A COMPARISON OF THE EFFICACY AND SIDE EFFECTS BETWEEN 800mcg AND 400mcg MISOPROSTOL IN THE MANAGEMENT OF MISSED MISCARRIAGES

BY

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Introduction : Misoprostol, a cheap and stable prostaglandin E1 analogue is the most widely studied drug for medical management of early pregnancy loss. In Malaysia, misoprostol is licensed for the management of stable first trimester miscarriages less than 13 weeks by Mesyuarat Panel Kaji Semula Senarai Ubat KKM. Most studies involving misoprostol compares between surgical and medical management of first trimester miscarriage. There is no study done comparing the doses of misoprostol in treatment of miscarriage available. This study compares between 400mcg and 800mcg in patient with uncomplicated missed miscarriage.

Objectives: To evaluate the effectiveness an and side effects profile of two different dosages of misoprostol

Methodology: A randomised controlled, equivalence study comparing 400 mcg and 800 mcg misoprostol pervaginally on an outpatient basis. The allocated dose was repeated the next day orally if clinically the products of conception had not been passed. Complete miscarriage was evaluated using two methods: ultrasound criteria on Day 7 and clinical criteria whereby pt having symptoms and sign that needed surgical management (ERPOC). Equivalence was demonstrated if the 95% confidence interval [CI] of the observed risk difference between the two doses for complete miscarriage lay between -15.0 and 15.0%. Differences in side effects were evaluated using patient-completed questionnaires.

Results : 136 women were allocated to receive 400 mcg and 132 women to 800 mcg misoprostol for the management of missed miscarriage. The rate of induced complete miscarriage was equivalent using both ultrasound criteria and clinical criteria (95% CI, P = 0.352). Following the 400

mcg dose, the reported rate of fever was stastically lower (95% CI, p<0.001). Other side effects also lower with diarhhoea (95% CI, p = 0.031), tiredness (95% CI, p = 0.002) and headache(95% CI, p = 0.042)

Conclusion: 400 mcg is as efficacious as 800mcg in inducing complete miscarriage. It also showed less side effect profile with significant less fever, diarrhoea, tiredness and headache.

Dr Ahmad Amir bin Ismail: Supervisor

Dr Zainal Abidin Hanafiah: Co Supervisor

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Contents

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
Et al	and others
hCG	human chorionic gonadotrophin
WHO	World Health Organisation
HRPZ II	Hospital Raja Perempuan Zainab II
mcg	microgram
RCOG	Royal College of Obstetric and Gynaecology
TVS	transvaginal scan
IUD	intrauterine device
ERPOC	evacuation retained product of conception
ET	endometrial thickness
eg	for example

ABSTRACT

Introduction

Misoprostol, a cheap and stable prostaglandin E1 analogue is the most widely studied drug for medical management of early pregnancy loss. In Malaysia, misoprostol is licensed for the management of stable first trimester miscarriages less than 13 weeks by Mesyuarat Panel Kaji Semula Senarai Ubat KKM. Most studies involving misoprostol compares between surgical and medical management of first trimester miscarriage. There is no study done comparing the doses of misoprostol in treatment of miscarriage available. This study compares between 400mcg and 800mcg in patient with uncomplicated missed miscarriage.

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To evaluate the effectiveness an and side effects profile of two different dosages of misoprostol

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A randomised controlled, equivalence study comparing 400 mcg and 800 mcg misoprostol pervaginally on an outpatient basis. The allocated dose was repeated the next day orally if clinically the products of conception had not been passed. Complete miscarriage was evaluated using two methods: ultrasound criteria on Day 7 and clinical criteria whereby pt having symptoms and sign that needed surgical management (ERPOC). Equivalence was demonstrated if the 95% confidence interval [CI] of the observed risk difference between the two doses for complete miscarriage lay between -15.0 and 15.0%. Differences in side effects were evaluated using patient-completed questionnaires.

RESULTS

136 women were allocated to receive 400 mcg and 132 women to 800 mcg misoprostol for the management of missed miscarriage. The rate of induced complete miscarriage was equivalent using both ultrasound criteria and clinical criteria (95% CI, P = 0.352). Following the 400 mcg dose, the reported rate of fever was stastically lower (95% CI, p<0.001). Othe side effects also lower with diarhhoea (95% CI, p = 0.031), tiredness (95% CI, p = 0.002) and headache(95% CI, p = 0.042)

Conclusion

400 mcg is as efficacious as 800mcg in inducing complete miscarriage. It also showed less side effect profile with significant less fever, diarrhoea, tiredness and headache.

