เปรียบเทียบยามัยโสพรอสทอล 50 ไมโครกรัมกับยาไดโนพรอสโทน 3 มิลลิกรัมสอดทางช่องคลอดครั้งเดียวในการเตรียมปากมดลูกเพื่อการคลอดโดยการทดลองทางคลินิกแบบสุ่มทดลอง

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A RANDOMIZED COMPARISON OF ONE SINGLE DOSE OF VAGINAL 50 MCG MISOPROSTOL WITH 3 MG DINOPROSTONE IN PRE-INDUCTION CERVICAL RIPENING

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มานิต ศรีประโมทย์: เปรียบเทียบยามัยโสพรอสทอล 50 ไมโครกรัมกับยาไดโนพรอสโทน 3 มิลลิกรัม สอดทางช่องคลอดครั้งเดียวในการเตรียมปากมดลูกเพื่อการคลอดโดยการทดลองทางคลินิกแบบสุ่มทดลอง (A RANDOMIZED COMPARISON OF ONE SINGLE DOSE OF VAGINAL 50 MCG MISOPROSTOL WITH 3 MG DINOPROSTONE IN PRE-INDUCTION CERVICAL RIPENING). อาจารย์ที่ปรึกษา: ศาสตราจารย์นายแพทย์จิตร สิทธิอมร, อาจารย์ที่ปรึกษาร่วม: รองศาสตราจารย์นายแพทย์รณชัย อธิสุข, ผู้ช่วยศาสตราจารย์สมรัตน์ เลิศมหาฤทธิ์ ; 75 หน้า ISBN 974-333-452-1

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยามัยโสพรอสทอล 50 ไมโครกรัมกับยาไดโนพรอสโทน 3 มิลลิกรัม สอดทางช่องคลอดครั้งเดียว ในการเตรียมปากมดลูกเพื่อการคลอดในสตรีตั้งครรภ์ครบกำหนด ซึ่งมีข้อบ่งชี้ในการคลอดแต่ปากมดลูกยังไม่พร้อม

รูปแบบการทดลอง: การทดลองทางคลินิกแบบสุ่มทดลอง

สถานที่ทำการวิจัย: วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ประเทศไทย

กลุ่มตัวอย่าง: สตรีตั้งครรภ์เดี่ยวที่มีอายุครรภ์ตั้งแต่ 37 สัปดาห์ขึ้นไป จำนวน 143 ราย มีข้อบ่งชี้ในการชักนำให้เจ็บครรภ์คลอด มีคะแนนบิชอบ 0-6 ทารกอยู่ในท่าศีรษะปกติ อัตราการเต้นของหัวใจทารกปกติ ถุงน้ำทูนหัวยังไม่แตก ไม่มีการหดรัดตัวของมดลูก ไม่มีข้อห้ามในการคลอดทางช่องคลอด ไม่มีข้อห้ามต่อการใช้ยาพรอสตาแกลนดิน

การกระทำ: ผู้ป่วยทั้งที่ไม่เคยคลอดและเคยคลอด แต่ละกลุ่มแบ่งผู้ป่วยเป็น 2 กลุ่มการศึกษา โดยวิธีการสุ่มแบ่งกลุ่ม โดยกลุ่มแรกได้รับยามัยโสพรอสทอล 50 ไมโครกรัม ในกลุ่มที่สองได้รับยาไดโนพรอสโทน 3 มิลลิกรัม ทั้งสองกลุ่มได้รับการบริหารยาโดยการสอดทางช่องคลอดครั้งเดียว หลังจากนั้น 24 ชั่วโมงให้ยาอ็อกซิโทซิน

การวัดผล: คะแนนบิชอบของปากมดลูกที่ 24 ชั่วโมงหลังได้รับยา การหดรัดตัวผิดปกติของมดลูก การคลอดทางช่องคลอดใน 24 และ 48 ชั่วโมง

ผลการวิจัย: ข้อมูลพื้นฐานและคะแนนบิชอบเริ่มต้น (คะแนนมัธยฐาน 3.5 เทียบกับ 4.0) ของผู้ป่วยทั้ง 2 กลุ่มไม่แตกต่างกัน ผู้ป่วยที่ได้ยามัยโสพรอสทอลมีคะแนนที่เพิ่มขึ้นเมื่อชั่วโมงที่ 24 มากกว่าผู้ป่วยที่ได้ยาไดโนพรอสโทนหนึ่งหน่วย (คะแนนเพิ่มเฉลี่ย 6.5 เทียบกับ 5.5; 95% CI 0.04 ถึง 2.1; p = 0.042) แต่ไม่มีความสำคัญทางคลินิก อัตราการเกิดกลุ่มอาการมดลูกหดรัดตัวมากกว่าปกติในกลุ่มได้รับยามัยโสพรอสทอลจะสูงกว่า (6.9% เทียบกับ 0%) แม้ว่าไม่มีนัยสำคัญทางสถิติ (p = 0.058)) แต่มีความสำคัญทางคลินิก เมื่อเปรียบเทียบการคลอดทางช่องคลอดในผู้ป่วยทั้ง 2 กลุ่ม พบว่าอัตราการคลอดใน 24 ชั่วโมงเท่ากับ 46.3% เทียบกับ 35.7% (p = 0.350) และอัตราการคลอดใน 48 ชั่วโมงเท่ากับ 88.9% เทียบกับ 89.3% ซึ่งแตกต่างอย่างไม่มีนัยสำคัญทางสถิติ (p >0.05) ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในวิธีการคลอด ระยะเวลาเริ่มให้ยาจนคลอดทางช่องคลอด น้ำหนักทารกแรกคลอด การถ่ายขี้เทา คะแนนแอ็ปการ์ที่ 1 และ 5 นาที และการรับทารกไว้ในหออภิบาล

สรุป: ยามัยโสพรอสทอล 50 ไมโครกรัมสอดทางช่องคลอดครั้งเดียวมีประสิทธิผลทางคลินิกในการเตรียมปากมดลูกเพื่อการคลอดไม่แตกต่างจากยาไดโนพรอสโทน 3 มิลลิกรัม แม้ว่าจำนวนผู้ป่วยที่ศึกษายังไม่มากพอที่จะตรวจความแตกต่างของอัตราการเกิดมดลูกหดรัดตัวผิดปกติระหว่างผู้ป่วยทั้ง 2 กลุ่ม แต่ผู้ป่วยที่ได้ยามัยโสพรอสทอลเกิดกลุ่มอาการมดลูกหดรัดตัวมากกว่าปกติมากกว่าผู้ป่วยที่ได้รับยาไดโนพรอสโทน จึงจำเป็นที่จะต้องเฝ้าระวังการหดรัดตัวของมดลูกและเสียงหัวใจทารกในผู้ป่วยที่ได้รับยามัยโสพรอสทอล

ภาควิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต Manit Sriprametee

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่ออาจารย์ที่ปรึกษา Chitr Sithi-amorn

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ลายมือชื่ออาจารย์ที่ปรึกษาร่วม Somrat Lertmaharit

4175379530 : MAJOR HEALTH DEVELOPMENT PROGRAMME

KEY WORD: PRE-INDUCTION CERVICAL RIPENING / MISOPROSTOL / DINOPROSTONE

MANIT SRIPRAMOTE: A RANDOMIZED COMPARISON OF ONE SINGLE DOSE OF VAGINAL 50 MCG MISOPROSTOL WITH 3 MG DINOPROSTONE IN PRE-INDUCTION CERVICAL RIPENING. THESIS ADVISOR: PROFESSOR CHITR SITTHI-AMORN, M.D., M.Sc., Ph.D., THESIS COADVISOR: ASSOCIATE PROFESSOR RONACHAI ATISOOK, M.D., M.Sc., ASSISTANT PROFESSOR SOMRAT LERTMAHARIT, M.Med.Stat. 75 pp. ISBN 974-333-452-1

Objective: To compare the efficacy and safety of one single dose of 50 mcg misoprostol and one single dose of 3 mg of dinoprostone vaginal administration for pre-induction cervical ripening in term-pregnant women who had the indication for induction of labor but with unripe cervices.

Design: A randomized double-blind controlled trial.

Setting: Bangkok Metropolitan Medical College and Vajira Hospital, Bangkok, Thailand.

Subjects: The 143 singleton pregnant women after 37 completed weeks' gestation presented with an indication for induction of labor. All patients had a Bishop score of 0-6, cephalic presentation, normal fetal heart tracing, intact membranes without uterine contraction, no contraindications for labor induction and to prostaglandins.

Intervention: The subjects were stratified to either nullipara and multipara group. The subjects in each stratum were allocated by randomization with blocks of size four to receive a single dose of 50 mcg misoprostol or 3 mg dinoprostone, administered vaginally. After 24-hour waiting, oxytocin augmentation was given in both groups.

Main outcome measure: The Bishop score of cervix at 24 hours after insertion of the study drugs, the occurrence of the abnormal uterine contraction, and the number of vaginal delivery within 24, 48 hours.

Results: The demographic data and the initial Bishop score (median score 3.5 versus 4.0) were comparable in both groups. The change of score at 24 hours was one unit higher in misoprostol-treated patients compared to dinoprostone-treated patients (mean change score 6.5 versus 5.5; with 95% CI 0.04 to 2.1, $p = 0.042$) but was not of clinical importance. There was a higher frequency of hyperstimulation syndrome in the misoprostol group (6.9% versus 0%) during 8 hours of cervical ripening. Although the difference was not statistically significant ($p = 0.058$) but was clinically important.. Comparing vaginal deliveries between both groups, the frequencies of delivery within 24 hours were 46.3% versus 35.7% ($p = 0.350$), and within 48 hours were 88.9% versus 89.3% ($p > 0.05$), non-significantly different. No significant differences were noted between misoprostol and dinoprostone in terms of mode of delivery, interval from start of medication to vaginal delivery, neonatal birth weight, meconium passage, 1- or 5-minute Apgar score, and admission to neonatal intensive care unit.

Conclusion: The efficacy of a single 50-mcg dose of vaginally administered misoprostol, is not clinically different to 3 mg dinoprostone in cervical ripening. Although the study was not sufficiently large to detect the differences in abnormal uterine contraction between two groups, there was a higher frequency of hyperstimulation syndrome in the misoprostol group compared to dinoprostone group. The close utero-fetal monitoring in misoprostol-treated patients is needed.

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CHAPTER 1

BACKGROUND AND RATIONALE

Labor induction is a necessary procedure for completion of pregnancy in 10% to 20% of patients. Half of these patients have a cervix that is unfavorable for the induction of labor. It is well known that labor induction in the presence of an unfavorable cervix is often prolonged, tedious and may lead to induction failure.[1] This results in discouraging parturients and obstetricians, long occupation of delivery rooms and a potential increase in unnecessary cesarean deliveries. In patients with an unfavorable cervix, cervical ripening agents are often applied before oxytocin is initiated including Laminaria tents and prostaglandins.[2]

The only agent approved for pre-induction cervical ripening and induction of labor in patients with an unripe cervix is prostaglandins E_2 (PGE_2, dinoprostone).[3] There are drawbacks to the administration of dinoprostone which include the cost, unstability at room temperature that needs refrigeration to preserve its potency, and their ability to induce excessive uterine contractility, which can cause perinatal and maternal morbidity.

Misoprostol, a synthetic prostaglandins E_1 analogue, used for prevention and treatment of gastric and duodenal ulcers, has been recently studied and many recent reports including a meta-analysis, have found that misoprostol safely and effectively ripens the cervix in patients with an unfavorable cervix. Misoprostol decreases the cesarean delivery rate and increases the incidence of vaginal delivery within 24 hours of its administration.[4, 5] The mean cesarean delivery rate in misoprostol compared to PGE_2 or oxytocin is 15.6% versus 21.5% with pooled odds ratio 0.67 (95%CI, 0.48 to

0.93) and the mean vaginal delivery rate within 24 hours is 70.3% versus 50.9% with pooled odds ratio 2.64 (95%CI, 1.87 to 3.71) respectively.[4] Additionally, the drug is cheap, simple to administer, easy to store, and stable at room temperature.

Most studies have shown an increased incidence of uterine tachysystole and hyperstimulation with the use of misoprostol.[6-8] However, the proportion of poor neonatal outcomes as consequences of increased uterine activity is not significantly increased. The meta-analysis, as well as most individual studies, have shown an increased incidence of tachysystole with the use of misoprostol which occurs 22.8% compared to 10.3% in the control groups (pooled odds ratio 2.70 and 95%CI, 1.80 to 4.04).[4]

The majority of dosing regimens studied to date use multiple administrations of misoprostol, with various doses and intervals, to safely ripen the cervix and induce labor.[3-14] The proper dose of misoprostol for cervical ripening without adversely effecting the fetus has not been established. The uterotonic adverse effects potentially occur by frequent administration of misoprostol. The one-time dose of misoprostol for cervical ripening before labor induction with oxytocin should reduce the complications, which may occur during administration of multiple dosing regimens. There are fewer studies of one single dosing regimen for pre-induction cervical ripening.

We designed this randomized study to evaluate the efficacy and safety of 50 mcg vaginal misoprostol compared with 3 mg dinoprostone once only in 24 hours for pre-induction ripening in patients with unripe cervices.

CHAPTER 2

LITERATURE REVIEW

2.1 Cervical ripening

The cervix is fundamentally afibrous connective tissue structure. The collagen, as determined by hydroxyproline analysis, is about 85% in the non-pregnant cervix. In pregnancy at ten weeks this concentration is reduced to 70%, and at term the collagen content is only 30%.[15] The increase in collagenase activity results in decreased collagen concentration and a reduction in the cross-linking collagen fiber. This causes fragmentation and increased solubility of collagen itself. [15] There is a concomitant shift in the ground substance from glycosaminoglycans to hyaluronic acid.[16] The cervix becomes more hydrophilic and total water content increases. [16]

Clinical characteristics of the ripening cervix include softening, effacement, dilatation, increased pliability, and decreased resistance. Such cervical changes may be represented numerically (quantified) by scoring systems such as the Bishop scores which is widely used in forecasting the success of labor induction and delivery. [1]

2.2 Bishop scoring system and cervical assessment

Bishop[1] has been credited with being the first to report an objective pelvic scoring method. This method has gained wide acceptance for several reasons. It was the first to use quantitative methods. The score, which was simple and clinically applicable, is composed of five factors easily evaluated during a pelvic examination.

Each factor is given a numerical value and the values are summed. The pelvic score ranged from 0 to 13. The higher the number, the greater the ripeness of the cervix. Bishop[1] found that with a score of 9 or greater, there were no induction failures and the

Bishop scoring system used for assessment of inducibility (1964)

Score	0	1	2	3
Dilatation (cm)	Closed	1-2	3-4	≥ 5
Effacement (%)	0-30	40-50	60-70	≥ 80
Consistency	Firm	Medium	Soft	_
Cervical position	Posterior	Middle	Anterior	_
Station of the presenting part	-3	-2	-1, 0	+1, +2

average duration of labor was 4 hours. There was still, however, some degree of subjectivity in the scoring of effacement [17]

Several evaluations of the Bishop score have been reported. [18-23] On conclusion, the relative associations between successful labor induction and the five parameters appear to be varied, with the strongest correlation observed with cervical dilation, whereas the association with cervical position and station of the presenting part is less robust. By its nature, cervical examination is somewhat subjective, but the use of objective criteria and numerical scoring of this information has substantially reduced this source of error.[17] The Bishop score and its variations have been used widely and accepted in clinical practice. Its advantage lies in its simplicity, reproducibility, and predictability in successful induction. Although criticized for the equal weight given to each of the five elements, none of the modifications to the original score has been shown to improve predictability. Although the Bishop score was initially evaluated only on multiparous women, it has been extended to nulliparous women with an equal degree of predictive value. To date, the Bishop scoring system remains as the best and simplest method available to determine the duration and safety of induced labor.[17]

2.3 Cervical ripening agent

Oxytocin is the only intravenous approved agent for the induction of labor. It is well known that labor induction in the presence of an unfavorable cervix is often prolonged, tedious and may lead to induction failure.[1] This results in discouraging parturients and obstetricians, long occupation of delivery rooms and a potential increase in unnecessary cesarean deliveries. To minimize these complications, a number of agents have been used to ripen the cervix before induction, including Laminaria tents, estrogen gels, relaxin, and prostaglandins.[2, 24] The PGE_2 derivatives dinoprostone, tablet or gel, is the only intravaginal agent approved by the Food and Drug Administration for pre-induction cervical ripening and induction of labor in patients with unripe cervix. This preparation is expensive, and may become unstable when stored in room temperature.

