostaglandins and their use as agents for induction of labour, a wide variety of different formulations, routes of administration and dosage regimens have been investigated. Currently, prostaglandin PGE_2 (dinoprostone) is the most widely used for the purpose of induction, with the preferred route of administration per vagina. A variety of vehicles have been developed for the delivery of this agent, including lactic acid-based pessaries, water-soluble gels and most recently, a slow -release hydrogel polymer.

Chapter 2

THE ROLE OF PROSTAGLANDINS IN LABOUR

Prostaglandins are lipid molecules that act as intermediaries in several physiologic and pathologic processes. Prostaglandins of the E (PGE_1, PGE_2) and F ($PGF_{2\alpha}$) series have potent uterotonic effects and are commonly used as labour induction and cervical ripening agents. Recent advances in molecular biology and biochemical techniques have allowed deeper understanding of the role prostaglandins play in the process of parturition.

Prostaglandin Synthesis

Biologically active eicosanoids are formed from polyunsaturated fatty acids. Arachidonic acid is the most common naturally occurring precursor and must be released from cell membrane stores, where it exists in an esterified form. The liberation of arachidonic acid from membrane phospholipids is generally considered the initial step in the synthesis of prostaglandins.[2] This release from the esterified position is accomplished by the action of phospholipases, primarily phospholipase A_2 (PLA_2). PLA_2 catalyzes the liberation of arachidonic acid from phosphatidylethanolamine, phosphatidylserine and phosphatidylysine.[2] PLA_2-type II is the most abundant of four subtypes of the enzyme in the placenta, fetal membranes and decidua. The activity of PLA_2 is increased in the amnion and placenta during labour.[3] The action of phospholipase C (PLC) is indirect, catalyzing the hydrolysis of

Oral administration of prostaglandins in obstetrics has virtually been abandoned because of the severe gastrointestinal side effects associated with existing preparations. Administration of prostaglandins for induction of labour has been limited to intracervical and intravaginal routes. An oral induction agent that is safe, effective, inexpensive and well-tolerated by patients would likely be attractive to patients and health care providers. Several researchers have conducted randomized trials comparing vaginal misoprostol to standard therapy and have found it to be a safe and effective prostaglandin for induction of labour. No previous masked randomized comparisons of oral and vaginal misoprostol (50μg every four hours) for labour induction have been published in the English language literature.

phosphatidylinositol into diacylglycerol and inositoltriphosphate. Diacylglycerol is then metabolized by diacyl- and monoacylglycerol lipases into glycerol and free fatty acids, including arachidonic acid.[2] At least ten distinct PLC isoforms have been cloned and sequenced.[4]

The second step in prostaglandin synthesis is the oxygenation and reduction of arachidonic acid to form an unstable intermediate, endoperoxide (PGH_2).[5] This step is catalyzed by prostaglandin endoperoxide H synthase (PGHS). Two forms of PGHS have been identified: PGHS-1 and PGHS-2, each having cyclooxygenase and peroxidase activities.[6] The principal feature distinguishing PGHS-1 and PGHS-2 is the regulation of their expression. PGHS-1 is a gene product constitutively expressed under normal physiological conditions. Levels of PGHS-1 increase late in gestation and peak at term, but do not rise in response to labour.[7] PGHS-2 is an inducible enzyme that is expressed after stimulation of the amnion and chorion by cytokines, growth factors or tumour promoters.[7,8] Recent studies suggest that the increased production of prostaglandins by intrauterine tissues during labour results from an increase in the expression of the PGHS-2 isoform.[9-11]

The third enzymatic step in prostaglandin synthesis is the conversion of the endoperoxide intermediate to one of the biologically active prostaglandins (D_2, E_2, $F_{2\alpha}$, I_2) or thromboxane A_2. Individual cell types contain one primary isomerase, reductase or synthase that converts the endoperoxide to a specific prostaglandin characteristic of that cell. An additional factor involved in modulating levels of active prostaglandins is the regulation of the rate at which these compounds are metabolized. Chorionic cytotrophoblasts contain abundant levels of the prostaglandin-metabolizing enzyme prostaglandin 15-hydroxydehydrogenase (PGDH), which catalyses oxidative inactivation of E and F series prostaglandins.[12]

Prostaglandin Receptors

Prostaglandins exert their action through specific membrane receptors. The regulation of uterine smooth muscle contraction is controlled by the quantity and distribution of prostaglandin receptors as much as by the tissue concentration of biologically active prostaglandins. The prostaglandin E receptor has four subtypes: EP_1, EP_2, EP_3 and EP_4. These couple to two major effector pathways.[13] EP_1 and EP_3 receptors promote muscle contraction through mechanisms that include increased calcium utilization and inhibition of intracellular cyclic adenosine monophosphate (cAMP). EP_2 and EP_4 act through increased cAMP formation to cause a relaxation of smooth muscle .[14] Prior to term, the action of EP_2 receptor is a factor in maintaining myometrial quiescence.

The expression of myometrial prostaglandin receptors increases during late gestation.[15] At term, EP_1 and EP_3 receptors in the uterine fundus act to promote uterine contractions. EP_2 and EP_4 receptors are concentrated in the lower uterine segment and cervix and may facilitate cervical effacement and dilation. Misoprostol is a synthetic prostaglandin E_1 analogue that is rapidly absorbed following oral administration. It is de-esterified to the active metabolite misoprostol acid. Misoprostol acid binds to EP_3 and EP_4 receptors.[16] When used as a labour induction agent, it can effect contraction of the uterine fundus and relaxation of the lower uterine segment and cervix.

Challis et al.[17] described compartmentalization of prostaglandin synthesis and metabolism within the human fetal membranes, decidua and myometrium in late gestation. In the amnion, prostaglandin H_2synthase (PGHS) activity predominates, with an increase in the expression of the PGHS-2 isoform at the time of labour. Prostaglandin E_2 is the principal

prostaglandin formed in the amnion. The chorion contains high concentrations of PGHS and the prostaglandin-catabolizing enzyme 15-hydroxyprostaglandin dehydrogenase (PGDH). A reduced activity of PGDH has been shown to be associated with preterm labour. [18]

During labour, PGDH undergoes a reduction in activity in the portion of fetal membranes overlying the cervical os.[19] The reduced activity of this enzyme in the region of the cervix is believed to potentially facilitate passage of active PGE_2 from the amnion across the chorion, thereby facilitating cervical ripening. Furthermore, abnormal persistence of this enzyme might hinder the ripening process by diminishing the concentration of prostaglandins within the cervix.[20] The maternal decidua is a source of significant prostaglandin synthesis; however, the levels of PGHS-1 and PGHS-2 do not change during gestation or with labour onset. It has therefore been postulated that one of the phospholipases may be the primary rate-determining factor in decidual prostaglandin synthesis.[11]

Prostaglandins and Parturition

Our knowledge of the mechanism of parturition in humans is increasing but not all relevant pathways have been completely elucidated. Prostaglandins clearly play an important role in the human labour process; however, a precise and complete description of their mechanism continues to be sought. They appear to be active in the triggering or facilitation of a complex sequence of events involving the fetus, fetal membranes and maternal tissues.[11-22]

The role of the human fetus in initiating labour is not well defined. In animal studies, it has conclusively been shown that the fetal sheep triggers the onset of labour through activation of the fetal hypothalamic-pituitary-adrenal axis (HPA), resulting in increased

secretion of cortisol from its adrenal gland.[21] Fetal cortisol acts on the placenta to upregulate prostaglandin synthesis, and to change the pattern of steroidogenesis, such that progesterone levels fall and estrogen levels rise. Once activated, the ovine myometrium is able to respond effectively to stimulation provided by the increased production of uterotonic agents such as oxytocin and prostaglandins. While a similar mechanism has not conclusively been demonstrated in humans, homology to the human parturition process is hypothesized.

In humans, the bioactivity of circulating corticotropin-releasing hormone (CRH) is diminished during pregnancy by the presence of a high-affinity CRH-binding protein (CRH-BP) in maternal blood.[23] This blocks the action of CRH in promoting ACTH release from pituitary cells and inhibits the stimulatory effect of CRH on prostaglandin production by intrauterine tissues. CRH-BP levels fall near term, with a corresponding increase in the activity of CRH. Studies in primates[23-29] have suggested that cortisol of fetal origin acts to promote delivery. Cortisol activates amniocytes, cytotrophoblasts and decidual cells to express CRH, further enhancing prostaglandin production by these cells. In addition, elevations in CRH may act synergistically with oxytocin or prostaglandins to stimulate myometrial contraction.[28] Recent studies have demonstrated that exogenous glucocorticoid administration stimulates expression of CRH by placenta, decidua and fetal membranes, which in turn enhances prostaglandin synthesis and impairs prostaglandin metabolism in these tissues, promoting parturition.[23]

Prostaglandins and Cervical Ripening

In 1947 Danforth[30] characterized the connective tissue component of the cervix and recognized that changes in its structure and biochemistry were key elements of cervical ripening. The mechanism of cervical ripening involves a series of biochemical events distinct from those responsible for myometrial activation and similar to those observed in tissue inflammation.[31] The trigger responsible for initiating the biochemical events that lead to cervical ripening has not yet been identified. Prostaglandins play an important role in cervical ripening; however, the molecular actions of prostaglandins to effect cervical ripening has not been fully defined.

Smooth muscle and fibroblasts make up the cellular component of the human cervix. The extracellular matrix is composed of substances secreted by fibroblasts, such as collagen, glycosaminoglycan and glycoproteins. The glycosaminoglycans are comprised of repeating units of hexosamines or uronic acid linked as polymer chains. Chondroitin sulfate and dermatan sulfate are sulphated glycosaminoglycans while hyaluronate and chondroitin are unsulfated glycosaminoglycans. The glycosaminoglycans attach in branched patterns to glycoproteins to form very large molecules known as proteogylcans.[32] Elastin is another important component of the extracellular matrix of the human cervix. Elastin fibers are organized parallel to and between collagen fibers and are capable of being stretched in any direction. During pregnancy and particularly labour the uterine cervix undergoes dramatic changes in histological characteristics and biochemical composition.

Early in gestation, cervical hyperplasia results from turnover of both smooth muscle cells and fibroblasts. As pregnancy advances, physiological cell death occurs, inducing

migration of neutrophils, macrophages and mast cells into cervical tissue.[31] These cells produce inflammatory cytokines that are responsible for stimulating the production of metalloproteinases that cause collagen degradation at term. Nitric oxide may induce prostaglandin production by stimulating cyclooxygenase activity .[33]

Ellwood et al.[34] described the production of prostanoids by the human cervix in pregnancy, demonstrating that the cervix produces E_2, I_2, and F prostaglandins. The production of these compounds was furthermore shown to increase at term. Norstom et al.[35] postulated that prostaglandins might exert their effects on the cervix by modulating fibroblast activity, thereby controlling the biophysical and biochemical properties of the extracellular matrix. They observed that cervical fibroblasts from women treated with prostaglandins undergo the same morphologic changes observed in women at the time of spontaneous labour.

Murota et al.[36] demonstrated that prostaglandins are capable of stimulating the production of hyaluronic acid by cervical fibroblasts. The resulting tissue hydration alters the glycosaminoglycan/proteoglycan composition in favour of cervical ripening. As pregnancy advances closer to term, multiple factors work together in complex interactions that cause collagen dispersion and ripening of the cervix. At the onset of labour, these substantial changes in hyaluronic acid, cytokines and collagenases, combined with the mechanical force of uterine contractions extend cervical elastin and allow dilation of the cervix required for parturition.

Chapter 3

MECHANICAL METHODS OF LABOUR INDUCTION

Sweeping Membranes

Stripping or sweeping of the fetal membranes was first described by James Hamilton in 1810.[37] The technique involves mechanically separating the membranes from the lower uterus by sweeping a finger circumferentially around the interface of the fetal membranes with the lower uterine segment at the time of pelvic examination. Sweeping of the membranes aims to initiate labour through a cascade of physiological events, the exact mechanism of which is unknown. McColgin et al.[38] concluded that membrane stripping causes acute elevation in plasma prostaglandin $F_2\alpha$ and endocervical phospholipase A_2 activity. This release of local prostaglandins is believed to initiate cervical ripening and the onset of active labour.

The Cochrane Library systematic review of stripping or sweeping of membranes for inducing labour or preventing post-term pregnancy assessed the effects of membrane sweeping to promote or induce labour on maternal and perinatal outcomes.[39] Sweeping of membranes, performed in low-risk women at term, was associated with a decreased incidence of pregnancy continuing beyond 41 or 42 weeks' gestation (relative risk (RR) 0.42, 95% confidence interval (CI) 0.19-0.93) but was not an effective induction method. The reviewers concluded that the routine use of sweeping the membranes at term did not seem to produce clinically important benefits.

Studies of sweeping membranes[40-49] suffer from heterogeneity in study design and selection bias. Some of these studies have flaws in their design or analysis, as well as deficiencies in reporting of results. The frequency with which sweeping was performed varied from study to study. The first study by Swann et al.[46] described sweeping membranes daily for three days. The authors reported an increase in the spontaneous delivery rate from 26% to 69%. This study was not formally randomized and did not stratify based on parity or Bishop score. McColgin et al.[41] examined membrane stripping performed weekly beginning at 38 weeks' gestation and found a significant decrease in the number of post-dates pregnancies. Patient demographics were not described, making it impossible to assess comparability of the two groups.

The study by Weissberg and Spellacy[42] suffered from selection bias with an excess number of study group participants having documented Bishop scores greater than six. Several of the studies[43, 44] enrolled only post-dates patients defined as beyond 40 completed weeks' gestation. Crane et al.[45] studied the effectiveness of sweeping membranes at 38-40 weeks' gestation based on the ability to pass a finger through the internal os and strip the membrane by sweeping the examiner's index finger twice in a circumferential manner. No significant difference in the median number of days to delivery was detected between the groups (33% sweeping, 38% control, P = .39).

Concerns may arise that membrane sweeping may not have been conducted properly in a number of these studies. As well, multiple episodes of sweeping potentially may be more effective than a single sweep. It is possible that sweeping membranes is more effective in post-dates than term patients or more effective in multiparous than nulliparous patients. The heterogeneity of results in published studies comparing sweeping membranes

to no intervention does not allow firm conclusions to be drawn about the relative merits of sweeping membranes for the purpose of labour induction with any degree of confidence.

Balloon Catheters

Obstetricians have used balloon catheters for more than 100 years to induce labour. Recently, Foley catheters have been used for this purpose.[50] After thorough cleansing of the vagina and cervix, the catheter is inserted into the endocervix and passed above the level of the internal cervical os. The balloon is then inflated with 30-50 ml of sterile saline and left in place for 24 hours or until spontaneous expulsion.[50-52] Some authors suggest the application of traction to the catheter or the infusion of saline through the catheter to accelerate the ripening process.[53-56]

The mechanism believed to be responsible for cervical ripening is direct pressure and overstretching of the lower uterine segment, causing local secretion of prostaglandin. This mechanism is attested to by an increase in prostaglandin levels in maternal blood.[57] Balloon catheters are absolutely contraindicated in patients with a low-lying placenta or antepartum hemorrhage. Other relative contraindications include cervicitis and ruptured membranes. No randomized trials assessing the Foley catheter for cervical ripening have included patients with a history of previous cesarean delivery.

Several investigators compared the balloon catheter to intravaginal prostaglandin gel, finding the catheter to be significantly more effective than placebo, and as effective as prostaglandin in ripening an unfavourable cervix, as measured by the Bishop Score and duration of labour.[58-62] No significant difference was found in the cesarean delivery rate. Spontaneous labour; however, occurred significantly more frequently in the prostaglandin

group. Atad et al.[60] reported their experience with a special double balloon catheter and concluded that it was as good as prostaglandin E_2 (dinoprostone) vaginal tablets and better than oxytocin in terms of change in Bishop score, interval to delivery and cervical ripening failure rates.

St. Onge et al.[61] compared 0.5 mg intracervical prostaglandin E_2 gel (n = 30) with Foley catheter (n = 36) in a small randomized clinical trial. The authors concluded that there was no difference in efficacy between intracervical prostaglandin (n = 28) and intracervical Foley catheter (n = 34) as measured by the mean change in the Bishop score. The induction to delivery interval was significantly shorter in the Foley catheter group (P = .01).

Chamberlain et al.[62] compared outpatient intracervical prostaglandin E_2 gel (n = 67) with intracervical Foley catheter insertion overnight (n = 62). Both the intracervical Foley catheter and the intracervical prostaglandin E_2 gel led to similar changes in Bishop score. The Foley catheter was more commonly associated with cervical dilatation of three to four centimetres despite the requirement for significantly more oxytocin to induce labour (P = .003). There was no difference in route of delivery or adverse maternal events.

A few randomized trials have compared intracervical Foley catheter plus extra-amniotic saline infusion to intravaginal or intracervical prostaglandin E_2 for cervical ripening in women with an unfavourable cervix.[53-56] The results of these studies were contradictory and inconclusive. In two studies, fewer ripening failures occurred in the Foley catheter group.[53,54] Lyndrup et al.[56] reported that prostaglandin E_2 was more efficient in inducing regular uterine contractions in nulliparous women; furthermore, Foley balloon catheter ripening was associated with a longer latent phase of labour. Two of these trials [53,55] found

no difference in cesarean delivery rates and two reported an increased cesarean delivery rate in those patients randomized to the balloon catheter group.[54,56]

The advantages of cervical ripening with extra-amniotic balloon catheters include: simplicity, low cost, reversibility and lack of severe maternal or fetal side effects when compared with intravaginal prostaglandin E_2. The disadvantages include pain and discomfort, decreased maternal mobility and a greater need for oxytocin augmentation. The data further indicates that prostaglandin use is more likely to result in spontaneous labour and less likely to result in failed induction. The heterogeneity of results in published studies comparing prostaglandin E_2 with Foley catheter does not allow firm conclusions about their relative merits to be drawn with any confidence.

Synthetic Hygroscopic Dilators

Hygroscopic dilators made from either natural or synthetic materials are inserted into the cervical canal under direct visualization using an aseptic technique. The dilators are placed in the endocervix and kept in place by sterile gauze placed in the vagina. These devices take up fluid from the surrounding tissue, gradually swell and ultimately cause dilation of the cervical canal. The stretching of the cervix causes local prostaglandin release. These devices are usually contraindicated in cases of ruptured membranes, cervicitis and vaginal bleeding. Their use in patients with a history of previous cesarean has not been studied.

Research groups[63-64] have investigated synthetic hygroscopic dilators such as Dilapan® (Gynotech, Middlesex, NJ) and Lamicel® (Cabot Medical Group, Langhorn, PA) to assess their effectiveness as cervical ripening agents. Dilapan® was shown to cause a

significant change in Bishop score within six to twelve hours of insertion. This change was comparable to prostaglandin and better than placebo. In a large randomized clinical trial of 444 women at term, the use of prostaglandin was associated with a higher rate of successful induction, shorter labour, less use of oxytocin and fewer infections in the mother and newborn when compared to Dilapan®[64].

Natural Hygroscopic Dilators

Natural laminaria are made from dried seaweed. In controlled studies, the overnight insertion of laminaria was found to cause significant change in the Bishop score in patients with unfavourable cervixes.[65-69] In two of these studies, patients with preinduction ripening with laminaria had higher rates of successful induction and shorter induction-to-delivery intervals compared with controls receiving only oxytocin.[65,66] These findings were contrary to findings of two other groups.[67,68] A recent randomized clinical trial comparing laminaria to extra-amniotic saline infusion reported that laminaria shortened the interval to delivery by eliminating the need for a preinduction ripening interval.[67] No significant difference was noted in rates of cesarean delivery or adverse maternal or neonatal outcomes.

Induction of labour is often indicated when the benefits to either the mother or the fetus outweigh the benefit of continuing the pregnancy. Obstetricians routinely use various mechanical methods to ripen the cervix; however, no single mechanical approach has enjoyed universally superior success or acceptance. The consistency of the cervix is clearly related to the rate of success of labour induction and to the duration of the induction-to-delivery interval. Women with the most unfavourable cervixes still face high rates of induction failure and cesarean delivery. The safety of mechanical methods for induction of

labour has not been established. There is a need for properly designed and conducted randomized clinical trials to evaluate the efficacy and safety of many of the mechanical methods of labour induction reviewed here.

Chapter 4

PHARMACOLOGIC INDUCTION AGENTS

Pharmacological Induction Agents

Pharmacological techniques for induction of labour were first described over 400 years ago.[70] One of the first recorded references described the use of juniper berries, cinnamon and castor oil to hasten birth. In 1906, Sir Henry Dale discovered uterotonic bioactivity in extracts of the posterior pituitary gland. William Blair Bell administered a crude preparation of these extracts to pregnant women and reported the first clinical studies on oxytocin use for induction of labour in 1909.[71] Pierce and Du Vigneaud determined the structure of oxytocin in 1950, for which Du Vigneaud was later awarded a Nobel Prize in chemistry. Charles Lieb[72] first discovered prostaglandins in 1930 but it was not until the late 1960s and early 1970s that prostaglandins E_1 and E_2 were first used clinically for induction of labour.

Since the discovery of prostaglandins and their use as agents for induction of labour, a wide variety of different formulations, routes of administration and dosage regimens have been investigated. Currently, prostaglandin PGE_2 (dinoprostone) is the most widely used for the purpose of induction, with the preferred route of administration per vagina. A variety of vehicles have been developed for the delivery of this agent, including lactic acid-based pessaries, water-soluble gels and most recently, a slow -release hydrogel polymer.

Dinoprostone

Dinoprostone (PGE_2) intracervical and intravaginal gel has been the prostaglandin agent of choice for several decades and is currently the only pharmacological agent approved by the U.S. Food and Drug administration and the Therapeutic Products Program of Health Canada. It is available in three forms: a 0.5 mg endocervical gel (Prepidil®; Upjohn Pharmaceuticals, Kalamazoo, MI), a 1.0 mg or 2.0 mg vaginal gel (Prostin®; Upjohn Pharmaceuticals, Kalamazoo, MI) and a controlled-release prostaglandin vaginal insert available in the United States (Cervidil®; Forest Pharmaceuticals, St. Louis, MO), Canada and Europe (Propess®, Ferring Pharmaceuticals AB, Malamo, Sweden).[72-74]

A meta-analysis of selected randomized trials comparing dinoprostone with placebo or with no treatment has concluded that the use of prostaglandins for cervical ripening is effective and reduces the induction-to-delivery interval as well as the operative vaginal delivery rate.[75] There was a higher rate of uterine hypertonus and uterine tachysystole in those patients who received prostaglandin (PGE_2) compared to oxytocin and a trend toward higher rates of abnormal fetal heart rate patterns. There are no randomized trials evaluating the required duration of fetal heart rate (FHR) and uterine contraction monitoring after prostaglandin gel dosing.