ABSTRAK

Pendahuluan

Misoprostol adalah prostaglandin E1 analogue yang stabil, murah dan merupakan ubat yang paling banyak dikaji dalam rawatan keguguran awal kandungan melalui kaedah perubatan. Di Malaysia penggunaan misoprostol yang telah diberi kelulusan oleh Mesyuarat Panel Kaji Semula Senarai Ubat KKM adalah untuk rawatan keguguran yang stabil pada usia kandungan kurang dari 13 minggu. Beberapa panduan mengenai dos misoprostol yang sepatutnya digunakan adalah berdasarkan kajian perbandingan antara kaedah surgeri dan perubatan,dan bukannya dari kajian perbandingan antara berlainan dos. Di sinilah kajian ini berbeza di mana perbandingan antara 400mcg dan 800mcg untuk rawatan keguguran akan dilakukan.

Objektif

Untuk membandingkan keberkesanan dan kesan sampingan antara dua dos misoprostol dalam rawatan keguguran awal kandungan

Kaedah kajian

Kajian perbandingan antara 400mcg dan 800mcg misoprostol dilakukan secara rawak dan sekata di klinik sakit puan.Misoprostol dengan dos yang ditentukan akan dimasukkan di dalam vagina pada hari pertama dan diulangi keesokannya secara oral jika tiada tanda-tanda keguguran janin berlaku. Keguguran lengkap ditentukan melalui kaedah bunyi ultra pada hari ketujuh and keperluan untuk sugeri melalui tanda-tanda klinikal. Perbandingan tentang kesan sampingan dilakukan melalui boring Questionnaires yang telah diberikan kepada pesakit.

Keputusan kajian

Seramai 136 peserta telah ditentukan untuk menerima 400mcg dan 132 peserta yang lain menerima 800mcg untuk rawatan keguguran awal kandungan. Tiada perbezaan statistik yang dapat dikesan melalui perbandingan keberkesanan antara dua dos ini (95% CI, P = 0.352). Dengan dos 400mcg,kesan sampingan demam dapat dikurangkan (95% CI, p<0.001), cirit birit (95% CI , p = 0.031), keletihan (95% CI , p = 0.002) dan sakit kepala(95% CI , p = 0.042).

Kesimpulan

Misoprostol dengan dos 400mcg boleh disyorkan untuk rawatan keguguran awal kandungan di klinik sakit puan.

INTRODUCTION

Up to 20% patient with early pregnancy loss opt for medical management (Shymaly et al , 2009). It involves administering a medication to induce complete miscarriage, allowing an expedient evacuation of the uterus compared to expectant management while avoiding surgical management. It is considered a promising alternative because it is also expected to reduce hospitalization cost.

Misoprostol, a cheap, stable prostaglandin E1 analogue and requires no refrigeration, is the medication most widely studied for this purpose, despite its use in gynecological practice remaining ‘off label’. In Malaysia, indication of misoprostol that had been licensed by Mesyuarat Panel Kaji Semula Senarai Ubat KKM is for the management of stable first trimester miscarriages less than 13 weeks. It has been recognized as safe, effective and acceptable. Its efficacy depends upon the dosage and the route of administration. It can be administered both orally and vaginally and has been proven that more effective when administered vaginally.

A number of different regimens have been dibed by various studies. This is one of the reason it still has not been widely implemented into clinical practice in developed counties. However most of the dosages recommended were based on the studies comparing surgical and medical management of early pregnancy loss, and not from studies comparing the doses. In the other hand, the recent studies comparing the doses were mostly done on all types of miscarriages, including inevitable and incomplete miscarriage. This study was different when comparison between 400mcg(the lowest dosage ever recommended) and 800mcg (the high dosage) were done on patient with uncomplicated missed miscarriage only.

Recent studies showed that 800mcg intravaginal misoprostol had successful rate of 85% to induce complete miscarriage. IT is also noted that in 35% of patient, second dose of misoprostol is needed after 24 hours. Although these studies show a range of efficiency, higher success has been achieved when clinicians wait for 1-2 weeks after misoprostol administration before judging success or failure.

Previous studies showed that self administrations of vaginal misoprostol at home is safe and has the advantage of avoiding an additional visit to the clinic and providing privacy, afamiliar atmosphere and family support for the women. I hope that, this study will contribute for the decision of opyimal recommended dosage of misoprostol with good efficavy and less side effct, and protocols for medical management of missed miscarriage with misoprostol in outpatient setting of Gynaecology clinic HRPZ II.

