EDITORIAL

The Use of Misoprsotol in Pregnancy

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Misoprsotol is a Prostaglandin$_{E1}$ analogue that had been approved by the Food and Drug Administration (FDA) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of non steroidal anti-inflammatory drugs. It has also become an important drug in obstetrical practice because of its uterotonic and cervical ripening actions. Misoprsotol is useful in the treatment of miscarriage, cervical ripening before surgical evacuation in cases of embryonic death, fetal death and particularly in induction of labour. The drug may also be used to treat and even prevent postpartum hemorrhage. However misoprostol is not approved for any of these indications in the United States of America (USA), the manufacturing country or elsewhere. Current products labeling include a warning that misoprostol is contraindicated during pregnancy because of its abortifacient properties. However the Food and Drug Administration (FDA) recognizes that, in certain circumstances the "off-label" uses of approved drugs are appropriate, rational and accepted medical practice[(1)]. Prescribing a medication for an off-label indication is common in the treatment of pregnant women and is not considered experimental if based on scientific evidence [(2)].

The purpose of this article is to review the large body of evidence supporting the use of misoprostol in pregnancy. This includes reviewing pharmacokinetics and physiology, mechanism of action, off-label conflicts, efficacy, dosage variations, different routes of administration and safety of misoprostol in pregnancy and postpartum haemorrhage under pregnancy three trimesters course.

Pharmacokinetics and Physiology

Misoprostol (Cytotec, Searle Illinois, USA) is a methyl ester of prostaglandin$_{E1}$ additionally methylated at C-16. It acts as an effective myometrial stimulant selectively binding to EP-2/EP-3 prostanoid receptors. It is manufactured as an oral 100 μ gm unscored and 200 μ gm scored tablets. It is cheap and easy to store. After oral administration, misoprostol is rapidly absorbed and converted to its active metabolite, misoprostol acid. Plasma concentrations peak in approximately 30 minutes, and decline rapidly thereafter [(3)]. The bioavailability of misoprostol is decreased by concomitant ingestion of food or antacids. Misoprsotol is primarily metabolized in the liver, and less than 1% of its active metabolite is excreted in urine [(4)]. Misoprsotol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system. The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering and fever. All of these effects are dose dependent. Although often Prostaglandins (Prostaglandin$_{E2}$ and Prostaglandin$_{F2\alpha}$) can cause myocardial infraction and bronchospasm, misoprostol does not [(5)]. Toxic doses of misoprostol have not been determined, however, cumulative doses of up to 2200 μ gm administered over 12 hours have been tolerated by pregnant women, with no serious adverse effects [(6)]. Misoprostol is not reported to cause major adverse effects. The effects of misoprostol on the reproductive tract are increased, and gastrointestinal adverse effects are decreased if the oral preparation of misoprostol is administered vaginally [(7, 9)]. When misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentration of misoprostol acid peaks in one to two hours and then declines slowly [(3)]. While in fact vaginal application of misoprostol results in slow increase and lower plasma peak of misoprostol acid than does oral administration, but overall exposure to the drug is increased [(3)]. Among women who were 9 to 11 weeks pregnant and given misoprostol, intrauterine pressure began to

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increase 8 minutes after oral administration and 21 minutes after vaginal administration and was maximal 25 minutes after oral administration, and 40 minutes after vaginal administration. Uterine contractility initially increased and then plateaued one hour after oral administration, where as uterine contractility increased continuously for four hours after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration [7].

Off-label use scenario

Manufacture's warning regarding unapproved uses of misoprostol was sent to the editor of New England Journal of Medicine: (G.D. Searle has been invited to clarify its position and actions in this regard. We at Searle share the overriding concern that physicians be supported in providing the most appropriate care for their patients. We also wish to emphasize our commitment to working collegially with all relevant parties. Our product Cytotic (Misoprostol) was approved by FDA in 1988 for the prevention of gastric ulcers. This is the only approved indication for misoprostol, and we are prohibited by FDA regulations from promoting or even suggesting its use for any other purpose. Since 1988 the misoprostol label has always carried a "black box" warning against its use in pregnant women [10].) We fully support the role of the physicians using their professional judgment to prescribe an approved product for a use outside of its FDA approved indication in the best interest of their patients on the basis of published researches, expert clinical opinion or their own clinical experience)[10].