Numerous recent reports, including a meta-analysis,[4,5] have found that misoprostol safely and ripens the cervix and induces labor in patients with an unfavorable cervix.

2.4 Pharmacology of misoprostol

Misoprostol is a synthetic PGE_1 analogue, the chemical name is methyl-11α, 16-dihydroxy-16methyl-9-oxoprost-13E-en-1-oate. Misoprostol inhibits acid and pepsin secretion including increase resistance of gastric mucosa and is used to prevent and treat esophago-gastro-duodenal ulcer and hemorrhagic lesion.[25]

Misoprostol is stable in the room temperature. After oral administration, 88% of misoprostol is absorbed with peak level at 30 minutes and is metabolized in the liver. The first half-life time is around 1.57-1.7 hours. Most of the drugs are excreted in urine within 24 hours and small amount excreted in fecal route. The drug level may increase up to two times in patients with renal insufficiency. The recent study of

absorption kinetics of misoprostol with vaginal administration of 400 mcg has shown that serum levels of the principal metabolite rose gradually, reached maximum levels between 60 and 120 minutes (80±27 minutes), and declined slowly, to an average of 62% of the peak level at 240 minutes after administration. [26]

The investigation of disposition of misoprostol and its active metabolite in patients with normal and impaired renal function after single oral misoprostol 400 mcg showed that the drug should be avoided in end staged renal disease because of high drug level may cause the adverse effects. There were no significant differences of drug level in the normal and impaired renal function groups that creatinine clearance level over 20 ml/min. [27]

2.5 Misoprostol in cervical ripening

Misoprostol, as a gastric cytoprotective agent, has been marketed in the United States since 1988 for the prevention of peptic ulcer.[25] It is marketed in oral formulation of 100- or 200-mcg tablets with a maximal recommended dose of 1600 mcg per day.

Early studies demonstrated that oral misoprostol caused uterine contraction in early pregnancy.[28] Subsequent studies showed that vaginal misoprostol can terminate first and second trimester pregnancy.[29-31] Sanchez-Ramos et al.[4] analyzed published randomized controlled trials assessing the safety and efficacy of misoprostol for cervical ripening and labor induction (table 2.1). To determine the combinability of individual studies, the authors performed a formal test of homogeneity of treatment effect across the eight studies. Their meta-analysis confirmed that misoprostol was an effective agent for cervical ripening and labor induction in patients at term, showing the decrease in cesarean rate and increase in the incidence of vaginal delivery within 24 hours of its administration. The mean cesarean delivery rate in patients given misoprostol compared to PGE_2 or oxytocin is 15.6% versus 21.5% with pooled odds ratio (OR) 0.67 (95% CI, 0.48 to 0.93) and the mean vaginal delivery rate within 24

hours is 70.3% versus 50.9% with pooled odds ratio 2.64 (95% CI,1.87 to3.71) respectively (table 2.2).[4]

Table 2.1 Meta-analysis of misoprostol therapy for cervical ripening and labor induction [4]

Study	Year	No. of Patients	Maximum Dosage	Control	Dose
Sanchez-Ramos et al.[6]	1993	129	50 mcg every 4 hr	Oxytocin, PGE_2	600 mcg
Fletcher et al. [32]	1993	45	100 mcg	Placebo	100 mcg
Fletcher et al. [33]	1994	63	100 mcg	PGE_2	100 mcg
Campos et al.[34]	1994	152	50 mcg	Oxytocin	50 mcg
Wing et al.[7]	1995	135	50 mcg every 3 hr	PGE_2	300 mcg
Wing et al. [3]	1995	275	25 mcg every 3 hr	PGE_2	200 mcg
Varaklis et al. [8]	1995	68	25 mcg every 2 hr	PGE_2	150 mcg
Chuck & Huffaker [35]	1995	99	50 mcg every 2 hr	PGE_2	250 mcg
Total		966			

Table 2.2 Meta-analysis of misoprostol: vaginal delivery within 24 hours [4]

Study	Misoprostol	Control	Odds ratio (95%CI)
Sanchez- Ramos et al. [6]	58/64 (91.0%)	54/65 (83.0%)	1.97(0.68 to 5.69)
Campos et al.[34]	66/77 (85.7%)	48/75 (64.0%)	3.37(1.53 to 7.46)
Wing et al. [7]	48/68(70.6%)	32/67(47.8%)	2.62(1.29 to 5.33)
Wing et al.[3]	72/138(52.2%)	41/137(29.9%)	2.55(1.56 to 4.19)
Total	244/347(70.3%)	175/344(50.9%)	2.64(1.87 to 3.71)

The most common side effect in patients given misoprostol is diarrhea, which is mild and transient, occurs in 5-40%. Other side effects include nausea (1%), vomiting (1%), headache (5%) and lower abdominal pain (13-20%). The manufactures recommend caution when using any prostaglandin products in patients with glaucoma, asthma, severe hepatic or renal impairment.

Uterine tachysystole and hyperstimulation are the major concerns. Uses in pregnant patients are stated to be contraindicated because of its uterotonic effect and risk of miscarriage. However, there have been no reports of fetotoxic, teratogenic, and carcinogenic effects in animal studies.[25] The meta-analysis, as well as most individual studies,[3-14] have shown an increased incidence of tachysystole with the use of misoprostol which occurs 22.8% compared to 10.3% in the control group (pooled OR 2.70 and 95%CI, 1.80 to 4.04) (table 2.3).

Table 2.3 Meta-analysis of misoprostol: incidence of tachysystole [4]

Study	Misoprostol	Control	Odds ratio (95%CI)
Sanchez-Ramos et al.[6]	22/64(34.4%)	9/65(13.8%)	3.26(1.36 to7.80)
Fletcher et al. [32]	1/24(4.2%)	0/21	2.74(0.11 to 71.1)
Campos et al.[34]	19/77(24.7%)	10/75(13.3%)	2.13(0.96 to 4.95)
Wing et al. [7]	25/68((36.8%)	8/67(11.9%)	4.29(1.76 to10.42)
Wing et al. [3]	24138(17.4%)	14/137(10.2%)	1.85(0.91 to 3.75)
Varaklis et al. [8]	2/36(5.5%)	0/32	4.71(0.91 to 3.75)
Total	93/407(22.8%)	41/97(10.3%)	2.7(1.80 to 4.04)

However, the incidences of abnormal 5-minute Apgar scores and poor perinatal outcomes were similar in misoprostol and control group.[4,5]

Misoprostol can cause excessive uterine activity and uterine rupture. Uses of misoprostol for second trimester termination of pregnancy has been associated with rare cases of uterine rupture, particularly when combined with oxytocin infusion. [36] The possibility of uterine rupture as a rare complication of labor induction with misoprostol must be considered. When misoprostol is used in women with previous cesareans, there is a high frequency of disruption of prior uterine incisions. Wing et al.[37] reported disruption of the prior uterine incision in two of 17 misoprostol-treated women. A case of uterine rupture during induction of labor at term with low dose

vaginal misoprostol after the second 25 mcg dose of misoprostol has been reported.[38] In this patient, a post-abortal curettage was the only previous uterine instrumentation.

It appears that the uterotonic effect is dose-dependent and may be a drug cumulative drug effect.[3, 38] The optimal dosing schedule has yet to be determined in an attempt to be efficacious and minimize the contractile problems.

The majority of dosing regimens studied to date are multiple administrations with various doses and intervals to safely ripen the cervix and induce labor. The doses of misoprostol vary from 25, 50, and 100 mcg and intervals vary from a single vaginal insertion to applications every 2, 3, 4, 6 and 8 hour.[3-14, 39] Multiple doses are potentially prone to the adverse effects. One single dose of misoprostol for pre-induction cervical ripening should reduce the harmful events. As the cervix is ripened, the oxytocin is added. The oxytocin is time-honored medicine with proved efficacy and it is easy to reverse.

There are fewer studies in patients of single dosing regimens in cervical ripening.[32,33,40-42] They reported a single dose of 100 mcg misoprostol six to 24 hourly and all showed the efficacy, although uterine tachysystole occurred in 1.7 – 38%.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research questions and objectives

3.1.1 Research questions

Primary question

In pre-induction cervical ripening of term-pregnant women with an unripe cervix, did one single dose of 50 mcg vaginal misoprostol show at least 25 % difference in the mean change of Bishop score, assessed 24 hours after medication, compared to one single dose of 3 mg dinoprostone?

Secondary questions

Comparing one single dose of 50 mcg misoprostol to one single dose of 3 mg dinoprostone:

1. Was there any difference in the mean change of Bishop score, assessed 8 hours after administration of the study drug?
2. Was there any difference in the incidence of abnormal uterine contraction occurring within 8 hours after administration of the study drug?
3. Was there any difference in the incidence of vaginal delivery within 24, 48 hours after administration of the study drug?

3.1.2 Research objectives

General objective

To compare the efficacy and safety of one single dose of 50 mcg misoprostol and one single dose of 3 mg dinoprostone administered vaginally with 24 hours waiting for pre-induction cervical ripening in term-pregnant women who had the indication for induction of labor but with unripe cervices.

Specific objectives

1. To compare the mean change of Bishop score, assessed 24 hours after medication in patients given one single dose of 50 mcg misoprostol and one single dose of 3 mg dinoprostone.
2. To compare the mean change of Bishop score, assessed 8 hours after administration of the study drug.
3. To compare the incidence of abnormal uterine contraction occurred within 8 hours after administration of the study drug.
4. To compare the incidence of vaginal delivery occurring within 24, 48 hours after administration of the study drug.

3.1.3 Hypothesis

Research hypothesis

In pre-induction cervical ripening, one single dose of 50 mcg misoprostol showed at least a 25 % difference in the mean change of Bishop score, assessed 24 hours after medication compared to one single dose of 3 mg dinoprostone.

Statistical hypothesis

1. Null hypothesis

In pre-induction cervical ripening, the mean change of Bishop score assessed 24 hours after one single dose of 50 mcg misoprostol was equal to the change from one single dose of 3 mg dinoprostone.

2. Alternative hypothesis

In pre-induction cervical ripening, the mean change of Bishop score assessed 24 hours after one single 50 mcg of misoprostol was at least 25% different from one single 3 mg of dinoprostone.

3.2 Conceptual framework

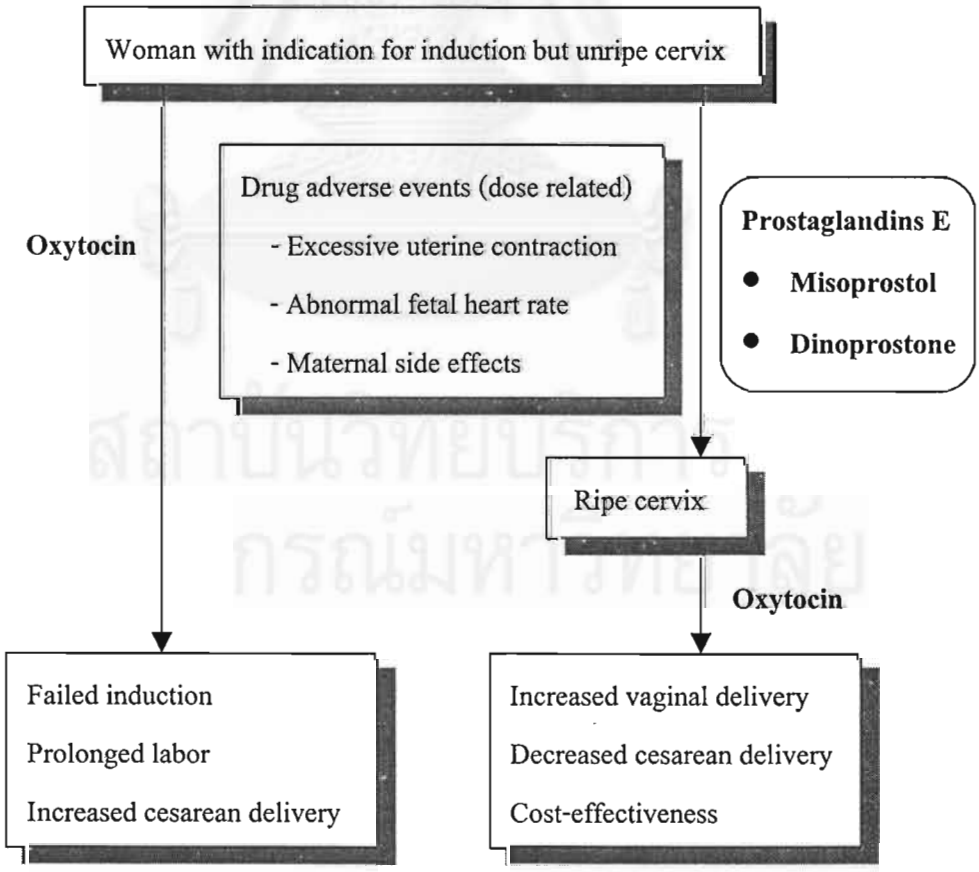

Figure 3.1 Flow chart of conceptual framework of the study

3.3 Key words

Pre-induction cervical ripening, misoprostol, dinoprostone.

3.4 Operational definition

Gestational age

The gestational age determined by the conformity of the calculation from last menstrual period, serial prenatal examination and prenatal ultrasonographic examinations.

Nullipara

The pregnant woman who had never delivered vaginally.

Multipara

The pregnant woman who had delivered vaginally for one to five times.

Bishop scoring system

A cervical scoring system used for assessment of labor inducibility , which numerically measured cervical dilatation, cervical effacement, cervical consistency, cervical position, and the station of the fetal presenting part. The definitions of each parameter of the Bishop scoring system in this study based on Cunningham et al.[43]

1. Cervical dilatation

The amount of cervical dilatation was ascertained by estimating the average diameter of the cervical opening at the level of internal os. The examining finger was swept from the margin of the cervix on one side to the opposite side, and the diameter traversed was expressed in centimeters.

2. Cervical effacement

The degree of obliteration or shortening of cervical canal from a length of about 2 centimeters, uneffaced cervix, to a mere circular orifice with almost paper thin edge. When the length of the cervix was reduced buy one half, it is 50% effaced, when the cervix became as thin as the adjacent lower uterine segment, it was completely, or

100%, effaced.[43] When the cervical ring was not equally effaced, the average degree was judged.

3. Cervical consistency

The *firm* consistency was considered when it was firm or firmer than the nasal ala. The *medium* cervix was soft close to the lip. The *soft* cervix was scored when soft and dilatable.

4. Cervical position

The relationship of the cervical os to the fetal head was categorized as posterior, middle, or anterior position.