Recent studies have noted a higher rate of successful induction, greater change in Bishop score and shorter induction-to-delivery interval with the use of vaginal gel (Prostin®) compared to intracervical gel (Prepidil®).[76] There is insufficient evidence to make firm conclusions about the relative effects of prostaglandins and oxytocin on substantive maternal and neonatal adverse outcomes.

Controlled-Release Insert

The controlled-release insert consists of a polymer base containing 10 mg of dinoprostone with a polyester retrieval system. The insert is placed in the posterior fornix of the vagina and releases 0.3 mg per hour of prostaglandin E_2 over a twelve-hour period. It is removed with the onset of labour, at spontaneous rupture of membranes, with excessive uterine activity or after twelve hours. Theoretical advantages include ease of administration and the ability to remove the medication if excessive uterine activity occurs.

Although widely used, these preparations may cause excessive uterine activity leading to placental insufficiency and abnormal fetal heart rate changes, and are associated with greater cost and more elaborate storage requirements. Dinoprostone must be refrigerated until shortly before administration. The average wholesale price of Prepidil® is $48.98 per 0.5 mg dose, Prostin® $54.00 per 2.0 mg dose and $84.00 for the 10 mg vaginal insert.

Several authors[77-79] have compared Cervidil® to placebo and demonstrated that it is effective in cervical ripening but is associated with a higher incidence of excessive uterine activity and hyperstimulation when compared to prostaglandin E_2 intracervical gel. In a recent meta-analysis performed by our research group,[80] we examined the effectiveness and safety of controlled-release prostaglandin for cervical ripening in nine randomized trials that compared controlled-release vaginal prostaglandin (with a retrieval string) with any other cervical ripening agent or with placebo. After assessing the homogeneity of results, the summary odds ratio and confidence intervals were determined.

Compared with placebo, controlled-release prostaglandin resulted in cervical change (summary odds ratio (OR) = 3.99, 95% (CI) = 2.71, 5.86), a higher rate of vaginal delivery in 12 hours (OR = 29.01, 95% CI = 7.08, 118.87) and less need for oxytocin (OR = 0.14, 95% CI 0.06, 0.32) but a higher incidence of excessive uterine activity ($P < .001$) and hyperstimulation ($P = .004$). When compared with Prepidil®, there was a higher rate of excessive uterine activity with controlled-release prostaglandin ($P = .03$), but less need for oxytocin (OR = 0.09, 95% CI = 0.01, 0.53). With Prepidil® plus immediate oxytocin, there was a lower rate of active labour in twelve hours compared with controlled-release prostaglandin (OR = 0.27, 95% CI= 0.10,0.72).

There was a lower rate of vaginal delivery in 12 hours and a higher incidence of oxytocin use with controlled-release prostaglandin as compared with misoprostol (OR = 0.53, 95% CI = 0.34, 0.83 and OR = 1.58, 95% CI 1.08, 2.32, respectively). The induction-to-delivery interval was shorter with controlled-release prostaglandin than with placebo or Prepidil® but longer than with Prepidil® plus augmentation with immediate oxytocin or misoprostol. Although no differences in maternal or fetal morbidity were noted, the sample size was not adequate to evaluate these outcomes. Controlled-release prostaglandin is an effective cervical ripening agent as compared with Prepidil® but may result in an increased incidence of excessive uterine activity. Controlled-release prostaglandin may not be as effective as misoprostol or Prepidil® plus immediate oxytocin. The American College of Obstetricians and Gynecologists recommends that the fetal heart rate and uterine activity be continuously monitored electronically for the duration of insert placement.[81]

Misoprostol

Misoprostol (Cytotec®; Searle, Oakville, ON), a synthetic prostaglandin (PGE_1) analogue, is marketed in an oral formulation of 100 μg or 200 μg tablets.[82] It is currently approved by the U.S. Food and Drug Administration for use in the treatment and prevention of gastrointestinal ulcer disease resulting from non-steroidal anti-inflammatory use. Misoprostol is an inexpensive prostaglandin capable of initiating uterine contractions; therefore, it has been extensively investigated for use as an induction agent in pregnancy. A single 100 μg tablet costs $ 0.30; therefore, a single 50 μg dose may cost as little as $0.15. Misoprostol is also temperature-stable and does not have special storage requirements. Vaginal misoprostol is currently widely used in the United States for cervical ripening and labour induction; however, investigations continue regarding the optimal dose, dosing regimen and route of administration.

Review of Vaginal Misoprostol Literature

Since the first clinical trial of vaginal misoprostol for labour induction reported by Margulies et al. in a letter to the Lancet in 1992, there has been growing interest in misoprostol for use as a labour induction agent.[83] In this randomized trial, 64 women beyond 28 weeks' gestation undergoing induction of labour were given 50 μg doses of intravaginal misoprostol or intravenous oxytocin. Successful induction was defined as vaginal delivery within 24 hours of the start of induction. More women in the misoprostol group achieved successful vaginal delivery within 24 hours than in the oxytocin group (79% compared with 62%). The mean time (± standard deviation) to vaginal birth delivery 407 (± 265) minutes in the misoprostol

group and 577 (± 605) minutes in the oxytocin group P = 0.02. There were no differences in mean birth weight or Apgar scores. No adverse fetal or neonatal outcomes were reported; however, this small study did not have sufficient power to form conclusions about maternal or fetal risks. The authors concluded that intravaginal misoprostol was more effective than oxytocin for labour induction in the third trimester of pregnancy.

Several randomized trials [83-97] comparing vaginal misoprostol to standard therapy (dinoprostone) found misoprostol to be safe and effective for induction of labour. In 1993 Sanchez-Ramos and colleagues[84] compared 50 μg of intravaginal misoprostol administered every four hours to intravenous oxytocin in 129 women with uneffaced and undilated cervixes. The interval from the start of induction to delivery was significantly shorter in the misoprostol -treated group (11 versus 18 hours, P = .004); however, the frequency of uterine tachysystole (defined as six contractions in a 10 minute period, repeated over two consecutive 10 minute periods) in the misoprostol group was approximately three times that found in the oxytocin treatment group (34.4% versus 13.8%, P < .05). No differences were found in delivery route, neonatal or maternal morbidity.

The authors concluded that vaginal misoprostol was safe and effective for labour induction and recommended further investigation to detail the optimal route, dose and dosing regimen. The frequency of excessive uterine activity was evaluated as a secondary outcome in the study, and did not form a basis for calculation of sample size. Investigators who reviewed fetal tracings were not blinded to group assignment. The non-blinded study design and the subjective nature of the evaluation and classification fetal heart rate tracings introduces bias

and raises concerns about inter-observer and intra-observer variation. This study did not have sufficient power to draw firm conclusions about the safety of misoprostol.

In 1995, Wing et al.[85] compared the administration of intravaginal misoprostol 50 μg every three hours with intracervical dinoprostone 0.5 mg every six hours in 135 women with unfavourable cervixes (Bishop score less than 4). Misoprostol was found to be more effective for labour induction. The mean time (± standard deviation) to vaginal birth was 903 (± 482) minutes in the misoprostol-treated subjects and 1410 (± 482) minutes in the control group ($P < .001$). The misoprostol-treated subjects required oxytocin augmentation much less frequently than those treated with dinoprostone 33.8% versus 65.7%, ($P < .001$). More than 70% of women in the vaginal misoprostol group delivered vaginally within 24 hours compared with 47% of dinoprostone-treated women ($P < .01$).

Misoprostol was associated with a 36% incidence of tachysystole (defined as greater than six or more uterine contractions occurring in 10 minute window for two consecutive 10-minute periods) compared with a 12% incidence of tachysystole in the dinoprostone treated group ($P < .001$). A 30% incidence of passage of meconium in utero was noted in the misoprostol group compared with a 10% passage of meconium in the dinoprostone-treated group ($P < .05$). No significant difference in maternal or neonatal outcomes was found between the two groups.

The limitations of this study include, lack of blinding, an empiric dosing regimen and lack of rigor in defining the treatment of study group and controls. The 50 μg dose of

misoprostol every three hours was extrapolated from a previously published study of misoprostol.[84] There was a difference in the time intervals from last dose of medication to allowable administration of oxytocin which could have potentially biased the primary outcome. Oxytocin administration was permitted three hours after the last dose of misoprostol and six hours after the last dose of dinoprostone. The frequency of excessive uterine activity and meconium staining were evaluated as secondary outcomes in this study. Investigators who reviewed fetal tracings were not blinded to group assignment. The non-blinded study design and the subjective nature of the evaluation and classification fetal heart rate tracings introduces bias and raises concerns about inter-observer and intra-observer variation. This study did not have sufficient power to draw firm conclusions about the safety of misoprostol.

In 1996, Mundle et al.[86] compared 50 μg vaginal misoprostol administered every four hours to standard labour induction methods (dinoprostone and or oxytocin) in 222 low-risk women undergoing cervical ripening and labour induction at term. The mean time to vaginal delivery (± standard deviation) was 753 (± 588) minutes for vaginal misoprostol versus 941 (± 506) minutes for intracervical or intravaginal dinoprostone. Oxytocin augmentation was used less frequently in the misoprostol group (RR = 0.48, 95% CI 0.31, 0.74). There were no significant differences in cesarean rate. Maternal and neonatal outcomes were not significantly different.

The major weaknesses of this study were lack of blinding and rigor in defining the standard protocol. The control group could receive one of several options: Prepidil® 0.5 mg intracervically every six hours, Prostin® 1 or 2 mg intravaginally every six hours or a dilute

solution of oxytocin administered intravenously. The choice of the agent to be used in the control group was to be chosen by the individual attending physician caring for that patient based on whichever option the physician felt was optimal for the care of that particular patient. This study did not have sufficient power to draw firm conclusions about the safety of misoprostol.

In a subsequent clinical trial involving 276 women, Wing et al.[87] used a lower dose of misoprostol, comparing 25μg of intravaginal misoprostol every three hours with 0.5 mg of dinoprostone administered intracervically every six hours in an attempt to reduce the occurrence of tachysystole and meconium passage noted in the misoprostol group in their earlier trial.[85] Misoprostol was found to be effective for labour induction in women with unfavourable cervixes (Bishop score less than 4). The mean time (± standard deviation) to vaginal birth was 1323 (± 844) minutes in the misoprostol-treated subjects and 1532 (± 706) minutes in the control group ($P < .05$). The misoprostol-treated subjects required oxytocin augmentation much less frequently than those treated with dinoprostone 46% versus 73%, ($P < .001$).

The dosing regimen of misoprostol 25 μg every three hours was associated with a 17% incidence of tachysystole (defined as greater than six or more uterine contractions occurring in 10 minute window for two consecutive 10-minute periods) compared with 14% incidence of tachysystole in the dinoprostone treated group ($P = 0.08$). A 17% incidence of passage of meconium in utero was noted in the misoprostol group compared with a 14%

passage of meconium in the dinoprostone-treated group ($P > .05$). No significant difference in maternal or neonatal outcomes was found between the two groups.

Limitations of this study include lack of blinding and a discrepancy in treatment between the study and control groups. Allowable dosing intervals from last dose to start of oxytocin differed in the investigational protocol, 6 hours for dinoprostone and three hours for misoprostol. Pharmacokinetic studies would have strengthened this study considerably. The primary outcome was the achievement of successful induction. All other outcomes were secondary. This study did not have sufficient power to draw firm conclusions about the safety of misoprostol.

Sanchez-Ramos et al.[88] studied the safety and efficacy of vaginal misoprostol for cervical ripening and labour induction in a meta-analysis of trials published up to 1997. Of 16 trials identified, eight [84, 85, 87, 89-93] met their criteria and included 966 patients, 488 of whom received vaginal misoprostol for labour induction. Controls received oxytocin or vaginal dinoprostone. Those who received vaginal misoprostol had a higher incidence of vaginal delivery within 24 hours of application (OR 2.64, 95% CI 1.87, 3.71) and a lower cesarean rate (OR 0.67, 95% CI 0.48,0.93). Use of vaginal misoprostol was associated with a higher incidence of tachysystole (OR 2.70, 95% CI 1.80, 4.04) but not of hyperstimulation (OR 1.91, 95% CI 0.98, 3.73).

The number of subjects allocated to the misoprostol group ranged from 24-138 with control groups of similar size. Five of the eight trials included were conducted in the United States[84, 85, 87, 92, 93] while the other three were conducted in South America.[89-91] The proportion of

nulliparous patients were similar and all patients enrolled in the control group received dinoprostone or oxytocin with the exception of one small trial where control patients received placebo.

The primary problem with this meta-analysis was the heterogeneity in study design. The dose of misoprostol varied from 25 μg every two hours[92] to 100 μg[89, 90] as a single dose. There was no one standard treatment for the control groups. In one study, placebo was used in the control group.[89] In two studies,[84, 91] dinoprostone 0.5 mg intracervically could be used with or without oxytocin. In the remaining four studies controls received dinoprostone 0.5 mg intracervically.[85, 87, 92, 93] In one study the dose of intravaginal dinoprostone was 3 mg.[90]

Continuous electronic fetal monitoring was performed on all patients in six studies while the other two studies used fetal monitoring intermittently.[89, 90] None of the individual trials had sufficient power to detect a reduction in cesarean delivery rate; however, a reduction in overall cesarean rate was observed when the studies were considered together. The reduction in cesarean rate in this meta-analysis depended heavily on one study.[91] When the analysis was repeated after excluding each trial, it appeared that the Campos study was an important contributor to the overall heterogeneity due to its large discrepancy in cesarean rates between the misoprostol (3.8%) and control groups (25.3%).

In an attempt to define the optimal dosing regimen of vaginal misoprostol, Wing et al.[94] compared 25 μg of intravaginal misoprostol every three hours with 25 μg of intravaginal misoprostol administered every six hours in 522 women with unfavourable cervixes (Bishop score < 4). In this trial, the six-hour regimen was found to be less efficacious than the three-

hour regimen. The mean time (± standard deviation) to vaginal birth was 903 (± 482) minutes in the three-hour dosing group and 1410 (± 869) minutes in the six-hour dosing group ($P < .001$). The overall frequencies of uterine contraction abnormalities were 14.6% with the three-hour dosing interval and 11.2% with the six-hour dosing interval ($P < .05$). A low incidence of uterine hypertonus and hyperstimulation was observed with both regimens (4.2% with the three-hour dosing and 4.6 with the six-hour dosing regime). The frequency of meconium passage was lower with the longer dosing interval than that observed in earlier studies (10%). No adverse fetal outcomes were reported; however, there was one maternal death from amniotic fluid embolus and two cesarean hysterectomies for uterine atony. This study did not have sufficient power to draw conclusions about maternal or fetal safety.

Sanchez-Ramos et al.[95] compared 50 μg of vaginal misoprostol with the slow-release dinoprostone vaginal insert. The vaginal insert was administered as a single application for a maximum of 12 hours. Misoprostol-treated women delivered in a shorter time interval than the dinoprostone treated women ($P < .001$) but experienced more tachysystole (21.3% versus 7.0%, $P = .004$). No differences in route of delivery, intrapartum complications or adverse neonatal outcomes occurred between the two groups. The authors concluded that both agents were effective and safe but that misoprostol appeared more effective and offered substantial cost savings.

Wing et al.[96] compared the efficacy of 25 μg of misoprostol administered every four hours to a 24-hour exposure of the dinoprostone vaginal insert. Two hundred women were enrolled. There were no significant differences in the interval from start of induction to

delivery. There were no significant differences in delivery route or use of oxytocin between the two groups. Approximately 50% of women in both treatment arms delivered vaginally within 24 hours. Uterine tachysystole and hyperstimulation occurred more often in the dinoprostone-treated subjects (18.4% versus 7.1%, P = .02).

The Cochrane Pregnancy and Childbirth Group[97] reviewed twenty-six selected randomized trials of vaginal misoprostol. They studied the effectiveness and safety of vaginal misoprostol compared with placebo, oxytocin or prostaglandin E_2 for cervical ripening or induction of labour at term. The primary outcomes were the rate of vaginal delivery within 24 hours, the incidence of uterine hyperstimulation with associated changes in the fetal heart rate, the rate of cesarean delivery and the incidence of serious adverse effects in the fetus or the mother.

When compared to dinoprostone, failure to achieve vaginal delivery within 24 hours was reduced in four of five trials (RR 0.70, 95% CI 1.17-1.99). The reported incidence of uterine hyperstimulation was increased with misoprostol (RR 1.59, 95% CI 1.02-2.48) as was meconium staining of the amniotic fluid (RR 1.38, 95% CI 1.06-1.79). Rates of vaginal instrumental delivery and cesarean delivery were inconsistent between trials. Overall, there was a reduction of instrumental deliveries with misoprostol (RR 0.75, 95% CI .58-.97). There were no significant differences in perinatal or maternal outcomes.

When comparing low dose regimens of misoprostol to higher doses regimens (25 μg every six hours compared to every three hours or 25μg compared to 50μg every three hours) neither group showed significantly more failures to achieve delivery within 24 hours

(RR 1.08, 95% CI .93-1.25). There was significantly more use of oxytocin for labour augmentation in the low dose group (RR 1.32, 95% CI 1.11-1.56). There was a trend toward less uterine hyperstimulation, fewer low Apgar scores at five minutes and fewer admissions to neonatal intensive care units. There were no differences in mode of delivery, meconium stained amniotic fluid or maternal side effects.

The Cochrane collaborative group concluded that in dosages of 25 μg every three hours or greater, misoprostol is more effective than dinoprostone and oxytocin for the induction of labour at term. No differences in perinatal outcomes were shown; however, the studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. Although vaginal misoprostol showed promise as a highly effective, inexpensive and convenient agent for labour induction, it could not be recommended for routine use at this time.[97-99]

Table 1: Summary of Randomized Trials of Vaginal Misoprostol for Labour Induction

Author	Year	No. Pts.	Misoprostol Dose	Control group	Results
Margulies[83]	1992	64	50 μg q2h	Oxytocin	Induc-delivery time shorter (miso.) (P = .02)
Sanchez[84]	1993	129	50 μg q4h	Oxytocin + PGE_2	Induc-delivery time shorter (miso.) (P = .004)
Fletcher[89]	1993	45	100 μg	Placebo	Induc-delivery time shorter (miso.) (P < .001)
Fletcher[90]	1994	63	100 μg	PGE_2 (3 mg)	Induc-delivery time not different (P = n.s.)
Wing [85]	1995	135	50 μg q3h	Prepidil ®	Induc-delivery time shorter (miso.) (P < .001)
Wing[94]	1995	276	25 μg q3h	Prepidil ®	Induc-delivery time shorter (miso.) (P < .001)
Varaklis[92]	1995	68	25 μg q2h	Prepidil ®	Induc-delivery time shorter (miso.) (P = .006)
Chuck[93]	1995	103	50 μg q4h	Prepidil ®	Induc-delivery time shorter (miso.) (P < .001)
Mundle[86]	1996	222	50 μg q4h	PGE_2	Induc-delivery time shorter (miso.) (P = .04)
Wing[87]	1996	522	25 μg q3h	25μg q6h	Induc-delivery time shorter (miso. q3h) (P < .001)
Wing[96]	1997	200	25 μg q4h	Cervidil®	Induc-delivery time not different (P = n.s.)
Sanchez[95]	1998	223	50 μg q3h	Cervidil®	Induc-delivery time shorter (miso.) (P < .001)

Review of Oral Misoprostol Literature

Only a few randomized trials assessing oral misoprostol for induction of labour at term have been published.[100-107] Ngai et al.[100] compared 200 μg oral misoprostol to 50 mg oral vitamin B_{12} placebo for cervical ripening in 80 women with prelabour rupture of membranes at term. Twelve hours after receiving the assigned treatment, oxytocin was administered as necessary. There was a significant difference in Bishop score 5.7 (± 1.8 SD) in the misoprostol group and 6.1 (± 1.9 SD) in the placebo group $P< .05$. The sample size was calculated to detect a difference in Bishop score 12 hours after administration of medication. The assumptions were α of .05 and $1-\beta = 95$. The sample size was initially calculated to be 100; however, an interim analysis was conducted after 80 patients were enrolled and the difference in Bishop score was found to be highly significant in both nulliparous and multiparous participants.

The strength of this study is its design as a double blind placebo controlled trial. The weaknesses include the choice of primary outcome. More clinically important and objective outcomes such as time to delivery would have been more relevant in this population of women with prelabour-ruptured membranes. The authors do not explain their decision to do an interim analysis after eighty patients were enrolled. An additional twenty patients would have met their sample size requirement. All patients in the study received oxytocin twelve hours after enrolment. This is a more aggressive approach than the current standard of care, which involves administration of oxytocin within 24 hours of membrane rupture.

Windrim et al.[101] studied the effectiveness, safety and gastrointestinal tolerance of misoprostol used orally for induction of labour and compared its use to established induction protocols. The primary outcome measure was time to delivery. Two hundred seventy-five women who presented for induction of labour were randomly assigned to receive either 50 μg

of misoprostol orally every four hours or treatment with physician-chosen combinations of either intracervical or vaginal prostaglandins every 4 to 6 hours or artificial rupture of membranes followed by oxytocin infusion. The mean time (± standard deviation) to vaginal birth was 926 ± (521) minutes compared to 909 ± (585) minutes with the established protocol P = 0.81, a non-significant difference. There were no clinically or statistically significant differences in maternal secondary outcome measures (cesarean rate, frequency of epidural use, perineal trauma or manual removal of the placenta). There was no difference in maternal gastrointestinal side effects. Neonatal outcomes including cord blood acid-base analysis were not different. This study identified oral misoprostol as a new option for labour induction and recommended further studies to confirm the safety and efficacy and to determine optimal dose and frequency of administration.

The sample size was calculated using a two-tailed α of 0.05 and a 1-β of 95. This is a smaller type two error than the β 0.20 usually chosen in similar trials. These authors chose this β of 5 to reduce the chance of missing a true difference between the two groups if a difference actually did exist. The major clinical consequence of conducting a trial with insufficient power to detect a difference in the time to delivery interval might be that patients could be offered a new induction agent that performed less well than the standard induction agent dinoprostone. The primary outcome was time to delivery, which is less substantive than more important clinical outcomes such as cesarean delivery rates and fetal asphyxia. To test such outcomes using misoprostol would require large sample sizes. A study of this nature would need to be multi-centred and would be prohibitively expensive.