1 LITERITURE REVIEW

Up to 20% patient with early pregnancy loss opt for medical management (Shymaly et al , 2009). It involves administering a medication to induce complete miscarriage, allowing an expedient evacuation of the uterus compared to expectant management while avoiding surgical management (Satiriadis et al , 2005). It is considered a promising alternative because it is also expected to reduce hospitalization cost.

Misoprostol, a cheap, stable prostaglandin E1 analogue and requires no refrigeration, is the medication most widely studied for this purpose, despite its use in gynecological practice remaining 'off label'. In Malaysia, indication of misoprostol that had been licensed by Mesyuarat Panel Kaji Semula Senarai Ubat KKM is for the management of stable first trimester miscarriages less than 13 weeks. It has been recognized as safe, effective and acceptable (Peterson et al, 2013 and Barcelo et al,2012). Its efficacy depends upon the dosage and the route of administration. It can be administered both orally and vaginally and has been proven that more effective when administered vaginally (Meckstroth et al, 2006).

1. CLINICAL REGIMENS

Misoprostol

Early studies of misoprostol used alone demonstrated rates of successful abortion of only 40–60% (Creinin et al, 1994, Bugalho et al, 1996). Subsequently, Carbonell et al, 1997 demonstrated improved success when tablets were moistened and placed vaginally. Up to three doses of 800 mg of misoprostol, place vaginally after moistening achieved success rates over 90% in gestations up to 9 weeks (Velaszo et al, 2000). In further dosing studies, Carbonell et al, 2001 found equal success and higher side-effects with 1000 mg, but much lower success (64%) with 600 mg. Initially, Carbonell's studies involved rather elaborate

protocols with douching prior to tablet insertion, and regimens of repeat administration. Jain et al, 2000 achieved success rates of 88–94% up to 8 weeks' gestation with simplified protocols using up to three doses of 800 mg of moistened, vaginal misoprostol. Although less complex than Carbonell's, these protocols still required multiple sonographic evaluations and visits to the clinic. Two of these trials compared 800 mg moistened vaginal misoprostol alone to a combination of mifepristone and misoprostol to 8 weeks' gestation. The first study comparedwomen who received misoprostol alone to women who had received 600 mg mifepristone and 400 mg oral misoprostol in a previous study at the same clinic as part of a multi-centre trial in USA. Successful abortion occurred in 88% with misoprostol alone and in 94% with the combination (Jain et al, 2000). A subsequent randomized controlled trial compared misoprostol alone to 200 mg mifepristone combined with 800 mg vaginal misoprostol, and found a success rate for the single drug of 88, versus 95.7% for the combination (Jain et al, 2002). Time to complete abortion was slower, and additional doses of misoprostol were required more frequently with misoprostol alone. Although gastrointestinal and other misoprostol side-effects were similar in these trials,moistening tablets prior to vaginal administration has been shown to lead to increased side-effects (Creinin et al, 1999).

Grading the evidence and recommendations for use of misoprostol alone is complex. According to US Preventative Task Force grading, level I evidence confirms that misoprostol alone is less effective than mifepristone plus misoprostol, suggesting a D-level recommendation against the use of this protocol when mifepristone is available. Although efficacy is lower, level I evidence supports the safety of medical abortion with one to three doses of 800 mg moistened vaginal misoprostol alone. Because mifepristone is unavailable or prohibitively expensive in many countries, the lower efficacy of misoprostol alone may be considered acceptable. When misoprostol alone is employed by women without the guidance

of a knowledgeable clinician, success rates may be lower and complications rates higher. Misoprostol is available in over 70 countries, is inexpensive and requires no refrigeration. For these reasons, an effective and simple regimen for medical abortion with misoprostol could benefit women who do not have access to other safe methods of abortion.

2. FACTORS INFLUENCING EFFICACY

Medical abortion is typically considered a success when a woman passes the pregnancy after medications and does not require surgical uterine evacuation for continuing pregnancy, incomplete abortion, prolonged or heavy bleeding, or patient request. In contrast, surgical abortion is usually considered a success if the pregnancy does not continue. Re-aspirations for the conditions listed above are not considered failures but complications. Given these definitions, medical abortion has a lower overall success rate than does surgical abortion. With improved dosing regimens at early gestation, however, success and continuing pregnancy rates of medical and surgical abortion are very similar (Child et al, 2001, Henshaw et al, 1994).In addition to medication factors, several patient and provider characteristics may affect efficacy rates of medical abortion.