5. Station of the presenting part

The level of the presenting fetal part in the birth canal was described in relationship to the ischial spine, which was half way between the pelvic inlet and the pelvic outlet. According to the Bishop scoring system, the station of the presenting part was "thirds" system. The designation was from -3 to +3 and assessed when there was no uterine contraction.

Each parameter was categorized and scored according to the extent of the assessment (table 3.1).

Table 3.1 Bishop scoring system

Score	0	1	2	3
Dilatation (cm)	Closed (internal os)	1-2	3-4	≥ 5
Effacement (%) from 2 cm	0-40	41-60	61-80	≥ 81
Consistency	Firm (nasal ala)	Medium (lip)	Soft and dilatable	_
Cervical position, relative to the presenting part	Posterior (to sacrum)	Middle	Anterior (direct to vaginal axis)	_
Station of the presenting part (when no contraction)	-3	-2	-1, 0	+1 to +3

Bishop score

The numerically cervical score evaluated by Bishop scoring system. The scores of all parameters were summed to obtain a cumulative score ranging from 0 to 13 points. The scores of patients whose labor entered active phase or delivered vaginally before the time of next score assessment were arbitrarily assigned to be 13 units.

Unripe cervix

A cervix with Bishop score 0-6.

Change of Bishop score

The change of Bishop score from the baseline score to the score at 8, 24 hours.

Active labor

Adequate uterine contraction of ≥ 3 regular contractions in 10 minutes with cervical dilatation ≥ 3 cm and 100% effacement.

Abnormal uterine contraction [44]

Abnormal uterine contractions assessed by cardiotocometer, occurred within 8 hours after start of the study drug.

- Tachysystole

The ≥ 5 contractions in ten minutes for two consecutive 10-minute periods.

- Hypertonus

A single uterine contraction that persisted for 90 seconds or more.

- Hyperstimulation syndrome

Tachysystole or hypertonus associated with non-reassuring FHR pattern.

Non-reassuring fetal heart rate (FHR) monitoring pattern [43]

Any non-reassuring FHR pattern within 8 hours of monitoring by tocometer as follows.

- Tachycardia

Baseline FHR was > 160 beats/min that persisted 15 minutes or longer in the absence of maternal infection. *Mild* tachycardia was between 161 and 180 beats/ min, and *severe* if ≥ 181.

- Bradycardia

Baseline FHR was < 120 beats / min that lasted 15 minutes or longer. *Mild* bradycardia was between 100 and 119, *moderate* if 80 to 99 and *severe* if less than 80 beats / min.

- Late deceleration

A symmetrical decrease in FHR beginning at or after the peak of the contraction and returning to baseline only after the contraction had ended. The repetitive patterns occurred in more than 35 % of uterine contractions.

- Repetitive moderate to severe variable deceleration

Persistent or recurrent variable wave forms that did not reflect the shape or intensity of associated uterine contraction curves.

1. The *moderate* variable decelerations were the decreasing of FHR to less than 70 beats /min and lasting 30-60 seconds.
2. The *severe* (significant) variable decelerations were the decreased FHR to less than 70 beats/min and lasting more than 60 seconds.

- Prolonged deceleration

An isolated deceleration lasted more than 60 seconds and less than 15 minutes.

- Decreased beat-to-beat variability

Decreased beat-to-beat variability was defined as the FHR baseline that was flat or nearly flat with diminished short-term variability to $\leq$ 5 beats/min.

Start to vaginal delivery time

The time in hours counted from the start of the study drug to the vaginal delivery.

Maternal side effects

The untoward clinical features occurred in the pregnant woman after receiving the study drugs. They were nausea, vomiting, diarrhea, pyrexia, and postpartum hemorrhage.

Neonatal outcomes

The neonatal outcomes included birth weight, meconium stained amniotic fluid, Apgar score at one and five minutes, and admission to the neonatal intensive care unit (NICU).

3.5 Research design

This study was fully conducted as a double-blind randomized controlled trial.

3.5.1 Research design model

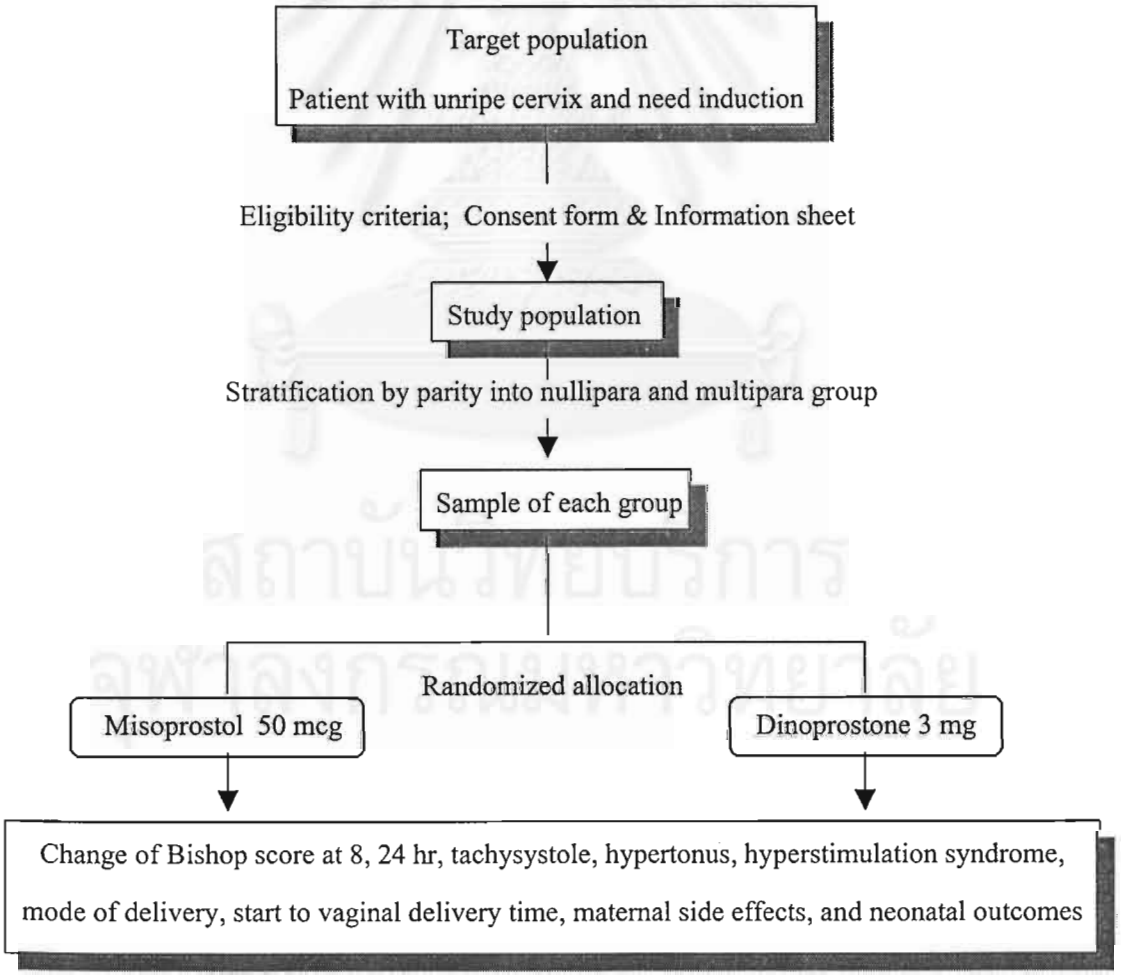

Figure 3.2 Flow chart of research design model

3.6 Population and sample

3.6.1 Target population

The pregnant women indicated for induction of labor with unripe cervices.

3.6.2 Study population

The non-private pregnant women who fulfilled the eligibility criteria at Bangkok Metropolitan Medical College and Vajira Hospital, the Bangkok Metropolis, Thailand.

3.6.3 Eligibility criteria

Inclusion criteria

1. Singleton pregnancy with gestational age ≥ 37 weeks in cephalic presentation and absence of true labor pain.
2. Unripe cervix (Bishop score 0-6).
3. Reactive fetal heart rate tracing.
4. Intact fetal membrane with no prior membrane strippling.
5. Obstetric or medical indications for induction of labor.
    1) Gestational age ≥ 41 weeks.
    2) Oligohydramnios.
    3) Intrauterine growth retardation.
    4) Pre-eclampsia.
    5) Chronic hypertension.
    6) Diabetes mellitus.

Exclusion criteria

1. Suspected cephalo-pelvic disproportion (CPD).
2. Estimated fetal weight > 4,000 grams.
3. Parity > 5.
4. Previous cesarean section and other uterine surgeries.
5. Suspected chorio-amnionitis.
6. Any contraindications to vaginal delivery.
    1) Placenta previa.
    2) Unexplained vaginal bleeding
    3) Vasa previa.
    4) Forelying umbilical cord.
    5) Active genital herpes infection.
7. Contraindications to the use of prostaglandins.
    1) Known hypersensitivity to misoprostol or prostaglandins.
    2) History of asthma, glaucoma.
8 Moderate to severe pre-existing medical diseases such as renal diseases, cardiovascular diseases, hepatic diseases.

3.6.4 Sample size estimation

The primary outcome measure was the change in Bishop score. The sample size formula for two independent means is: $n = 2[Z_{\alpha/2} + Z_{\beta}]^2 S_p^2/(\bar{X}_1 - \bar{X}_2)^2$. This formula is based on two-sample, independent-groups *t* test. The assumptions needed are (1) normally distributed observations in both groups, (2) equal variances or standard deviations in the two groups, (3) the observations occur independently.

The pilot study for assessment of Bishop score changes was performed. The pregnant women, whose characteristics were similar to the study group, received 3 mg

dinoprostone or 50 mcg misoprostol. Twenty four hours after receiving dinoprostone, ten women showed mean Bishop score change of 6.0 (SD 3.33). Sixteen misoprostol-treated women showed mean Bishop score change of 4.5 (SD 2.13). On Kolmogorov-Smirnov test of normality and Levene test of homogeneity of variances showed that both pilot groups were normally distributed and had equal variances. A 25% mean change difference of score, 1.5 units, was clinically important. Supposed in administering misoprostol to the woman with the most unripe cervix, Bishop score would change from zero to 4.5. This value was accepted as successful ripening.

A sample size per group was determined to give 90 % power of detecting a mean change difference of 25% in either direction between misoprostol and dinoprostone with alpha of 0.05.

$$n = 2[Z_{\alpha/2} + Z_{\beta}]^2 S_p^2 / (\bar{X}_1 - \bar{X}_2)^2$$

$$Sp^2 = 2.65^2$$

$$n = 2 [1.96 + 1.28]^2 (2.65)^2 / (6.0 - 4.5)^2 = 65.26 \text{ or } 66 \text{ per group}$$

3.6.5 Randomized allocation method

To prevent allocation bias, the patients were stratified by parity to nullipara and multipara group. Stratified randomization with random permuted blocks was used to allocate the treatment in this study.[45] The method was to produce a separate block randomization list for each stratum. It was essential that stratified treatment allocation was based on block randomization within each stratum other than simple randomization. Otherwise there would be no control of balance of treatments within strata, and so the object of stratification would be defeated in clinical trials which were not very large.

The patients in each stratum were assigned by a random number table with blocks of size four to receive a single dose of 50 mcg misoprostol or 3 mg

dinoprostone. The allocation was concealed by placing the patients' assignments in consecutively numbered opaque envelopes that were drawn in ascending consecutive order. Eligible subjects were assigned to a sequential study number.

The codes in the envelopes were broken at the end of the study or when serious complications occurred, such as frequent occurrence of abnormal uterine contraction, uterine rupture from the uterotonic effect of the studied drugs.

3.7 Intervention

3.7.1 Preparation of the medication

Misoprostol 50 mcg

The misoprostol available in Thailand is Cytotec oral tablet (200 mcg, Searle, Illinois, USA). For preparation of misoprostol 50 mcg, Cytotec was weighed on electronic balance "Ohaus- model AP 210S" (Ohaus Corporation, USA). The minimal readability of the Ohaus balance was 100 mcg. The mean weight of each tablet was 0.2090 gram, composed of active ingredient, misoprostol 200 mcg, and supporting inactive powder. After weighing, Cytotec was bisected into two nearly equal pieces. Each half was gradually trimmed and weighed to be exactly one-fourth of its original tablet. The prepared drug was kept in a clean dry bottle at room temperature.

Dinoprostone 3 mg

Each dinoprostone vaginal tablet was in the original foil (Prostin-E2, Upjohn, USA) and was kept in the refrigerator.

3.7.2 Procedure

The protocol was approved by the Institutional Review Board and conducted at Bangkok Metropolitan Medical college and Vajira Hospital, the tertiary health center hospital of the Bangkok Metropolis, Thailand. Obstetric and gynecologic residents under the supervision of the staff provided the patient care.

The procedures in this study were:

1. After determining the indication for induction, a resident performed a digital cervical examination in each patient, assigned the Bishop score and notified the investigators.
2. One of two investigators reassessed the selection criteria in each patient. Informed consent was signed after proper counseling and describing the detail of the study including the nature of the subject's involvement in it. (appendix 1, 2).
3. An intravenous line was placed. The cardiotocometer was started for 30 minutes before drug administration to ensure the normal FHR tracing and absence of regular uterine contraction within 10 minutes.
4. One of two investigators assessed the initial Bishop score at 8.00 o'clock.
5. A resident, who is not involved in the outcome assessment, inserted the randomized drug into the posterior vaginal fornix. The placement of the drug was seen through the vaginal speculum.
6. The patient was left in supine or lateral position for at least one hour. Vital signs and side effects were monitored every one hour.
7. The cardiotocometer continuously monitored fetal heart activity and uterine contraction for 8 hours.
8. One of two investigators, blinded to the study drugs, assessed the Bishop score at 16.00 o'clock. Otherwise, the pelvic examination before 24 hours of drug insertion was not allowed unless there was active labor.

9. Oxytocin infusion as well as amniotomy was not employed within 24 hours of drug insertion.
10. Treatment of uterine abnormality was given in both groups when there were tachysystole or hypertonus of pressure amplitude > 30 mmHg with or without non-reassuring FHR. The terbutaline 250 mcg was administered intravenously. This tocolytic agent was repeated if there were recurrent episodes of uterine abnormality. The intra-uterine resuscitation was given in patient having non-reassuring FHR pattern, consisted of a change in maternal position to lateral or supine position, five liters of oxygen via nasal cannula, and close observation. The patients with abnormal contraction would be monitored continuously until delivery. The cesarean section would be performed in the patient with persistent hyperstimulation syndrome, or threatened uterine rupture.
11. One of two investigators reassessed the cervical Bishop score at 24 hours after medication and prescribed the oxytocin to augment the labor.
12. Artificial rupture of the membranes was performed, when the patient entered active labor and was clinically safe.
13. The other management was conducted according to routine intrapartum and postpartum care by the residents. All medical personnel are blind to the allocation of the study drug.

3.8 Observation and outcome measurement

3.8.1 Primary outcome measure

The primary outcome was the change of Bishop score at 24 hours after insertion of the study drug. The Bishop scoring system was used to assess the cervical

ripeness, which numerically measured cervical dilatation, cervical effacement, cervical consistency, cervical position, and the station of the fetal presenting part.

Validity of Bishop scoring system

The Bishop scoring system is the best and simplest method to determine the duration and safety of induced labor.[17] The system has content validity, although the correlation between each parameter and successful labor induction appear to be varied. Another limitation is the subjectivity of cervical examination, but the use of objective criteria and numerical scoring has substantially reduced this source of error.

Pretesting for reliability of Bishop scoring system

The reliability is the extent to which repeated measurements of a relatively stable phenomenon fall closely to each other. The pretest for the reliability of the Bishop scoring system was conducted in the Department of Obstetrics and Gynecology, Bangkok Metropolitan Medical College and Vajira Hospital. The two investigators were standardized and tested for inter-rater reliability.