The major weaknesses of this study were lack of blinding and lack of rigor in defining the standard protocol. The control group could receive one of several options: Prepidil® 0.5 mgs intracervically every six hours, Prostin® 1 or 2 mgs intravaginally every six hours or a dilute solution of oxytocin administered intravenously. The choice of the agent to be used in the control group was to be chosen by the individual attending physician caring for that patient based on whichever option the physician felt was optimal for the care of that particular patient.

Toppozada et al.[102] compared vaginal and oral misoprostol for induction of labour in a small-randomized trial. Twenty patients assigned to receive 100μg of vaginal misoprostol were compared to twenty assigned to 100μg oral misoprostol. When no response was noted three hours following the first 100μg dose, 200μg was then administered every 3 hours until a maximum dose of 1000μg was reached. Doubling the dose via the vaginal route was only needed in one instance. One subject in the vaginal group and three in the oral group had cesarean delivery because of failed induction. The authors concluded that vaginal misoprostol resulted in a shorter time to delivery ($P < .005$). However, more abnormal fetal heart rate patterns and uterine hyperstimulation occurred ($P < .05$). The validity of the results of this study is limited by its small sample size and the heterogeneity in misoprostol dosing regimens. The study does not have sufficient power to draw conclusions about maternal or fetal safety.

Table 2: Summary of Randomized Trials of Oral Misoprostol for Labour Induction

Author	Year	No. Pts.	Misoprostol Vaginal Dose	Misoprostol Oral Dose	Comparison Group	Results
Ngai[100]	1996	80		200 μg once	Placebo	Change in Bishop score greater (miso.) (P < .05)
Windrim[101]	1997	275		50 μg q4h	PGE_2 gel q6h	Time to delivery not different (P = .81)
Toppozada[102]	1997	40	100 μg q3h	100 μg q3h		Time to delivery longer in oral (P < .005)
Bennett[103]	1998	206	50 μg q4h	50 μg q4h		Time to delivery longer (oral) (P = .004) Hyperstimulation lower in oral (P = .04)
Adair[104]	1998	178	50 μg q6h	200 μg q6h		Time to delivery not different (P = .12) Tachysystole greater (oral) (P < .01)
Wing[105]	1999	220	25 μg q4h	50 μg q4h		Time to delivery longer (oral) (P = .005) Tachysystole not different (P = .39)
Butt[106]	1999	108		50 μg q4h	Oxytocin	Time to delivery longer (miso.) (P = .007)

Chapter 5

RESEARCH QUESTION AND METHODS

Research Question

The primary research question in this study was whether there existed a four-hour difference in the interval to vaginal birth with oral misoprostol (50 μg) compared with vaginal misoprostol (50 μg) administered every four hours for induction of labour in women at term with intact membranes. As a secondary outcome, we also studied whether the route of administration influences the frequency of excessive uterine activity resulting in abnormal fetal heart rate tracings. Other secondary outcomes included neonatal morbidity (as determined by cord blood acid-base disturbances and American College of Obstetricians and Gynecologists criteria for birth asphyxia.), cesarean birth, maternal gastrointestinal side effects and patient satisfaction.

Scientific Rationale and Originality

Prostaglandins are known to be effective induction agents when administered vaginally. A meta-analysis of randomized clinical trials found vaginal misoprostol to be safe and effective in cervical ripening and labour induction in women at term with intact membranes.[88] No masked randomized clinical trials comparing oral misoprostol 50 μg every four hours to vaginal misoprostol 50 μg every four hours were found in a Medline search of the English language literature.

Research Design

This study was a masked randomized placebo-controlled trial.

Sample Size Calculation

For the primary outcome, time to vaginal birth, a sample size of 172 was calculated using a two-tailed $\alpha = .05$, $\beta = .20$, $\Delta = 240$ minutes, and σ derived from pooling of results from a cohort of women who received vaginal misoprostol [86] (588 minutes) and the oral misoprostol intact membrane stratum [IGI] (521 minutes) in previous studies by our group (PEPI, Version 2,1995; Computer Programs for Epidemiologic Analysis, Stone Mountain, Georgia). Since our previous studies had consistent cesarean rates of 12.2% with 99% confidence interval (CI) (8.8, 16.5%), we added 20% (34 patients) to allow for anticipated cesarean births in our sample. A sample size of 206 was deemed appropriate to detect the clinically important difference (240 minutes), determined by a survey questionnaire of patients and medical personnel.

Setting

The study was conducted at the Grace General Hospital, St. John's, Newfoundland, Canada, from March 3, 1997 to October 8, 1997. This referral centre for perinatal care serves an almost entirely white population of 500,000 and is the site of 2500 of the province's 6000 annual births. Our induction rate is just over 20%, with approximately 520 inductions per year.

Inclusion and Exclusion Criteria

Patient inclusion criteria were: an indication for induction, single live fetus, gestation longer than 37 completed weeks, intact membranes and cephalic presentation. Patients who presented with any one of the following were ineligible: non-reassuring fetal heart rate tracing (FHR), previous uterine surgery, known hypersensitivity to prostaglandins, age less than 18 years, contraindication to vaginal birth or unwilling to consent.

Recruitment

Before starting the trial, the research protocol and study design was presented to obstetricians, residents and labour and delivery nurses at the annual Obstetrical Resident Research Day. The research nurse provided in-service education to the labour and delivery staff and prenatal educators who were involved in the study. All pregnant women who attended prenatal classes were informed of the study and given written information about the protocol. Eligible patients were informed when induction of labour was indicated. At presentation for induction, patients were enrolled in the study by the attending physician, who explained the protocol and potential risks and benefits before obtaining written consent.

Randomization

Opaque envelopes containing a card indicating group allocation were prepared by an administrative staff member using computer-generated random number tables with randomization in blocks of four. Stratification was based on parity and Bishop score. Allocation of each consenting patient to the induction method was determined at the time of induction by opening the next sequentially numbered envelope. A pharmacy technician

prepared study medications and placebos. For each patient, eight powdered 50 μg doses of misoprostol were placed individually in paper packets and stored in an airtight plastic container. Eight doses of an indistinguishable powdered cellulose placebo were similarly prepared and separately packaged for each patient. Oral or vaginal use was specified on the label.

Allocation Concealment

To conceal appearance and taste, all oral powders were mixed with 30 ml of apple or orange juice according to patient preference. Vaginal powders were suspended in hydroxyethyl gel just before use and delivered to the posterior fornix using a vaginal applicator. When a subject required more than eight doses, another identically prepared medication and placebo package was provided. To maintain allocation concealment, research personnel who prepared the envelopes and medications were not involved in any other aspect of the study. The induction method was concealed from all caregivers, participants and investigators until data analysis was completed. The code for group assignment was not broken until data analysis was complete.

Intervention

After enrolment, subjects were examined to determine Bishop score and stratified to either the low (less than 7) or high (7 or more) Bishop score group, and according to nulliparity or multiparity. Each patient was then randomly assigned to receive either oral misoprostol (50 μg) and vaginal placebo or vaginal misoprostol (50 μg) and oral placebo every

four hours until the occurrence of one of the following: a contraction frequency of three per 10 minutes, a non-reassuring FHR tracing, spontaneous rupture of membranes or delivery. All study inductions were conducted immediately after randomization on an inpatient basis, to allow continuous electronic FHR and uterine contraction monitoring for at least one hour after each dose. Decisions regarding amniotomy, analgesia, epidural anesthesia and oxytocin augmentation were made by the attending physician.

Compliance

All participants enrolled in the study were accounted for, with none lost to follow-up. After each delivery, the study package was returned to the pharmacy technician to ensure each participant had received the assigned treatment.

Primary Outcome

Substantive maternal and neonatal primary outcomes, such as rates of cesarean birth and birth asphyxia, are relevant when evaluating any induction agent. To test such outcomes using misoprostol would require sample sizes of 3400 and 5300, respectively because of the infrequency of these events. A study of this nature would need to be multi-centred and would be prohibitively expensive. For this study, the primary outcome measure was chosen to address clinical effectiveness. The primary objective was to compare the efficacy of misoprostol administered orally to misoprostol administered vaginally in patients requiring cervical ripening for the induction of labour at term. The purpose was to determine if route of administration impacts upon the induction–to-delivery interval.

Secondary Outcomes

To determine whether hypertonus, tachysystole or hyperstimulation were associated with route of administration of misoprostol, all FHR graphs were reviewed before study induction groups were unmasked. Each of the physician authors (two maternal fetal medicine attending physicians and two senior obstetrical residents) independently classified monitoring strips using terminology defined by Curtis et al.[107] as follows: hypertonus, a contraction lasting more than 90 seconds; tachysystole, a contraction frequency of more than five in a ten-minute period; hyperstimulation, exaggerated uterine response with late FHR decelerations or tachycardia greater than 160 beats per minute. Planned treatment of tachysystole and hyperstimulation included change in maternal position to the left lateral decubitus position, oxygen administration by nasal prongs and intravenous ritodrine as needed. Fetal scalp blood sampling was performed when indicated by non-reassuring FHR graphs, at the discretion of the attending physician.

To assess fetal safety issues, cord blood samples for arterial and venous acid-base analysis were taken after each delivery. Neonatal outcomes such as Apgar score at one and five minutes were recorded. All neonates were evaluated to assess if they met the American College of Obstetricians and Gynecologists (ACOG) criteria for birth asphyxia.[108] To assess patient satisfaction, all patients enrolled in the study were asked to complete a modified labour agentry scale questionnaire.[109]

Data Analysis

Data were analyzed on an intent-to-treat basis by parametric and nonparametric statistics, using Statistix 4.1 (Analytic Software, Tallahassee, Florida). Decision levels and hypotheses to be tested were preset to minimize bias. Hypothesis testing was performed on the primary outcome. Other comparisons were considered hypothesis-generating. Statistical significance of the primary outcome measure was assessed using Student's t-test and was considered significant at $P < .05$. Rank order nonparametric statistics using the Mann-Whitney U test, where cesarean birth is a failure to deliver vaginally and ranked longer than any vaginal birth, allowed inclusion of all births in a secondary analysis with median time to vaginal birth as the measure of central tendency.

Secondary outcomes were analyzed by parametric and nonparametric statistics as appropriate. Descriptive statistics were used for demographic baseline data. The significance level for all secondary and hypothesis-generating analyses was set at $P < .001$ to account for multiple testing, a conservative approach.

Confidentiality and Ethical Issues

Specific steps were taken to protect the rights of participants in the clinical trial. All pregnant women who attended prenatal classes were given written information early in their pregnancy. All participants who presented at the time of induction were given written information sheets explaining their participation in the clinical trial. The physician responsible for initiating the induction obtained written informed consent. Members of the research team reviewed records concerning labour, delivery and hospital stay. No records bearing the name

of any research participant was provided to anyone other than the research team involved in the study. No participant was identified in publication.

The risks associated with the study were carefully explained at the time of obtaining written consent. All patients were informed of the potential risk of excessive uterine activity associated with the use of prostaglandins. The planned medical treatment available and the possibility of cesarean delivery were explained in detail. Participants were also informed of the potential gastrointestinal side effects associated with administration of oral prostaglandins. The Human Investigation Committee of the Faculty of Medicine, Memorial University of Newfoundland, and the Grace General Hospital approved the research proposal.

Study Protocol for Misoprostol Induction

The study protocol for this randomized controlled trial was posted in the labour and delivery area and served to guide medical and nursing personnel involved in recruitment of patients and administration of study medications.

Misoprostol (Cytotec®) is a prostaglandin E_1 methyl analogue with potent cervical ripening and uterotonic effects. Randomized clinical trials in our centre have found misoprostol to be more effective than standard induction regimes. Patients being delivered by a family physician require consultation with an obstetrician before recruitment.

Contraindications

- Major uterine surgery
- Cephalopelvic disproportion

- Non-reassuring fetal heart rate tracing
- Fetal malpresentation
- Known hypersensitivity to misoprostol or prostaglandins
- Any contraindication to vaginal delivery
- Age less than 18 years.

Note

The use of prostaglandins for cervical ripening or induction in a patient with a history of a previous cesarean delivery has not been approved by the Society of Obstetricians and Gynecologists of Canada (SOGC) or by the American College of Obstetricians and Gynecologists. (ACOG).

Procedure

1. The patient should be fully informed of the indication for induction.
2. The proposed use of misoprostol should be explained.
3. Written informed consent should be obtained.
4. All misoprostol inductions will be done as in-patients.
5. A written order is necessary for the initiation of the induction by misoprostol.
6. A specific order is necessary for each additional dosage of misoprostol, after physician evaluation of the appropriateness of this dosage.
7. Vital signs are to be checked prior to administration of medication.
8. Fetal heart rate tracing (FHR) prior to misoprostol should be obtained.
9. All patients should have a Bishop Score determined and recorded prior to the start of the induction.

10. The data sheet should also be stamped with the patient's admission card.
11. Fetal heart rate tracings should be done continuously for two hours after each dose of misoprostol.
12. Repeat misoprostol dosage may be continued until one of the following occurs: labour is established, a contraction frequency of 3 per 10 minutes.
13. Amniotomy (ARM) can be performed in either group at the discretion of the attending physician.
14. Following ARM, misoprostol can no longer be used.
15. Augmentation with oxytocin is permitted following the use of misoprostol.
16. Oxytocin should not be started within four hours of misoprostol administration.
17. Misoprostol may be ordered in a dose of 50 micrograms up to every four hours as needed.
18. All newborns should have cord blood gases obtained (venous and arterial).
19. The misoprostol induction data sheet should be completed for ongoing monitoring and quality assurance of our misoprostol protocol.

Budget and Grant Applications

In an attempt to procure funding for this study, our research group submitted a proposal to the Medical Research Council of Canada (see appendix F). Unfortunately, this application was unsuccessful. A subsequent research proposal submitted for the Memorial University and Health Care Corporation research award was successful and resulted in a

research grant of $25,000. The Health Care Corporation hired a departmental part-time research nurse to assist with the study. The Budget is attached as appendix G.

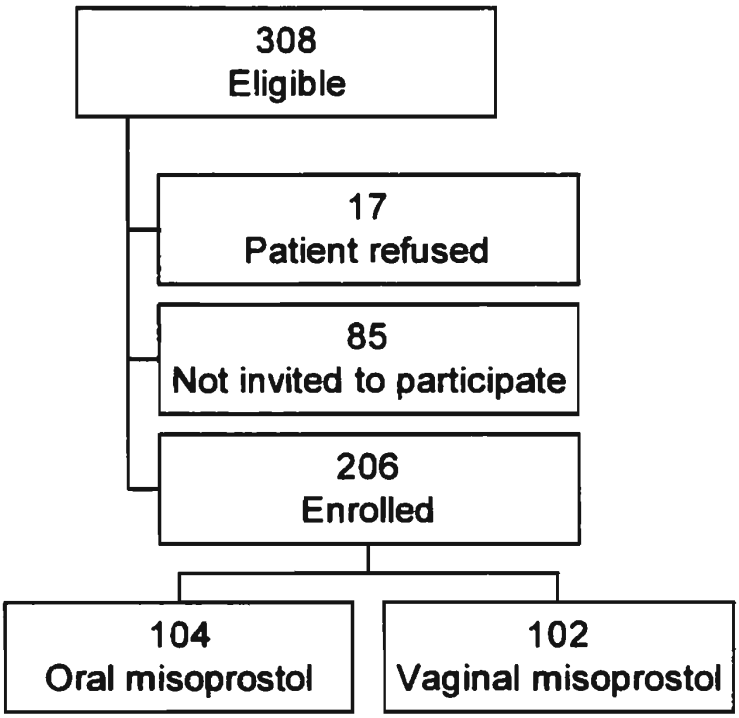
Chapter 6

RESULTS

Study Population

During the study period, 393 patients presented for induction of labour, of whom 308 were eligible. Seventeen patients refused enrolment because they did not want to be involved in a research protocol and the remaining 85 were not invited to participate because alternate methods of induction including amniotomy, oxytocin or dinoprostone were preferred by their attending physicians. Among 206 women enrolled, there were 104 in the oral group and 102 in the vaginal group (Figure 1). No participant or neonate was lost to follow-up.

Figure 1: Study population



Primary Outcome

The mean time (± standard deviation) to vaginal birth with oral misoprostol was 1072 (± 593) minutes compared with 846 (± 385) minutes with the vaginal protocol, a statistically significant difference (P = .004). The median time to vaginal birth in the oral misoprostol group was 1125 minutes compared with 926 minutes in the vaginal misoprostol group (P = .38, Mann Whitney U test). When given orally, a median of two and a maximum of nine doses were used. Only seven subjects took more than five oral doses. When misoprostol was placed vaginally, a median of two and a maximum of five doses were used. Maternal preinduction and

neonatal demographic data are given in Table 3. There were no significant differences in demographic characteristics between the two groups.

Table 3: Demographic characteristics

	Vaginal Misoprostol n = 102	Oral Misoprostol n = 104
Nulliparous	74	69
Maternal age (years)	28.7 (4.9)	27.5 (5.0)
Gestation (days)	284.2 (8.3)	285.4 (7.6)
Gravidity	1.6 (0.8)	1.7 (1.0)
Parity	0.3 (0.6)	0.5 (0.8)
Bishop score < 7	81	79
Postterm	65	69
Hypertension	18	12
Oligohydramnios	8	13
Other	11	10
Birth weight (grams)	3645 (566)	3585 (612)

Data given as number or mean (standard deviation)

Peripartum data are given in Table 4, with relative risk (RR) and 95% CI. There were no significant differences in oxytocin (RR 0.67, CI 0.38, 1.18), epidural (RR 0.89, CI 0.51, 1.56) or other analgesia use (RR 0.59, CI 0.21, 1.64). No significant differences were observed in meconium staining of amniotic fluid (RR 0.78, CI 0.41, 1.47), frequency of need for episiotomies (RR 1.23, CI 0.62, 2.42) or tearing of the perineum (RR 0.98, CI 0.72, 2.33).

Table 4: Peripartum data

	Vaginal (n = 102)	Oral (n = 104)	Relative Risk	95% Confidence Interval
Intrapartum frequency				
Oxytocin use	59	70	0.67	0.38, 1.18
Epidural use	61	65	0.89	0.51, 1.56
No analgesia use	6	10	0.59	0.21, 1.64
Meconium	21	29	0.78	0.41, 1.47
Episiotomy	22	19	1.23	0.62, 2.42
Laceration	54	59	0.98	0.56, 1.69
Third or fourth degree Laceration	2	0		
Intact perineum	34	29	1.29	0.72, 2.33

Data for mean vaginal birth intervals are given in Table 5. There was a significant difference in time to vaginal birth depending on route of administration. Those subjects randomized to the vaginal misoprostol route had a significantly shorter time to delivery (846 ± 385 minutes versus 1072 ± 593 minutes in the oral misoprostol group, P = .004). Furthermore, the induction-to-full dilatation interval was also significantly shorter in the vaginal misoprostol group (763 ± 361 minutes versus 1003 ± 578 minutes in the oral misoprostol group, P = .002). There were no statistically significant differences in the time of first, second and third stages of labour between the two groups. This indicates that the observed difference in time to delivery was not simply due to an increased time pushing during the second stage of labour.

Table 5: Labour interval to vaginal birth

	Vaginal Misoprostol	Oral Misoprostol	P*
Induction to vaginal birth	846 (385)	1072 (593)	.004
Induction to full dilatation	763 (361)	1003 (578)	.002
1st stage of labour	342 (204)	365 (223)	.48
2nd stage of labour	83 (89)	69 (76)	.26
3rd stage of labour	12 (14)	9.9 (8.4)	.21

Data given in minutes as mean (standard deviation)

* Student's t-test

Secondary Outcomes

Birth Route

There was no significant difference in birth route between the two groups (χ_3^2 = 2.53, P = .47). With oral misoprostol, there were 58 spontaneous vaginal deliveries, 21 vacuum deliveries, 9 forceps-assisted deliveries and 16 cesarean births (15.3%). With vaginal misoprostol, there were 56 spontaneous vaginal deliveries, 15 vacuum deliveries, 8 forceps-assisted deliveries and 23 cesarean births (22.5%). Non-reassuring FHR tracing was the indication for two cesareans in the oral misoprostol group and six cesareans in the vaginal misoprostol group (RR 2.47, CI 0.49, 12.49).

Excessive Uterine Activity

Fetal heart rate and uterine activity tracing data were analyzed using nonparametric statistics based on number of masked physician reviewers making that classification of a given

tracing (Table 6). The inherent subjectivity involved in analyzing fetal heart graph and uterine contraction monitoring strips led us to analyze the data based on agreement between physicians. All four physician-reviewers blinded to group assignment agreed that 25 women in the vaginal misoprostol group and 5 women in the oral misoprostol group experienced tachysystole (P = .01), and four women in the vaginal misoprostol group and no women in the oral misoprostol group experienced hyperstimulation (P = .04).

Table 6: Classification of excessive uterine activity

	0 Reviewers classified graph as:	1 Reviewer classified graph as:	2 Reviewers classified graph as:	3 Reviewers classified graph as:	4 Reviewers classified graph as:	P *
Tracing classification						
Hypertonic > 90 sec						
Oral misoprostol	1	8	15	26	54	0.68
Vaginal misoprostol	0	12	11	29	49	
Hypertonic > 120 sec						
Oral misoprostol	7	22	24	20	31	0.57
Vaginal misoprostol	8	21	22	28	22	
Tachysystole > 10 min						
Oral misoprostol	23	14	18	25	23	0.21
Vaginal misoprostol	16	15	18	21	31	
Tachysystole > 20 min						
Oral misoprostol	52	21	16	10	5	0.01
Vaginal misoprostol	41	17	7	11	25	
Hyperstimulation						
Oral misoprostol	84	14	5	1	0	0.04
Vaginal misoprostol	70	17	6	4	4	

* Mann-Whitney U test.

Although there was more frequent 20-minute tachysystole ($P < .04$) in the vaginal misoprostol group, these results were not statistically significant by our preset level for secondary analyses, but the trend warrants attention.

Neonatal Outcomes

Neonatal outcomes in both groups were similar (Table 7). Umbilical cord arterial and venous blood acid-base analysis was performed on 89 of the 104 participants in the oral misoprostol group and 92 of the 102 participants in the vaginal misoprostol group (90% of neonates). Two neonates from the vaginal misoprostol group had cord pH less than 7.00; however, no neonate met the American College of Obstetricians and Gynecologists (ACOG) criteria for birth asphyxia.[108] While it is reassuring that no neonate experienced an adverse outcome, this study did not have sufficient power to draw conclusions about fetal safety. The significance level for all secondary and hypothesis-generating analyses was set at $P < .001$ to account for multiple testing.

