health technology assessment

REPORT

MISOPROSTOL IN PREGNANCY

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EXECUTIVE SUMMARY

INTRODUCTION

In Malaysia, the commonly used prostaglandins are Gemeprost (Cervagem®) and Dinoprostone (Prostin®). Although effective and safe, they are expensive and require special storage (Song J 2000). The search for an effective, easily stored, and affordable cervical ripening and uterotonic agent has led to the use of misoprostol.

Misoprostol has been approved (licensed) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of non steroidal anti inflammatory drugs. This drug is registered by the Drug Control Authority of Malaysia for the same indication. Misoprostol has not been approved for any other indications. Use under these circumstances would be considered off label. Unlike the off label use of other drugs, the use of misoprostol for labor induction has sparked considerable controversy.

POLICY QUESTION

The Obstetrical and Gynecological Society of Malaysia requested a health technology assessment be carried out on the use of "Misoprostol in Pregnancy". The reason for such a request is recently there has been wide interest by the media on the alleged misuse and the alleged dangers of misoprostol.

TARGET AUDIENCE

This report is meant for policy makers to consider allowing the use of misoprostol on pregnant mothers.

OBJECTIVES

To determine safety, effectiveness, cost effectiveness and legal aspects of misoprostol for various uses in the first, second and third trimester for cervical ripening and induction of labour ~~and~~ as well as the management of post partum hemorrhage.

RESULTS

MISOPROSTOL IN THE FIRST TRIMESTER

Effectiveness

The evidence suggests that in the first trimester, misoprostol is an effective cervical priming agent prior to surgical abortion. It is as effective as gemeprost when used for this purpose. It is also effective in evacuating the uterus in missed abortions. There is limited evidence to support its use in incomplete abortions and as an abortifacient.

Safety

There are studies that found an association between the use of misoprostol for attempted abortion and subsequent Mobius syndrome in live born infants. However there is a need for proper large controlled trials to confirm whether this is a strong association of correlation or not.

MISOPROSTOL IN THE SECOND TRIMESTER

Effectiveness

For second trimester abortions, there is insufficient evidence for effectiveness of misoprostol as a cervical priming agent. However, there is sufficient evidence for its effectiveness for termination of pregnancy and it is also cost effective.

MISOPROSTOL FOR CERVICAL RIPENING AND INDUCTION OF LABOUR

Effectiveness

In the third trimester, there is sufficient evidence of effectiveness for oral misoprostol for induction of labour. However, the data on optimal regimens are lacking.

Safety

There is evidence that demonstrates that effective oral regimens of misoprostol result in unacceptably high incidence of complications such as uterine hyperstimulation and possibly uterine rupture. There is insufficient large clinical trials to assess maternal and perinatal outcomes.

MISOPROSTOL IN POST PARTUM HAEMORRHAGE

Effectiveness

There is insufficient evidence to support the use of misoprostol in prevention of postpartum hemorrhage.

Safety

A number of studies have reported concerns with the usage of misoprostol in third stage of labour.

COST EFFECTIVENESS

There is sufficient evidence that demonstrates that it is a cost effective alternative to use misoprostol in the first trimester, second trimester and third trimester.

LEGAL IMPLICATIONS

From the legal aspect, misosprostol cannot be used in pregnancy since it has been registered only for treatment of gastric and duodenal ulcers refractory to H_2-receptor antagonists

RECOMMENDATIONS

Based on the current evidence to date, there is sufficient safety and legal concerns not to recommend misoprostol for cervical priming, termination of pregnancy, induction of labour or postpartum hemorrhage.

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1. INTRODUCTION

The practice of obstetrics and gynecology has over the years been revolutionized by the use of prostaglandins. Being highly active organic chemical compounds, they not only affect myometrial contractility but also accelerate physiological ripening of the cervix (Scheepers et al, 1999). Prostaglandins have been used in the induction of labour, cervical ripening in pregnancies at term, medical termination of pregnancies and cervical priming in cases of surgical termination of pregnancies.

In Malaysia, the commonly used prostaglandins are Gemeprost (Cervagem®) and Dinoprostone (Prostin®). Cytotec, a stable, orally active, synthetic analogue, is the only product containing misoprostol. registered by the Drug Control Authority of Malaysia. Although effective and safe, prostaglandins are expensive and require special storage (Song, 2000).

Misoprostol is prostaglandin E1. Its uterotonic and cervical ripening properties have become increasingly known, a wealth of information has emerged from studies and published literature worldwide regarding its potential use in obstetrics and gynecology (Goldberg et al 2001). However, Misoprostol has not been approved for any of these indications. Use under these circumstances, its use for this would be considered *off label*. Unlike the *off label* use of other drugs, the use of misoprostol for labor induction has sparked considerable controversy.