The standardization was as followed.

1. Defined the detail of five parameters and weights of the categories of each parameter.
2. Assessed the cervix and scored the cervical ripeness of the patients.
3. Calculated the reliability coefficient of Bishop score.
4. Corrected the cause of low reliability.

Two investigators blindly examined twenty patients, whose characteristics were similar to the study population. Bishop score was tested for reliability by calculating the intraclass correlation coefficient (ICC) (appendix 3). The inter-observer reliability of Bishop score was almost perfect with ICC of 0.92.

Secondary outcome measures

The secondary outcome variables were as follows.

1) The change of Bishop score at 8 hours after insertion of the studied drug.
2) The uterine tachysystole, hypertonus, and the hyperstimulation syndrome. The fetal heart action and uterine activity were monitored through the maternal abdominal wall by the external detectors, the external electronic fetal monitoring (cardiotocometer, Hewlett Packard series 50A). The FHR pattern was detected using the ultrasound Doppler principle. The transducer with a sensor is placed on the maternal abdomen at a site where fetal heart action was best detected. The uterine activity was detected by a sensor device on the most contractile area of the uterine fundus. Both sensors were held in position by the belts. The fetal tracing was interpreted by a chief resident who is in charge of delivery room. After delivery, the fetal monitor strips of each patient were reviewed by one blind perinatologist.
3) The mode of delivery.
4) The time interval from the start of study drug to vaginal delivery.
5) Vaginal delivery within 24, 48 hours.
6) The maternal side effects, i.e. nausea, vomiting, diarrhea, pyrexia, and postpartum hemorrhage.
7) The neonatal outcomes: birth weight, Apgar score at one and five minutes, presence of meconium stained amniotic fluid, and admission to the NICU.

3.9 Data collection

The baseline data and outcome variables were collected in the data collection form (appendix 4).

3.9.1 Primary source

The investigators assessed the cervical ripeness. The examinations were performed exactly before the start of medication, at eight hours, and at 24 hours after administration of the studied drug and recorded in the collection form.

3.9.2 Secondary source

The resident blinded to the study drugs recorded the progress of labor, the delivery, and postpartum. The investigators collected the baseline data and secondary outcomes as noted in the labor record and post-partum record from the patient file.

3.10 Data analysis

Data were analyzed on an intention-to-treat basis by parametric and nonparametric statistics, using SPSS 7.5. Descriptive statistics were used for demographic baseline data and summarized as mean with standard deviation (SD), or median with range, or proportion and compared in both groups (table 3.2). Continuous variables were examined for normal distribution (Kolmogorov-Smirnov test, probability plots) before using parametric statistics. Differences between continuous variables were evaluated with the unpaired *t* test for variables that were normally distributed and the Mann-Whitney *U* tests for variables that were not normally distributed (table 3.2).

Categorical variables were evaluated by Chi squared (χ^2) test, or Fisher's exact test as appropriate. All tests were two-sided. The primary outcome measure was considered significant only if $p < 0.05$. Other analyses for secondary outcomes should be considered hypothesis generating. The significance for all secondary outcomes was $p < 0.001$ to account for multiple testing, a conservative approach.

Table 3.2 Statistical analyses for demographic data and outcome variables

Variables	Data summary/ Test of differences	Statistical test
Demographic data		
Age (yr)	Mean, SD	
Height (cm), weight (kg), Hct (vol %)	Mean, SD	
Gravidity, parity	Proportion	
Gestational age (wk)	Mean, SD	
Indication for induction	Proportion	
Initial Bishop score	Mean, SD	
Primary outcome		
Bishop score at 24 hours	Mean, SD, 95% CI	Unpaired *t* test
Change of score at 24 hours	Mean, SD, 95% CI	Unpaired *t* test
Secondary outcomes		
Bishop score at 8 hours	Mean, SD, 95% CI	Unpaired *t* test
Change of score at 8 hours	Mean, SD, 95% CI	Unpaired *t* test
Abnormal uterine contraction	Proportion, OR (95% CI)	Chi-square
Tachysystole	Proportion	Chi-square
Hypertonus	Proportion	Chi-square
Hyperstimulation syndrome	Proportion	Chi-square
Need of terbutaline	Proportion	Chi-square
Vaginal delivery in 24, 48 hours	Proportion, OR (95% CI)	Chi-square
Mode of delivery	Proportion	Chi-square
Start to vaginal delivery time (hr)	Mean, SD	Unpaired *t* test
Maternal side effects		
Nausea, vomiting, diarrhea, pyrexia	Proportion	Chi-square
Postpartum hemorrhage	Proportion	Chi-square
Neonatal outcomes		
Birth weight (gm)	Mean, SD	Unpaired *t* test
Meconium stained amniotic fluid	Proportion	Chi-square
Apgar score at 1, 5 minutes	Mean, SD	Unpaired *t* test
Admission to intensive care unit	Proportion	Chi-square

Item of analysis

1. Data summary.
2. Statistical test of differences and association between two groups.
3. Problem cases. The solution for drop out case was to compute and compare the value of interest as the worst outcome, the best outcome, and the group average.
4. Interim analysis when there were frequent side effects or severe complications, such as frequent occurrence of abnormal uterine contraction, uterine rupture from the uterotonic effect of the studied drugs.
5. Interpretation when there was statistical significance or non- significance about clinical importance, power and 95% confidence interval.

3.11 Ethical considerations

1. Described the detail of the study and the nature of subject's involvement in it and clearly replied to the questions and misunderstandings.
2. The research proposal were approved by the Institutional Review Board.
3. The increase in uterine hyperstimulation was a matter concern. The investigators closely monitored the fetal heart rate pattern and maternal status after use of misoprostol. If adverse effects occur, they would be immediately managed.
4. The patients were completely free to refuse participation or drop out at any time.
5. Information sheet and consent form for every patient.

3.12 Limitation

The Bishop score indicates the cervical ripeness. The higher the number, the greater the ripeness and inducibility of labor. Most investigators classify the cervix into three groups, depending on the degree of inducibility: favorable, intermediate favorable and unfavorable cervix. In the favorable cervix (score more than 8), there were no induction failures.[1] The beneficial effect of the use of prostaglandin cervical priming in women with intermediate Bishop score at entry (score 4-6) has been reported, resulting in an improved chance of vaginal delivery.[46] The women who have the Bishop score at entry of 3 or less have significantly higher rates of failed induction and of cesarean delivery than those with Bishop score above 3.[47] It is worth to ripe the intermediate and unfavorable cervix prior to induction of labor. In this study we defined an unripe cervix as a cervix with the Bishop score 0-6. The result could not be applicable to 0-3 score. The cervix with score 0-3 and 4-6 subgroups were evaluated separately.

3.13 Benefits of the study

The need to ripen the cervix prior to the onset of induction of labor has become an important issue in Obstetrics and also the cost-benefit. One misoprostol tablet costs 50 times less than one dinoprostone tablet. The result of the study would impact the obstetric practice if one single dose misoprostol was as efficacious as dinoprostone especially if it was with acceptable side effects.

3.14 Obstacles

1. The pregnant women receiving cervical ripening agent need closely monitoring. The continuous electronic monitoring was burden to health personnel in

the labor room. The study of absorption kinetics of misoprostol with vaginal administration of 400 mcg had shown that serum levels of the principal metabolite rose gradually, reached maximum levels between 60 and 120 minutes, and declined slowly, to 62% of the peak level at 240 minutes after administration.[26] The majority of tachysystole manifested within 6 hours of administration.[3] In this study, electronic monitoring continued for eight hours unless there was no adverse effect.

2. The dinoprostone vaginal tablet was expensive. Funding was needed for the coverage of the sample size.

3.15 Administration and time schedule

The study took three months for literature review, pilot study, and proposal development . The rate of patient accrual was three to four cases per week so it took around 12 months for data collection. The data were analyzed and followed by the thesis writing. The corrected thesis would be submitted in time.

	1998	1999				2000
	Sep-Dec	Jan-Mar	Apr-June	July-Sep	Oct- Dec	Jan – April
- Formulate the problem	----					
- Literature review	----------					
- Proposal development and submission	--------					
- Collect the data	----------	----------	----------	----------	----------	
- Data analysis					-----	
- Thesis writing					--------	
- Thesis submission and defense						------

CHAPTER 4

RESULTS

From November 1998 to December 1999, there were 6,851 deliveries in the labor ward. The 143 pregnant women who had indications for induction of labor and fulfilled the eligibility criteria were enrolled in the study. By the parity-stratify randomization, the patients were allocated to receive misoprostol in 72 cases and dinoprostone in 71 cases. In misoprostol group, 5 out of 72 (5/72, 6.9%) patients delivered within 8 hours and 32/72 (44.4%) delivered within 24 hours as presented in figure 4.1. All patients in misoprostol group delivered during hospitalization.

In dinoprostone group, 3/71 (4.2%) patients delivered within 8 hours and 23/71 (32.4%) delivered within 24 hours. Two patients in dinoprostone group withdrew from the study. Both refused further treatment when they did not enter true labor after two days of admission. The 24-hour Bishop score, which was the primary outcome, was obtained and analyzed. However, secondary outcomes, such as mode of delivery, were unknown. We omitted these patients in the analysis of the secondary outcomes.

The number of patients analyzed for the primary outcome in both groups, 68 versus 68, covered the number of sample size calculated, i.e. 66 per group (chapter 3).

4.1 Demographics

Demographic baseline data are presented in table 4.1. The maternal characteristics of two groups were comparable with respect to age, height, weight, hematocrit, gestational age, gravidity and parity. Approximately two-thirds of both groups were nulliparae.

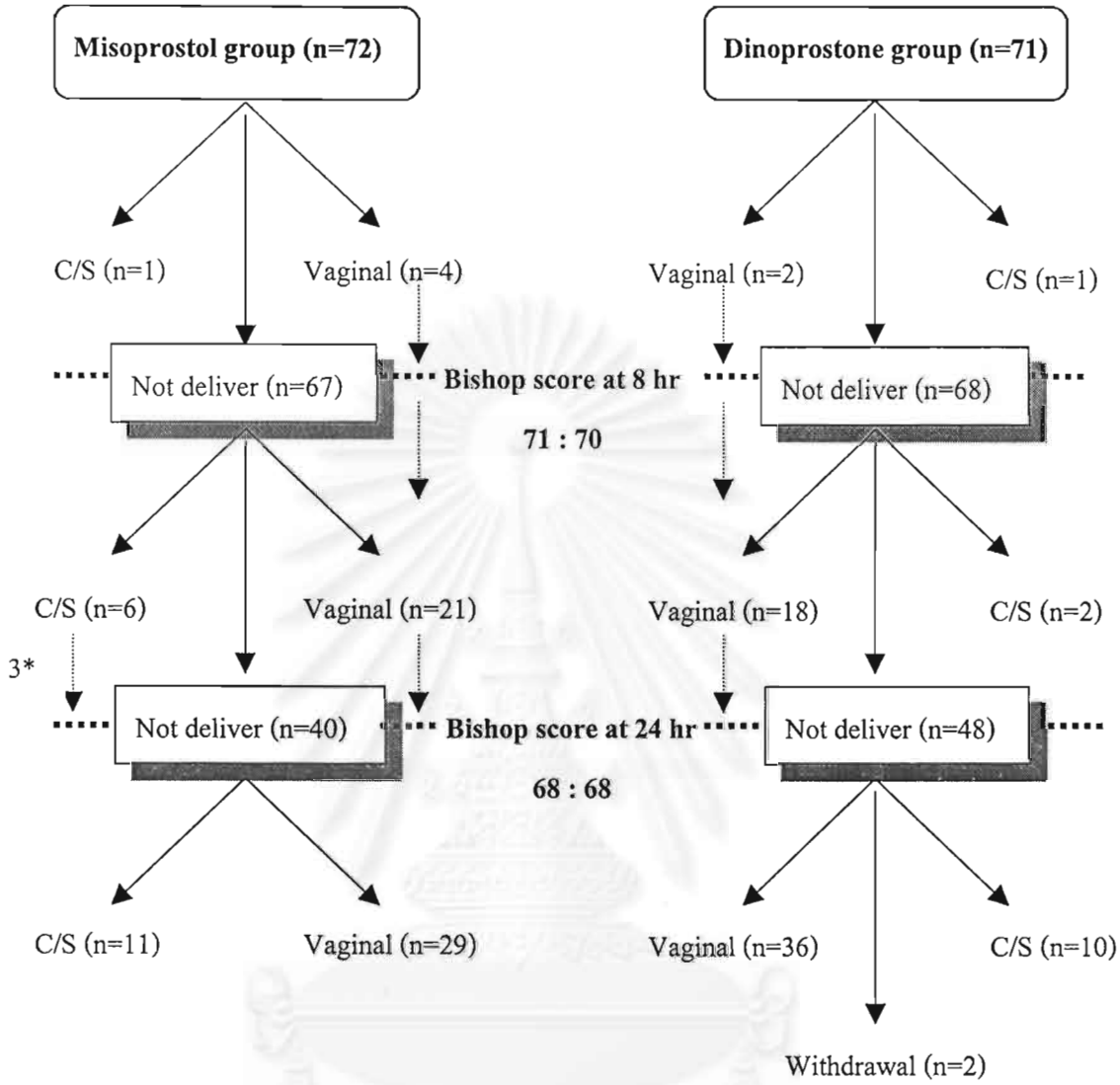

Figure 4.1 Flow chart of deliveries of patients receiving misoprostol or dinoprostone.

The Bishop scores of subjects whose labor entered active phase or delivered vaginally before 24 hours were arbitrarily assigned to be 13 units. The dotted down-arrow indicated the patients whose the Bishop scores were included in the analysis of score change. At eight hours after administration of the study drug, 71 subjects in misoprostol group and 70 subjects in diprostone group were assessed for the Bishop score. At 24 hours after administration of the studied drug, 68 subjects in misoprostol group, including three cesareans* during 8-24 hours, and 68 patients in dinoprostone group were assessed for the Bishop score. (C/S = delivered by cesarean section).

Table 4.1 Comparison of demographic data between two groups.

	Misoprostol (n=72)	Dinoprostone (n=71)	*P*
Age (yr)			
Mean (SD)	24.7 (5.25)	24.5 (4.30)	
Median (range)	24 (15-38)	24 (16-37)	0.902**
Height (cm)			
Mean (SD)	154.6 (6.38)	154.4 (5.40)	0.831*
Median	154.0 (140.0-173.0)	154.0 (144.0-170.0)	
Weight (kg)			
Mean (SD)	67.0 (10.83)	65.9 (10.39)	
Median (range)	65.1 (54.7-94.3)	63.3 (50.0-106.0)	0.566**
Hct (vol%)			
Mean (SD)	34.3 (3.26)	34.8 (3.42)	0.428*
Median	34.2 (27.4-42.3)	35.0 (26.0-44.0)	
Gestational age (wk)			
Mean (SD)	40.9 (1.33)	41.1 (1.05)	
Median (range)	41 (37-42)	41 (38-42)	0.278**
Number of primigravidae	42 (58.3%)	36 (50.7%)	0.454#
Number of nulliparae	47 (65.3%)	48 (67.6%)	0.906#

* Unpaired *t* test. ** Mann-Whitney *U* test. # χ^2 with continuity correction.

Table 4.2 Comparison of primary indications for induction of labor between two groups.