Gestational duration is an important predictor of outcome. The most recent meta-analysis of medical abortion found that, as gestation advanced from 7 to 9 weeks, success rates declined from 95 to 84%. Large studies of 800 mg vaginal misoprostol achieve success rates over 95%, with failure due to ongoing pregnancy in only about 1% of women (Ashok et al,2000, 2002 and El Rafaey et al, 1994, 1995). Several large trials have reported that parous women have an increased failure rate compared to nulliparous women (Child et al,2001, Ashok et al, 2002, Schaff et al, 2000). Some studies also have noted decreased success in women with prior elective abortions compared to women without prior abortions. The reasons for these trends are unknown. One analysis found decreased success using

mifepristone plus a prostaglandin with increasing beta human chorionic gonadotropin (hCG) value and body mass index (Grimes et al,1990). Experience with medical abortion improves counselling and familiarizes clinicians with the course of medical abortion. When both patient and clinician are familiar with normal variations in bleeding, pain and other side-effects, intervention is less frequent. This decline in surgical intervention with experience has been documented in studies of methotrexate (Borgatta et al, 2000), and is suggested by the lower success rates found in the initial US multi-centre trial, compared to countries where providers were experienced.

3. PHARMACOLOGY OF MISOPROSTOL

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue. It was developed for the prevention and treatment of peptic ulcers because of its gastric acid anti-secretory properties and its various mucosal protective properties (Watkinson et al, 1988). It has become an important drug in obstetric and gynecological practice because of its uterotonic and cervical priming action. In comparison to other prostaglandin analogues, misoprostol has the advantages of being cheap, widely available and stable at room temperature and having few side effects. Its clinical applications include medical abortion, medical evacuation for miscarriages, cervical priming before surgical procedure, induction of labor and management of postpartum hemorrhage.

STRUCTURE AND CHEMISTRY OF MISOPROSTOL

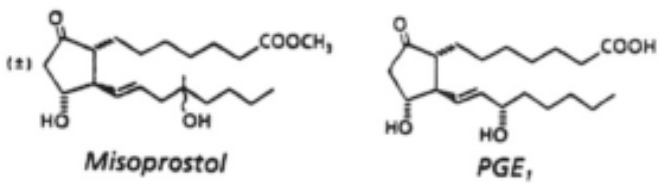

Fig. 1 shows the structures of misoprostol and the naturally occurring prostaglandin E1.

The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert et al. However, naturally occurring prostaglandins have three drawbacks that hindered their clinical application. These problems were: (1) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally, (2) numerous side effects, and (3) chemical instability leading to a short shelf life.Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, whilst the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug.

3.1 Pharmacokinetic properties of the various routes of administration of misoprostol.

Misoprostol tablets were developed to be used orally. Other routes of administration, however, including vaginal, sublingual, buccal and rectal, have also been used extensively in obstetric and gynecological applications. Over the past decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol.

3.2 Oral route

Early studies concentrated on the pharmacokinetic properties after oral administration. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid. Following a single dose of 400 mcg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes declines rapidly by 120 minutes and remains low thereafter (Meckstroth et al,2006)

3.3 Vaginal route

It was found in clinical studies that vaginal administration was more effective than oral administration in medical abortion (El rafaey et al,1995 and Ho PC et al.1997]. Zieman et al performed the first pharmacokinetic study comparing oral and vaginal routes of administration. In contrast to the oral route, the plasma concentration increases gradually after vaginal administration, reaching its maximum level after 70-80 minutes before slowly declining with detectable drug levels still present after 6 hours. Although the peak concentration after oral administration is higher than for vaginal administration, the 'area under the curve' is higher when given vaginally. The greater bioavailability of vaginal misoprostol may help to explain why it is more effective in medical abortion. It has been shown that the coefficient of variation of the AUC after vaginal administration is greater than that after oral administration (Zieman et al,1997). This means that the vaginal absorption of misoprostol is inconsistent. In clinical practice, remnants of tablets are sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to the variation between women in the amount and pH of the vaginal discharge. Variation in the amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa. Numerous attempts have been made to improve the absorption of vaginal misoprostol. The addition of water to the misoprostol tablets is a common practice. However, this has been shown not to improve the bioavailability of vaginal misoprostol (Tang OS et al, 2002).

3.4 Sublingual route

Recently, sublingual administration of misoprostol has been studied for medical abortion and cervical priming. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. A pharmacokinetic study compared the

absorption kinetics of oral, vaginal and sublingual routes of administration of misoprostol (Tang OS et al, 2002). It found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes.