2. BACKGROUND

With respect to termination of pregnancy, the reintroduction of the medical approach is relatively new. The termination of pregnancy using pharmacological agents alone, without resorting to surgical means is termed medical abortion (Ankum, 2001).

For terminating 1st trimester pregnancy, in many countries, vacuum aspiration is still the first choice, since it is quick and cheap (Fong et al 1998). Prior to surgical abortion in the first trimester, cervical priming is critical to prevent cervical lacerations, hemorrhage and uterine perforation. Cervical priming is defined as softening, effacement and gradual dilatation of the cervical os. Priming can be achieved biochemically with the use of prostaglandins (e.g. Gemeprost) or hydrophilic dilators (e.g. Dilapan®, Laminaria ®) (Fong, 1998). Gemeprost is the method of choice in most public hospitals. However, due to expense and inconvenience of administration of drugs, pre-abortion cervical priming is used sporadically and selectively (Vimala et al, 2003).

In incomplete abortions, the mainstay of management is surgical evacuation of retained products of conception. The medical approach is relatively new.

Missed abortion in the first trimester is conventionally managed with surgical evacuation, usually with suction aspiration. Medical treatment could also be used to evacuate the uterus prior to suction evacuation.

In the second trimester of pregnancy, cervical dilatation and induction of labour to expel the fetus is necessary. Gemeprost is widely used in public hospitals currently for this purpose.

The main problems experienced during induction of labour are ineffective labour, and excessive uterine activity which may cause fetal distress. Both problems may lead to an increased risk of caesarean section. Labour can be induced by administration of oxytocin, prostaglandins, prostaglandin analogues; smooth muscle stimulants such as herbs or castor oil; mechanical methods such as digital stretching of the cervix and sweeping of the membranes; hygroscopic cervical dilators, extra-amniotic balloon catheters, artificial rupture of the membranes, and nipple stimulation (Mitri 1987).

Oxytocin has the disadvantage of a high failure rate when the cervix is unfavourable, as well as requiring monitored continuous intravenous infusion.

Artificial rupture of membranes is also less effective or may not be possible when the cervix is unfavourable. It may increase the risk of infection if labour does not proceed promptly. The rupture of membranes may also increase the vertical transmission of specific maternal infections such as HIV.

Unsuccessful labour induction is most likely when the cervix is unfavourable and, in this circumstance, prostaglandin preparations have proved to be beneficial (Kierse 1993; MacKenzie 1997). Uterine hyperstimulation has been identified as a particular problem during labour induction with prostaglandins, and has been treated with tocolysis (Egarter 1990).

Misoprostol has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors (Senior, 1993). It has been used widely for obstetric and gynaecological indications despite the fact that it has not been registered for such use. It has therefore not undergone the extensive testing for appropriate dosage and safety required for registration

3. POLICY QUESTION

The Obstetrical and Gynecological Society of Malaysia requested a health technology assessment be carried out on the use of “Misoprostol in Pregnancy”. The reason for such a request is recently there has been wide interest by the media on the alleged misuse and the alleged dangers of misoprostol.

4. TARGET AUDIENCE

This report is meant for policy makers to consider allowing the use of misoprostol on pregnant mothers.

5. OBJECTIVE

To determine safety, effectiveness, cost effectiveness and legal aspects of misoprostol for various uses in the first and second trimester as well as in the third trimester for cervical ripening or induction of labour and post partum hemorrhage.

6. METHODOLOGY

The Medline database was searched with no limits applied. The key words used included *misoprostol, cytotec, abortion, miscarriage, effectiveness, efficacy, termination of pregnancy* and *priming*. These words were used in various combinations. The Cochrane Database of Systematic Reviews and Evidence Based Medicine Database of Abstracts of Reviews (DARE) were also searched using keywords *misoprostol* and *abortion*. The Royal College of Obstetricians and Gynaecologists, United Kingdom website database was also searched using the keyword *misoprostol*. When using the above keywords and looking at the aspect of effectiveness/ efficacy, about 240 abstracts were retrieved and 56 were found relevant. Among these, 23 full articles were reviewed.

When looking at the aspect of cost effectiveness, key words used in Medline included *misoprostol, cytotec, abortion, miscarriage, cost, cost effectiveness termination of pregnancy* and *priming.* The Cochrane Database of Systematic Review and Evidence Based Medicine Database of Abstracts of Reviews (DARE) were also searched using keywords misoprostol and abortion and cost effectiveness. Of this, about 24 abstracts were analyzed and 8 were found relevant. Among these, 4 full articles were reviewed.