	Misoprostol (n=72)	Dinoprostone (n=71)	*P*
Gestational age ≥ 41 wk	46 (63.9%)	50 (70.4%)	0.549#
Oligohydramnios	18 (25.0%)	13 (18.3%)	df = 2
Pre-eclampsia	8 (11.1%)	6 (8.5%)	
Chronic hypertension	0	1 (1.4%)	
Diabetes mellitus	0	1 (1.4%)	

χ^2, *P* by gestational age, oligohydramnios and pre-eclampsia.

Table 4.2 compares the primary indications for labor induction in the two groups, which were similar. The gestational age ≥ 41 weeks and oligohydramnios accounted for the majority of cases, which were 64 out of 72 (64/72, 88.9%) in misoprostol group compared to 63/71 (88.7%) in dinoprostone group.

The initial Bishop score is presented in table 4.3. The scores in both groups were not normally distributed, (Kolmogorov-Smirnov test, $p < 0.001$ in both groups). Therefore, the Mann-Whitney *U* test was used in statistical test of difference.

The median score were 3.5 with the range of 0-6 in misoprostol group which was comparable to 4.0 (0-6) in dinoprostone group. The patients with score less than four were 36/72 (50%) in misoprostol group compared to 33/71 (46.5%) in dinoprostone group, which was not significantly different. .

Table 4.3 Comparison of initial Bishop score between two groups.

	Misoprostol (n=72)	**Dinoprostone (n=71)**	***P***
0	1 (1.4%)	1(1.4%)	
1	4 (5.5%)	3 (4.2%)	
2	12 (16.7%)	12 (16.9%)	
3	19 (26.4%)	17 (23.9%)	
4	17 (23.6%)	12 (16.9%)	
5	4 (5.6%)	8 (11.3%)	
6	15 (20.8%)	18 (25.4%)	
Mean (SD)	3.7 (1.57)	3.9 (1.63)	
95 % CI	3.3 to 4.0	3.5 to 4.3	
Median (range)	3.5 (0-6)	4.0 (0-6)	0.481**
Score less than 4	36 (50.0%)	33 (46.5%)	0.800#

** Mann-Whitney *U* test. # χ^2 with continuity correction.

4.2 Effects in eight hours.

Delivery within eight hours

There were four vaginal deliveries within 8 hours after insertion of misoprostol (table 4.4). One cesarean section was performed due to fetal distress characterized by severe variable deceleration. The fetal tracing showed normal FHR prior to the administration of misoprostol. Thirty minutes from the start of the drug, the tracing displayed mild variable deceleration, with unremarkable uterine contraction (1-2 contractions in 10 minutes). The intrauterine resuscitation was given and the FHR tracing still showed infrequent deceleration pattern. Two hours later, the tracing showed uterine hypertonus with persistent severe variable deceleration. The staff in charge of the labor ward decided to perform emergency cesarean section for fetal distress with oligohydramnios and thick meconium stained amniotic fluid without the administration of the tocolytic agent. The baby was delivered with normal Apgar score.

In dinoprostone group, there were two vaginal deliveries and one cesarean delivery. The cesarean section was performed due to persistent bradycardia with oligo-hydramnios, which occurred four hours after drug insertion. No abnormal uterine contraction was observed in this case.

Table 4.4 Comparison of delivery within 8 hours between two groups.

	Misoprostol (n=72)	Dinoprostone (n=71)	*P*
Not delivered	67 (93.1%)	68 (95.8%)	
Vaginal delivery	4 (5.5%)	2 (2.8%)	>0.05[#]
Cesarean delivery	1 (1.4%)	1 (1.4%)	
Fetal distress	1*	1	

* Hyperstimulation syndrome, oligohydramnios and thick meconium stained amniotic fluid.

[#] Fisher's exact test, *P* by vaginal and cesarean delivery.

Change of bishop score at 8 hours

One cesarean section in each group operated for fetal distress before entering the active phase. The Bishop score at 8 hours could not be assessed in these two patients. Therefore, there were 71 and 70 patients in misoprostol and dinoprostone groups were assessed for Bishop score at 8 hours (figure 4.1).

Table 4.5 shows the Bishop score at 8 hours after insertion of the study drugs. The 8-hour scores and change of score in both groups were not normally distributed, (Kolmogorov-Smirnov test, $p < 0.05$ in both groups). Therefore, the Mann-Whitney *U* test was used in statistical test of difference.

The initial median score in misoprostol group was 3.5 (0-6) units which changed to be 7 (0-13) compared to the score change from the initial median score of 4 (0-6) to be 7 (1-13) in dinoprostone group (table 4.3 and 4.5). The median change score in misoprostol group was 1 unit more than in dinoprostone group (table 4.5), but the difference was not of statistical significance, ($p = 0.169$).

Table 4.5 Comparison of Bishop score at 8 hours between two groups.

	Misoprostol (n=71)	**Dinoprostone (n=70)**	***P***
8 - hour score			
Mean (SD)	7.1 (3.44)	6.5 (2.95)	
95% CI	6.3 to 7.9	5.8 to 7.2	
Median (range)	7 (0-13)	7 (1-13)	0.294**
Change of score			
Mean (SD)	3.5 (3.09)	2.6 (2.29)	
95% CI	2.7 to 4.2	2.1 to 3.2	
Median (range)	3 (0-10)	2 (0-7)	0.169**

** Mann-Whitney *U* test. $^{\#}\chi^2$ with continuity correction.

4.3 Effects in twenty-four hours

Delivery during 8-24 hours

Between 8-24 hours after insertion of the study drugs (figure 4.1), there were 21 out of 67 (21/67, 31.3%) vaginal deliveries and 6/67 (9.0%) cesarean sections in misoprostol group compared to 18/68 (26.5%) vaginal deliveries and 2/68 (2.9%) cesarean deliveries in dinoprostone group, a non-significant difference (p = 0.437). The primary indications in misoprostol group were fetal distress (4/6), arrest pattern (2/6). The indications in dinoprostone group were fetal distress (2/2). No cesarean section was done due to hyperstimulation during this period.

Change of Bishop score at 24 hours – the primary outcome

The scores of subjects whose labor entered active phase or delivered vaginally before 24 hours were arbitrarily assigned to be 13 units. Three out of six cesarean cases in misoprostol group entered the active labor. Therefore, the Bishop scores at 24 hours were assessed in 68 cases of each group (figure 4.1).

Table 4.6 shows the Bishop score at 24 hours after insertion of the study drugs. The 24-hour scores in both groups were not normally distributed, (Kolmogorov-Smirnov test, $p < 0.001$ in both groups). The Mann-Whitney U test was used to test the difference of 24-hour score. The 24-hour median score in misoprostol group were 10 (3-13) compared to 10 (1-13) in dinoprostone group, a non-significant difference.

For the 24-hour score change, which was the primary outcome, the probability plots (P-P plots, SPSS 7.5) of both groups revealed points clustered around a straight line, which indicated the normal distribution. Therefore, unpaired t test was used to test the difference of 24-hour score change between two groups.

The mean change score from initial score to 24-hour score in misoprostol-treated patients was 6.5 (SD, 3.01) compared to 5.5 (SD, 2.93) in dinoprostone-treated patients. The score change in misoprostol group was one unit more than that of dinoprostone group (95%CI, 0.04 to 2.1), a statistically significant difference (p = 0.042). This confidence interval meant that with probability 0.95 the true score change difference lied between 0.04 to 2.1. The interval not includes zero meant that the difference was significant because the difference was in the same direction. However, there was a 1 in 20 chance that the true difference was outside this interval.

Table 4.6 Comparison of Bishop score at 24 hours between two groups.

	Misoprostol (n=68)	**Dinoprostone (n=68)**	**Difference(95% CI)**	***P***
24 - hour score				
Mean (SD)	10.1 (2.91)	9.4 (3.32)		
95% CI	9.4 to 10.8	8.6 to 10.2		
Median (range)	10 (3-13)	10 (1-13)		0.173**
Change of score				
Mean (SD)	6.5 (3.01)	5.5 (2.93)	1.0 (0.04 to 2.1)	0.042*
95% CI	5.8 to 7.2	4.8 to 6.2		
Median (range)	7 (0-12)	5 (0-11)		

* Unpaired t test. ** Mann-Whitney U test.

The subgroup of patients with initial score 0 to 3 and 4 to 6 were analyzed separately (table 4.7). In 0-3 score group, the mean change in score at 24 hours in misoprostol-treated patients group was 1.5 units higher than dinoprostone-treated patients with 95 % CI, -0.1 to 3.1 (p = 0.072), a non-significant difference. In 4-6 score group, the mean change in score at 24 hours in misoprostol group was 0.6 units higher than dinoprostone group with 95 % CI, -0.6 to 1.8 (p = 0.346), a non-significant difference.

Table 4.7 Comparison of Bishop score at 24 hours between two groups stratified by intial score of 0-3 and 4-6.

	Misoprostol	Dinoprostone	Difference(95% CI)	*P*
Score 0-3	**(n=33)**	**(n=31)**		
Initial median score	3 (0-3)	2 (0-3)		0.900**
24 - hour median score	9 (3-13)	8 (1-13)		0.065**
Mean change (SD)	7.3 (3.17)	5.8 (3.37)	1.5 (-0.1 to 3.1)	0.072*
95% CI	6.2 to 8.5	4.6 to 7.1		
Score 4-6	**(n=35)**	**(n=37)**		
Initial median score	5 (4-6)	5 (4-6)		0.212**
24 - hour median score	11 (3-13)	10 (4-13)		0.726**
Mean change (SD)	5.7 (2.67)	5.1 (2.51)	0.6 (-0.6 to 1.8)	0.346*
95% CI	4.8 to 6.6	4.3 to 6.0		

* Unpaired *t* test. ** Mann-Whitney *U* test.

Competing event with best/worst/average outcome analysis

The 24-hour scores were not assessed in four cesarean deliveries in misoprostol group and three in dinoprostone group. The exclusion of such patients from the analysis may lead to controversy.[48] Assigned the most optimistic outcome, score change to 13 to these patients, the analysis revealed a non-significant difference in change of 24-hour score between two groups, 6.5 (SD, 3.40) versus 5.7 (SD, 2.99), (p = 0.133). When repeated the analysis with the most pessimistic outcome, no change of score, the difference was also non-significant, 6.11 (SD, 3.36) versus 5.3 (SD, 3.07), (p = 0.114). With the average outcome, there was statistically significant difference in mean change of score, 6.5 (SD, 3.01) versus 5.5 (SD, 2.86), (p = 0.047).

Delivery within 24 hours

Table 4.8 shows the delivery within 24 hours. The delivery rate in misoprostol group was higher, 44.4% versus 32.4%, with odds ratio (OR)1.7 (95% CI, 0.9 to 3.3), a non- significant difference, ($p = 0.191$). The CI included one meant that the difference was not of significant because the interval was in opposite directions. However, the OR could be nothing or nearly double that. This illustrated the small numbers of patients. The cesarean deliveries were higher in misoprostol group, 7/32 (21.9%) versus 3/23 (13%) of the deliveries, which was not significantly different ($p = 0.494$).

Table 4.8 Comparison of delivery within 24 hours between two groups.

	Misoprostol (n=72)	Dinoprostone (n=71)	OR (95%CI)	*P*
Delivery	32 (44.4%)	23 (32.4%)	1.7 (0.9 to3.3)	0.191[#]
- Vaginal delivery	25 (34.7%)	20 (28.2%)		0.494[##]
- Cesarean delivery	7 (9.7%)	3 (4.2%)		
Fetal distress	5	3		
CPD/arrest pattern	2	0		

[#] χ^2 with continuity correction. [##] Fisher's exact test, *P* by vaginal and cesarean delivery.

Table 4.9 shows the data of cesarean delivery for fetal distress within 24 hours

Table 4.9 Comparison of data of cesarean delivery for fetal distress within 24 hours between two groups.

	Misoprostol (n=5)	Dinoprostone (n=3)
Gestational age ≥ 41 wk	4	0
Oligohydramnios	3	3
Non-reassuring fetal heart rate	4	3
Hyperstimulation syndrome*	1	0
Thick meconium stained amniotic fluid	2	0

Each case may have more than one item. * Delivered by C/S three hours after medication.

after drug insertion. Oligohydramnios was the most common fining, occurred in 3/5 patients in misoprostol group and 3/3 in dinoprostone group. These six patients had unremarkable uterine contraction and operations were performed during 8-24 hours.

4.4 Abnormal uterine contraction

Table 4.10 shows the abnormal contraction within 8 hours (tracing displayed in appendix 5). Abnormal contraction occurred more in misoprostol, 7/72 (9.7%) versus 5/71 (7.0%), with odds ratio of 1.4 (95% CI, 0.4 to 4.7), a non-significant difference (p = 0.782). The rate of hyperstimulation syndrome was higher in misoprostol group, 5/72 (6.9%) versus none, but non-significantly different, (p = 0.058).

Table 4.10 Comparison of abnormal uterine contraction within 8 hours between two groups.

	Misoprostol (n=72)	**Dinoprostone (n=71)**	**OR (95%CI)**	***P***
Abnormal uterine contraction	7 (9.7%)	5 (7.0%)	1.4 (0.4 to 4.7)	0.782[#]
- Tachysystole	2	4		
- Hypertonus	0	1		
- Hyperstimulation syndrome	5	0		0.058[##]
• Contraction				
Tachysystole	2			
Hypertonus	2			
Tachysystole + hypertonus	1			
• Fetal heart rate				
Tachycardia	3			
Bradycardia + prolonged DC	1			
Late DC	1			
Start to occurrence (hr), median (range)	2.4 (0.6-7.0)	2.3 (0.8-3.5)		0.808**
Terbutaline requirement	3 (42.9%)	2 (40.0%)		

[#] χ^2 with continuity correction. [##] Fisher's exact test. ** Mann-Whitney U test.

Median time from start of misoprostol to first occurrence of abnormal contraction was 2.4 hours. The 3/7 (42.9%) cases in misoprostol group developed abnormal contraction later than four hours with the latest occurrence of 7.0 hours. This patient had unremarkable uterine contraction after receiving misoprostol until she developed abrupt tachysystole with fetal tachycardia seven hours later. Two doses of 250 mcg terbutaline were given, one hour apart. After intra-uterine fetal resuscitation, the contraction and fetal heart rate tracing were normalized. The labor progressed until it arrested at 7-cm cervical dilatation and cesarean section was performed for CPD. She delivered the baby, weighed 3,850 gm with normal Apgar score.

Five patients in dinoprostone group developed abnormal contraction, which occurred within 3.5 hours without abnormal fetal heart rate tracing.

Terbutaline was given to treat 3/7 (42.9%) patients with abnormal contraction in misoprostol group (one case of tachysystole and two cases of hyperstimulation syndrome) and 2/5 (40%) in dinoprostone group (two cases of tachysystole). Three patients with tachysystole responded to one dose of terbutaline while two patients with hyperstimulation responded to two doses.

The 11/12 (91.7%) patients with abnormal contraction responded to conservative treatment without a recurrent episode of abnormal contraction. One patient with hyperstimulation syndrome delivered by cesarean section for fetal distress, oligohydramnios and thick meconium stained amniotic fluid as shown in table 4.4.

4.5 Delivery after twenty-four hours

Two patients in dinoprostone group withdrew after 24 hours of drug insertion (figure 4.1). Therefore the delivery data of these two patients were not included in the analysis. Table 4.11 shows the delivery after 24 hours of two study groups. The most common indications for cesarean deliveries in both groups were CPD and arrest of labor. Five patients failed for induction. Their median initial Bishop score was 3 (2-

4). One cesarean section was performed for fetal distress. The indication for induction was 42 weeks with oligohydramnios. Her initial score was one and reached five after 24 hours of misoprostol insertion. Oxytocin was given on the second day. The labor progressed to active phase and developed persistent late deceleration. The cesarean section was performed and the baby was delivered with normal Apgar score.