Table 7: Neonatal outcome

	Vaginal Misoprostol	Oral Misoprostol	P
ACOG criteria for birth asphyxia:	*N*	*N*	
Apgar 5 min < 3	0	0	
Cord pH < 7	2	0	.16*
Base deficit > 16	2	0	.16*
Cord blood:	*Mean*	*Mean*	
Cord pH	7.28 (0.10)	7.30 (0.09)	.08†
Base deficit	5.28 (4.14)	4.44 (3.32)	.13†
Apgar scores:	*Median*	*Median*	
Apgar 1 minute	9 (8,9)	9(8,9)	.59‡
Apgar 5 minute	9 (9,10)	9 (9,10)	.23‡
	N	*N*	
Apgar 1 minute < 7	17	7	.03$^{\chi}$
Apgar 5 minute < 7	0	1	.32*

* Fishers' exact test

† Student's t test: mean (standard deviation)

‡ Mann-Whitney U test: median (1st and 3rd quartile)

$^{\chi}$ Chi square test

Labour Satisfaction

Ninety women in the oral group and 83 in the vaginal group completed a labour satisfaction questionnaire administered 24 hours postpartum (84% response rate). Analysis of the responses to all questions failed to detect any statistically significant difference in patient satisfaction or overall score. All participants in the study reported positive labour and delivery experiences. None of the participants reported adverse gastrointestinal effects. There was no reported diarrhea in either group and no difference in occurrence of vomiting (18 in the oral and 19 in the vaginal group, P = .81).

Chapter 7

METHODOLOGICAL ISSUES AND DISCUSSION

Design Problems

The results of this study are convincing because of the strength of its masked randomized design and the lack of protocol violations. The problems encountered in conducting the trial stemmed from two major sources: financing the trial and accomplishing blinding. From the point of view of financial support, it became apparent very early that the Canadian manufacturer of misoprostol (Searle Canada, Oakville Ontario) was not interested in supporting research on induction of labour. This related to medicolegal liability inherent to research in pregnancy and a potential adverse effect on pharmaceutical marketing in the event of publicized complications or lawsuits. Because of its reticence to be involved in pregnancy-related research, the manufacturer declined to provide a placebo. Estimates obtained from the manufacturer placed the cost of placebo production at more than $200,000.

Even if misoprostol was identified to be an ideal pharmacological induction agent, the market size and additional generated revenue would be small, as each potential patient would require only small doses briefly, during an infrequent event in her lifetime. For these reasons, the manufacturer is unlikely to ever be proactive in this area of research or to seek Canadian Health Protection Branch approval of misoprostol for induction of labour. This approval will have to be sought by investigators once more evidence is obtained

Since a major expected benefit of using misoprostol for labour induction is cost savings, it was decided to pursue the possibility of realizing such a cost savings to obtain financing for this trial from the Health Care Corporation of St. John's. A review of pharmacy records from previous misoprostol studies conducted at the Grace General Hospital provided data to support an expected savings by using misoprostol instead of dinoprostone for labour induction, justifying financial support of this trial by the Health Care Corporation.

The Corporation approved the hiring of a part-time pharmacy technician to work exclusively on the trial to provide a placebo for the study and to maintain records, ensuring that each participant received the appropriate treatment. This technician was responsible for the preparation of code-labelled indistinguishable drug-placebo packages according to the specifications of the study protocol. Study drug packages contained eight doses of the designated treatment, as the maximum number of doses required by any subject in our prior research studies was seven. The induction method was concealed from all caregivers and investigators until data analysis was completed.

The Health Care Corporation also approved the hiring of a part-time research nurse to provide support to the Department of Obstetrics and Gynecology for the duration of the trial. The research nurse reviewed all aspects of the study protocol and acted as a liaison with the pharmacy department. Educational sessions were arranged for prenatal instructors, residents and attending physicians to familiarize all participating caregivers with the study protocol. Data collection, including the administration of a postpartum labour satisfaction questionnaire to all participants, was the primary responsibility of the research nurse.

In addition to financial support from the Health Care Corporation, funding was sought from the Medical Research Council of Canada. Two separate grant applications were submitted; unfortunately, neither application was successful. An application to the Memorial University of Newfoundland Faculty of Medicine was successful in securing a $25,000 research grant, and was awarded the Cox Research Award. These additional funds were instrumental in financing the remainder of the projected costs of the trial. Efforts to secure financing for this trial delayed its start date by approximately one year.

Recruitment

During the study period, 393 women presented for induction of labour. Of this group, 85 were ineligible according to the study protocol, 17 did not wish to participate in a study and 85 were not invited because the attending physician chose alternate methods of induction. Two hundred and six of the 223 women (> 90%) invited to participate agreed to participate in the study. Since only 206 of a potential 308 were recruited, a possible selection bias is introduced into the study. Non-participants were documented but their demographic characteristics were not. This is because physicians other than the investigators were providing primary medical care. We did not have permission from non-participants to review their medical records.

Differences are widely acknowledged to exist between patients who agree to participate as subjects in research studies and those who do not. Significantly different outcomes have frequently been documented even between non-participants in studies and participants randomized to an equivalent control arm. Therefore, one must interpret these

results (and those of most trials) bearing in mind that generalizability to the clinical population may not be complete. In this case, 85 patients were not invited to participate in the study because their attending physician preferred alternate methods of induction including amniotomy, oxytocin or dinoprostone. It is likely that several of these women had a favourable cervix (high Bishop score) at presentation, leading the attending physician to believe that an amniotomy followed by oxytocin was a more appropriate treatment than randomization to either form of misoprostol induction. Thus, any conclusions reached concerning the relative merits of the forms of misoprostol induction studied here must be understood to apply to a relatively similar population to that randomized.

Classification of Excessive Uterine Activity

Although there is no direct relationship between continuous electronic fetal monitoring and fetal well-being, non-reassuring fetal heart rate changes associated with excessive uterine activity warrant intervention either to reduce uterine activity or to deliver the fetus. Because of confusion stemming from inconsistent definitions of excessive uterine activity, Curtis recommended a standard terminology. While it allows for classification of labour graphs, the terminology is nevertheless arbitrary, particularly with respect to tachysystole and hypertonic contractions.

Despite concerns of possible uterine hyperstimulation, substantive adverse newborn outcomes such as neonatal acidosis, meconium aspiration, and birth asphyxia have been rare and have not differed between misoprostol and control groups in previous published studies. In our study, two neonates in the vaginal misoprostol group had cord blood pH less than 7.00

but no asphyxia occurred. Among the 39 cesarean births, six of the eight done for fetal safety reasons were in the vaginal misoprostol group. While these differences are not statistically significant, the question is clinically relevant, making it a worthwhile primary goal in the design of a future clinical trial. The frequency of excessive uterine activity associated with route of administration was evaluated as a secondary outcome in the present study, and did not form a basis for calculation of sample size.

Inherent in the evaluation of excessive uterine activity is the concern about inter-observer and intra-observer variation. We believe that agreement about the occurrence of hyperstimulation among all four reviewers blinded to each others' results and to group assignment provides strong evidence for the existence of four cases of hyperstimulation in the vaginal misoprostol group and no cases of hyperstimulation in the oral group. The finding that two neonates in the vaginal misoprostol group that had a cord pH less than 7.00 further supports the conclusion that vaginal misoprostol has a greater propensity to cause excessive stimulation of uterine contractility.

Pharmacokinetics of Crushed Misoprostol

The pharmacokinetics of misoprostol suspended in gel and given vaginally has not been directly evaluated. No study has evaluated the pharmacokinetics of crushed misoprostol given orally. In our study, this group had the lowest incidence of tachysystole and hyperstimulation. Understanding the timing of excessive uterine activity is important because it addresses concerns about fetal safety. Appropriate and timely intervention can then be

initiated. Such information is also essential for the rational design of further trials to determine the safest dose, form, and route of misoprostol administration.

A Future Study of Excessive Uterine Activity

To further study the relationship between misoprostol and excessive uterine activity, our research group has planned a cohort study. The primary objective is to determine the incidence and timing of excessive uterine activity with induction of labour with misoprostol. Different routes and formulations of misoprostol will be compared to prostaglandin E_2 intracervical or intravaginal gel, oxytocin, and spontaneous labour.

Study Design

The study will include women enrolled in each of three randomized trials evaluating misoprostol for labour induction.[101,103,105] The studies were conducted from March 30, 1994 to September 22, 1994 and October 25, 1996 to December 19, 1997 at the Grace General Hospital in St. John's, Newfoundland. A cohort of women who presented in spontaneous labour during the same period will also be evaluated.

Inclusion criteria are: a single live fetus in cephalic presentation, gestation longer than 37 weeks and fetal heart rate and uterine activity graphs available for review. Exclusion criteria include: non-reassuring fetal heart rate tracing prior to induction (or on admission in the spontaneous labour cohort), prior uterine surgery, contraindication to vaginal birth, age less than 19 years and known hypersensitivity to misoprostol or other prostaglandins.

One of these trials enrolled only women with term premature rupture of membranes[106], while the other two trials included only those women with intact membranes.[101,103] The details of the three trials are previously published. For those women undergoing induction of labour, the cohorts will be as follows: misoprostol 50 μg crushed and suspended in hydroxyethyl gel given vaginally every four hours, misoprostol 50 μg crushed and mixed with juice given orally every four hours, misoprostol 50 μg tablet given orally every four hours for premature rupture of membranes [PROM]), intravenous oxytocin beginning at 2 milliunits (mu) /min and increasing by 2 mu/min every 15 to 30 minutes for PROM, misoprostol tablet 50 μg vaginally every four hours, prostaglandin E_2 intracervical gel 0.5 mg every six hours or prostaglandin E_2 intravaginal gel 1 mg or 2 mg every 6 hours. The cohort of women in spontaneous labour in the study will include a group of women who had at least six hours of fetal heart rate and uterine activity monitoring and who would have otherwise met the criteria for induction of labour.

Methods

The fetal heart rate and uterine activity graphs will be independently and individually analyzed by three maternal fetal medicine specialists and one physician enrolled in a Maternal Fetal Medicine Fellowship. Tachysystole will be defined as a contraction frequency of more than five in a ten-minute period for two consecutive ten-minute periods. Hyperstimulation will be defined as tachysystole with late fetal heart rate decelerations or fetal tachycardia greater than 160 beats per minute. Tachysystole or hyperstimulation will be noted if at least two of those reviewing the graph agree with the diagnosis.

For those women receiving the crushed forms of misoprostol, reviewers were blinded to group assignment and the code was not broken until completion of analysis of graphs. For the other cohorts, although the reviewers were not blinded, they will not actively seek to reveal the cohort allocation until analysis of graphs is completed. The timing of the excessive uterine activity will be determined relative to the misoprostol dosing schedule. If tachysystole or hyperstimulation occurred after subsequent doses of misoprostol, the timing of each episode will be determined relative to the number of doses given. Those women who experience tachysystole or hyperstimulation only after oxytocin augmentation is initiated, or during the second stage of labour with pushing, will not be included in the determination of timing of excessive uterine activity, as this may lead to confounding.

Sample Size Calculation

The sample size required is based on the estimated incidence of tachysystole in the misoprostol and oxytocin cohorts.[101,103,106] Using a two-tailed $\alpha = .05$ and $\beta = .20$, fifty-one women in each cohort will be needed to detect a significant difference between 35% incidence in one cohort and a 10% incidence in another cohort. Data will be analyzed using Statistix 4.1 (Analytical Software, Tallahassee, FL). Continuous variables will be assessed using Student's t test and analysis of variance, while categorical variables will be analyzed by χ^2 and Fisher exact test where appropriate. Statistical significance will be set at $P < .05$. Because of multiple testing, all comparisons other than the primary outcomes will be considered only as hypothesis generating.

Chapter 8

IS ORAL MISOPROSTOL THE IDEAL INDUCTION AGENT?

Obstetricians routinely use various mechanical methods and pharmacological agents to induce labour; however, no single approach has been universally successful. Oxytocin is an effective induction agent; nonetheless, it is not optimal therapy for a patient with an unripe cervix. Administration requires an intravenous infusion with continuous monitoring of fetal heart rate and uterine contractions. Prostaglandins are effective cervical ripening agents, achieving a shorter induction-to-delivery interval and a lower rate of operative intervention when compared to oxytocin.

Oral administration of prostaglandins has essentially been abandoned because of undesirable gastrointestinal effects, which have limited their use to vaginal and intracervical routes. Termination of prostaglandin-related excessive uterine activity remains problematic. An oral induction agent that is safe, effective, inexpensive and well tolerated by patients would likely be attractive to patients and health care providers. Anticipated benefits include avoidance of intravenous lines in some parturients, less frequent need for vaginal examination and greater freedom for upright positioning. Ambulation might even facilitate labour progress.

Misoprostol

Misoprostol (Cytotec®; Searle, Oakville, ON), a synthetic prostaglandin (PGE_1) analogue, is marketed in an oral formulation of 100 μg or 200 μg tablets.[82] It is currently

approved by the U.S. Food and Drug Administration for use in the treatment and prevention of gastrointestinal ulcer disease resulting from non-steroidal anti-inflammatory use. Misoprostol is an inexpensive prostaglandin capable of initiating uterine contractions; therefore, it has been extensively investigated for use as an induction agent in pregnancy. A single 100 μg tablet costs $ 0.30; therefore, a single 50 μg dose may cost as little as $0.15. Misoprostol is also temperature-stable and does not have special storage requirements.

Pharmacokinetics of Oral and Vaginal Misoprostol

Misoprostol is primarily metabolized in the liver, with less than one percent of its active metabolite excreted in urine. Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system. The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering and fever, all of which are dose dependent. Although other prostaglandins (prostaglandin E_2 and prostaglandin $F_2\alpha$) can cause myocardial infarction and bronchospasm, misoprostol does not. Toxic doses of misoprostol have not been determined.

Zieman et al.[110] compared the pharmacokinetics of misoprostol (400 μg) administered by vaginal and oral routes to 10 non-pregnant and 10 pregnant first trimester volunteers, concluding that significant differences exist. Among women who were 9 to 11 weeks pregnant and given misoprostol before a surgical abortion, intrauterine pressure began to increase an average of 8 minutes after oral administration and 21 minutes after vaginal administration and was maximal 25 minutes after oral administration and 46 minutes after vaginal administration. Uterine contractility initially increased and reached a plateau one hour

after oral administration whereas uterine contractility increased continuously for four hours after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration. Systemic bioavailability of vaginally administered misoprostol was found to be three times that of misoprostol administered orally. With vaginal administration, peak plasma levels were reached more slowly but were sustained in excess of four hours.

In a confirmatory study, Danielsson et al.[111] reported that uterine activity increased continuously for four hours after vaginal administration of misoprostol, and warned that this could lead to a cumulative effect with subsequent dosing. When contractions of abnormally high intensity or frequency occur, insufficient recovery resulting in FHR abnormalities could necessitate operative delivery or lead to fetal asphyxia. It could reasonably be argued that the greater frequency of abnormal fetal heart rate patterns observed in patients who receive vaginal misoprostol are a result of excessive uterine activity, reflective of this greater bioavailability.

Induction agents, ideally, should mimic spontaneous labour while avoiding excessive uterine activity. Inherent in the evaluation of excessive uterine activity is the concern about inter-observer and intra-observer variation. We believe that agreement about the occurrence of hyperstimulation among all four reviewers blinded to each others' results and to group assignment provides strong evidence for the existence in this study of four cases of hyperstimulation in the vaginal misoprostol group and no cases of hyperstimulation in the oral group. The finding that two neonates in the vaginal misoprostol group that had a cord pH less than 7.00 further supports the conclusion that vaginal misoprostol has a greater propensity to cause excessive stimulation of uterine contractility. Uterine hyperstimulation was a secondary outcome and was not considered in calculation of sample size. The significance level for all

secondary and hypothesis-generating analyses was set at $P < .001$ to account for multiple testing.

Misoprostol-Current and Future Use

Despite accumulating evidence of effectiveness and obvious cost advantage in over 44 randomized clinical trials, the U.S. Food and Drug Administration and the Therapeutic Products Program of Health Canada have not yet approved misoprostol for induction of labour. However, they do recognize that in certain circumstances, off-label uses of approved products are appropriate, rational and accepted medical practice. Misoprostol administered vaginally for labour induction is currently in widespread use in the United States. Its use in most Canadian tertiary care centres is limited to research protocols.

The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice recently concluded that vaginal misoprostol administered appears to be effective in inducing labour in pregnant women who have unfavourable cervixes; however, the initial dose should be limited to 25 μg every three to fours hours because of concerns of the greater incidence of tachysystole observed with the use of higher doses. It further concluded that prospective studies are necessary to define optimal dosing regimens.[112] The Society of Obstetricians and Gynecologists of Canada (SOGC) has not published a recommendation on the use of misoprostol as an induction agent.

Misoprostol is an effective induction agent whether it is given orally or vaginally. Misoprostol is much less expensive than dinoprostone and, unlike dinoprostone, which

requires refrigeration until just before use, it is stable at room temperature. Oral administration of misoprostol is appealing for several reasons, including convenience and a non-invasive mode of delivery. Fewer cervical exams could also potentially result in lower peripartum infection rates, particularly in women with prelabour-ruptured membranes. Oral administration of misoprostol, if proved safe and effective, could potentially reduce overall hospitalization time by permitting administration of the medication in an outpatient setting. No studies using misoprostol as an outpatient preinduction cervical ripening agent have been published. Use for this indication is not currently recommended because of the need for close surveillance of uterine activity after administration of misoprostol. In addition to these potential benefits, oral misoprostol shares with vaginal misoprostol the advantages of cost-effectiveness and efficacy in labour induction.

The oral route of misoprostol administration is an important one that has not been fully investigated, and the question of whether oral may be the preferred route of misoprostol administration remains to be answered. Sanchez-Ramos et al.[99] conducted a systematic review of published randomized trials comparing oral and vaginal misoprostol administration for cervical ripening and labour induction. In total, 1,191 patients were randomized to receive misoprostol orally (n = 602) or by the vaginal route (n = 589). The oral doses ranged from 50 μg to 200 μg every four to six hours. Vaginal misoprostol was administered in doses ranging from 25 μg every four hours to 100 μg every three hours.

No significant difference was noted in the proportion of patients who delivered within 12 and 24 hours. Similarly, the intervals from start of induction to vaginal delivery were

not different. No difference was noted in the incidence of abnormal Apgar scores or rates of admission to neonatal intensive care units. Interestingly, the rate of cesarean delivery was significantly lower in the oral misoprostol group (15% versus 22%, Mantel-Haenszel pooled odds ratio 0.64).

Although meta-analysis provides a systematic and explicit method for demonstrating early evidence with regard to the effectiveness of treatments, it is not as valuable as a large randomized trial. Three principal concerns must be addressed when assessing the validity of a meta-analysis: publication bias, quality assessment of the randomized clinical trials included and study heterogeneity. Several sources of inter-study heterogeneity can be identified in the Sanchez-Ramos review. There were variations in treatment protocols, small sample size in two of the seven studies[100,101] and a lack of uniform stratification according to Bishop score and parity. It is important that the results of a meta-analysis not depend excessively on the results of a single study. To assess inter-study heterogeneity, the analysis should be repeated after sequentially excluding each trial, seeking to determine whether any one trial contributed excessively to the overall reduction in cesarean delivery rate.

The enormous economic and clinical advantages of misoprostol for cervical ripening and labour induction suggest that the unanswered questions about the impact of oral misoprostol on cesarean delivery rates and fetal safety should be addressed in a properly designed, well-conducted multi-centre trial. Our research group has planned such a trial, and is currently seeking funding to allow it to proceed.

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A Masked Randomized Comparison of Oral and Vaginal Administration of Misoprostol for Labor Induction

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Objective: To test the null hypothesis that administering misoprostol orally or vaginally will result in no difference in time to vaginal birth, and to determine whether different frequencies of tachysystole and hyperstimulation are associated with route of administration.

Methods: Two hundred six women after 37 completed weeks' gestation who presented with an indication for induction were randomly assigned to receive misoprostol (50 μg) either orally or vaginally every 4 hours as needed to induce labor. Placebo use and allocation concealment accomplished blinding until data analysis was completed. Sample size was calculated to allow a two-tailed α of .05 and power (1 − β) of 80%. All fetal heart rate and uterine activity graphs were classified according to Curtis' criteria before induction groups were unmasked.

Results: Analysis involved 104 women in the oral group and 102 in the vaginal group. The mean time (± standard deviation) to vaginal birth with oral misoprostol was 1072 (±593) minutes compared with 846 (±385) minutes with the vaginal protocol ($P = .004$). There were no significant differences in cesarean rate, epidural use, or neonatal outcomes. More frequent tachysystole for 20 minutes ($P < .01$) and hyperstimulation ($P < .04$) were observed with vaginal misoprostol. No neonatal asphyxia occurred in either group.

Conclusion: Misoprostol effectively induces labor, given orally or vaginally. There is a shorter interval to vaginal birth with vaginal application; however, the more frequent occurrence of fetal heart rate graph abnormalities in this group suggests that, until the optimal dosing interval for vaginal use is determined, the preferred route of misoprostol administration might be oral. (Obstet Gynecol 1998;92: 481–6. © 1998 by The American College of Obstetricians and Gynecologists.)

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Misoprostol (Cytotec; Searle, Oakville, Ontario, Canada), a synthetic prostaglandin (PG) E_1 analogue currently used for treatment of gastric and duodenal ulcers, can initiate uterine contractions. It is marketed in an oral formulation of 100- or 200-μg tablets with a maximum recommended dose of 1600 μg per day.[1] Induction of labor by placing a portion of such a tablet in the vagina has been studied extensively[2–8]; however, few randomized trials[9,10] assessing oral misoprostol for

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induction of labor at term have been published. Our research group compared oral misoprostol to vaginal dinoprostone (PGE_2) and found oral misoprostol to be an effective induction agent with no important adverse maternal or neonatal outcomes.[9] The median medication cost per patient receiving misoprostol was at least 100 times lower than the median medication cost per patient in controls receiving dinoprostone.[8,9]

Despite accumulating evidence of effectiveness and obvious cost advantage, misoprostol is not yet approved for induction of labor at term in most North American health care centers or by a national agency. Some authors have reported that tachysytole[11] might be a frequent occurrence when vaginal misoprostol is used to initiate uterine activity,[5,6,12,13] which has led to concerns about potential increased rates of operative delivery and neonatal asphyxia. Any new induction technique must address these safety concerns.