As most of the studies were included in the systematic reviews and meta analysis, and the most recent and updated systematic reviews were "Vaginal misoprostol for cervical ripening and induction of labour" by Hofmeyr, GJ; Gulmezoglu, AM (21.11.02 updated) and "Oral misoprostol for induction of labour" by Alfirevic, Z (21.02.04 updated), these 2 systematic reviews were used for the purpose of the analysis. The former included 70 trials while the latter 13 trials.

As the Randomised Controlled Trials reviewed in both the systematic reviews were not large enough to exclude the possibility of the rare but serious adverse event - uterine rupture, which has been reported anecdotally following misoprostol use in women, the EBM – CDSR, CCRCT, DARE, and Pubmed were searched using the keywords – "*misoprostol* and *uterine rupture*". 79 searches were found and 34 were relevant out of which 21 were references in the 2 Systematic Reviews. Of the other 13 articles, the abstracts of 3 of the articles we were unable to be retrieved (Goer H, McLean MT, Wagner M –all comments/letters).

7. TECHNICAL FEATURES

The US FDA approved the use of Mifepristone (RU486) in conjunction with Misoprostol for early pregnancy termination (49 days or less). In September 2000, the product labelling included a warning that misoprostol is contraindicated in pregnancy because of abortifacient properities. However in May 2002, FDA changed the warning to misoprostol being contraindicated for use as an anti-ulcer drug in pregnant women.

Misoprostol has not been approved by FDA for any obstetric or gynecologic indication, (Goldberg & Wing, 2003). In Malaysia, Mifepristone is not registered for use.

The information described below for Misoprostol is based on information derived from Cytotec Tablets.

Misoprostol is a methyl ester of prostaglandin E1 additionally methylated at C-16**.** It has been approved (licensed) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of non steroidal anti inflammatory drugs. This drug is registered by the Drug Control Authority of Malaysia for the same indication.

Misoprostol is a synthetic prostaglandin E_1 analogue that is water soluble and appears as viscous liquid. The uterotonic effect of misoprostol is an inherent property of prostaglandin E1. Misoprostol can induce or augment uterine contractions, interacting with myometrial cell receptors to cause strong myometrial cell contractions leading to expulsion of embryonic or fetal tissue. It also results in cervical softening and dilatation.

Misoprostol is rapidly absorbed orally and vaginally. This drug has rapid and extensive absorption after oral administration and undergoes de-esterification to its free acid which is responsible for its clinical activity. The half life of misoprostol is 30 minutes.

Oral administration (PO):	Time to peak plasma conc.	= 30 min
	Onset of uterine tonus	= 8 min
	Time to peak uterine tonus	= 25 min
Vaginal administration (PV):	Time to peak plasma conc.	= 80 min
	Onset of uterine tonus	= 21 min
	Time to peak uterine tonus	= 46 min

Approximately 80% of the orally administered dose of misoprostol is excreted in the urine within 24 hours, 56% being excreted within the first 8 hours.

Oral misoprostol has similar efficacy as vaginal misoprostol and adverse uterine effects (hyperstimulation, tachysystole) can be minimized by carefully selecting the appropriate dose and frequency (Toppozada et al, 1997; Carlan et al, 2001; How et al, 2001). Sublingual misoprostol was found to be more efficacious than oral misoprostol in one study, but it was found that the sublingual tablets did not dissolve completely in 9.5% of patients (Shetty et al, 2002)

The vaginal dose should be 25mcg or less, repeated at least 3-hourly intervals to minimise uterine hyperstimulation, going up to 5 or 6 doses before considering rescue interventions with other modalities such as vaginal prostaglandin gel. Higher doses are associated with a greater incidence of uterine hyperstimulation, tachysystole or interventions secondary to fetal distress. An oral dose of 50 to 100mcg at 4 hour intervals of up to 5 doses appears to be acceptable in terms of efficacy, safety and patient preference.

The toxic dose of misoprostol in humans has not been determined, and it is not known if misoprostol is dialysable. As misoprostol is metabolised like a fatty acid, it is unlikely that dialysis would be the appropriate treatment for overdosage.

There has been no carcinogenicity or mutagenecity reported of this drug. However, congenital abnormalities and fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient.