Table 4.11 Comparison of delivery after 24 hours between two groups.

	Misoprostol (n=40)	**Dinoprostone (n=46)**	***P***
Vaginal delivery	29 (72.5%)	36 (78.3%)	0.712#
Cesarean delivery	11 (27.5)%	10 (21.7%)	
CPD/arrest pattern	8	7	
Failed induction	2	3	
Fetal distress	1	0	

χ^2 with continuity correction.

4.6 Mode of delivery

Table 4.12 shows the comparison of mode of delivery between two groups. In

Table 4.12 Comparison of mode of delivery between two groups.

	Misoprostol (n=72)	**Dinoprostone (n=69)**	***P***
Vaginal delivery	54 (75.0%)	56 (81.2%)	0.497#
Cesarean delivery	18 (25.0%)	13 (18.8%)	
Failed induction	2	3	
Oligohydramnios	1	2	
Severe pre-eclampsia	1	1	
Fetal distress	6	3	
CPD/arrest pattern	10	7	

χ^2 with continuity correction.

misoprostol group, 54/72 (75%) of patients delivered vaginally compared to 56/69 (81.2%) in dinoprostone group, a non-significant difference (p = 0.497). Oligohydramnios was the most common finding in cesarean section for fetal distress, which occurred 4/6 (66.7%) in misoprostol group and 3/3 (100%) in dinoprostone group. All cesarean sections for failed induction had secondary indications.

Start to vaginal delivery time

Table 4.13 shows the frequency of vaginal delivery within 24, 48 hours and start to vaginal delivery time of the two groups. For the patients who delivered vaginally, the rate of vaginal delivery within 24 hours was higher in misoprostol group, 46.3% versus 35.7%, but with non-significant difference. The rate of vaginal delivery within 48 hours was comparable in both groups, 88.9% versus 89.3%.

The median time interval in misoprostol group was 2.8 hours shorter than dinoprostone, but the difference was not of statistical significance (p = 0.155).

Table 4.13 Comparison of vaginal delivery and start to delivery time between two groups.

	Misoprostol (n=54)	Dinoprostone (n=56)	OR (95%CI)	*P*
Vaginal delivery within 24 hours	25 (46.3%)	20 (35.7%)	1.6(0.7 to 3.3)	0.350#
Vaginal delivery within 48 hours	48 (88.9%)	50 (89.3%)	1.0(0.3 to 3.2)	>0.05#
Start to vaginal delivery (hr)				
Mean (SD)	25.5 (16.46)	28.4 (15.7)		
Median (range)	25.8 (4.8-77.5)	28.6 (7.8-85.0)		0.155*

χ^2 with continuity correction. * Mann-Whitney U test.

4.7 Maternal side effects

In both groups, there were no maternal adverse events of nausea, vomiting, diarrhea, pyrexia, and postpartum hemorrhage.

4.8 Neonatal outcomes

In this study, there were no poor perinatal outcomes in both groups. Table 4.14 compares the neonatal outcomes between two groups. There were no statistically significant differences in birth weight, meconium stained amniotic fluid, one-minute and five-minute Apgar score, or admission to NICU between the two groups. One neonate in dinoprostone group was admitted in NICU with anemia and pneumonia. The patient's indication for induction of labor was pre-eclampsia. The labor progression and FHR tracing were unremarkable. She delivered the baby vaginally with normal Apgar score. The baby was discharged with the mother on day 8.

Table 4.14 Comparison of neonatal outcomes between two groups.

	Misoprostol (n=72)	**Dinoprostone (n=69)**	***P***
Birth weight (g)			
Mean (SD)	3186.8 (426.26)	3230.1 (365.72)	
Median (range)	3170 (2250-4500)	3250 (2450-4150)	0.336**
Meconium stained			
(moderate to thick)	3 (4.2%)	2 (2.9%)	>0.05##
Apgar score 1 min			
Mean (SD)	9.2 (0.94)	9.1 (1.32)	
Median (range)	9 (6-10)	10 (5-10)	0.508**
< 7	2 (2.8%)	5(7.2%)	0.268##
Apgar score 5 min			
Mean (SD)	10.0 (0.20)	9.90 (0.43)	
Median (range)	10 (9-10)	10 (8-10)	0.622**
< 7	0	0	
NICU admission	0	1 (1.5%)	0.489##

NICU = neonatal intensive care unit. ** Mann-Whitney *U* test. ## Fisher's exact test.

CHAPTER 5

DISCUSSION

Dinoprostone is the agent of choice to ripen the cervix before the induction of labor. However, it is usually expensive and not available in many developing countries. Misoprostol, on the other hand, is quite cheap, available in over 70 countries and more stable than dinoprostone tablet.[49]

The majority of studies to date have used misoprostol in multiple administrations with various doses and intervals to safely induce labor. The trials of multiple dosing regimen have shown that vaginal misoprostol in doses ranging from 25 mcg three hourly, to 50 mcg fourly (most studies) and 100 mcg six to 12 hourly, appear to be more effective than oxytocin or dinoprostone used in the usual recommended doses.[50] The accumulative effect of multiple doses of misoprostol may have a resulting dangerous degree of uterine hyperactivity and are potentially prone to the adverse effects.[42] The one-time dose of misoprostol for cervical ripening before labor induction with oxytocin should reduce the complications which may occur during administration of multiple dosing regimens. There are few studies in the literature to report a single dose of 100 mcg misoprostol with six to 24-hour waiting for cervical ripening.[32, 33, 40-42] A single dose of 50 mcg misoprostol with waiting 24 hours for cervical ripening has never been reported. The 24-hour waiting might yield more efficacious for cervical ripening.

The primary goal of the study was to compare the efficacy of a single dose of 50 mcg of intravaginal misoprostol assessed at 24 hours with the standard cervical ripening agent.

5.1 Modification of thesis proposal during implementation

According to the initial proposal, there were some modifications in the enrolled patients and procedures due to some limitation and feasibility.

When we designed proposal, we considered the unripe cervix as a cervix with the Bishop score 0-3. The patients who have indication for induction of labor with score less than four are much less than anticipated. This might affect the adequate sample size to be recruited in time. The beneficial effect of the use of prostaglandin cervical priming in women with intermediate Bishop score at entry (score 4-6) has been reported, resulting in an improved chance of vaginal delivery.[46] Thus, we defined an unripe cervix as a cervix with the Bishop score 0-6. The cervix with score 0-3 and 4-6 subgroups would be analyzed separately.

Electronic monitoring for uterine contraction and fetal heart rate pattern was performed for 8 hours after administration of the studied drugs instead of 4 hours as planned in the proposal. The reason was the occurrence of the abnormal contraction during four to eight hours.

5.2 Methodology consideration

5.2.1 Design features

This study was a randomized, double-blind controlled clinical trial which minimized the selection bias, measurement bias, other known and unknown confounders. The parity is a well-known confounder to influence the change in Bishop score after administration of prostaglandins. Using the stratified randomization by parity could prevent the allocation bias and parity was well balanced in both groups.

Stratified randomization with random permuted blocks was used to allocate the treatment in this study.[45] The method is to control of balance of treatments within

strata. A disadvantage of blocked randomization is that, from a strictly theoretical point of view, analysis of data is more cumbersome than if simple randomization is used. However, most investigators ignore the fact that the randomization was blocked. Altman supported that stratified randomization would achieve approximate balance of important characteristics without sacrificing the advantages of randomization.[48]

5.2.2 Effectiveness of randomization procedures

Inspection of the baseline data (table 4.1 – 4.3) revealed no significant differences between two groups with regard to demographic characteristics, indications for induction and the initial Bishop score. The comparable baseline data of treatment groups with allowed valid between-group comparisons.

5.3 Efficacy

5.3.1 Cervical ripening effect

With one-time dose of 50 mcg of vaginal misoprostol, the median Bishop score change at eight hours was 3 units in misoprostol group compared to 2 units in dinoprostol group. Gottschall et al.[42] reported the same median change of Bishop score in a randomized trial for pre-induction cervical ripening compared 100 mcg misoprostol with 5 mg of PGE_2. The gradual change in the Bishop score was similar in both groups, but misoprostol was better as shown in table 4.5, 4.6. In misoprostol group, the median score was double the initial score at eight hours and triple at 24 hours. The increase in score at eight and 24 hours also observed with one-time dose of 3 mg of dinoprostone, but with a lesser degree. The findings supported the improved efficacy in cervical ripening of prostaglandins for 24-hour waiting. Herabutya et al.[41] also reported the gradual change of the score with the 12 and 24 hours of waiting in the

study evaluated the effectiveness of 100 mcg vaginal misoprostol compared with 1.5 mg PGE_2 gel applied in endocervix once only in 24 hours.

The mean change of 24-hour score in misoprostol was one unit more than that of dinoprostone, 6.5 (SD, 3.01) versus 5.5 (SD, 2.93), (table 4.6), although of statistically significant difference but of no clinical importance. The one unit change may be from the measurement error. The mean change difference of 25% or approximately 1.5 units was considered to be clinically important, as described in the part of sample size estimation (chapter 3).

We did not assign the subgroup analysis for patients with the initial Bishop score of 0-3 and 4-6 in advance because of limited number of study population. However, the analyses for both subgroups showed larger changes of 24-hour Bishop score in misoprostol-treated patients than in dinoprostone-treated patients, but the differences were not of statistical significance. The powers of the study in both subgroups were approximately 50.0 %, which reflected inadequate sample sizes.

Competing event

The cesarean delivery prior to active labor and before the assessment of 24-hour Bishop scores was the competing event. The exclusion of such patients from the analysis may affect the outcome analysis and may lead to controversy.[48] Although we got enough patients according to pre-specified sample size calculation for the primary outcome, we performed best/worst/average case analyses. The analyses showed the dissimilar significant difference to the analysis in which the patients are excluded. Therefore, we could not be confident in the finding that the score change at 24 hours in misoprostol group was more than that of dinoprostone group as presented in table 4.6. However, all analyses yielded more mean change of Bishop score in misoprostol-treated patients than in dinoprostone-treated patients. This might reflect the efficacy of misoprostol to be at least equal to or more than dinoprostone.

5.3.2 Effect on vaginal delivery

The evidences confirmed that misoprostol was an effective agent for cervical ripening and labor induction in patients at term, showing the increase in the incidence of vaginal delivery within 24 hours of its administration.[4, 50] Hofmeyr et al.[50] reported in their systematic review that the vaginal delivery rate within 24 hours was higher in patients given misoprostol compared to PGE_2 or oxytocin, 83.3% versus 65.1% with pooled relative risk 2.08 (95%CI, 1.52 to 2.86). Wing and Paul [3, 7, 12, 13] had the largest experience in the literature involving more than 900 patients. Their trials used misoprostol dosages ranging from 25 to 50 mcg 3 hourly to 6 hourly. The induction-to-delivery times varied from 18.3 to 27.3 hours. Sanchez-Ramos et al.[4] reported the start-to-delivery time varied from 9.2 (SD, 3.5) to 23.4 (SD, 14.5) hours and the pooled estimate of the interval was 4.6 hours fewer than the control (95% CI, -3.5 to -5.7).[4]

The trials using a single dose of 100-mcg misoprostol with 6-24 hour wating time and augmented with oxytocin reported 80% to 95% delivered vaginally within 24 hours, the mean start to vaginal delivery times varied from 16 to 19 hours.[40-42]

In this study, 46% of the vaginal deliveries occurred in 24 hours and 89% occurred in 48 hours with one single dose of 50 mcg misoprostol (table 4.13). The median start to vaginal delivery time was 25.8 hours. The longer start to delivery time may be explained by two reasons. Firstly, we assigned 24 hours waiting before oxytocin augmentation. Secondly, the usage of one-time small dose of misoprostol to reduce the complications, may associate with longer intervals.

5.3.3 Effect on cesarean delivery

None of the individual trials evaluating the effectiveness of misoprostol for cervical ripening and labor induction had sufficient statistical power to detect a significant reduction in the cesarean rate.[4] However, the increased power resulting

from the combination of many studies in the meta-analyis resulted in detection of a statistically significant treatment effect. Women who received misoprostol for cervical ripening and labor induction had a significantly lower overall cesarean rate than control (15% versus 21.5%; OR 0.67; 95% CI 0.48 to 0.93).[4] The ability of misoprostol to effect changes in the Bishop score, as well as adequate uterine activity, may contribute to this cesarean rate.

In this study, the cesarean rate in misoprostol group was higher than dinoprostone group, but with a non-significant difference (table 4.12). The indications for cesarean section were not related to the studied drugs except the one who developed hyperstimulation syndrome (table 4.4). The cesarean delivery for fetal distress was related to oligohydramnios, which was the indication for induction in 7/9 (77.8%) of all patients. All cesarean deliveries for failed induction had secondary indications (table 4.12), which influenced the obstetrician's decision for operation.

5.4 Adverse events

Misoprostol appears to be an extremely low incidence of maternal side effects. The only adverse effect noted in the studies of misoprostol was an increased incidence of abnormal uterine contraction.[4, 50] In this study, the most common adverse event was tachysystole / hypertonus with or without FHR abnormalities. Other side effects including nausea, vomiting, diarrhea, pyrexia, postpartum hemorrhage, and poor neonatal outcomes as the consequence of increased uterine activity were not found in both groups.

5.4.1 Abnormal uterine contraction

Uterine hyperactivity is a major concern with the use of misoprostol. Wing et al.[7] reported the highest rate of uterine tachysystole at 36.7% and a hyperstimulation

rate of 7.4% with use of a dose of 50 mcg repeated every 3 hours for a maximum of six doses. The accumulative effect of multiple doses of misoprostol, as reported in other series, may have a resulting increase in uterine tone. Hofmeyr et al.[4] recently have reported in their systematic review that the use of misoprostol was associated with increased both uterine hyperstimulation without fetal heart rate changes (RR 1.67, 95% CI 1.30 to 2.14) and with associated fetal heart rate (RR 1.45, 95% CI 0.04 to2.04).

The studies using a single dose of 100 mcg misoprostol and further augmented by oxytocin reported tachysystole rates of 4.2% to 37% and hyperstimulation syndrome rates of 0 to 9.4%. [32, 33, 40- 42]

In this study, with the use of a single 50 mcg dose of intravaginal misoprostol, we had a low rate of abnormal uterine contraction of 9.7% which was uterine tachysystole in 2.8% and hyperstimulation syndrome in 6.9% (table 4.10). Although the study did not show a difference in abnormal contraction between two study drugs, the power of the study was not sufficient to eliminate the possibility of a type II error. Five out of 72 patients (6.9%) with hyperstimulation syndrome occurred in the misoprostol group, compared to none of 71 patients (0%) in dinoprostone group. This difference was borderline non-significant and was clinically important. This reflects close utero-fetal monitoring on administration of misoprostol.

Abnormal uterine contraction is not the indication for operative delivery. The management for this condition is conservative approach. [3, 7, 12, 13, 42] In this study, all cases of abnormal contraction with the except of one responded to conservative treatment. She underwent a cesarean delivery for fetal distress with hyperstimulation syndrome (table 4.4). The fetal distress in this patient associated with oligo-hydramnios and thick meconium stained amniotic fluid. Diminished amniotic fluid volume may predispose the patient to the relatively high frequency of abnormal FHR patterns. The misoprostol may have a resulting increase in uterine tone, further diminishes uterine perfusion and worsens the fetal status. One cesarean delivery for fetal distress with oligohydramnios, but without abnormal uterine contraction, was also

performed in dinoprostone group. The patient who has oligohydramnios should be closely monitored whatever inducing medication given.