Substantive maternal and neonatal primary outcomes, such as rates of cesarean birth and birth asphyxia, are relevant when evaluating any induction agent. To test such outcomes using misoprostol would require sample sizes of 3400 and 5030, respectively, because of the infrequency of these events. Before conducting such a large and costly project, it is necessary to determine the most appropriate route of misoprostol administration. For this purpose, we designed a masked randomized trial with time to vaginal birth as the primary outcome measure.

Our primary research question was whether there is a 4-hour difference in the interval to vaginal birth with oral compared with vaginal use of 50 μg of misoprostol administered every 4 hours for induction of labor in women at term with intact membranes. We also determined whether the frequency of excessive uterine activity resulting in abnormal fetal heart rate (FHR) tracings is influenced by route of administration. Other secondary outcomes included neonatal morbidity (as measured by cord blood acid-base analysis and ACOG criteria for birth asphyxia[14]), cesarean birth, maternal gastrointestinal side effects, and patient satisfaction.

Methods

The study was conducted at the Grace General Hospital, St. John's, Newfoundland, Canada, from March 3, 1997 to October 8, 1997. This referral center for perinatal care serves an almost entirely white population of 500,000 and is the site of 2500 of the province's 6000 annual births. Our induction rate is just over 20%, with approximately 520 inductions per year. The research proposal was approved by the Human Investigation Committee of the Faculty of Medicine, Memorial University of Newfoundland, and the hospital.

Patient inclusion criteria were indication for induction, single live fetus, gestation longer than 37 completed weeks, intact membranes, and cephalic presentation. Patients who presented with any one of the following were ineligible: nonreassuring FHR tracing, previous uterine surgery, known hypersensitivity to prostaglandins, age less than 18 years, or contraindication to vaginal birth. All pregnant women who attended prenatal classes were informed of the study and given written information about the protocol. Eligible patients were informed when induction of labor was indicated. At presentation for induction, patients were enrolled in the study by the attending physician, who explained the protocol and potential risks and benefits before obtaining written consent.

Opaque envelopes containing a card indicating group allocation were prepared by an administrative staff member using computer-generated random number tables with randomization in blocks of four. Allocation of each consenting patient to induction method was determined at the time of induction by opening the next sequentially numbered envelope. Study medications and placebos were prepared by a pharmacy technician. For each patient, eight powdered 50-μg doses of misoprostol were placed individually in paper packets and stored in an airtight plastic container. Eight doses of an indistinguishable powdered cellulose placebo were similarly prepared and separately packaged for each patient. Oral or vaginal use was specified on the label.

To conceal appearance and taste, all oral powders were mixed with 30 mL of apple or orange juice according to patient preference. Vaginal powders were suspended in hydroxyethyl gel just before use and delivered to the posterior fornix using a vaginal applicator. After each delivery, the study package was returned to the pharmacy technician to ensure each participant had received the assigned treatment. When a subject required more than eight doses, another identically prepared medication and placebo package was provided. To maintain allocation concealment, research personnel who prepared the envelopes and medications were not involved in any other aspect of the study. The induction method was concealed from all caregivers, participants, and investigators until data analysis was completed.

After enrollment, subjects were examined to determine Bishop score[15] and stratified to either the low (less than 7) or high (7 or more) Bishop score group. Each patient was then randomly assigned to receive either oral misoprostol (50 μg) and vaginal placebo or vaginal misoprostol (50 μg) and oral placebo every 4 hours until the occurrence of one of the following: a contraction frequency of three per 10 minutes, a nonreassuring FHR tracing, spontaneous rupture of membranes, or deliv-

ery. All study inductions were conducted immediately after randomization, on an inpatient basis, to allow continuous electronic FHR and uterine contraction monitoring for at least 1 hour after each dose.

Decisions regarding amniotomy, analgesia, epidural anesthesia, and oxytocin augmentation were made by the attending physician. To assess patient satisfaction, all patients enrolled in the study were asked to complete a modified labor agentry scale questionnaire.[16] Planned treatment of tachysystole and hyperstimulation included change in maternal position to the left lateral decubitus, oxygen administration by nasal prongs, and intravenous ritodrine, as needed. Fetal scalp blood sampling was performed when indicated by nonreassuring FHR graphs. Cord blood samples for arterial and venous acid-base analysis were taken after each delivery.

To determine whether hypertonus, tachysystole, or hyperstimulation were associated with the route of administration of misoprostol, all FHR graphs were reviewed before study induction groups were unmasked. Each of the physician authors (two maternal fetal medicine attending physicians and two senior residents) independently classified monitoring strips using terminology defined by Curtis et al[11] and Wing et al[6] as follows: hypertonus, a contraction lasting more than 90 seconds or more than 120 seconds; tachysystole, a contraction frequency of more than five in a 10-minute period or two consecutive 10-minute periods; hyperstimulation, exaggerated uterine response with late FHR decelerations or fetal tachycardia greater than 160 beats per minute. The code for group assignment was not broken until completion of data analysis.

For the primary outcome, time to vaginal birth, a sample size of 172 was calculated using a two-tailed α = .05, β = .20, Δ = 240 minutes, and σ derived from pooling of results from our[8] vaginal misoprostol cohort (588 minutes) and our previous oral misoprostol[9] intact membrane stratum (524 minutes) (PEPI, Version 2, 1995; Computer Programs for Epidemiologic Analysis, Stone Mountain, GA). Since our previous studies[8,9] had consistent cesarean rates of 12.2% with 99% confidence interval (CI) 8.8, 16.5% we added 20% (34 patients) to allow for anticipated cesarean births in our sample. A sample size of 206 was deemed appropriate to detect the clinically important difference (240 minutes) determined by a survey questionnaire of patients and medical and nursing personnel.

Data were analyzed on an intent-to-treat basis by parametric and nonparametric statistics, using Statistix 4.1 (Analytical Software, Tallahassee, FL). Decision levels and hypotheses to be tested were preset to minimize bias. Hypothesis testing was performed on the primary outcome. Other comparisons were considered hypothesis generating. Statistical significance of the primary outcome measure was assessed using Student's *t*-test and was considered significant at $P < .05$. Rank order nonparametric statistics using the Mann-Whitney U test, when a cesarean birth is a failure to deliver vaginally and ranked longer than any vaginal birth, allowed inclusion of all births in a secondary analysis with median time to vaginal birth as the measure of central tendency. Secondary outcomes were analyzed by parametric and nonparametric statistics, as appropriate.

Continuous variables were examined for normal distribution (Wilk-Shapiro/Rankit Plot) before using parametric statistics.[17] Descriptive statistics were used for demographic baseline data. Baseline data from nonvolunteers were analyzed to assess generalizability. The significance for all secondary and hypothesis-generating analyses was $P < .001$ to account for multiple testing, a conservative approach.

Table 1. Demographic Characteristics

Characteristic	Vaginal misoprostol (n = 102)	Oral misoprostol (n = 104)
Nulliparous	74	69
Maternal age (y)	28.7 (4.9)	27.5 (5.0)
Gestation (d)	284.2 (8.3)	285.4 (7.6)
Gravidity	1.6 (0.8)	1.7 (1.0)
Parity	0.3 (0.6)	0.5 (0.8)
Bishop score less than 7	81	79
Indication for induction		
Post-term	65	69
Hypertension	18	12
Oligohydramnios	8	13
Other	11	10
Birth weight (g)	3645 (566)	3585 (612)

Data given as number or mean (standard deviation).

Table 2. Peripartum Data

Variable	Vaginal (n = 102)	Oral (n = 104)	Relative risk	95% confidence interval
Intrapartum frequency				
Oxytocin use	59	70	0.67	0.38, 1.18
Epidural use	61	65	0.89	0.51, 1.56
No analgesia used	6	10	0.59	0.21, 1.64
Meconium	21	29	0.78	0.41, 1.47
Perineal trauma				
Episiotomy	22	19	1.23	0.62, 2.42
Laceration	54	59	0.98	0.56, 1.69
Third- or fourth-degree laceration	2	0		
Intact perineum	34	29	1.29	0.72, 2.33

Table 3. Labor Intervals to Vaginal Birth

Interval	Vaginal misoprostol	Oral misoprostol	P*
Induction to vaginal birth	846 (385)	1072 (593)	.004
Induction to full dilation	763 (361)	1003 (578)	.002
First stage of labor	342 (204)	365 (223)	.48
Second stage of labor	83 (89)	69 (76)	.26
Third stage of labor	12 (14)	9.9 (8.4)	.21

Data are given in minutes as mean (standard deviation).
* Calculated by Student *t* test.

Results

During the study period, 393 patients presented for induction of labor, of whom 308 were eligible. Seventeen patients refused enrollment because they did not want to be involved in a research protocol and the remaining 85 were not invited to participate because alternate methods of induction, including amniotomy, oxytocin, or dinoprostone, were preferred by their attending physicians.

Of 206 women, there were 104 in the oral group and 102 in the vaginal group. No participant or neonate was lost to follow-up. The mean time (±standard deviation) to vaginal birth with oral misoprostol was 1072 (±593) minutes compared with 846 (±385) minutes with the vaginal protocol, a statistically significant difference ($P = .004$). (The median time to vaginal birth in the oral misoprostol group was 1125 minutes compared with 962 minutes in the vaginal misoprostol group [$P = .38$, Mann-Whitney *U* test].) Maternal preinduction and neonatal demographic data are given in Table 1. Peripartum data are given in Table 2, with relative risk (RR) and 95% CI. There were no significant differences in oxytocin, epidural, or other analgesia use. Data for mean vaginal birth intervals are given in Table 3.

Table 5. Neonatal Outcome

Outcome measure	Vaginal misoprostol	Oral misoprostol	P
ACOG criteria for birth asphyxia			
Apgar at 5 min ≤3	0	0	
Cord pH <7	2	0	.16*
Base deficit >16	2	0	.16*
Mean cord pH	7.28 (0.10)	7.30 (0.09)	.08†
Mean base deficit	5.28 (4.14)	4.44 (3.32)	.13†
Median Apgar at 1 minute	9 (8, 9)	9 (8, 9)	.59‡
Median Apgar at 5 minute	9 (9, 10)	9 (9, 10)	.23‡
Apgar at 1 min <7	17	7	.03§
Apgar at 5 min <7	0	1	.32*

* Fisher exact test.
† Student *t* test: mean (standard deviation).
‡ Mann-Whitney *U* test: median (first and third quartile).
§ χ^2 test.

There was no significant difference in birth route between the two groups ($\chi_3^2 = 2.53$, $P = .47$). With oral misoprostol there were 58 spontaneous vaginal deliveries, 21 vacuum deliveries, nine forceps-assisted deliveries, and 16 cesarean births. With vaginal misoprostol there were 56 spontaneous vaginal deliveries, 15 vacuum deliveries, eight forceps-assisted deliveries, and 23 cesarean births. Nonreassuring FHR tracing was the indication for two cesareans in the oral misoprostol group and six cesareans in the vaginal misoprostol group (RR 2.47, 95% CI 0.49, 12.49).

Fetal heart rate and uterine activity tracing data were

Table 4. Classification of Excessive Uterine Activity

Tracing classificaiton	0 Reviewers classified graph as	1 Reviewers classified graph as	2 Reviewers classified graph as	3 Reviewers classified graph as	4 Reviewers classified graph as	P*
Hypertonic >90 sec						
Oral misoprostol	1	8	15	26	54	.68
Vaginal misoprostol	0	12	11	29	49	
Hypertonic >120 sec						
Oral misoprostol	7	22	24	20	31	.57
Vaginal misoprostol	8	21	22	28	22	
Tachysystole >10 min						
Oral misoprostol	23	14	18	25	23	.21
Vaginal misoprostol	16	15	18	21	31	
Tachysystole >20 min						
Oral misoprostol	52	21	16	10	5	.01
Vaginal misoprostol	41	17	7	11	25	
Hyperstimulation						
Oral misoprostol	84	14	5	1	0	.04
Vaginal misoprostol	70	17	6	4	4	

* Mann-Whitney *U* test.

analyzed using nonparametric statistics based on number of masked physician reviewers making that classification of a given tracing (Table 4). Although there was more frequent 20-minute tachysystole ($P < .01$) and hyperstimulation ($P < .04$) in the vaginal misoprostol group, these results were not statistically significant by our preset level for secondary analyses, but the trend warrants attention. Neonatal outcomes in both groups were similar (Table 5). Umbilical cord arterial and venous blood acid-base analysis was performed on 89 of the 104 participants in the oral misoprostol group (86% of neonates) and 92 of the 102 participants in the vaginal misoprostol group (90% of neonates). Two neonates from the vaginal misoprostol group had cord pH less than 7.00; however, no neonate met the ACOG criteria for birth asphyxia.[14]

A postpartum questionnaire was completed by 90 women in the oral group and 83 in the vaginal group (84% response rate). Analysis of the responses to the 49 questions failed to detect any statistically significant difference in patient satisfaction or overall score. All participants in the study reported positive labor and delivery experiences. None of the participants self-reported adverse gastrointestinal effects on the questionnaire. There was no diarrhea noted in either group, and no difference in occurrence of vomiting (18 in the oral and 19 in the vaginal group, $P = .81$). When given orally, a median of two and a maximum of nine doses were used. Only seven subjects took more than five oral doses. When misoprostol was placed vaginally, a median of two and a maximum of five doses were used. Baseline data from nonvolunteers did not differ significantly from volunteers.

Discussion

Obstetricians routinely use various mechanical methods and pharmacologic agents to induce labor; however, no single approach has been universally successful. Oxytocin is an effective induction agent but it is not optimal for patients with an unripe cervix.[18,19] Administration requires intravenous infusion with continuous monitoring of FHR and uterine contractions. When compared to oxytocin, prostaglandins (dinoprostone) are effective cervical ripening agents, achieving a shorter induction-delivery interval and a lower rate of operative intervention.[20] Oral administration of prostaglandins essentially has been abandoned because of undesirable gastrointestinal effects, which have limited their use to vaginal and intracervical routes.[19] Termination of prostaglandin-related excessive uterine activity remains problematic.[21]

An oral induction agent that is safe, effective, inexpensive, and well-tolerated by patients would be attractive to patients and health care providers. Anticipated benefits include avoidance of intravenous lines in some parturients, less frequent need for vaginal examination, and greater freedom for upright positioning. Ambulation might even facilitate labor progress.[22] Induction agents should mimic spontaneous labor while avoiding excessive uterine activity. When contractions of abnormally high intensity or frequency occur, insufficient recovery resulting in FHR abnormalities could necessitate operative delivery or lead to fetal asphyxia.[11]

Several randomized trials[2-8] comparing vaginal misoprostol to standard therapy found misoprostol to be safe and effective for induction of labor. Sanchez-Ramos and colleagues[12] studied the safety and efficacy of vaginal misoprostol for cervical ripening and labor induction in a meta-analysis of published trials to 1997. Of 16 trials identified, eight met their criteria for inclusion and included a total of 966 patients, 488 of whom received vaginal misoprostol for labor induction. Controls received oxytocin or vaginal dinoprostone. Those who received vaginal misoprostol had a higher incidence of vaginal delivery within 24 hours of application OR 2.64, 95% CI 1.87, 3.71) and a lower cesarean rate (OR 0.67, 95% CI 0.48, 0.93). Use of vaginal misoprostol was associated with a higher incidence of tachysystole (OR 2.70, 95% CI 1.80, 4.04) but not of hyperstimulation (OR 1.91, 95% CI 0.98, 3.73).

Only a few randomized trials assessing oral misoprostol for induction of labor at term have been published.[9,10] Toppozada et al[13] compared vaginal and oral misoprostol for induction of labor in a small randomized trial. Twenty patients assigned to receive 100 μg of vaginal misoprostol were compared to 20 assigned to oral misoprostol. When no response was noted 3 hours after the first 100-μg dose, 200 μg was administered every 3 hours until a maximum dose of 1000 μg was reached. Doubling the dose administered vaginally only occurred once. One subject in the vaginal group and three in the oral group had cesarean deliveries because of failed induction. The authors concluded that vaginal misoprostol resulted in a shorter time to delivery ($P < .005$), but more abnormal FHR patterns and uterine hyperstimulation occurred ($P < .05$).

Zieman et al[23] compared pharmacokinetics of misoprostol (400 μg) administered by vaginal and oral routes to ten nonpregnant and ten pregnant first-trimester volunteers and concluded that significant differences exist. Systemic bioavailability of vaginally administered misoprostol is three times that of misoprostol administered orally. The greater bioavailability of vaginal misoprostol might explain why we observed a shorter time to vaginal birth in the vaginal group. The greater frequency of abnormal FHR patterns observed in this group might be the result of excessive uterine activity because of this greater bioavailability.

Although there is no direct one-to-one relationship

between continuous electronic fetal monitoring and fetal well being, nonreassuring FHR changes associated with excessive uterine activity warrant intervention, either to reduce uterine activity or to deliver the fetus. Because of confusion from varied definitions of excessive uterine activity, Curtis et al[11] recommended a standard terminology. Although it allows for classification of labor graphs, the terminology is arbitrary, particularly with respect to tachysystole and hypertonic contractions.

Despite concerns of possible uterine hyperstimulation, substantive adverse newborn outcomes such as neonatal acidosis, meconium aspiration, and birth asphyxia have been rare and have not differed between misoprostol and control groups.[1–10,12,13] In our study, two neonates in the vaginal misoprostol group had cord blood pH less than 7.00, but no neonatal asphyxia occurred. Among the 39 cesarean births, six of eight done for FHR abnormalities were in the vaginal group. Although these differences are not statistically significant, the question is clinically relevant, making it worthwhile to design a clinical trial to answer this question. The frequency of excessive uterine activity associated with route of administration is a secondary outcome in the present study and did not form a basis for calculation of sample size.

Misoprostol is effective in inducing labor whether it is given orally or vaginally. There is a shorter interval to vaginal birth with vaginal application; however, the more frequent FHR graph abnormalities in this group might be attributable to excessive uterine activity. Oral administration is an appropriate alternative for labor induction with misoprostol, considering fetal safety and the ongoing study of optimal vaginal dosing interval.

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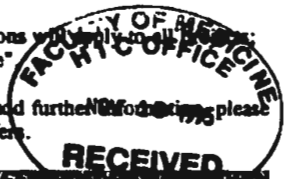
APPENDIX B: HUMAN INVESTIGATION COMMITTEE APPLICATION FORM

MEMORIAL UNIVERSITY OF NEWFOUNDLAND - FACULTY OF MEDICINE

HUMAN INVESTIGATION COMMITTEE - APPLICATION FORM



This form is designed to cover as large a variety of proposals as possible: not all questions will apply to all proposals; however, please consider each question carefully before writing it off as "Not Applicable".

Please type your answers. If the space provided is not adequate and it is necessary to add further information, please submit this in **single spaced typing**, indicating clearly to which question the addition refers.

1. Name of Principal Investigator: *Kelly A.Bennett*

   Mailing Address/Telephone No.: *73 Logy Bay Road, St. John's, NF (739-0329)*

2. Name(s) of Co-Investigator(s): *Dr. David Young*

3. Name of supervisor, if Principal Investigator is a student: *Dr. David Young*

4. Title of investigation: **(PLEASE HI-LIGHT KEY WORDS)**

   Vaginal Misoprostol Versus Oral Misoprostol For Induction Of Labour: A Randomized Controlled Trial

5. What is the proposed starting date? (Must be at least 4 weeks later than date of receipt of this application by the H.I.C. Office.)

   January 1996

6. What is the anticipated date of completion of the study? *January 1997*

7. Please fill in the appropriate information:

Hospital/Community Setting Involved	Involves Patients/ Residents	Involves Records	Involves Facilities	Submitted to Participating Hospital Ethics Committees
Grace General Hosp.	*Yes*	*Yes*	*Yes*	*Yes*
Labour & Delivery				
Unit				

This application may be forwarded to participating institutions if requested.

8. State, briefly, the objectives of the investigation:

The primary objective of this study is to compare the efficacy of misoprostol (a prostaglandin) adminstered orally to misoprostol administered vaginally in patients requiring cervical ripening for the induction of labor. The purpose is to determine if route of administration impacts upon the time of induction to delivery. It is our contention that an oral medication would be desirable to women as it could decrease the number of vaginal examinations they might require through the induction process.

9. What is the scientific background and rationale for the study? What benefits may be anticipated? Have any relevant human or animal studies already been conducted? Please specify. (Attach another sheet of paper, if required.)

Prostaglandins are known to be effective induction agents. Several studies have shown vaginal misoprostol to be safe and effective in cervical ripening and labour induction in patients with intact membranes, including our center's RCT. Misoprostol is about one percent as costly as other agents.

A recent RCT completed at the Grace General Hospital has shown oral misoprostol to be an effective induction agent. No randomized trials have compared oral administration to vaginal administration. This study attempts to clarify whether vaginal or oral administration is the preferred route of delivery.

10. Which of the following are to be employed in the investigation? List only those that are NOT part of normal patient care.

(a) Samples to be taken from subjects: State type of sample, frequency and amount.

No

(b) List the procedures and any tests or substances to be administered to patients: special diets, drugs (state dose and frequency), isotopic tracers, etc.

Group I. *Misoprostol 25 ug PO every two hours until labour established, spontaneous rupture of membranes or delivery.*

Group II. *Misoprostol 25 ug PV every two hours until labour established, SROM or delivery.*

(c) Questionnaires: Attach copy of questionnaire to be used.

Attached.

(d) Is this application for a clinical trial? (X) Yes ( ) No
If yes, what "phase" of the trial does this study represent? What is the design of the trial (e.g. open, double blind, etc.)?

Open.
Phase 3.
Randomized control trial

11. Does the study involve the use of any radioactive material? ( ) Yes (X) No
If yes, specify.

A positive response to this question will be communicated to the Radiation Control Committee.

12. Give a brief description of the design of the study. (Please also attach one copy of a protocol if available.) This should include details of subject selection, sample size calculation (if applicable), outcome measurement and details of analysis.

The investigators intend to conduct a randomized controlled trial comparing oral and vaginal misoprostol as induction agents. In order to account for the effect of parity on induction of labour randomization will be stratified. Two groups will be established, nulliparous patients and multiparous patients. Randomization to oral and vaginal misoprostol would be done by using sequentially numbered opaque envelopes with study allocation. These would be prepared by administrative staff not involved in patient care using random number tables with randomization in blocks of four. Group assignment would be concealed from care givers until the time of induction. All study patients will be admitted to hospital and induction will be carried out on an inpatient basis with continuous fetal monitoring for one hour after administration of the prostaglandin and during established labour.