Misoprostol is inexpensive and easily stored at room temperature

8. RESULTS AND DISCUSSION

8.1. EFFECTIVENESS OF MISOPROSTOL IN THE FIRST TRIMESTER

8.1.1. CERVICAL PRIMING BEFORE SURGICAL ABORTION

Several randomized controlled trials comparing efficacy of misoprostol as a cervical priming agent to placebo found that misoprostol significantly increases baseline cervical dilatation. (Ngai, 1995; Ngai, 1999; de Jonge, 2000; Vimala, 2003). .

Vacuum aspiration was found to be easier in groups treated with misoprostol compared to placebo. In one study, pre treatment with misoprostol increased baseline cervical dilatation and significantly reduced duration of the procedure (Saxena, 2003). In the other study, misoprostol resulted in 85% change in cervical score in pre-treated patients (Okanlomo, 1999). A randomized double blind placebo controlled trial comparing misoprostol to laminaria tents found no statistically significant difference in dilatation between misoprostol and laminaria (MacIsaac, 1999).

Four randomized controlled trials compared misoprostol to gemeprost. The two larger trials with 199 and 406 patients each found misoprostol and gemeprost to be equally effective in producing cervical dilatation (Platz-Christensen, 1995; Henry, 1999). A smaller trial with 64 patients found misoprostol to be more effective than gemeprost (Ngai, 1995). A local study in Hospital Taiping compared misoprostol to gemeprost as priming agents in missed abortions in 100 patients, 71% in the first trimester, and the remaining in the second trimester (Eeson et al, 1998).. There was no significant difference in cervical dilatation ability found between gemeprost and misoprostol.

8.1.2. MEDICAL ABORTION

Several clinical trials using misoprostol as an abortifacient reported complete abortion rates varying from 84 % to 96% (Carbonell et al, 1997 a; Carbonell et al, 1997 b; Carbonell et al 1998; Carbonell et al, 1999; Esteve, 1999; Bugalho, 2000; Velazco, 2000; Carbonell et al, 2001 a; Carbonell et al, 2001 b; Tang, 2001; Tang, 2002; Zikopoulos, 2002; Singh,2003). However, the periods of gestation vary in all these studies from 42 to 91 days. Those with higher rates were followed up for longer periods following initial dosing with patients experiencing prolonged bouts of bleeding. One study obtained a

96% complete abortion rate after following up the patient for 43 days (Singh, 2003). In another study, a complete abortion rate of 88.7% was obtained (Velazco, 2000).

However, misoprostol has also been considered inadequate to produce a high and acceptable abortive efficacy, since an abortion rate of 64% was obtained in a clinical trial (Carbonell et al, 2000). In a randomized controlled trial of 80 patients using misoprostol, complete abortion rates of 85% using moistened tablets and 65% with unmoistened tablets were achieved, with 40% of patients preferring a surgical method in future because of the high failure rate (Ngai, 2000).

The Cochrane Database of Systematic Reviews (2003) studied medical and surgical methods of first trimester pregnancy termination and found limited evidence on acceptability of medical methods of termination. The National Evidence Based Clinical Guidelines on Care of Women Requesting Induced Abortion (Royal College of Obstetricians & Gynaecologists, 2000) reviewed 15 randomized controlled trials of misoprostol for various uses in abortion, and does not recommend its use alone for medical abortion.

8.1.3. INCOMPLETE ABORTION

In a randomized controlled trial comparing misoprostol to surgical evacuation for incomplete abortion, a 95% success rate was achieved at the expense of a significantly higher mean number of bleeding days (Sahin, 2001). In a similar larger study, 50% of patients treated with misoprostol required surgical evacuation (Chung, 1999).

Another randomized controlled trial comparing misoprostol to expectant management obtained a success rate of 83.3% in the misoprostol group with patients experiencing 14.6 mean bleeding days (Ngai, 2001).

Trials using misoprostol alone quoted various complete abortion rates ranging from 61% to 85% (Ngai, 2001; Pang, 2001; Pandian, 2001).

A review in the Cochrane Database of Abstracts of Reviews of Effectiveness (2003) of various options of medical management of incomplete abortion found insufficient evidence to support this mode of treatment.

A local unpublished RCT by Zainuddin et al from Universiti Kebangsaan Malaysia comparing rate of complete evacuation using vaginal misoprostol with curettage in women with spontaneous first trimester incomplete miscarriage, obtained a success rate of 80.5% with misoprostol.