The duration of uterine monitoring after administration of misoprostol is to be considered. Some patients appear to quite sensitive to misoprostol, demonstrating prolonged contraction responses after a dose of the agent, sometimes in excess of 20 hours after the drug.[3] The pharmacokinetic study of 400 mcg vaginal misoprostol has shown that serum levels of the principal metabolite was an average of 62% of the peak level at 240 minutes after administration.[26] The majority of tachysystole manifested within 6 hours of administration.[3] In this study, the tachysystole occurred later than 4 hours in approximately 40% with the latest occurrence of 7 hours. This emphasizes the continuous monitoring to early detect the adverse event of uterine hyperactivity and abnormal FHR even in one time 50-mcg misoprostol.

5.5 Economic consideration

The need to ripen the cervix prior to the induction of labor has become an important issue in Obstetrics and also in economic consideration. Although the abnormal contraction occurs more frequently with the use of misoprostol, the induction of labor by other agents including oxytocin and dinoprostone require close observation as with the administration of misoprostol. The cost of observation consists of the cost of utero-fetal monitoring and the cost in the management of the abnormal contraction. The cost of utero-fetal monitoring is comparable across the ripening agents. The cost in the management of abnormal contraction depends on the severity of adverse event. The most severe form is the uterine rupture, which is rarely occurred in case of continuous monitoring. Hence, when the abnormal contraction occur, almost cost in the treatment of this adverse event is the terbutaline cost, which is 9.5 baht per dose.

With regard to the cost of ripening agents, cost-benefits from the administration of misoprostol are evident. One tablet of 3 mg dinoprostone (Prostin E2) costs 550

baht, whereas one tablet of 200 mcg misoprostol (Cytotec) costs 11 baht; this translates to approximately 3 baht per dose of misoprostol. If these figures are applied to the 143 patients in this study, there are 78,221 baht savings in the misoprostol-treated patients versus the dinoprostone-treated patients for cervical ripening alone. This has significant implications for treatment of patients in developing countries.

5.6 Limitation in this study

The limitation in this study is the empiric-dosing regimen. The single dosing regimen studied was empiric and based on other reports. The proper dose of misoprostol for cervical ripening without adversely effecting the fetus has not been established. The 25 mcg dose given 3 hourly appears to be the minimum dose one can use.[3, 50] The reported single dosing regimens was 100 mcg misoprostol with six to 24-hour waiting.[32, 33, 40-42] One-time, low dose misoprostol should reduce the complications which may occur during administration of multiple dosing regimens. We expected more cervical ripening with longer waiting. Hence, we studied a single 50 mcg dosing regimen with 24-hour waiting.

5.7 Generalizability and application

The sample population in this study covered most pregnant women with indications for induction of labor but unripe cervices. In this study we defined an unripe cervix as a cervix with the Bishop score 0-6 and the sample size estimation was based on patient with this characteristic. The result could not be applicable to subgroups of patients having the score of 0 to 3, which occupied approximately one half of patients (table 4.3).

This trial studied the ripening efficacy of the drugs administered only single dose. The result would not be applicable for women who need urgent termination of

This trial studied the ripening efficacy of the drugs administered only single dose. The result would not be applicable for women who need urgent termination of pregnancy or whose indications for induction of labor can not be waited beyond 24 hours. Multiple dosing regimens or single dosing regimen with oxytocin augmentation after 6 hours are recommended for those patients.

Though misoprostol shows promise as an effective, inexpensive and convenient agent for cervical ripening and labor induction, it cannot be recommended for routine use. It is possible that, if sufficient numbers are studied, an unacceptably high number of serious adverse events including uterine rupture and asphyxial fetal deaths may occur.[50]

Based on the findings of the abnormal uterine contraction in this study, the patient who receives one dose of 50 mcg misoprostol for pre-induction cervical ripening should be closely monitored by cardiotocometer for at least eight hours. Special precaution should be paid on the patients with oligohydramnios or suspected utero-placental insufficiency.

5.8 Further study

Many studies are going on to further evaluate the optimal misoprostol dose, dose interval, and total number of doses administered in multiple dosing regimens. We are among the few groups in the literature to report a single dose of misoprostol for cervical ripening and labor induction. Our colleagues chose to use a single dose of misoprostol to reduce the dangerous degree of uterine hyperactivity from multiple dosing regimens. Further studies of single dosing regimen in our institutes are:

1. A single dose of 50 mcg misoprostol with oxytocin augmentation after six hours.
2. Further studies with large power to detect the uncommon complications and subgroups that can most benefit from misoprostol.

CHAPTER 6

CONCLUSION

This study was a randomized, double-blind, controlled trial. The objective was to compare the efficacy and safety of one single 50 mcg administration of misoprostol with one single 3 mg of dinoprostone administered vaginally with 24 hours waiting for pre-induction cervical ripening in term-pregnant women who had the indication for induction of labor but with unripe cervices.

The study was conducted at Bangkok Metropolitan Medical College and Vajira Hospital, Bangkok, Thailand. The singleton pregnant women of $\geq$ 37 weeks of gestation, who had indications for termination of pregnancy and initial Bishop score less than seven. All eligible patients were stratified by parity into nullipara and multipara groups and each stratum were randomly allocated to receive a single dose of 50 mcg misoprostol or 3 mg dinoprostone, administered vaginally. After waiting 24 hours for cervical ripening, oxytocin augmentation was given in both groups.

The Bishop scoring system was the instrument used to assess the cervical ripeness. The primary outcome measure was the change of Bishop score at 24 hours after insertion of the study drugs. The secondary outcomes were the occurrence of the abnormal uterine contraction, the number of vaginal delivery within 24, 48 hours.

Among 143 patients enrolled, 72 received misoprostol and 71 received dinoprostone. The demographic data in terms of age, height, weight, hematocrit, gravidity, parity, and indications for induction of labor were comparable in both groups. There were no significant differences in initial Bishop score (median score 3.5 versus 4.0), change of score at 8 hours (median change score 3.0 versus 2.0). The change of score at 24 hours was one unit higher in misoprostol group (mean change

score 6.5 versus 5.5, with 95% confidence interval 0.04 to 2.1, $p = 0.042$). This difference was statistically significant but without clinical importance. As cesarean delivery was the competing event to the 24-hour score, the best/worst/average outcome analyses were performed and revealed dissimilar results, which may affect the confidence of the positive results. Abnormal contraction occurred in both groups, 9.7% versus 7.0%, with higher frequency of hyperstimulation syndrome in misoprostol group (6.9% versus 0%) during 8 hours of cervical ripening. Although the difference in hyperstimulation syndrome was not statistically significant ($p = 0.058$) but this is clinical important. Nearly all patients with abnormal contraction (91.7%) responded to conservative treatment. Comparing vaginal deliveries between both groups, the frequencies of delivery within 24 hours were 46.3% versus 35.7% ($p = 0.350$), and within 48 hours were 88.9% versus 89.3% ($p > 0.05$), a non-significant difference. The start to vaginal delivery time was 3 hours shorter in the misoprostol group (median interval 25.8 hours versus 28.6 hours), but this difference was not statistically significant ($p = 0.155$). The cesarean delivery rate was higher in the misoprostol group (25.0% versus 18.8%), but is not of significant difference ($p = 0.497$) and related to oligohydramnios. No significant differences were noted between two groups in terms of mode of delivery, neonatal birth weight, meconium passage, 1- or 5-minute Apgar score, or admission to NICU. Although the study did not show differences in the secondary outcomes between the two groups, the power of the study was not sufficient to eliminate the possibility of type II error.

A single 50-mcg of misoprostol is not clinically different to 3-mg dinoprostone in cervical ripening. The increase in hyperstimulation syndrome with fetal heart rate changes following misoprostol is a matter of concern. Although no differences in abnormal contraction, vaginal delivery within 24 hours, and neonatal outcomes were shown, the studies were not sufficiently large to exclude the possibility of uncommon adverse effects. Further studies with large power to detect the uncommon complications and subgroups that can most benefit from misoprostol are needed.

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APPENDICES

APPENDIX 1

Consent form

1. I have been informed that the Department of Obstetrics and Gynecology, Bangkok Metropolitan Medical College and Vajira Hospital is conducting a study " A randomized comparison of 50 mcg misoprostol and 3 mg dinoprostone in pre-induction cervical ripening."
2. I am completely informed about the research objectives, the procedures and also the content of this study.
3. I have the indication to deliver my pregnancy. I will receive the cervical ripening drug to accomplish the labor more successfully. The drug is either misoprostol or dinoprostone inserted intravaginally.
4. I also have been informed the adverse effects that may occur and the possibly unfavorable therapeutic outcomes of my patient. I will be closely monitored along the action or the drug to ensure that my baby and I will be in good health state.
5. I understand that my agreement of my patient's participation in this study is entirely voluntary and that I may withdraw my consent to participate at any time without penalty and without in anyway affecting the health my patient receives.
6. All information about the specific treatment will be kept confidential. No one will be identified individually in any publish reports. Only the investigator will have assess to the study.
7. I have been an opportunity to ask questions about this study. Any questions that I have asked have been answered to my satisfaction. If I have further questions about this study, I may contact the investigator in this hospital on Tel. ext.2430.

Subject's name .....

Physician's signature .....

Witness' signature.....

Date of participation .....

APPENDIX 2

Information sheet

Title of study A randomized comparison of 50 mcg misoprostol with 3 mg dinoprostone in pre-induction cervical ripening.

Place The Department of Obstetrics and Gynecology, Bangkok Metropolitan Medical College and Vajira Hospital

Investigator Manit Sripramote, M.D., Santhana Sharoenkul M.D.

Objective To compare the efficacy and safety of one single 50 mcg of misoprostol and one single 3 mg of dinoprostone administered vaginally for pre-induction cervical ripening in term-pregnant women who had an indication for induction of labor but with unripe cervices.

Why study?

Labor induction is a necessary procedure for completion of pregnancy in 10% of pregnant woman. Some have an unfavorable cervix for the induction of labor and result in the prolonged, tedious labor or induction failure. This results in discouraging parturient and obstetrician, long occupation of delivery rooms and a potential increase in unnecessary cesarean deliveries.

The only agent approved for pre-induction cervical ripening and induction of labor in patients with an unripe cervix is dinoprostone. There are drawbacks to the administration of dinoprostone which include the high cost, unstability at room temperature that needs refrigeration to preserve its potency

Misoprostol, used for prevention and treatment of gastro-duodenal ulcers, has been recently studied for cervical ripening and labor induction. Misoprostol decreases the cesarean delivery rate and increases the incidence of vaginal delivery within 24 hours of its administration. Additionally, the drug is 50 times cheaper than dinoprostone, simple to administer, easy to store, and stable at room temperature.

There have been no reports of fetotoxic, teratogenic, and carcinogenic effects in animal studies. Nowadays many obstetricians use and study this drug. Uterine tachysystole and hyperstimulation are the major concerns. Most studies have shown an increased incidence of hyperstimulation with the use of misoprostol which occurs 2.7 times the control group. However, the proportion of adverse perinatal outcomes as consequences of increased uterine activity is not significantly increased.

The proper dose of misoprostol for cervical ripening without adversely effecting the fetus has not been established. The uterotonic adverse effects potentially occur by frequent administration of misoprostol. The objective of this study was to compare the efficacy and safety between one single dose of 50 mcg misoprostol with 3 mg dinoprostone for pre-induction ripening in patients with unripe cervices.

Benefit of the study

1. Misoprostol will be the other alternative for cervical ripening and inducing the labor if the study prove its efficacy and safety.
2. If misoprostol is efficacious with acceptable safety, it is more cost-effective.

Who will be the participant?

The pregnant woman with the indication to deliver but the cervix is not favorable. The indications are (1) gestation $\geq$ 41 weeks (2) oligohydramnios (3) intrauterine growth retardation (4) hypertension (5) other medical or obstetric indications that may harm her health or her baby if the pregnancy goes further.

The physician will assess the indication whether you are recruited in the study.

What will happen to the participant?

The participant will randomly receive any one of the study drugs trans-vaginally, misoprostol or dinoprostone.

The procedures in this study are:

1. At 7 am an intravenous line is placed. The tocometer is started for 30 minutes to ensure the normal fetal heart rate.

2. The investigator will assess the cervix at 8 am.
3. A resident places the drug into the vagina.
4. The participant lies on bed and is closely monitored for 8 hours.
5. If the uterine hyperstimulation occurs, it will be treated immediately.
6. The investigator assesses the cervix at 4 pm on the same day and at 8am on the next day. The oxytocin will be given to augment the labor.
7. The participant will deliver safely.

The experienced medical personnel in the labor room will closely monitor you with standard medical care.

Need to be the participant?

The physician will completely informed about the content of the study, the adverse effects that may occur and the possibly unfavorable therapeutic outcomes. Have your own decision to participate the study. Your agreement of participation in this study is entirely voluntary and you may withdraw your consent to participate at any time without penalty and without in anyway affecting your further medical care.

Any adverse effects?

While receiving misoprostol or dinoprostone, the participant may develop uterine contraction with progressive discomfort. The sensation seems like labor pain. The doctor will prompt detect the excessive uterine contraction and treat immediately. Other side effects include diarrhea, nausea, vomiting, headache, and lower abdominal pain. These events are mild and transient and rarely occur in the study dose.

Any expense and payment?

This research program does not pay you to participate the study. The program will support you for the cost of the study drug and the hospital charge for the complication of the procedures or the adverse events that may occur.

How to contact the investigator?

Feel free to ask questions about this study. If you have further questions about this study, you may contact the investigator in this hospital on Tel. 2430151, ext.2430.

APPENDIX 3

Pretesting for the reliability of the Bishop scoring system

Two obstetricians blindly examined twenty pregnant women, whose characteristics were similar to the study population. Bishop scores were tested for reliability by calculating the intraclass correlation coefficient (ICC) .

The ICC could be obtained from the approach of analysis of variance (ANOVA). From two-way ANOVA model, overall variation among various measurements was partitioned into 3 distinct sources i.e., between observers, between subjects and unexplained error (residual). The ICC was computed as:

$$ICC = \sigma^2 sample / \sigma^2 sample + \sigma^2 error$$

Statistical test of the inter-rater reliability

The Bishop score

By using the statistical program SPSS 7.5, overall variation among various measurements were obtained from the approach of the statistics ANOVA.

Bishop score by 20 subjects, 2 observers (SPSS-ANOVA)

Source of variation	Sum of squares	Df	Mean squares	F	Sig.
Subjects	377.88	19	19.89	23.80	0.000
Observers	0.63	1	0.63	0.75	0.398
Residual (error)	15.88	19	0.84		
Total	394.38	39	10.11		

σ^2 error = mean square error (MSE) = 0.84

σ^2 sample = [MSS - MSE] / 2 = [19.89-0.84] / 2 = 9.53

σ^2 observer = [MSO – MSE] / 5 = [0.63-0.84] / 20 = -0.01

F statistics for observers was not significant (p= 0.398), so the calculation did not need the variance between observers. When F statistics for observers were significant (p< 0.05), the variance of observers were included in the observation variance.

ICC = σ^2 sample / σ^2 sample + σ^2 error

= 9.53 / 9.53+0.836 = 0.92

Interpretation of the agreement index

<	Poor
0-0.2	Slight
0.2-0.4	Fair
0.4-0.6	Moderate
0.6-0.8	Substantial
0.8-1.0	Almost perfect

The standard of acceptable reliability for stability is 0.5.[51, 52] For clinical assessment of Bishop score in individual patient, the ICC after pre-testing should more than 0.8. The ICC reliability coefficient shows the ratio of the true score variance to observed score variance. Thus reliability of 0.92 indicated that an estimated 8 % of the observed variance was due to error in measurement. The ICC of the Bishop score in this pretest study was 0.92, which was in " almost perfect range".