See attached for continuation.

13. Number of subjects: Will pregnant women be excluded? State how subjects will be selected.

780 subjects will be recruited from general practicioners and obstetrical practices in St. John's. Patients will be eligible if they present with an indication for induction of labor, a single fetus, cephalic presentation and intact membranes. There must be no contrainduction to vaginal birth.

14. Number of controls: State how they will be selected.

Exclusion criteria will be: nonreassuring fetal heart tracing, prior uterine surgery, documented hypersensitivity to misoprostol or other prostaglandins or contraindication to vaginal birth.

15. What (a) risks, (b) discomforts or (c) inconveniences are involved?

(1) Possible gastrointestinal side effects associated with prostaglandin include: nausea, vomiting, diarrhea. (2) A rare complication of prostaglandin use is uterine hyperstimulation. A Medical Protocol for addressing this situation is established.

16. Are there any immediate benefits arising out of the study for the subjects? (Specify)

Fewer pelvic examinations might ultimately need to be preformed. Data from a study done at our insitution revealed a statistical and clinically significant reduction of over three hours ($p=0.018$) in time from induction to vaginal birth with vaginal misoprostol administered 50 ug every four hours PV.

17. What steps will be taken to preserve confidentiality?

The investigators listed will be the only people to handle charts and health records. No patient identifying information will be released for publication or presentation.

18. Explain procedure for obtaining consent.

Who will make the initial contact with the subject? *Attending Physician*

Who will obtain the consent of the subject? *Investigators listed, obs/gyn residents/research nurse (if funding support obtained)*

19. Will subjects include minors ( ) Yes (X) No

emancipated minors only

mentally incompetent persons ( ) Yes (X) No

legally incompetent persons ( ) Yes (X) No

If so, what steps will be taken to protect their rights?

20. What mechanism will there be for debriefing or feedback to subjects? *A questionnaire will be given to all participants in order to obtain feedback. A personel interview of all participants will be conducted by the principle investigator following delivery.*

21. (a) Will volunteers receive reimbursement for expenses ( ) Yes (X) No

time lost from work ( ) Yes (X) No

payment for participation in the study? ( ) Yes (X) No

** Please specify on separate sheet according to Guidelines for the Remuneration of Research Subjects.

(b) Will there be any third party remuneration for referral of patients? ( ) Yes (X) No

** Please specify on separate sheet according to Guidelines for Payment of Finders' Fees.

** AVAILABLE IN THE OFFICE OF RESEARCH & GRADUATE STUDIES (MEDICINE)

22. Please enclose a copy of the budget for this study, including an indication of source of funding.

Will the budget be administered through the University Finance Office? ( ) Yes (X) No
If no, specify. *If research funding obtained it would be administer through the University.*

Will the investigator accrue any benefits by virtue of participation in this study? ( ) Yes (X) No

23. Is this part of a multi-centre study? ( ) Yes (X) No

24. Will data become the exclusive property of a pharmaceutical company or other outside agency? If yes, please elaborate. ( ) Yes (X) No

25. It is the responsibility of the investigator to ensure that permission is obtained from clinicians, departments, institutions or communities whose patients/residents will be involved in the study. Have the appropriate contacts been made?

Yes

26. Have you read "Guidelines on Research Involving Human Subjects" (MRC. 1987) (X) Yes ( ) No

Date of submission: *November 15, 1995*

Signature of principal investigator: *Kelly Bennett* Kelly Bennett

Signature of supervisor, in case of student application: Donald Young

Revised 1990/10

Memorial
University of Newfoundland

Office of Research and Graduate Studies (Medicine)
Faculty of Medicine
The Health Sciences Centre

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1997 03 13

Reference #95.150

Dr. Kelly Bennett
Department of Obstetrics/Gynecology
Grace General Hospital

Dear Dr. Bennett:

Thank you for taking the time to complete the annual update form for the research study entitled **"Vaginal Misoprostal Versus Oral Misoprostal for Induction of Labor: A Randomized Controlled Trial"**.

At a meeting held on **February 27, 1997**, the Human Investigation Committee granted approval of this study until **February 1998** at which time you will be contacted for a further update.

Sincerely,

H.B. Younghusband, PhD
Chairman
Human Investigation Committee

HBY\jglo

cc: Dr. K.M.W. Keough, Vice-President (Research)

St. John's, NF, Canada A1B 3V6 • Tel.: (709) 737-6762 • Fax: (709) 737-5033 • email: rgs@morgan.ucs.mun.ca

APPENDIX C: DATA COLLECTION FORMS

Group	
Chart #	
Age	
Gravida, Para	
Gestation (days)	
Bishop - Position	
- Consistence	
- Effacement	
- Dilation	
- Station	
# Doses of Narcotic	
Epidural	
PG # of Doses	
Mg. Miso - Vag.	
Mg. Miso. Oral	
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 Diarrhea**

QUESTIONNAIRE SENT _____ YES _____ NO

R.O.M. (Time)	
Meconium:	Yes No
1st Stage (mins.)	
2nd Stage (mins.)	
Induction to delivery (mins.)	
Induction to fully (mins.)	
Stage III	
Apgar 1	
Apgar 5	
Cord Ph	
Cord B.E.	
Gender	
Weight	
# Pelvic Exams	

INITIAL BISHOP SCORE - PLEASE CIRCLE

Parameters	0	1	2	3
Cervical Position	Posterior	Mid	Anterior	_
Cervical Consistency	Firm	Medium	Soft	_
Cervical Effacement (%)	0-30	40-50	60-70	>80
Cervical Dilatation (cm)	0	1-2	3-4	>5
Station of Fetal Head	-3	-2	-1/0	+1

Total Score =

Time and date:

Assessment by:

Prostaglandin	Dosage	Time	Date
1			
2			
3			
4			
5			
6			
7			
8			

Oxytocin:

Time Started:

Biship Score:

Dose:

Gravidity:

Parity:

Gestational Age:

Time of Delivery:

APPENDIX D: POSTPARTUM MISOPROSTOL QUESTIONNAIRE

Applicant's Name: Kelly Angela Bennett

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 labor 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 labor 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 labor and delivery.	1 2 3 4 5 6 7 8 9 10
4. Some unnecessary interventions were carried out on mother or baby during labor and delivery.	1 2 3 4 5 6 7 8 9 10
5. Our wishes were always respected during labor and delivery.	1 2 3 4 5 6 7 8 9 10
6. I feel happy about this labor and delivery experience.	1 2 3 4 5 6 7 8 9 10
7. I felt in control of what happened during labor 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 labor and delivery	1 2 3 4 5 6 7 8 9 10
9. If the staff had been more capable during labor 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 labor 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 labor and delivery.	1 2 3 4 5 6 7 8 9 10
12. The doctor gave all the attention needed during labor 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 labor and delivery.	1 2 3 4 5 6 7 8 9 10
14. Sufficient attention was paid to comfort during labor and delivery.	1 2 3 4 5 6 7 8 9 10
15. I would have liked the management of labor and delivery to have been done differently.	1 2 3 4 5 6 7 8 9 10

Applicant's Name: Kelly Angela Bennett

16. There was too much equipment used during labor and delivery.	1 2 3 4 5 6 7 8 9 10
17. The staff were sometimes rude to me during labor and delivery.	1 2 3 4 5 6 7 8 9 10
18. There were too many staff or students involved in the labor 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 labor 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 restriction on mothers walking around during labor.	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 deliver 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 labor.	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 labor.	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

Applicant's Name: Kelly Angela Bennett

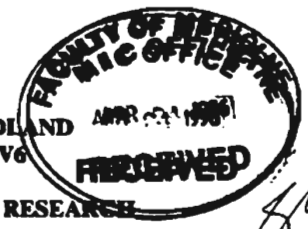
35. Recovery time in labor and delivery was too rushed.	1 2 3 4 5 6 7 8 9 10
36. The nurse made the labor and delivery a better experience.	1 2 3 4 5 6 7 8 9 10
37. I wish all doctors were as good as ours.	1 2 3 4 5 6 7 8 9 10
38. The doctor made the labor and delivery a better experience.	1 2 3 4 5 6 7 8 9 10
39. I did not experience diarrhea during my induction. labor and delivery.	1 2 3 4 5 6 7 8 9 10
40. I did not experience stomach cramps during my induction. labor and delivery.	1 2 3 4 5 6 7 8 9 10

ADDITIONAL COMMENTS:

APPENDIX E: CONSENT FORM

all editorial changes made. 8 April '96. 26 April '96.

FINAL



FACULTY OF MEDICINE
MEMORIAL UNIVERSITY OF NEWFOUNDLAND
ST. JOHN'S, NEWFOUNDLAND A1B3V6

CONSENT TO PARTICIPATE IN BIO-MEDICAL RESEARCH

Title: Double Blind Placebo Controlled Randomised Trial Comparing Oral Versus Vaginal Misoprostol For Labour Induction.

Investigators: Dr. K. Bennett and Dr. D. Young

You are being asked to participate in a research study. Participation in the study is entirely voluntary. You may decide not to participate or may 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 during the study at all times should you have any problems or questions about the study.

Description and Background Information:

You understand you have been scheduled for induction of labour. You are aware that prostaglandins, although primarily used as cervical ripening agents, also stimulate labour. These medications can be administered either by mouth or vaginally.

Misoprostol is a prostaglandin used for the treatment of stomach ulcers. Recent research has shown that misoprostol placed vaginally effectively induces labour. Our own research has demonstrated that misoprostol by mouth is no less effective or safe than usual labour induction. This trial will attempt to decide if misoprostol by mouth can be used as effectively as vaginal misoprostol.

Study Design:

If you choose to enter this study you will be randomized (chosen as if by flipping a coin) into one of two groups. All patients will receive a pill by mouth and a vaginal preparation. One of these preparations will contain misoprostol, the other preparation will not contain any medications. Every patient will receive an active medication either by mouth or vaginally. Neither patients nor investigators will know group assignment. There will be no additional examinations or blood tests. After delivery your chart will be reviewed by the research team for information regarding your delivery and baby. You understand that you will remain under the care of your physician who will manage your labour/delivery as deemed necessary. Your participation is voluntary.

You may choose to withdraw from study at any time. Prior to discharge we will be asking you to complete a brief questionnaire on the satisfaction of care during your stay in hospital and throughout the labour and delivery.

Alternative Treatments:

The alternative should you choose not to enter the study, would be induction via prostaglandin containing cream given per vagina.

Voluntary Participation:

You have discussed the information provided with your physician and he/she has answered any questions about your care.

Confidentiality/Access to Medical Records:

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

Liability Statement:

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

(Signature of Participant)	**(Date)**
(Signature of Witness)	**(Date)**
(Signature of Investigator)	**(Date)**

File Copy
Sent April 30.96
B.

Memorial
University of Newfoundland

Human Investigation Committee
Research and Graduate Studies
Faculty of Medicine
The Health Sciences Centre

29 April 1996

Reference #95.159

Dr. Kelly Bennett
c/o Dr. David Young
Obstetrics & Gynecology
Grace General Hospital

Dear Dr. Bennett:

This will acknowledge receipt of your revised consent form for the research study entitled **"Double-Blind, Placebo-Controlled, Randomized Trial Comparing Oral Versus Vaginal Misoprostol For Labour Induction"**.

I have reviewed the revised consent form and find it to be satisfactory. We will keep a copy in the HIC Office.

Yours sincerely,

H.B. Younghusband, PhD
Chairman
Human Investigation Committee

cc: Dr. K.M.W. Keough, Vice-President (Research)
Dr. Maureen Dunn, Chairperson, Ethics Committee, Grace Hospital
Ms. Denise Dunn, c/o Medical Director's Office, Grace Hospital
Dr. E. Parsons, Medical Director, H.S.C.

St. John's, Newfoundland, Canada A1B 3V6 • Tel.: (709) 737-6974 • Fax: (709) 737-5033

APPENDIX F: MEDICAL RESEARCH COUNCIL GRANT APPLICATION

Name of principal applicant and amount requested (1st year) / Nom du candidat principal et somme demandée (1er année)

Young, David $ 81,522

A- Information Page (For MRC Office Use Only) / Page de renseignements (à l'usage du Bureau du CRM seulement)

Surname, given Names / Nom, prénoms	Year of birth / Année de naissance	Competition Date / Date du concours
Young, David	1947	03/01/97
Crane, Joan	1965	

B- Classification Code: / Code de classification: 17 PREGNANCY/BIRTH

C- Area of Research / Domaine de recherche REPR REPRODUCTION/PREGNANCY

D- Descriptors: In your own words, select a few general terms which best describe your research. See guidelines for an example. / Descripteurs: Décrire votre recherche en quelques termes généraux. Voir l'exemple dans les marches à suivre

MISOPROSTOL
LABOUR INDUCTION

E- Suggested Grant Committees / Comités de subvention suggérés

Clinical Investigation C

Clinical Trials C

F- Suggested External Referee(s) / Évaluateur(s) de l'extérieur suggéré(s)

Names / Addresses / Telephone No. / Noms / adresses / Nos de téléphone	Areas of Expertise / Domaines de compétences
1. Dr. Mary Hannah Associate Professor Faculty of Medicine University of Toronto Dept. of Obs/Gyn 76 Grenville Street Toronto, Ont. M5S 1B2 (416) 323-7317	Perinatal Clinical Trials Maternal Fetal Medicine
2. Dr. Jerome Dansereau Associate Professor Faculty of Medicine University of British Columbia B.C. Women's Hospital 1T62-4500 Oak St. Vancouver, B.C. V6H 3N1 (604) 875-2424	Maternal Fetal Medicine
3. Dr. Greg Ryan Assistant Professor Dept. of Obs/Gyn University of Toronto Mount Sinai Hospital 775-600 University Ave. Toronto, Ont. M5G 1X5 (416) 586-8415	Maternal Fetal Medicine
4. Dr. Renato Natale Professor Dept. of Obs/Gyn University of Western Ontario St. Joseph's Health Centre PO Box 5777, Stn Cte CSC London, Ont. N6A 4V2 (519) 646-6091	Maternal Fetal Medicine

G- If necessary, indicate those referees to whom you would prefer that your application NOT be sent. (Provide addresses) / S'il y a lieu, indiquer les noms des évaluateurs auxquels vous préférez que votre demande NE soit PAS envoyée. (Indiquer leurs adresses)

H- Collaborators (other than co-applicants) & Institution / Collaborateurs (en plus des co-candidats) et établissement

Dr. Kelly Bennett, Resident V, Dept. of Ob/Gyn., Memorial University of Newfoundland

Dr. Rory Windrim, Professor, Dept. of Ob/Gyn., Memorial University of Newfoundland

Dr. Kim Butt, Resident IV, Dept. of Ob/Gyn., Memorial University of Newfoundland

I- Give the name and address of a scientist in your field you would like to see on a future MRC committee. Include his/her area of expertise and proposed committee. / Nom d'un scientifique dans votre domaine de recherche que vous souhaiteriez voir faire partie d'un comité d'évaluation du CRM à l'avenir. Indiquer son champ d'expertise et le comité proposé.

Medical Research Council of Canada / Conseil de recherches médicales du Canada

OPERATING GRANT APPLICATION / **DEMANDE DE SUBVENTION DE FONCTIONNEMENT**

Applicant(s): / Candidat(e):	Position / Poste	Department / Département	College/Faculty/School / Collège/Faculté/École
Young, David	Prof & Chair	Obs and Gyn 40	Medicine 101
Crane, Joan	Asst Prof	Obs and Gyn 40	Medicine 101

Institution / Établissement		This grant, if awarded, should be paid through: / La subvention, si elle est accordée, devra être versée par l'intermédiaire de:	
Memorial University of Newfoundland	CJAA	Memorial University of Newfoundland	CJAA

Title of research / Titre de la recherche: Induction of Labour with Oral Misoprostol.

Category of Operating Grant applied for: / Catégorie de subvention de fonctionnement demandée:

New ◉ Nouvelle

Renewal ○ Renouvellement

If renewal, specify MRC Grant # / S'il s'agit d'une demande de renouvellement, indiquer le no de subvention du CRM:

Amount requested in first full year / Somme demandée pour la première année complète

Operating Base	$ 81,522	Base de fonctionnement
Equipment		Appareils
Total	$ 81,522	Total

Period of support requested: / Durée de l'aide demandée

◉ 1 ○ 2 ○ 3 ○ 5 Years / Années

Indicate if proposal involves: / Indiquer si le projet comporte:	Y	N	N
	Yes / Oui		Form / Formulaire: Attached Ci-joint / To follow A suivre
Human experimentation / des expériences sur des humains	☒		☒ / ☐
Animal experimentation / des expériences sur des animaux	☐		☐ / ☐
A requirement for containment / des exigences de confinement	☐		☐ / ☐

And if so, what level / Préciser le niveau, le cas échéant

MRC Studentship award voucher requested / Parrainage de stagiaire de recherche du CRM demandé ☐

Mailing address of principal applicant / Adresse postale du candidat principal

Dr. David Young
Grace General Hospital
241 LeMarchant Road
St. John's, NF
A1E 1P9

Telephone Number	Numéro de téléphone	709-778-6157
Fax	Télécopieur	709-753-1862
E-mail	Courrier électronique	obgynmun@public.nfld.com

Language in which the research proposal is written: / Le projet de recherche est rédigé en: English ◉ Français ○

I wish to receive correspondence in: / Je désire recevoir la correspondance en: English ◉ Français ○

The undersigned agree that the general conditions governing the award of a research grant, as set out in the MRC Grants and Awards Guide, apply to any grant made pursuant to this application and are hereby accepted by the applicant(s) and the institution which employs the applicant(s):

Les soussignés conviennent que les conditions générales régissant l'octroi d'une subvention de recherche, telles qu'énoncées dans le Guide de subventions et bourses du CRM, s'appliquent à toute subvention accordée à la suite de la présente demande, et sont par la présente acceptées par le (ou les) candidat(s) et l'établissement qui emploie le (ou les) candidat(s).

Signatures: Applicant(s)/Candidat(e)	President or Principal / Recteur	Head of Department / Directeur du département	Dean of Faculty / Doyen de la faculté
David Young	Barbara Cox	David Young	Vivian M. Skanes
J Crane			
	Name / Nom: Barbara Cox	Name / Nom:	Name / Nom: VIVIAN M SKANES
Date: Feb 28/97	Date: Feb. 28, 1997	Date: Feb 28/97	Date: Feb. 28, 1997

MRC/CRM 11e (ver 1.1)

PROTECTED WHEN COMPLETED

-1-

Office of Research

Name of principal applicant and amount requested (1st year) / Nom du candidat principal et somme demandée (1er année)

Young, David $ 81,522

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Surname, given Names / Nom, prénoms	Year of birth / Année de naissance	Competition Date / Date du concours
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PREGNANCY/BIRTH

C- Area of Research / Domaine de recherche REPR

REPRODUCTION/PREGNANCY

D- Descriptors: In your own words, select a few general terms which best describe your research. See guidelines for an example. / Descripteurs: Décrivez votre recherche en quelques termes généraux. Voir l'exemple dans les marches à suivre

MISOPROSTOL
LABOUR INDUCTION

E- Suggested Grant Committee / Comité de subvention suggérés

Clinical Investigation C

Clinical Trials C

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3. Dr. Greg Ryan Assistant Professor Dept. of Obs/Gyn University of Toronto	Mount Sinai Hospital 775-600 University Ave. Toronto, Ont. M5G 1X5 (416) 586-8415	Maternal Fetal Medicine
4. Dr. Renato Natale Professor Dept. of Obs/Gyn University of Western Ontario	St. Joseph's Health Centre PO Box 5777, Stn Cte CSC London, Ont. N6A 4V2 (519) 646-6091	Maternal Fetal Medicine

G- If necessary, indicate those referees to whom you would prefer that your application NOT be sent. (Provide addresses) / S'il y a lieu, indiquer les noms des évaluateurs auxquels vous préférez que votre demande NE soit PAS envoyée. (Indiquer leurs adresses)

H- Collaborators (other than co-applicants) & Institution / Collaborateurs (en plus des co-candidats) et établissement

Dr. Kelly Bennett, Resident V, Dept. of Ob/Gyn., Memorial University of Newfoundland

Dr. Rory Windrim, Professor, Dept. of Ob/Gyn., Memorial University of Newfoundland

Dr. Kim Butt, Resident IV, Dept. of Ob/Gyn., Memorial University of Newfoundland

I- Give the name and address of a scientist in your field you would like to see on a future MRC committee. Include his/her area of expertise and proposed committee. / Nom d'un scientifique dans votre domaine de recherche que vous souhaiteriez voir faire partie d'un comité d'évaluation du CRM à l'avenir. Indiquer son champ d'expertise et le comité proposé.

Name of principal applicant and amount requested (1st year) / Nom du candidat principal et somme demandée (1er année)

Young, David $ 81,522

Applicant(s) / Candidat(s)	Institution where the research is done / Établissement où s'effectue la recherche
Young, David Crane, Joan	Memorial University of Newfoundland
	Tel.No of principal investigator / No de tél. du chercheur principal 709-778-6157
	Fax / Télécopieur 709-753-1862

Title of the research (one line only) / Titre de la recherche (une ligne seulement)

Induction of Labour with Misoprostol.

Abstract
(Suitable for preparation of a Press Release)

Suitable for non-scientific audience. Please summarize in general terms why the research is important, what disease may be impacted and what results are expected.

Résumé
(Formulé de façon à permettre la rédaction d'un communiqué de presse)

A l'intention du lecteur non scientifique. Résumer en termes généraux pourquoi la recherche est importante, les maladies qui peuvent être affectées et les résultats qu'on en attend.

Labor induction is a frequent obstetric intervention (≈20%). Prostaglandins (PGs) are effective agents, but gastrointestional (GI) intolerance has limited use to non-oral routes. The traditional oxytocin "drip" requires intravenous (IV) use and discourages mobility. Misoprostol, a modified PG, is marketed for oral treatment of GI disorders, but initiates uterine contractions, an undesirable GI side effect. Recently, there has been a research "boom" on misoprostol in pregnancy to effectively and safely empty the uterus, by using this "side effect". Almost all this research has been per vagina. We are one of two or three groups worldwide who have published on oral misoprostol to induce term labor to study effectiveness, GI tolerance, and safety for mother/ baby. Cost per patient has been less than one hundredth that of other PGs, even less than IV oxytocin.

This project will advance our research for term labor induction with two randomized controlled trials (RCTs): one comparing oral to vaginal misoprostol with amniotic membranes intact, the other oral misoprostol to IV oxytocin with prelabor ruptured membranes. We will assess time to vaginal birth, mother/baby well-being, mother's satisfaction, and any GI effects. With further research we hope to find misoprostol a safe cost effective oral induction agent.