8.1.4 MISSED ABORTION

Randomized controlled trials comparing misoprostol to surgical evacuation in missed abortion found rates of 60 % to 76.9% in the misoprostol groups (Demetroulis, 2001; Muffley, 2002). However, randomized controlled trials comparing misoprostol to placebo in missed abortion during the first trimester found misoprostol to be significantly more

effective than placebo with successful abortion rates ranging from 63% to 80% (Kovavisarach, 2002; Wood, 2002). A clinical trial using misoprostol alone in missed abortion showed a complete evacuation rate of 56.8% (Ayres de Campos, 2000).

A review of studies involving the use of misoprostol in missed abortions in the first trimester found expulsion rates of 80 to 90%, although no large studies were identified (Creinin, 2001).

8.2. SAFETY OF MISOPROSTOL IN THE FIRST TRIMESTER

8.2.1. CERVICAL PRIMING BEFORE SURGICAL ABORTION

Vimala (2003) in a randomized control trial showed that the use of sublingual misoprostol at a dose of 400mcg prior to surgical evacuation was associated with slightly higher pre-evacuation bleeding, abdominal pain and nausea and vomiting, although the overall blood loss was however less compared to placebo.

A RCT by Ngai (1999) however found no significant differences in the postoperative complications rate and bleeding comparing oral and vaginal misoprostol and placebo. These findings was also confirmed in other studies (El-Rafeay, 1994; Ngai, 1995; Fong, 1998;)

8.2.2. ABORTION

With respect to safety, post abortion bleeding is one of the main concerns with the use of misoprostol in the first trimester. Most studies report a slight drop in the haemoglobin level but this finding is not clinically significant (Carbonell, 1997; Carbonell, 1998; Esteve, 1999; Carbonnel, 2001; Wood, 2002; Cochrane Database of Systemic Review, 2003).

A randomized control trial comparing misoprostol and surgical evacuation in abortion found that with medical management there was a significantly lower incidence of immediate and short term complications, with fewer major complications even 6 months after treatment. However, approximately 50% of patients on misoprostol subsequently required surgical evacuation. (Chung, 1999),

The other side effects reported were abdominal pain, nausea and vomiting, diarrhoea, transient hyperthermia and headache (Faunders, 1996; Haberal, 1996; Ayres-de-Campos, 2000).

Another serious side effect is the failure of misoprostol to cause abortion, reported by a Brazilian study where 17 out of 42 patients who failed to abort with misoprotol subsequently delivered babies with Congenital Talipes Equinovarus and cranial nerve defects, while 10 other babies had arthrogryposis (Claudette, 1998) Similarly Pastuszak et al (1998) found that failed abortion with misoprostol resulted in infants with Mobius Syndrome, congenital facial paralysis with or without limb defects. It has been postulated that this is due to vascular disruption, due to brain-stem ischemia induced during

contractions.

8.3. COST EFFECTIVENESS OF MISOPROSTOL IN THE FIRST TRIMESTER

Schaub (1995) in a randomized controlled trial comparing misoprostol versus sulprostone as a cervical priming agent before surgical evacuation, found the cost to be lower using misoprostol. Hughes et al, (1996) in a RCT also found that the cost of treating first trimester miscarriages was lower when misoprostol was used.

8.4. EFFECTIVENESS OF MISOPROSTOL IN THE SECOND TRIMESTER

8.4.1. CERVICAL PRIMING

In a retrospective review of 110 patients at gestations 14 to 18 weeks, the efficacy of misoprostol was found to be similar to laminaria for cervical priming (Todd, 2002).

8.4.2. ABORTION

Effectiveness

Two small RCT found misoprostol as effective as PGE2 in terminating second trimester pregnancies (Owen, 1999; Jain, 1994). Similarly, a local study in Kuala Lumpur Hospital found misoprostol to be as effective as gemeprost in second trimester intrauterine deaths (Eng, 1997). However, another RCT found misoprostol more effective than gemeprost in second trimester terminations producing an 80% abortion rate within 24 hours compared to 59% with gemeprost (Wong, 1998).

Other trials using misoprostol alone achieved abortion rates ranging from 80 to 90.5% (Herabutya, 2000; Wong, 2000; Jain, 1999; Carbonell, 1998). The clinical guidelines of the Royal College of Obstetricians & Gynaecologists (2000) recommended misoprostol as an alternative to gemeprost in mid trimester abortions, to be used in combination with mifepristone.

In conclusion, there is sufficient evidence that Misoprostol is effective as an abortifacient in second trimester pregnancies, its efficacy being similar to prostaglandin E2 and gemeprost.