Code No....

APPENDIX 4

Data collection form

Baseline data	**Data entry**
1. Hospital number	1. [ ][ ][ ][ ][ ][ ][ ]
2. Assignment **1** Drug A **2** Drug B	2. [ ]
3. Age (yr)	3. [ ][ ]
4. Height (cm).....	4. [ ][ ][ ]
5. Weight(kg)	5. [ ][ ][ ]
6. Gravidity.....	6. [ ]
7. Parity.....	7. [ ]
8. Gestational age (mark x) ☐ by date (.....wk...day)	8. [ ][ ]
☐ by US (.....wk ...day) ☐ by serial ANC (.....wk...day)	
9. Hematocrit (%).....	9. [ ][ ]
10. Indication for induction (circle one)	10.[ ]

1 Gestational age ≥ 41 wk **5** Chronic hypertension

2 Oligo-hydramnios **6** DM

3 IUGR **7** Others.....

4 Pre-eclampsia

Bishop scoring system

Score	0	1	2	3
Dilatation (cm)	Closed (internal os)	1-2	3-4	≥ 5
Effacement (%) from 2 cm	0-40	41-60	61-80	≥ 81
Consistency	Firm (nasal ala)	Medium (lip)	Soft and dilatable	_
Cervical position (relative to the presenting part)	Posterior (to sacrum)	Middle	Anterior (direct to vaginal axis)	_
Station of presenting part (when no contraction)	-3	-2	-1, 0	+1 to +3

Outcomes

Bishop score

	Initial score	8 hr score	24 hr score
Time/date	...../.....	...../.....	...../.....
Dilatation	...../.....	...../.....	...../.....
Effacement	...../.....	...../.....	...../.....
Consistency	...../.....	...../.....	...../.....
Position	...../.....	...../.....	...../.....
Station	...../.....	...../.....	...../.....
Total score	11. [ ][ ]	12. [ ][ ]	13.[ ][ ]
14-15. Score difference 8-0 hr, 24-0 hr		14. [ ][ ]	15.[ ][ ]

Uterine contraction and fetal heart rate tracing

16. Tachysystole	**0** No	**1** Yes at.....o'clock			16.[ ]
17. Hypertonus	**0** No	**1** Yes at.....o'clock			17.[ ]
18. Hyperstimulation syndrome	**0** No	**1** Yes (with non-reassuring FHR pattern)			18.[ ]
a Tachycardia	**0** No	**1** 161-180	**2** >180		
b Bradycardia	**0** No	**1** 100-119	**2** 80-99	**3** <80	
c Late deceleration	**0** No	**1** Yes			
d Variable DC	**0** No	**1** 30-60 sec		**2** >60 sec	
e Prolonged DC	**0** No	**1** Yes			
f Decreased BBV	**0** No	**1** Yes			
19. Need of terbutaline	**0** No	**1** Yes at.....o'clock			19.[ ]

Delivery

20. Mode of delivery 20.[ ]

1 Spontaneous **3** Forceps extraction

2 Vacuum extraction **4** C/S

21. Indication of C/S (circle ≥ one) 21.[ ]

0 Not C/S **3** CPD

1 Failure of ripening **4** Arrest pattern

2 Fetal distress **6** Others.....

22. Start to vaginal delivery time (min) ..... 22.[ ][ ][ ][ ]

23. ***Maternal side effects*** (circle ≥ one) 23.[ ]

0 No **3** Pyrexia

1 Nausea & vomiting **4** Antepartum hemorrhage

2 Diarrhea **5** Postpartum hemorrhage

Neonatal outcomes

Delivery date ..... time .....

24. Birth weight (gm)..... 24.[ ][ ][ ][ ]

25. Meconium passage **0** No **1** Light **2** Moderate **3** Thick 25 [ ]

26. Apgar score at 1 min ..... 26.[ ][ ]

27. Apgar score at 5 min ..... 27.[ ][ ]

28. Admission to NICU 28.[ ]

0 No **1** Yes with indication .....

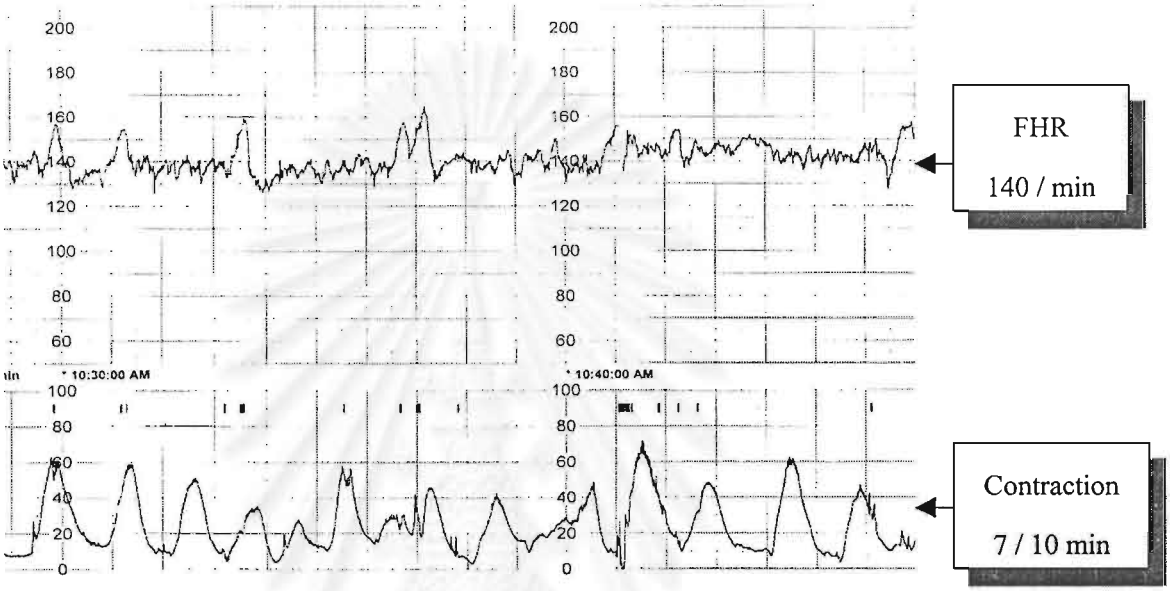
Name.....

Date.....

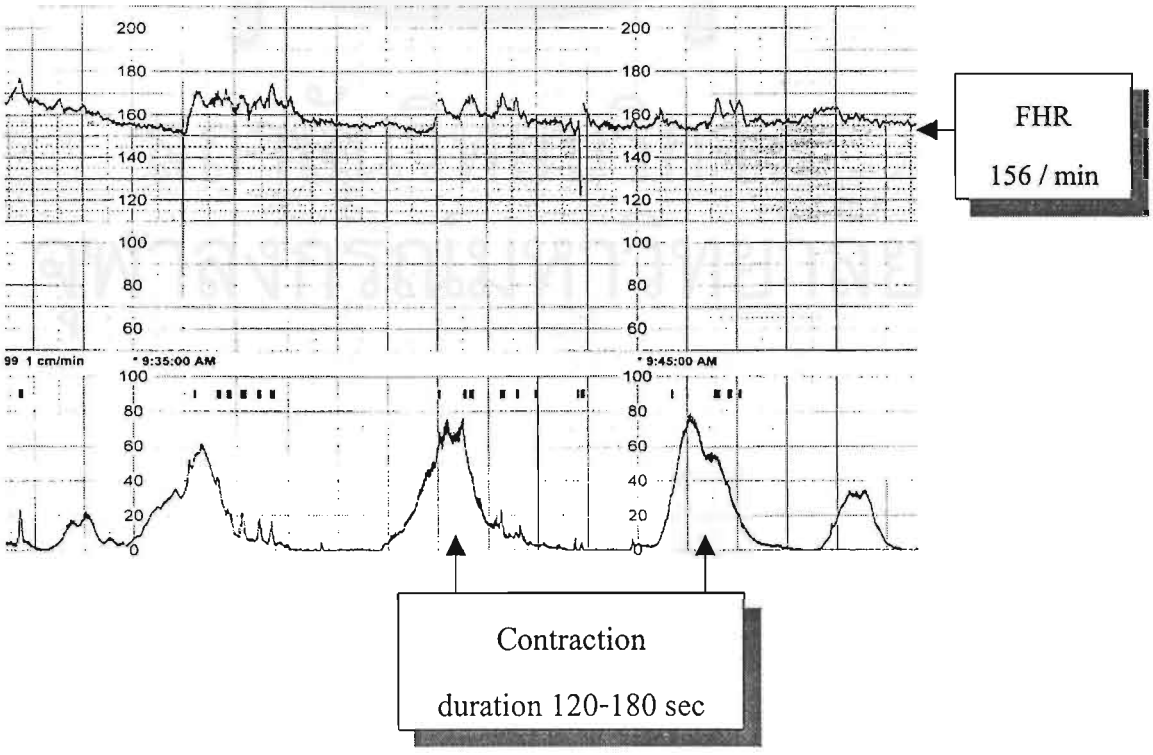
APPENDIX 5

Uterine contraction and fetal heart rate tracing

1. Uterine tachysystole with normal fetal heart rate

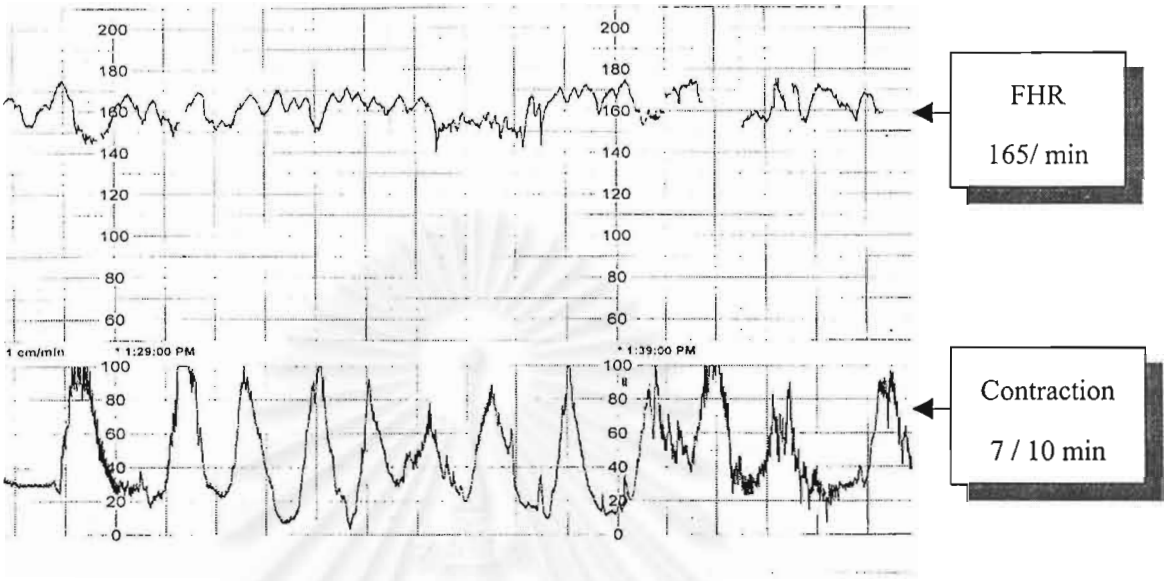


2. Uterine hypertonus with normal fetal heart rate



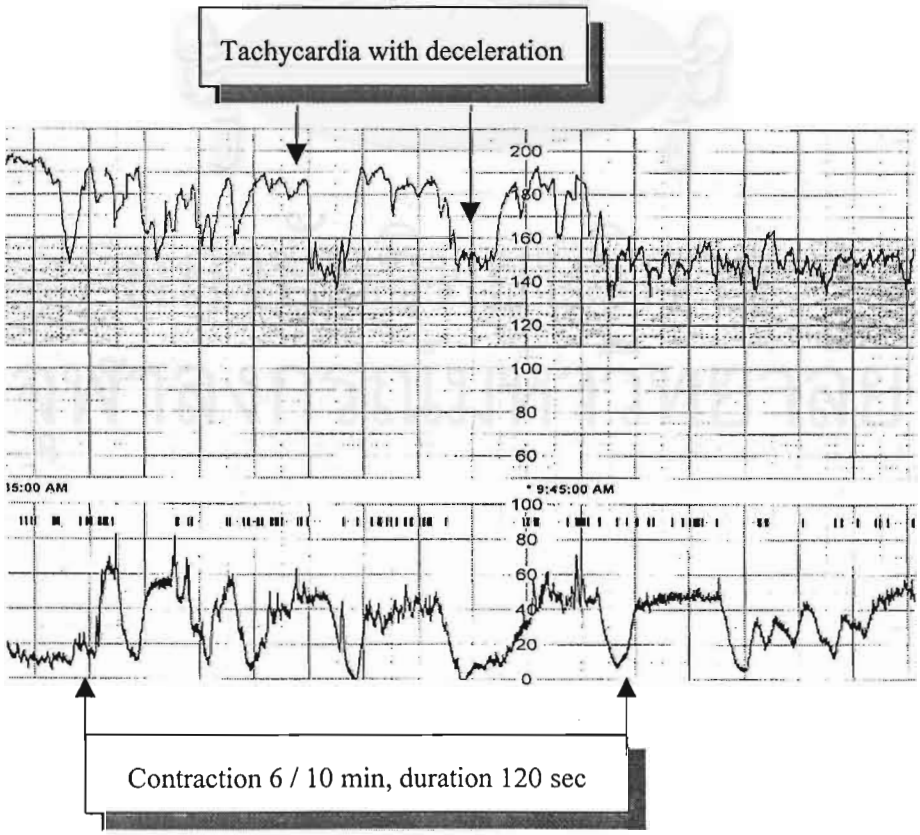
3. Hyperstimulation syndrome

Uterine tachsystole with fetal tachycardia



4. Hyperstimulation syndrome

Uterine tachysystole and hypertonus with fetal tachycardia and deceleration



VITAE

Dr. Manit Sripramote was born on July 7, 1950 in Thonbui Province, Thailand. He graduated from the Faculty of Medicine of Siriraj Hospital (FMSH), Mahidol University in 1978 after accomplishing six years of undergradate study and one-year internship. After three-year Obstetrics and Gynecology Training Coursre at FMSH, he has been working at Bangkok Metropolitan Medical College and Vajira Hospital (BMMCVH). Due to his hard work, commitment and achievement, his position came to be office level nine, the chief of Gynecology and Pathology and recently Professor in Obstetrics and Gynecology. His research responsibility was the Chairman of Resident Research Committee, advisory support of Obstetrics and Gynecology Residency Training Program in BMMCVH.

He was ambitious to learn full course of clinical epidemiology. In 1998, he has been sponsored by the Bangkok Metropolis and admitted in the Master Degree Program / Clinical epidemiology in Faculty of Medicine of Chulalongkorn University, Bangkok, Thailand. This clinical epidemiology course is run by Thai CERTC (Clinical Epidemiology Regional Training Center) Consortium of INCLEN (International Clinical Epidemiology Network) principally sponsored by the Rockefeller foundation, New York, USA.

He was interested in the obstetrics practice and the research of labor induction. During this course, he has conducted a randomized controlled trial on misoprostol and dinoprostone in pre-induction cervical ripening.

Since 1999, BMMCVH established the Clinical Epidemiology and Research Development Centre and assigned him to be the chief of the unit. This clinical epidemiological training course will enable him to involve more teaching and research program at his institute.