The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration; it takes 75 minutes (Tang OS et al, 2002). Therefore, it appears that the sublingual and oral routes have the quickest onset of action. After 400 mcg of misoprostol, a sublingual dose achieves a higher peak concentration than that of oral and vaginal administration. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. The rapid onset and high peak concentration means that of all the possible routes the systemic bioavailability, as measured by the AUC in the first 6 hours, is greatest for sublingual administration. On the other hand, although vaginal absorption has been shown to be slower and the peak concentrations lower than that for the other routes, the serum level of misoprostol is sustained at that low level for a longer period of time. In fact, at the end of 6 hours the serum level of misoprostol acid after vaginal administration is higher than those of the sublingual and oral routes. Therefore, the effect of misoprostol may linger for more than 6 hours after a single dose, though the threshold serum level for clinical action is unknown.

3.5 . Buccal route

Buccal administration is another way of giving misoprostol. The drug is placed between the teeth and the cheek and allowed to be absorbed through the buccal mucosa. Clinical studies, although limited compared to other routes, have shown that the buccal route

is also effective for medical abortion, cervical priming and labor induction (Castleman et al,2006 andCarlan et al,2002). The buccal route is a promising way of administering misoprostol and more studies are required to compare it with other routes of administration.

3.6 Rectal route

The rectal route of administration has been studied recently for the management of postpartum hemorrhage. This route of administration is less commonly used for other applications.

An understanding of the pharmacokinetic properties of different routes of administration can help to design the best regimens for the various clinical applications. However, it may not be able to predict clinical outcomes for various clinical indications. Sublingual misoprostol, which has the shortest Tmax, is perhaps useful for clinical applications that require a fast onset of clinical action, such as postpartum hemorrhage or cervical priming. Vaginal misoprostol on the other hand, which has a high bioavailability and sustained serum level, is useful for indications that require a longer time for the manifestation of its clinical effects, like medical abortion. The absorption kinetics can also explain why some routes of administration are associated with a higher incidence of side effects. Sublingual administration, which gives the highest Cmax, is associated with highest incidence of side effects when compared to other routes.

4. DOSE AND TIMING OF MISOPROSTOL

Because side-effects increase with the dose of misoprostol, the lowest effective dose for each route of administration is ideal. Unfortunately, comparative dose-finding studies of misoprostol, used alone or in combination, are few. A comparison of misoprostol, given vaginally 1, 2, or 3 days after mifepristone, found no difference in efficacy (Tang OS et al,

2002). Some protocols require multiple doses of misoprostol after mifepristone. A second oral misoprostol dose appears to lead to higher overall efficacy, and may mitigate the influence of gestational length on efficacy with oral misoprostol (Hausknecht et al,1995 and Ashok et al, 2002). The ideal interval between the doses is not clear, however. A week-long course of oral misoprostol (400 mg twice daily), was not beneficial in reducing blood loss or improving efficacy (Finer et al, 2003)

5. PHARMACOKINETICS IN HUMAN BREAST MILK

Breastfeeding mothers may be given misoprostol for postpartum hemorrhage prevention and treatment. It is important therefore to consider its potential effects on the fetus. However, there are very few studies on the pharmacokinetics of oral misoprostol in breast milk. Misoprostol were detected in breast milk within 30 minutes of oral administration. The peak concentration was attained in 1 hour, which is slightly slower than the plasma level (30 minutes). The level in breast milk rapidly drops afterwards and is undetectable by 4-5 hours after ingestion. The misoprostol acid level in breast milk is only one-third of that in the plasma (Vogel et al, 2004 and Abdel-Aleem et al,2003). There is no data on the pharmacokinetics of misoprostol in breast milk for non-oral routes. However, it would be expected that the breast milk concentration would be lower after vaginal administration than after oral administration, but might last longer. The effect of a short exposure to low levels of misoprostol to the fetus is unknown.

6. EFFECTS ON THE UTERUS AND THE CERVIX

The uterotonic and cervical softening effects on the female genital tract were considered as side effects rather than therapeutic effects when misoprostol was first introduced. However, it is because of these effects that misoprostol is so widely used in obstetric and gynecological practice today.