Safety

Gonzales (2001) found in his study that the outpatient self-administration of oral misoprotol 200mcg was safe. Other studies have also confirmed that there are few side-effects like fever, nausea and vomiting as compared to cervagem or placebo (Herabutya, 2000; Srisombon, 1998; Eng, 1997; Srisombon, 1999; Batioglu, 1997; Bugalho, 1993; Sinthamoney, 2001; Schuker, 1999).

8.4.3. COST IMPLICATIONS

A RCT in Kuala Lumpur Hospital by Eng (1997) comparing the effectiveness and cost effectiveness of misoprostol vs. gemeprost as an abortifacient in the second trimester found that misoprostol was more cost effective (RM 1.08 vs. RM 105). Dickinson (1998) found a 200 fold pharmaceutical cost advantage when intra-vaginal misoprostol was used compared with gemeprost. Other investigators have also found that using misoprostol was much cheaper than using prostaglandin analogues (Jain, 1994; Lalley, 2001; Wridht-Francis, 1998).

8.5. EFFECTIVENESS OF MISOPROSTOL FOR CERVICAL RIPENING AND INDUCTION OF LABOUR

8.5.1. VAGINAL MISOPROSTOL

Compared to placebo, vaginal misoprostol was associated with increased cervical ripening and reduced failure to achieve vaginal delivery within 24 hours. However, uterine hyperstimulation, without fetal heart rate changes, was increased (Alfirevic, 2004).

Comparing vaginal misoprostol, vaginal prostaglandin E2 with intracervical prostaglandin E2 and oxytocin, it was found that with vaginal misoprostol, labour induction was associated with less epidural analgesia use and fewer failures to achieve vaginal delivery within 24 hours. However, there was more uterine hyperstimulation. Misoprostol when compared with vaginal or intracervical prostaglandin E2, resulted in less oxytocin augmentation although meconium-stained liquor was more common. Compared with intracervical prostaglandin E2, there was less unchanged or unfavourable cervix after 12 to 24 hours with misoprostol.

A local RCT by Kassim compared vaginal misoprostol with dinoprostone involving 130 primigravidas for induction of labour found both equally effective for cervical ripening at six hours after insertion.

8.5.2. ORAL MISOPROSTOL

A trial with 80 randomised women with pre-labour rupture of membranes at term showed that oral misoprostol when compared with placebo, reduces the need for oxytocin infusion from 51% to 13 % and shortens delivery time by 8.7 hours (Alfirevic, 2004).

Two small trials with 188 women in total compared oral misoprostol and oxytocin in women with term ruptured membranes and found no significant differences in pre-specified outcomes.

8.5.3. VAGINAL VERSUS ORAL MISOPROSTOL

In seven trials with 1278 randomised women oral misoprostol appeared to be less effective compared to vaginal misoprostol, as more women in the oral misoprostol group did not achieve vaginal delivery within 24 hours of randomisation (Alfirevic, 2004).

Comparing the use of a vaginal gel preparation of misoprostol versus tablet, the gel was associated with less hyperstimulation, but more use of oxytocin and epidural analgesia (Homefyr & Gulmezoglu, 2004).

8.5.4. DOSAGE VARIATION IN MISOPROSTOL

Lower doses of misoprostol were associated with greater need for oxytocin augmentation, less uterine hyperstimulation, with and without fetal heart rate changes, and a trend to fewer admissions to neonatal intensive care unit (Homefyr & Gulmezoglu, 2004).

8.6 SAFETY OF MISOPROSTOL IN INDUCTION OF LABOUR AND CERVICAL PRIMING

The clinical guideline by the Royal College of Obstetricians and Gynecologists (2001) highlights an area of major concern with regards to safety in that misoprostol is only available in 200 microgram formulation, when most trials of misoprostol in labour use 50 and 25 microgram doses, which involves cutting the tablet or making a suspension of the drug. As a result, uniform concentration of the active drug cannot be guaranteed in individual pieces, resulting in variable amounts of active drug being delivered. This guideline recommends more clinical trials with regards to safety of using vaginal or oral misoprostol using commercially produced low-dose tablets.

Similar conclusions was drawn by Hofmeyr and Gulmezoglu (2004) in their meta analysis for vaginal misoprostol for cervical ripening and induction of labour, who concluded that the clinical trials were not sufficiently large to assess the likelihood of uncommon, serious adverse perinatal and maternal complications due to misoprostol.

8.6.1.UTERINE RUPTURE

There have been several reports of uterine rupture following misoprostol labour induction with and without previous caesarean section (Bennett, 1997; Sciscione, 1998; Blanchette 1999; Matthews, 1999; Gherman, 1999; Daisley, 2000; Hill, 2000; Majoko 2002b).