Please check if you agree to the release of the following to a publicly accessible database:

Cocher les cases appropriées si vous êtes d'accord à ce que les renseignements suivants puissent être entrés dans des bases de données disponibles au public.

- the information on this page ☒ - les renseignements donnés sur cette page
- your project summary (page 10) ☒ - le résumé de votre projet de recherch à la page 10 du formulaire

Place & Date / Lieu et Date: St. John's, Nfld Feb 28/97

Signature: David Young

Name of principal applicant and amount requested (1st year) / Nom du candidat principal et somme demandée (1er année)

Young, David $ 81,522

Financial assistance requested for the first 12-month period / Aide financière demandée pour la première période de 12 mois

1. RESEARCH STAFF (excluding trainees)
PERSONNEL DE RECHERCHE (sauf les stagiaires)

	No. nº	Salary Salaire	Benefits Avantages sociaux	Total $	TOTALS / TOTAUX
Research Assistants / Assistants de recherche	1	$ 39,872	$ 9,968	$ 49,840	
Technicians / Techniciens	1	$ 22,600	$ 5,650	$ 28,250	
Other Personnel (specify) / Autre personnel (préciser)				$	
TOTAL PERSONNEL / SOMME TOTALE POUR LE PERSONNEL DE RECHERCHE					$ 78,090

2. RESEARCH TRAINEES
STAGIAIRES DE RECHERCHE

	No. nº	Amount Somme	
Postdoctoral Fellows (post PhD, MD etc.) / Stagiaires diplômés (post PhD, MD etc.)			
Graduate Students / Étudiants des cycles supérieurs		$	
Summer Students / Étudiants d'été		$	
TOTAL TRAINEES / TOTAL STAGIAIRES			$

3. MATERIALS, SUPPLIES, TRAVEL
MATÉRIEL, FOURNITURES, VOYAGES

Animals / Animaux		
Expendables / Articles de consommation courante	$ 585	
Services	$ 88	
Other (including travel) / Autres (y compris voyages)	$ 2,759	
TOTAL		$ 3,432

TOTAL OPERATING BASE
TOTAL DES FRAIS DE BASE DE LA SUBVENTION $ 81,522

4. EQUIPMENT / APPAREILS

TOTAL REQUEST / FIRST FULL YEAR
DEMANDE TOTALE / PREMIÈRE ANNÉE COMPLÈTE $ 81,522

Each budget item must include the applicable provincial and federal taxes. Federal taxes should be calculated using the following rebate percentages: universities 2.5%, hospitals 1.2%, other institutions 3.5%.

Chaque poste du budget doit inclure toutes les taxes provinciales et fédérales applicables. Les taxes fédérales doivent être calculées en tenant compte des taux de réduction suivants: universités, 2.5%; hôpitaux, 1.2%; et autres établissements, 3.5%.

-5-

Name of principal applicant and amount requested (1st year) / Nom du candidat principal et somme demandée (1er année)

Young, David $ 81,522

Human Resources

A. For each applicant indicate the hours per week to be spent on the proposed project.

Ressources humaines

B. Pour chaque candidat, indiquer le nombre d'heures par semaine qu'il consacrera au projet proposé.

Young, David	10 hrs/wk
Crane, Joan	20 hrs/wk

B. Employment history for the past 12 months of personnel to be employed on grant

For all personnel, list their current employment (at the time of application), actual salary rate($/annum, excluding benefits) and present source of funding.

Emplois au cours des douze derniers mois du personnel qui sera engagé grâce à cette subvention

Pour tout le personnel, indiquer l'emploi au moment de la demande, le salaire réel ($ par année, sans compter les avantages sociaux), et la source de financement.

Name / Nom	Employment / Emploi	Salary / Salaire $	Source of funding / Source de financement
Recruiting research assistant.			

C. Details of financial assistance required

Budget Justification

PERSONNEL Research Assistant

Position: Research Assistant
Credentials: Bachelor of Nursing, Level II pay scale (source: Collective Agreement NLNU, NHNHA and Treasury Board)
Department: Obstetrics & Gynecology, Faculty of Medicine, MUN

General Accountability:
This is a professional position providing research support to the office of Obstetrics & Gynecology. The position maintains a liaison with officials of the Faculty of Medicine, Nursing, Pharmacy and Hospital Administration. General supervision is provided by research applicant and Discipline Chair.

Young, David	$ 81,522

Duties:

- Function as full-time project co-ordinator.
- Collect and collate demographic, intrapartum and outcome data.
- Input data to computer.
- Inform potential participants about research project at prenatal classes.
- Participate in informed consent process.
- Administer postpartum satisfaction questionnaire.
- Educate nursing and medical staff such as family physicians, housestaff, and caseroom nurses, regarding study protocol.
- Conduct literature searches on related topics.
- Prepare presentations ie. slides.

Salaries:

Nursing (screening & monitoring), overtime, standby, beeper, mileage, annual leave	$ 39,872.10
Benefits (25% gross salary - CPP, PSPP, UIC, WCC, etc)	9,968.00

Pharmacy Technician

Position:	Pharmacy Technician I
Credentials:	Pharmacy Technician Certificate, Level III pay scale (source: Collective Agreement NAPE HS, NHNHA and Treasury Board).
Department:	Pharmacy, School of Pharmacy, MUN & Health Care Corporation (HCC) of St. John's

General Accountability:

This is a professional position providing research support to the office of Obstetrics & Gynecology. The position maintains a liaison with officials of the Faculty of Pharmacy and Hospital Administration. General supervision is provided by research applicant, Obstetrics & Gynecology Chair, and Director of Pharmacy, HCC.

Duties:

- Function as full-time pharmacy project manager.
- Prepare active drug and placebo as per randomization schedule.
- Maintain records of patient assignment.
- Act as pharmacy liaison with Grace Hospital site, HCC.

Salaries:

Overtime, standby, beeper, mileage, annual leave	22,600.00
Benefits (25% gross salary - CPP, PSPP, UIC, WCC, etc)	5,650.00
Total Salaries	**78,090.10**

Young, David		$ 81,522

EXPENDABLE

	Estimated cost of postage.	
	Total prior to taxes	50.00
	HST (10.31%)	5.16
	Total postage	**55.16**
	Estimated cost of phone/fax ($40/month).	
	$40.00/month x 12 months	480.00
	HST (10.31%)	49.49
	total phone/fax	**529.49**
SERVICES	**Estimated cost of photocopying.**	
	$0.02/copy x 4,000 copies	80.00
	HST (10.31%)	8.25
	total photocopying	**88.25**

OTHER EXPENSES

Material and Supplies

	Estimated cost of misoprostol (RCT I).	
	$0.77/patient x 206 patients	158.62
	HST (10.31%)	16.35
	total misoprostol (RCT I)	**174.97**
	Estimated cost of placebo (RCT I).	
	$1.00/patient x 206 patients	206.00
	HST (10.31%)	21.24
	total placebo (RCT I)	**227.24**
	Estimated cost of misoprostol (RCT II).	
	$0.77/patient x 54 patients	41.58
	HST (10.31%)	4.29
	total misoprostol (RCT II)	**45.87**
	Estimated cost of oxytocin (RCT II).	
	$5.22/patient x 54 patients	281.88
	HST (10.31%)	29.06
	total oxytocin (RCT II)	**310.94**
Travel	**Estimated cost for travel for presentation of results and exploring future related research opportunities.**	**2,000.00**
TOTAL EXPENSES		**$ 81,522.02**

Name of principal applicant, institution, and amount requested (1st year) / Nom du candidat principal, établissement, et somme demandée (1re année)

Young, David $ 81,522

Response to previous reviews

Applicants may respond here to reviews on a previous grant application. One additional page may be added.

Commentaires sur les évaluations antérieures

Les candidats peuvent commenter les évaluations d'une demande antérieure. Une page additionnelle peut être ajoutée.

Summary of Discussion

The committee was concerned that misoprostol was not being compared to current standard of care, cervical prostaglandin (PG) with or without IV oxytocin, and that though labor duration was an outcome of interest, safety should be the preeminent outcome.

As is stated in our research proposal, we agree that substantive maternal (e.g. Caesareans) and newborn (e.g. birth asphyxia) are the preferred primary outcome measures, however, the sample sizes needed to appropriately evaluate clinically important changes in these (see RATIONALE page 12.6) would require 3400 and 5030 subjects respectively. Such a clinical trial would need to be multicenter and, therefore, costly. Before beginning a multicenter RCT, the most appropriate misoprostol intervention needs to be defined. Oral misoprostol would offer a new approach that would appeal to many patients and caregivers. The RCTs we propose here are to evaluate an oral misoprostol protocol in labor induction against vaginal misoprostol with membranes intact (RCT I) and intravenous oxytocin with prelabor-ruptured membranes (RCT II). We feel our publications [14,21] have shown vaginal misoprostol as cost-effective compared with a cervical PG/IV oxytocin protocol and oral misoprostol no less. If the proposed oral misoprostol RCTs support existing evidence, then a multicenter RCT of sufficient sample size would be appropriate, with a primary outcome such as Caesarean or birth asphyxia, and versus the current standard of care.

Reviewer #1 "Dated December 9, 1996"

Our proposal has been extensively revised (RCT I and RCT II), and we believe is better organized and not repetitively presented. The demonstration of a cost-effective and safe oral induction agent is clinically relevant. The other two reviewers support this. Peer reviewers for our oral misoprostol publication [21], have suggested that this may lead a change in standard of care in North America, after further evidence.

Oral misoprostol is likely to be less costly even than IV oxytocin induction, where our costs for IV line, tubing, electrolyte solution and oxytocin average $5.22 per patient.

The Canadian manufacturer of misoprostol (Searle Canada, Oakville, Ontario) has not been interested in support of research in labor induction or pregnancy termination. This relates to medicolegal liabilities inherent to research in pregnancy, and marketing liabilities of being associated with a potential "abortion" drug. Even if misoprostol became the ideal pharmacological induction agent and the first line approach, the market size and additional generated revenue would be small, compared to the present safe and secure GI market. Unless the company adopts a "for the good of women" humanitarian attitude, it will never be proactive in this area of research and never seek Health Protection Branch approval for investigation of this new indication. Our research has been approved by our university and hospital human investigation and ethics committees, and subjects are fully informed. With further research evidence we would seek such HPB approval, in deference to the manufacturer. [There is a rumour that the company may begin marketing misoprostol only in combination with a nonsteroidal anti-inflammatory agent in a single pill (ARTHROTEC), which would eliminate use in pregnancy.]

Young, David	$ 81,522

A two-tailed sample size calculation was used because effect may be in either direction. Excessive uterine activity variables will be collected, as well as substantive newborn outcomes. Oxytocin use in our study and control groups have been specified.

In the past year we have been invited to present our research at national (SOGC) and regional meetings in Canada (Atlantic and Ontario), and at several tertiary centers - Calgary, Halifax, Toronto and Baltimore. Research with misoprostol in obstetrics and gynaecology in Canada is underway in Vancouver and Toronto. I hope this would persuade this reviewer of the general interest in the Canadian obstetrical community regarding misoprostol.

Reviewer #2 "Review of Protocol by Young D. 9609 CT - 34568 - CT B"

This review was quite encouraging to us, and made a number of beneficial suggestions. The reviewer felt that oral misoprostol is "a potentially important addition", and that "misoprostol may become the treatment of choice" for induction of labor. Our difficulties with obtaining funding from the manufacturer and through MRC/PMAC were understood.

Concern regarding brevity of the research plan, clarity of inclusion criteria, and stratification variables have all been addressed. We have not specified a maximum Bishop score, however, as we are exploring misoprostol use for the full spectrum of cervical "ripeness".

We have clarified how side affects will be assessed, by caregivers and subjects, and referenced our satisfaction questionnaire.

Because, following revision, the project will be completed within one year, we have not established an external Safety Monitoring Committee, however, any instance of neonatal asphyxia will be brought to attention of the study team within 24 hours of its occurrence, for ongoing monitoring.

The reviewer has suggested addition of a trials design expert to our team. Dr. Joan Crane is now added as a co-principal investigator. She is a maternal fetal medicine subspeciality graduate who has now joined our faculty and is at present completing her M.Sc thesis in clinical epidemiology at Dalhousie. The two collaborating senior residents, Drs. Kimberly Butt and Kelly Bennett are enrolled in the clinical epidemiology M.Sc program at Memorial University of Newfoundland. The resources of the Clinical Research Group in Clinical Epidemiology at MUN are available to us. The principal investigator has an M.Sc in Design, Measurement, and Evaluation from McMaster University, Department of Clinical Epidemiology and Biostatistics.

Reviewer #3 On a form entitled Committee Review's Report

We were pleased with this very positive review. Through the revision for resubmission, our sample size has been reduced so that completion within a year as a single center study is now feasible. We feel that following this project we will proceed with a multicenter trial as mentioned above.

I was deeply troubled by the final line of this review. It is apparent that the reviewer's original rating was "excellent" with a score of 4.4, but this is pencilled over to "good" and 3.0, with no indication as to who made this change. Presumably the committee has this authority.

Name of principal applicant, institution, and amount requested (1st year) / Nom du candidat principal, établissement, et somme demandée (1re année)

Young, David $ 81,522

Summary of research proposal

The objective(s), hypothesis, approach and research plan should be summarized. No abbreviations may be used.

Résumé du projet

Résumer l' (les) objectif(s), l'hypothèse, la démarche et le plan de recherche. Aucune place jointe n'est permise.

Rationale

Labor induction is a frequent obstetric intervention (≈20%). Prostaglandins (PGs) are effective agents, but gastrointestinal (GI) intolerance has limited their use to intracervical and vaginal administration of PGE_2 gels.

Misoprostol, PGE_1 analogue, is marketed for oral treatment of upper GI disorders. The past five years has seen mushrooming literature on its use to initiate uterine contractions for pregnancy termination in the first and second trimesters, and labor induction in the third. Vaginal administration has been almost exclusively used, has been cost-effective (less than one hundredth PGE_2) and without harm to mother or newborn. We have published a randomized controlled trial (RCT) on vaginal use [14]. An oral labor induction agent would be attractive to many patients and care providers. A single published RCT manuscript [22] has evaluated oral misoprostol as a one dose cervical priming agent prior to oxytocin induction, and our RCT[21] (in press) with 275 subjects addressed an induction protocol with repeat oral doses compared to a traditional induction regime (physician chosen combinations of intracervical or vaginal PGE_2, intravenous (IV) oxytocin, and artificial membrane rupture). Both RCT's found oral misoprostol effective, well tolerated, and without harm to mother or newborn.

Before embarking on a costly and necessarily multicenter RCT to evaluate more substantive outcomes (Caesareans or neonatal asphyxia) with sample sizes greater than 3000, we seek funding for two RCT's, for labor induction at term. RCT I - a double blind comparison of oral versus vaginal misoprostol, with intact membranes and RCT II - oral misoprostol versus IV oxytocin with prelabor ruptured membranes (PROM).

Primary Research Questions

RCT I - When compared with vaginal misoprostol (50 μg every 4 hours as needed) for labor induction at term with intact membranes, does oral administration differ by more than 4 hours in time from induction to vaginal birth?

RCT II - When compared with our established IV oxytocin labor induction protocol for term PROM, does oral misoprostol (dose as above) differ by more than 4 hours in time from induction to vaginal birth?

Secondary research questions address harm to the newborn (including cord blood acid base analysis, and ACOG birth asphyxia criteria[29-31]) and mother (Caesareans, peripartum interventions), maternal GI intolerance, and excessive uterine activity.

Research Plan

Subjects in both RCT's will be at gestations greater than 37 completed weeks, with a cephalic presenting live single fetus, who have an indication for induction, and no contraindication to induction, vaginal birth, or PG use.

Random allocation will be blocked and stratified (on Bishop score and parity). In RCT I, all subjects will receive a vaginal and oral application (misoprostol or placebo). In RCT II, the control group will receive IV oxytocin, based on recent TERMPROM trial[36,37]. Blinding of RCT II is not feasible for our center at present.

Sample size calculations were based on Δ = 240 minutes, α (2 tailed) = 0.05, β = 0.20, with σ from our publications [14,21]. Adjustment for anticipated Caesareans (<20%) were made. Sample size for RCT I is 206 and RCT II is 108. This recruitment within a year is supported by our prior research. [14,21]

Summary of progress under the current grant

Please identify the length of your current MRC grant (i.e. 1988-89).

New applicants are encouraged to summarize previous work relevant to this application.

No attachments may be used.

Résumé des progrès depuis le début de la subvention

Indiquer la durée de la subvention en vigueur (ex. : 1988-1989).

Les nouveaux candidats sont encouragés à résumer leurs travaux précédents qui ont rapport à leur demande.

Aucune pièce jointe n'est permise.

Our previous work of most direct relevance to this application has resulted in three publications in the past year[14,18,21]. These papers report our two prior randomized controlled trials (RCTs) of vaginal[14] and oral misoprostol[21] versus a widely established term labor induction protocol, and a literature review[18] and meta-analysis of vaginal misoprostol RCTs. These papers are described in the Research Proposal, pages 12 to 12.10 of this application, with the complete papers in the Appendix. Data on vaginal birth interval (VBI) in the membranes intact and membranes ruptured (PROM) strata of our oral misoprostol publication[21] will be presented and discussed here. Some of this data does not appear in the paper, but will be presented at the SOGC ACM 1997.

Of the 275 subjects randomized, 56 were in the PROM stratum. VBI (cesareans excluded from analysis) was a mean (± standard deviation) of 734 ± 468 min with oral misoprostol versus 557 ± 312 min for control subjects (IV oxytocin) (P=0.13). Nonparametric analysis using the Mann Whitney U test (including cesareans as the same VBI, but greater than any actual VBI) gives a median VBI of 800 min with oral misoprostol and 796 min for controls (P=0.96). No newborn in either group had birth asphyxia[29-31].

The intact membranes stratum contained 219 subjects. The control group permitted physician chosen combinations of intracervical/vaginal prostaglandins, artificial membrane rupture, and oxytocin infusion. The VBI (cesareans excluded) was a mean of 974 ± 524 with oral misoprostol versus 1002 ± 606 min in controls (P=0.73). Nonparametric analysis (including cesareans) gives a median VBI of 1030 min with oral misoprostol and 994 min with controls (P=0.34). Again, no newborn in either group had birth asphyxia. In neither stratum was a difference in VBI found. Even direction in effect time is not apparent.

Our vaginal misoprostol RCT[14] for term labor induction included only intact membrane subjects. Eligibility criteria were essentially the same as for the intact membranes stratum of our oral misoprostol RCT[21]. With the control group (as for intact membranes stratum above) mean VBI was 941 ± 506 min (excluding cesareans), with a median time of 931 min (including cesareans). Very similar data to that in the previous paragraph. Vaginal misoprostol lead to a mean VBI of 753 ± 588 min, with a median time of 681 min. Compared with the control group, these VBIs durations are less (P=0.018 t-test, and 0.017 U-test respectively).

This research proposal will describe two RCT's. RCT I will be a double blind comparison of oral versus vaginal misoprostol for term induction with intact membranes. It would be logistically more difficult, if not impossible for our center to carry out a double blind RCT of oral or vaginal misoprostol versus traditional induction methods, without placebos provided by pharmaceutical manufacturers (Searle Canada for misoprostol and Upjohn for dinoprostone), which is not forthcoming at present. The above date suggests oral misoprostol results are very similar to the control group particularly with membranes intact. A double blind trial of oral versus vaginal misoprostol is feasible for us and would provide unbiased outcome data, particularly on the more subjective uterine activity.

RCT II will be designed with sufficient power to come to a conclusion regarding oral misoprostol versus IV oxytocin (no better method yet shown[36,37]). Blinding of this RCT is not feasible for us.

Name of principal applicant, institution, and amount requested (1st year) / Nom du candidat principal, établissement, et somme demandée (1re année)

Young, David $ 81,522

Research proposal

A maximum of 10 pages may be added to this page in the case of one or two applicants; or 12 pages in the case of three or more applicants. Page limits do not include charts, photographs, diagrams nor references. Legends are limited to two lines.

Projet de recherche

On peut ajouter un maximum de 10 pages à celle-ci dans le cas de un ou deux candidats, ou 12 pages dans le cas de trois candidats ou plus. Le nombre de pages acceptées n'inclut pas les graphiques, les photographies, les diagrammes et les références. Les légendes ne doivent pas dépasser deux lignes.

Title

Induction of Labour with Oral Misoprostol.

Introduction of Labor with Prostaglandins (PGs)

Induction of labor near term is frequently necessary, (more than 20% of labors in many Canadian tertiary centers) for a variety of obstetric and medical indications. PGs, particularly dinoprostone (PGE_2), have been proven effective cervical ripening and labor induction agents.[1,2] Since 1971 there has been evidence from randomized controlled trials (RCTs) that oral PG administration is an effective method of labor induction.[2] Unfortunately, oral PGs, including dinoprostone tablets, lead to unacceptable gastrointestinal (GI) side effects, with up to a 10% incidence of vomiting and diarrhea[2]. With the development of commercial gel PG preparations designed for vaginal or intracervical application, without such side effects,the oral PG approach for labor induction has been virtually abandoned.

Misoprostol

Misoprostol (Cytotec; Searle Canada, Oakville, Ontario, Canada) is an inexpensive synthetic PGE_1 analogue marketed in North America in an oral tablet form, which is stable at room temperature. Two formulations, 100 μg and 200 μg, are available on physician prescription for prevention and treatment of nonsteroidal anti-inflammatory drug induced gastric ulcers and treatment of duodenal ulcers.[3] The frequency of GI side effects is low with oral administration of up to 1600 μg per day. Use in pregnancy is stated to be contraindicated because of its uterotonic effects and the risk of miscarriage. There has been no evidence of fetotoxic, teratogenic, or carcinogenic effects in animal studies.[3] Misoprostol costs less than one hundredth the price per dose of commercial PGs currently used in labor induction.

A role for vaginal misoprostol has been established in second trimester termination of pregnancy, using its uterotonic effects [4,5] in divided doses of 400 to 2200 μg per day. An RCT has compared misoprostol favorably to dinoprostone[6]. Our group first studied misoprostol in second trimester termination of pregnancy complicated by lethal fetal anomalies, and found vaginal use a cost-effective to intraamniotic hypertonic saline.[5] Misoprostol is also effective in first trimester medical termination, but only following administration of another abortifacient, such as mifepristone[6] or methotrexate[7].