6.1 Uterus

The effect of misoprostol on uterine contractility was well studied by Gemzell-Danielsson et al. and Aronsson et al.. After a single dose of oral misoprostol there is an increase in uterine tonus (Norman et al,1991). To produce regular contractions, however, a sustained plasma level of misoprostol is required and this requires repeated oral doses. The effect of vaginal administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration: an increase in uterine tonus. However,after 1-2 h, regular uterine contractions appear and they last at least up to 4 h after the administration of misoprostol . The development of regular contractions after vaginal administration may explain the better clinical efficacy of vaginal administration when compared to oral administration(Ho PC et al,1997).Recently, sublingual misoprostol was studied in first and second trimester medical abortion. Aronsson et al.compared the effects of misoprostol on uterine contractility following different routes of administration (Tang OS et al,2003). It was found that the increase in uterine tonus is more rapid and more pronounced following oral and sublingual treatment than after vaginal treatment. The mean time to increase in tonus is 8 and 11 min for oral and sublingual administration respectively compared with 20 minutes for vaginal administration.

The mean time to maximum tonus is also significantly shorter for oral and sublingual misoprostol compared to vaginal administration. One to two hours after the administration of misoprostol, the tonus begins to decrease. In the case of oral misoprostol, this is the end of the activity. For vaginal and sublingual treatment, however, the tonus is slowly replaced by regular uterine contractions. These regular uterine contractions are sustained for a longer period after vaginal administration than after sublingual treatment, with decreased activity occurring only after 4 hours (compared to 3 hours with sublingual).

The uterine effect of buccal and rectal administration was studied by Meckstroth et al. It was shown that the pattern of uterine tonus and contractility of buccal administration is very similar to vaginal administration. Rectal administration shows the lowest uterine activity in terms of tonus and contractility. Furthermore the mean onset of activity was 103minutes, significantly longer than by other routes. This studies on uterine contractility so far have shown that a sustained level, rather than a high serum level, is required for the development of regular uterine contractions. Studies have failed to define the threshold serum level for uterine contractility. It seems that a very low serum level of misoprostol is required for the development of regular uterine contractions. This is complicated further by the fact that the sensitivity of the uterus to prostaglandins increases with gestation. The clinical effects or actions required for different indications of use also vary. The strength of contraction that is required to achieve the clinical effects usually increases with gestation. For instance, stronger contractions are required for labor induction than medial abortion. For medical abortion, the

addition of mifepristone would certainly modify the action of misoprostol and lower the serum threshold level for uterine contractility. In addition to uterine contraction, the softening effect of misoprostol on the cervix also contributes to its clinical action.

6.2 Cervix

There were many clinical studies that have demonstrated the cervical priming effect of misoprostol in the pregnant state. Misoprostol has been used extensively for its cervical softening effect before induction of labor and surgical evacuation of the uterus. Studies have demonstrated that less force was required for mechanical dilatation of the cervix if misoprostol was applied before the procedure (Ngai et al,1995,Elrafaey et al,1994) While this softening effect on the cervix may be secondary to the uterine contractions induced by misoprostol, it is more likely to be due to the direct effect of misoprostol on the cervix. The

uterine cervix is essentially a connective tissue organ. Smooth muscle cells account for less that 8% of the distal part of the cervix. The exact mechanism leading to physiological cervical ripening is not known. The biochemical events that have been implicated in cervical ripening are a decrease in total collagen content, an increase in collagen solubility, and an increase in collagenolytic activity. Indeed, during cervical ripening there is an influx of inflammatory cells into the cervical stroma, which increases matrix metalloproteinases and thereby leads to the degradation of collagen and cervical softening . It has been proposed that these cells produce cytokines and prostaglandins that have an effect on extracellular matrix metabolism.It has also been shown that various prostaglandin analogues could decrease the hydroxyproline content of pregnant cervix(Rath et al,1982).

The histochemical changes in the pregnant cervix after misoprostol administration were studied using electron microscopy and proline uptake assay. The mean proline incorporation per mcg protein and collagen density, estimated by light intensity, was significantly less than the control. This indicated that the action of misoprostol appeared to be mainly on the connective tissue stroma with evidence of disintegration and dissolution of collagen (El Rafaey et al,1994).

Most of the studies on uterine contractility and cervical softening after misoprostol have been conducted on pregnant women. There is, however, evidence suggesting that these changes alsooccur innon-pregnant uterus. Some non-pregnant women experience uterine cramps after misoprostol and misoprostol has been shown to also have a cervical priming

effect in the non-pregnant state (Ziemann et al,1997).

Misoprostol is a safe and well-tolerated drug. Pre-clinical toxicological studies indicate a safety margin of at least 500-1000 fold between lethal doses in animals and misoprostol has not been shown to be embryotoxic, fetotoxictherapeutic doses in