A trial of misoprostol for labour induction in women with prior caesarean section had to be terminated prematurely because of disruption of the uterine incision in two of the first 17 women treated with misoprostol (Wing, 1998a).

In a retrospective review, uterine rupture was found to occur in 5.6% of women with previous caesarean delivery who had labour induced with misoprostol (Plaut, 1999). No uterine ruptures were detected among 48 women with previous caesarean section whose labour was induced with vaginal misoprostol 50 mcg four hourly in another retrospective review (Choy-Hee, 2001). Bique (1999) also did not find any uterine rupture in 165 grandmultiparas induced with vaginal misoprostol

Homefyr and Gulmezoglu (2004) conclude that the existing RCTs are not large enough to exclude the possibility of a serious adverse event like uterine rupture.

8.6.2 MATERNAL OUTCOMES

A metanalysis found that vaginal misoprostol in dosages ranging from 25 micrograms 2-3 hourly, to 50 micrograms 4 hourly (most studies), to 100 micrograms 6-12 hourly, appear

to be more effective than oxytocin or dinoprostone in the usual recommended doses for induction of labour, but with increased rates of uterine hyperstimulation both without and with associated fetal heart rate changes (Hofemyr, 2004). Wing and Paul (1997) compared differing dosing regimens of vaginally administered misoprostol for pre-induction cervical ripening and labor induction, and reported one maternal death due to amniotic fluid embolus as well as two cases of caesarean hysterectomy for atonic uterine hemorrhage.

Similar findings were obtained from a systematic review by Sanchez-Ramos et al (2000) looking at 44 prospective studies where women receiving misoprostol for cervical ripening and labor induction were twice as likely to experience tachysystole and hyperstimulation, with the incidence of these conditions closely related to the dose of misoprostol administered.

When oral versus vaginal routes of administration of misoprostol were compared there was no difference in uterine hyperstimulation with fetal heart rate changes. However, the caesarean section rate was lower in the oral misoprostol group (16.7%) compared to the vaginal (21.7%) misoprostol group. There were no reported cases of severe neonatal and maternal morbidity (Alfirevic, 2004).

Meta analysis showed the caesarean delivery rate was lower in misoprostol induced patients compared to those women receiving alternative induction regimens (Hofemyr et al 2004; Sanchez-Ramos et al 2000). While the indication for caesarean section was not a pre-specified outcome in this review, there were more operations for fetal distress and fewer for poor labour progress in the misoprostol groups.

8.6.3 PERINATAL OUTCOMES

There were more meconium stained liquor with misoprostol versus vaginal or intracervical prostaglandins, and Wing et al (1995), suggested the possibility of it being due to uterine hyperstimulation or a direct effect of absorbed misoprostol metabolites on the fetal gastrointestinal tract.

Sanchez-Ramos et al (2000) in their systematic review involving 5,735 pregnant women noted that there was no difference between the incidence of low 5-minute Apgar scores and admission to the NICU between the misoprostol and other modalities.

8.7. COST IMPLICATIONS OF MISOPROSTOL IN INDUCTION OF LABOUR AND CERVICAL PRIMING

Ramsey (2003) in a RCT on 111 women with unfavourable cervix who either received misoprostol, dinoprostone gel or dinoprostone insert for induction of labour concluded that misoprostol is more cost effective than the other two prostaglandins as an adjuvant to induction of labour. The relative cost of misoprostol (Cytotec - USD $2 for 50µg dose) as lowest compared to dinoprostone gel (Prepidil - $108 for 0.5 mg) and dinoprostone insert (Cervidil -$168 for 10mg). There were no significant differences in the mode of delivery or any adverse outcomes in all three study groups.

The Clinical Guideline by Royal College of Obstetricians and Gynecologists (2001) noted that vaginal misoprostol cost £0.18 for one 200 microgram tablet of misoprostol compared with £8.13 for a 3 mgm tablet of prostglandin E2. This guideline noted that there would be an indirect cost savings to the NHS, given the reduced rate of operative delivery.