Vaginal Misoprostol for Labor Induction

Several RCTs have now shown vaginal placement of misoprostol tablets to be an effective method of inducing labor, without an increase in adverse maternal or neonatal outcomes.[8-13] In 1993, Sanchez-Ramos et al[8], reported an RCT of vaginal misoprostol versus intravenous oxytocin infusion with decreased time to vaginal delivery. Subsequent trials have compared a variety of control groups

including intracervical and vaginal dinoprostone[9-14]. In an RCT involving 222 subjects at term with membranes intact, our group[14] found decreased time to vaginal delivery (by approximately three hours), less frequent oxytocin augmentation, a strong trend for less use of epidural analgesia, and no difference in Caesarean births with misoprostol. Median PG cost per patient with misoprostol was one hundredth that in the control subjects, who received our established induction protocol (physician-chosen combinations of intracervical or vaginal dinoprostone every six hours, artificial rupture of membranes (AROM), and oxytocin infusion).

Our group reported a meta-analysis of the published RCTs (5 papers[9-13], 3 abstracts[14-16] and one letter[17]) of vaginal misoprostol versus contemporary control groups (most including vaginal and/or cervical commercial prostaglandins). Over 600 subjects receiving vaginal misoprostol had been observed prospectively in such research.[18] Misoprostol has been effective. There was more frequent vaginal birth within 12 hours (Relative risk (RR) 1.60, 95% confidence interval (CI) 1.28 to 2.06) and within 24 hours (RR 1.36, CI 1.23 to 1.53). Oxytocin use was less (RR 0.53, CI 0.47 to 0.61). No significant change in Caesareans, low five minute Apgar scores, or rate of neonatal acidosis was found.[18]

Oral Misoprostol for Labor Induction

An orally administered labor induction agent would likely be attractive to both patients and health care providers. Avoidance of intravenous lines in some parturients, and less frequent need for vaginal examination might be anticipated, and considered more client friendly. Greater freedom for upright positioning and ambulation might even facilitate labor progress.

Because misoprostol is known[3] to be well tolerated orally when used for its primary indication, the management of upper gastrointestinal dysfunction, we studied the effectiveness, safety and side effects of misoprostol as an oral agent for induction of labor. Although no information exists on oral misoprostol pharmacokinetics in third trimester pregnancy, first trimester uterine contraction data[19] following oral administration suggest responses similar to that in nonpregnant use. After oral administration in males, the peak concentration and half time of misoprostol acid, the active metabolite, are 12 and 21 minutes respectively[20].

We have in press[21] an RCT of oral misoprostol (50 μg every four hours if needed) versus our standard approach to term labor induction (physician chosen combinations of intracervical, or vaginal dinoprostone, dilute intravenous oxytocin infusion, and AROM).[21] The 275 women were randomized into strata based on membrane status. Prelabor rupture of membranes (PROM) had occurred in 56. In summary, the time from induction to vaginal birth with oral misoprostol was not significantly different from that with our established protocols. There were no clinically or statistically significant differences in maternal secondary outcome measures (Caesarean rate, frequency of epidural use, perineal trauma, or manual removal of the placenta). Neonatal outcomes, including cord blood acid base analysis, were not different. There was no difference in frequency of maternal GI side effects in the two groups. Oral misoprostol may be a safe, cost- effective alternative to standard induction agents with a high degree of patient acceptability.

We are unaware of other publications using oral misoprostol for term labor induction with living fetuses. Ngai et al [22] have recently reported a double blind RCT with a single 200 μg oral

misoprostol dose versus placebo for cervical priming, in PROM 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, and 41 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 GI 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.

An abstract has just appeared from Vancouver[20] of a double blind RCT with oral misoprostol (50µg every 6 hours) versus vaginal dinoprostone (2mg every 6 hours), with study medication given up to 4 doses. They found no difference in induction to delivery interval (37.9 ± 41 hours versus 36.0 ± 75 hours), but failed induction was higher in the misoprostol group (16% versus 3%, $P<0.001$). These induction to delivery intervals (not stated if cesareans were included in this analysis) are obviously longer than those seen at our center, so we eagerly await their complete manuscript publication.

The median PG cost in our previous studies[14,21] was $0.33 for misoprostol and a conservative $70.00 for standard therapy. Maximum PG expenses for any single patient were under $1.00 and more than $180.00 for misoprostol and standard therapy, respectively.

Fetal Safety Issues

Inherent in labor induction is the potential for excessive uterine activity which may interfere with uteroplacental perfusion sufficiently to compromise the fetus. Because of confusion stemming from varied definitions of excessive uterine activity, Curtis[23] recommended a standard terminology: hypertonic - a contraction lasting more than 90 seconds; tachysystole - contraction frequency greater than five per ten minutes; hyperstimulation - hypertonic contraction or tachysystole with late fetal heart rate decelerations or fetal tachycardia. While this terminology is an obvious improvement, it is nevertheless arbitrary, with no research to support it based on fetal or newborn outcomes. Though the relationship between continuous electronic fetal heart rate (FHR) monitoring and fetal well being is not one to one, nonreassuring changes associated with excessive uterine activity warrant intervention either to reduce uterine activity, provide more direct assessment of fetal well being (fetal blood sampling, other biophysical assessment), or removing the fetus from this environment (delivery), if simple measures such as position change or maternal oxygen supplementation are not corrective.

Our meta-analysis[18] of data from existing RCTs has found tachysystole significantly more frequent with misoprostol (RR 2.21, CI 1.53 to 3.18), with uterine hyperstimulation nearly so (RR 1.84, CI 0.98 to 3.47). This meta-analysis included every vaginal misoprostol protocol. The maximum incidence of tachysystole in any single report was 37 percent[12] , and uterine hyperstimulation 11 percent. To place this in perspective, contemporary studies with oxytocin inductions report tachysystole and uterine hyperstimulation of similar or greater frequency.[24,25] A

recent RCT report[26] from the same authors[12] found less tachysystole (7%) and hyperstimulation, than with a dinoprostone vaginal insert, on changing from their original[12] every three hours to an every four hours protocol.

The Vancouver double blind RCT[26] found uterine hyperstimulation rates of 5% with oral misoprostol and 10% with vaginal dinoprostone, with fetal distress in labor of 23% in both groups, and cesarean rates of 25% and 22% (NS) - all reassuring results for oral misoprostol safety.

When oxytocin induction results in uterine hyperstimulation with nonreassuring FHR changes, discontinuing the infusion can reduce oxytocin blood levels quickly. Use of vaginal dinoprostone gels or misoprostol is more problematic. Authors[27] describe vaginal lavage and removing tablet remnants, however, intravenous β - adrenergic agonist regimens have been used[28] with apparent beneficial tocolytic response. Intravenous tocolysis is the approach necessary with oral misoprostol. Forced emesis would likely be ineffective, and distasteful. We have never used intravenous tocolysis in more than 400 misoprostol inductions.

Despite these concerns of possible uterine hyperstimulation, substantive worrisome newborn outcomes (neonatal acidosis, meconium aspiration, and ACOG Birth Asphyxia criteria[29-31]) have been rare, acceptable, and not different between misoprostol and control groups. It is imperative that such outcome data be collected in future studies to quantitate more precisely potential risks of misoprostol (and traditional approaches).

Prelabor Rupture of Membranes (PROM)

Approximately 8% of pregnancies present with term PROM. A longer PROM duration is thought to be associated with a higher risk of maternal and fetal infection. Over 60% of these women will begin labor spontaneously within 24 hours, and more than 95% within 72 hours. The etiology of PROM is not well understood. [32]

The assessment of suspected PROM involves history and physical examination, lab testing, and ultrasound imaging. A sterile speculum exam demonstrating fluid in the vagina, which is both nitrazine positive and ferning positive, is diagnostic. Nitrazine will detect alkaline amniotic fluid, whereas the vaginal pH in pregnancy is 4.5-6.0. Nitrazine can be falsely positive in the presence of blood, semen, vaginitis and antiseptic solutions. The typical ferning appearance of amniotic fluid, when a fluid drop dries on a slide and is visualized by microscope, is less often falsely positive. Ultrasound can quantitate intrauterine amniotic fluid volume. If doubt remains following these investigations, observation for further fluid leakage is appropriate.[32]

Concerns with prolonged PROM are related to an increased risk of maternal infection (such chorioamnionitis, post-partum endometritis and sepsis) and more seriously, neonatal infection. Early induction to avoid these complications raises worry about increasing Caesarean births. There is controversy about whether to induce immediately or manage expectantly; or whether to use oxytocin or PG, if induction is chosen.

Several studies have assessed induction with oxytocin or PG's vs expectant management. These studies have been small and potentially biased by the method of randomization. Neonatal outcomes were not assessed blindly. Overview of these trials was carried out in the Cochrane Collaboration Database - Pregnancy and Childbirth Module. Induction of labor with oxytocin was

associated with higher Caesarean rates (typical OR (95% CI): 1.85 (1.37-2.50)) and lower risk of neonatal infection (typical OR (95% CI); 0.27 (0.12-0.59)) than expectant management.[33] In trials comparing induction with PGs with expectant management, the findings suggested PGs would result in a similar Caesarean rate (typical OR (95% CI): 0.98 (0.65-1.50)), and lower rate of endometritis (typical OR (95% CI): 0.38 (0.20-0.70))[34] Overviews of EROM trials comparing oxytocin vs vaginal PGs suggest that induction of labor with PGs results in fewer Caesareans (typical OR (95% CI): 0.62 (0.42-0.91)[35].

Recently the TERMPROM Trial[36,37] was published. This remarkable study included 5042 patients from 72 centers in Canada, Britain, Australia, Sweden, Israel, and Denmark. Four groups were compared 1) induction with oxytocin, 2) induction with vaginal PGE_2 gel, 3) expectant care & induction with oxytocin if needed, and 4) expectant care & induction with PGE2 gel if needed. The primary outcome was neonatal infection. All infants were to have a CBC and blood culture performed and clinical assessment performed blind to the treatment allocation. There was no difference in the rates of neonatal infection (2.0 - 3.0 %) or Caesarean section (approximately 10%). Sample size had been chosen to detect a 50% reduction in an anticipated baseline neonatal infection rate of 4%. Because the actual baseline rate was less than 3%, the study power was unfortunately only 25%. The time to delivery was shortest in the induction with oxytocin group ($P< 0.0001$). There was a trend toward reduction in chorioamnionitis and postpartum fever in the oxytocin induced group. Other secondary outcome analyses suggested less neonatal antibiotic use and less frequent neonatal intensive care admission for more than 24 hours with oxytocin induction. Though the numbers involved are small, all four non-anomalous perinatal deaths were in the expectant groups ($P = 0.125$). Patient satisfaction was highest in the induced groups. In one publication, the authors concluded that induction with IV oxytocin was the preferred choice. [37]

Arguably the patient satisfaction and secondary outcome analysis of TERMPROM suggest the approach of immediate induction of labor is unsurpassed. The option of oral agent for labor induction in this situation begs further evaluation. The existing published information from Hong Kong [22] and our PROM stratum [21] is very preliminary.

RESEARCH PROTOCOL

Primary Research Questions:

This proposal seeks funding for two randomized controlled trials (RCTs) to answer the following:

RCT I. When compared with vaginal misoprostol (50 μg every four hours as needed) for induction of labor at term with intact membranes, does oral administration differ by more than four hours in time from induction to vaginal birth?

RCT II. When compared with our established intravenous oxytocin labor induction protocol for prelabor rupture of membranes at term, does oral misoprostol (50 μg every four hours as needed) differ by more than four hours in time from induction to vaginal birth?

Young, David	$ 81,522

Secondary Research Questions

1. Does oral misoprostol induction of labor increase harm to the newborn (as measured by cord blood acid base analysis, and ACOG criteria for birth asphyxia) or mother (Caesarean, peripartum trauma or interventions)?

2. Does oral misoprostol increase maternal GI problems (vomiting or diarrhea)?

3. What is the frequency of uterine tachysystole and hyperstimulation associated with the study induction protocols (as well as in a group of term parturients in spontaneous labor at term)?

Rationale

Our prior research has demonstrated cost-effectiveness and suggested safety first of vaginal misoprostol and then oral misoprostol in comparison with an established and widely followed labor induction protocol. Before considering a more costly and ambitious multicenter trial on a more substantive outcome such as Caesarean rate (2N = 3400 to detect a change from 12 to 9 %) or neonatal asphyxia (2N = 5030 to detect a change from 2 to 1%), we feel further research (in essence pilot studies) is required to better define the appropriate intervention to evaluate in such an exercise. Oral misoprostol induction would be most innovative.

The first RCT here proposed will provide an assessment of oral misoprostol against vaginal misoprostol as the initial approach to term labor induction with membranes intact. There is no such published trial to date. A double blind comparison will permit an unbiased assessment of all outcomes, including the occurrence of excessive uterine activity.

We feel the second RCT, with a different control group is warranted. With ruptured membranes, vaginal placement, retention, and absorption of a misoprostol tablet could all be problematic. Our interpretation of the TERMPROM trial prompts us to choose traditional intravenous oxytocin induction for the control. A double blind approach for this trial is possible, but not feasible, at this time in our center.

RCT I - Oral versus Vaginal Misoprostol (Double Blind)

Sample Specification

Subjects will be recruited from those patients who are placed on our hospital induction list for an obstetric or medical indication. Eligibility criteria are pregnant women at gestation greater than 37 completed weeks with membranes intact, and a single live fetus of cephalic presentation.

Exclusion criteria are nonreassuring fetal heart rate (FHR) tracing, prior uterine surgery, lethal or major fetal anomaly, suspected chorioamnionitis, known hypersensitivity to misoprostol or other PGs, or contraindication to vaginal birth.

Following approval of the attending physician, eligible subjects will be approached by our research nurse, an investigator, or an obstetrical resident or staff physician familiar with the study. Information pamphlets will be circulated to physician offices and prenatal education classes to inform women of our research. Our research protocol and consent form has been approved by the Human Investigation Committee, Faculty of Medicine, Memorial University of Newfoundland, and Health Care Corporation of St. John's Research Committee.

To address in part issues of generalizability and volunteer bias, demographic and outcome data will be collected on parturients who are ineligible, or decline randomization, but allow confidential use of this information.

Experimental Manoeuvre

With the exception of the experimental manoeuvre, all aspects of patient care will be determined by the patient's own physician. If eligibility criteria are met and informed consent obtained, allocation will be carried out. Group allocation will be assigned by opening the next sequentially numbered opaque envelope only when induction is to begin. Envelopes will contain a card indicating study drug package to be administered, which was determined using a computer generated random sequence and prepared by university research personnel not involved in the study. Randomization will be blocked in groups of four and stratified by cervical ripeness (Bishop score <7, or not). Study drug packages will be prepared by pharmacy and contain eight doses (maximum dose per subject used in our prior research has been seven) of a designated packet containing powdered misoprostol or methyl cellulose (visually indistinguishable), to be administered by oral syringe after dissolving in 30 cc of water, or in a 5 cc syringe containing hydroxyethyl gel for vaginal use. For a given subject either the oral powder or the vaginal syringe will contain active misoprostol. Our pharmacy has developed this approach based on a previously published protocol [9]. The oral preparation will be administered to a subject, immediately after the vaginal syringe has been emptied into the vaginal posterior fornix. We have successfully used these administrations in a number of patients. This approach has been necessary as the cost of a placebo tablet from the pharmaceutical manufacturer has been quoted as in excess of $200,000.

A vaginal exam for cervical assessment (Bishop score) and placement of study medication (by a staff physician or resident) will occur immediately before randomization. All study inductions will be carried out on an inpatient basis, with continuous electronic FHR and uterine contraction monitoring until uterine activity has resolved, or a minimum of 1 hour after any PG administration. Misoprostol study drugs will be repeated at 4 hour intervals until one of the following occurs: progressive labor, contraction frequency of three per 10 minutes, nonreassuring FHR tracing, or delivery. All decisions with regard to AROM, analgesia, epidural use, and oxytocin augmentation will be made by the attending physician. A staff physician will reassess the patient before each administration of misoprostol. The rationale for this schedule is our prior experience. [14,21] This dose frequency will not be exceeded. Study drug use will be discontinued after rupture of membranes. Oxytocin augmentation may not begin until 4 hours after discontinuing misoprostol. Intravenous oxytocin will begin at 2 mIU/min and be increased at 2 mIU/min increments every 30-60 minutes.

Outcome Measures

Maternal and newborn outcome measures are required. All study subjects will remain in their allocated group for outcome assessment - an "intent to treat" analysis.

The primary outcome is the time from onset of induction to vaginal birth. Although consent may be obtained earlier, randomization will not occur until the time induction is to begin. A difference of 240 minutes was chosen as clinically important to detect, on the basis of a questionnaire survey of pregnant and postpartum patients, nursing and physician staff.

Secondary outcomes include:

1. Labor intervals to vaginal birth - induction to full dilation, duration of membrane rupture, labor stages (first, second and third).

2. Labor intervals with Caesarean birth.

3. Maternal interventions and morbidity - frequency of IV use, vaginal exams (for study drugs and other), oxytocin use, analgesia use (epidural, narcotic, general, other), nonreassuring FHR, fetal blood sampling, episiotomy, perineal laceration (degree), intact perineum, manual removal of placenta, endometritis, fever >38 °C on two occasions more than six hours apart, postpartum stay, estimated peripartum blood loss, postpartum haemorrhage, blood transfusion, other significant illness and death.

4. Birth route: vaginal (spontaneous, vacuum or forceps), and Caesarean.

5. Frequency of uterine tachysystole (>6 contractions per 10 minutes).

6. Maternal satisfaction with labor evaluated by questionnaire (Labor Agentry Scale[29]).

7. Neonatal morbidity - cord artery acid base analysis, Apgar scores at one and five minutes, meconium prior to birth, ACOG criteria for birth asphysia [four findings: profound metabolic or mixed acidemia (cord artery pH less than 7.00), 5 minute Apgar score of 3 or less, neonatal neurologic abnormality, and dysfunction of one other major body system], time in intensive care and hospital, sepsis, pneumonia, meningitis, antibiotic treatment, other significant illness or death.

8. Maternal GI intolerance - frequency of nausea, vomiting or diarrhea by caregiver report and patient questionnaire.

Baseline demographic data collected on study subjects will include: indication for induction, parity, Bishop score, age, race, height, weight, group B streptococcus (GBS) status and neonatal birthweight.

Sample Size

The primary outcome measure time from induction to vaginal birth, is a continuous variable.

Δ = 240 minutes

α (2 tailed) = 0.05 Z_α = 1.96

β = 0.20 Z_β = 0.84

σ = standard deviation derived from pooling of results from our prior vaginal misoprostol cohort[14] (588 minutes) and oral misoprostol intact membranes stratum [21] (524 minutes).

N (group) $= 2 [(Z_\alpha + Z_\beta)\sigma/\Delta\}]^2$
= 86 (using PEPI, Version 2, 1995. Computer Programs for Epidemiologic Analysis, USD)
2N = 172

Our prior studies[14,21] had consistent overall Caesarean rates of 12.2 and 12.4%. Combined, this rate is 12.3% with 99% CI 8.8 - 16.5%. Adding 20% or 34 to the prior 2N would allow for anticipated Caesarean births in our sample.

$\therefore$ RCT I Sample Size = 206

Feasibility

There are approximately 2600 annual births at the Grace General Hospital, St. John's, Newfoundland. This provincial tertiary unit is the only birth center within 100 kilometers for a population of over 150,000. Our induction rate is just over 20% giving approximately 520 inductions per year. Our previous studies enrolled 222 and 219 subjects respectively[14, 21] for induction with intact membranes in 6 months each. It should be quite feasible to complete this clinical trial in one year, simultaneously with RCT II.

Data Analysis

Hypothesis testing will be performed only on the primary outcome. Other comparisons will be considered hypothesis generation. Presetting decision levels and hypotheses to be tested should minimize data dredging and post hoc significance bias. Analysis will be on an "intent to treat" basis. The primary outcome measure, time to vaginal birth, will be significant if $P<0.05$ (as per sample size calculation) using parametric statistics (Student's t).

APPENDIX G: BUDGET

Budget Justification

Personnel: Estimated costs for Research Assistant.

Position: Research Assistant

Credentials: Bachelor of Nursing, Level II pay scale (source: Collective Agreement NLNU, NHNHA and Treasury Board).

Department: Obstetrics & Gynecology, Faculty of Medicine, MUN

General Accountability:
This is a professional position providing research support to the office of Obstetrics & Gynecology. The position maintains a liaison with officials of the Faculty of Medicine, Nursing, Pharmacy and Hospital Administration. General supervision is provided by research applicant and Discipline Chair.

Duties:

- Function as full-time project manager.
- Collect and collate demographic, intrapartum and outcome data.
- Input data to computer.
- Inform potential participants about misoprostol and prostaglandin induction at prenatal classes.
- Participate in informed consent process.
- Administer postpartum satisfaction questionnaire.
- Educate nursing and medical staff such as family physicians, housestaff, and labour and delivery nurses, regarding study protocol.
- Conduct literature searches on related topics.
- Prepare presentations ie. slides.

Salaries:

Nursing (screening + monitoring)	
Overtime	
Course credits	
Standby	
Beeper	
Mileage	
Annual Leave	
Total	**$39,872.10**

Benefits
(25% Gross Salary - CCP, PPP, UIC, WWC, Group, etc.) 9,968.00

Total salaries $49,840.10

Material and Supplies: **Estimated cost of Misoprostol.**

Calculation: $0.77 /patient x 790 patients = $ 608.00
GST (2.31%) = 14.04
PST (12.84%) = 79.86
$ 701.90

Estimated cost of Placebo.

Calculation: $10.00 /patient x 790 patients = $7,900.00
GST (2.31%) = 182.49
PST (12.84% x cost of placebo) = 1,014.36
$9,096.85

Expendables: **Estimated cost of postage .**

Calculation: total prior to taxes = $ 50.00
GST (2.31%) = 1.15
PST (12.84% x cost of expendables = 6.42
$ 57.57

Estimate cost of phone/fax ($40/month).

Calculation: total prior to taxes = $ 480.00
GST (2.31%) = 11.09
PST (12.84% x cost of expendable) = 61.63
$ 552.72

Printing: **Estimated cost of photocopying.**

Calculation: $0.02 /copy x 4,000 copies = $ 80.00
GST (2.31%) = 1.85
PST (12.84% x cost of printing) = 10.27
$ 92.12

Travel: Travel for presentation of results and exploring future related research opportunities.

Calculation: Estimate travel = $ 2,000.00

Total per year $ 62,341.26