8.8 MISOPROSTOL FOR POST PARTUM HAEMORRHAGE

8.8.1 EFFECTIVENESS OF MISOPROSTOL IN THE PREVENTION OF POSTPARTUM HAEMORRHAGE

An updated Cochrane Systematic Review (2002); (4) and a more recent systematic review (Joy et al, 2003) which involved 287710 women noted that oral misoprostol was inferior to oxytocin and other uterotonics as part of active management of third stage of labour especially for low risk women. Similar findings were noted in double blind WHO multicentric RCT which recruited 18459 women in the study comparing oral misoprostol 600mcg versus intravenous oxytocin 10u. The results of the study demonstrated that intravenous or intramuscular oxytocin was preferable to oral misoprostol in the active management of postpartum hemorrhage (Gulmezoglu et al, 2001). Other studies that support the above findings include (Cook et al, 1999; Surebeck et al, 1999;

However, a multicentric RCT (Ng et al, 2001) comparing oral misoprostol (600 mcg) and i.m. syntometrine (1 ml) and another RCT (comparing oral misoprostol and standard management noted that there was no difference in mean blood loss or drop in BP in both groups. The misoprostol group required significantly higher additional oxytocics but had lower procedures on manual removal of the placenta.

A case series by O'Brien et al (1998) reported that misoprostol was able to control postpartum hemorrhage that was unresponsive to oxytocin and methylgonovine.

8.8.2 SAFETY OF MISOPROSTOL IN POSTPARTUM HAEMORRHAGE

Several studies have reported the main side effects of using misoprostol in 3rd stage of labour which were shivering and pyrexia and are dose related (el Refaey et al, 2000; Gulmezoglu et al, 2001; Ng et al, 2001; Gulmezoglu et al, 2002; Lumbiganon et al, 2002; Joy et al, 2003; Oboro & Tabowei, 2003).

Hofmeyr et al (2001) conducted a double blind RCT giving 600 mcg oral misoprostol in one arm and the other arm a placebo. This study noted not only the above side effects but an increase in both diastolic and systolic blood pressure in the women given misoprostol.

Two studies namely a prospective observational study and a randomised controlled trial noted that the use of misoprostol increased the incidence of shivering, pyrexia and diarrhea (el- Refaey, 1997; Lumbiganon et al, 2002).

8.9. LEGAL ISSUES

Only one product containing misoprostol, Cytotec® has been registered with the Drug Control Authority (DCA) of Malaysia, the approved indication being the treatment of gastric and duodenal ulcers refractory to H_2-receptor antagonists. No other indication has been applied for. In addition, there has been no application to the DCA for any generic products containing misoprostol.

It has been suggested that there is little incentive exists for the manufacturer to engage in an expensive process required to add an indication to the label of misoprostol when the legal, financial and political risks are high and the additional profits from marketing and sales are likely to be low (Goldberg & Wing, 2003).

In the day-to-day management of patients, health professionals are only allowed to use a product for the indications for which is has been approved. Use of a product for any other indication constitutes an "off-label-use". Although there is no legal provision for "off-label-use", it is recognized that physicians will use their own professional judgement to prescribe any pharmaceutical product in the interest of their patients based on published research, expert clinical opinion and their experience especially if the situation warrants it, for example, in a life threatening situation or when there are no alternatives available. It is advised that should a product be used for an off-label indication, the patient should be informed and consent obtained prior to use. Neither the product registration holder nor the Drug Control Authority can be held responsible should an untoward/ adverse reaction occur if the product is used for the treatment or management of any condition other than the approved indication.

The product insert of Cytotec® in Malaysia clearly indicates that the administration of Cytotec® by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec® has not been approved for the induction of labour in any country. Misoprostol is part of the FDA approved regimen for use with mifepristone to induce abortion in pregnancies of 49 days or less, but mifepristone has not been registered in Malaysia.

9. CONCLUSIONS

The evidence suggests that in the first trimester, misoprostol is an effective cervical priming agent prior to surgical abortion. It is as effective as gemeprost when used for this purpose. It is also effective in evacuating the uterus in missed abortions. There is limited evidence to support its use in incomplete abortions and as an abortifacient.

For second trimester abortions, there is insufficient evidence ~~of~~ for effectiveness of misoprostol as a cervical priming agent. However, there is sufficient evidence ~~of~~ for its effectiveness for termination of pregnancy and it is also cost effective.

In the third trimester, there is sufficient evidence ~~of~~ for effectiveness of oral misoprostol for induction of labour. However, the data on optimal regimens and safety are lacking.

There is insufficient evidence to support the use of misoprostol in prevention of postpartum haemorrhage. A number of safety concerns arise with the usage of misoprostol in third stage of labour.

From the legal aspect, misoprostol cannot be used in pregnancy since it has been registered only for treatment of gastric and duodenal ulcers refractory to H_2-receptor antagonists

RECOMMENDATIONS

Based on the current evidence to date, there is sufficient safety and legal concerns not to recommend misoprostol for cervical priming, termination of pregnancy, induction of labour or postpartum haemorrhage.

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