In spite of the fact that more than 200 studies were identified by many authors involving more than 16000 women who received misoprostol, and concluded that "Misoprostol is one of the most important medications in obstetrical practice" This was stated by Goldberg et al. in the New England Journal of Medicine, a review article issued in January 4, 2001[11] . They reviewed the evidence supporting the use of misoprostol in pregnancy three trimesters including fetal death for cervical ripening and induction of labour in terms of mechanism of action, dosage, efficacy, and safety. They also used the scheme of United States preventive services task force to grade the strength of their recommendations to promote the use of misoprostol.

As a result of FDA approval, any administration of misoprostol to a pregnant woman would be considered as "off-label" use of the drug. However Goldberg et al. stated again that cervical ripening as a preclude to induction of labour was frequently and effectively performed by misoprostol as a treatment of choice [11]. In November 1999 the American College of Obstetrics and Gynecology (ACOG) published an obstetric practice committee opinion together with a practice bulletin on induction of labour with misoprostol to provide guidelines on appropriate use of misoprostol [12, 13]. These publications stated that, misoprostol is an effective agent in cervical ripening and induction of labour. These recommendations are based on consistent scientific evidence and confirmed by extensive and successful use of misoprostol [14]. In August 23, 2002 G.D. Searle Company sent a letter to obstetricians. (The purpose of this letter is to remind you that administration of misoprostol is contraindicated in women who are pregnant). The warning further stated, " Sereale has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or of induction of labor, nor does Searle intend to study or support these uses. Therefore Searle is unable to provide complete risk information for Cytotec when it is used for such purposes." [15]. The strong prohibition of off-label use of misoprostol included the administration of the drug during all stages of pregnancy. No attempt on the part of the company to contact (ACOG) or any other scientific group to review the evidence regarding the benefits and risks of misoprostol in pregnant women before they sent the letter. This omission is particularly surprising in the face of the numerous published reports supporting the use of misoprostol for cervical ripening, among other things. Many obstetricians asked why Searle issued such a strong warning, especially when years of experience supported the efficacy of misoprostol for this purpose. The letter appeared to reflect a sense of urgency that was incompatible with the current peer-reviewed medical literature or practices across the country. The warning was also highly unusual because many other medications are used for "off-label" indications and such use has not precipitated similar responses from their manufactures. [15]. (ACOG) stated that "Many of our physician members have been able to convince their hospitals to continue to make misoprostol available for off-label

use. The real victims in this scenario are pregnant women who receive treatment in hospitals that will not allow the use of misoprostol. Alternative medications are expensive and relatively ineffective. Even worse, in some instances no alternative treatments are available. Searle seems to have ignored these women". (ACOG) notified its members in October 2000 that off-label use of misoprostol based on scientific evidence is justified [15].

Further more two letters were sent to The Lancet, June 2001one supporting misoprostol in obstetrics. (If a drug was proven to be equivalent to another drug but nearly 100 times cheaper, it would make sense to use the cheaper drug. If the manufacturer warned that they would not support use of the cheaper drug for an indication for which there was sample data from clinical trials about its efficiency, one might expect to know why. The drug is widely used worldwide in obstetrics. Goldberg and colleagues concluded among 2000 studies that the drug is effective, and results supported its continued us .[11]. Searle is still maintaining its position in the (USA). The looser are patients, the financial resources and the winners are?) [16]. The other one, opposing the use of misoprostol referring to FDA, Searle and Cochrane library. (None of the studies of misoprostol induction have large enough sample size to assess rare and serious risk such as uterine rupture and death. The Cochrane data base has reviewed misoprostol induction and recommends it not to be used because of insufficient data on the relative risk of rare adverse outcomes with the use of misoprostol)[17].

Misoprostol is obviously one of the important drugs in obstetric practice worldwide and its use is continuously increasing.

Misoprostol in the First Trimester

Medical abortion

The variation in rates of complete abortion among women given misoprostol may be due to differences in study design since rates are often lowest in randomized trials, or to efforts to increase vaginal absorption in some studies. In one study the success was high, the vagina was cleaned with saline, the drug was moistened with two or three drops of water or saline and then placed in the posterior fornix.[18] In a randomized study comparing dry and moistened tablets, there was no significant difference in the rate of complete abortion [19]. Misoprostol is not recommended for medical abortion neither for termination of viable pregnancy in the first trimester by the evidence of few available data.

Failed Pregnancy or Embryonic Death

Misoprostol helps to expel products of conception. In cases of anembryonic pregnancy or blighted ovum and embryonic death, the pregnancy is already destabilized with placental degeneration and decidual sloughing. If expulsion is delayed drug therapy may be indicated to evacuate the uterus in order to avoid surgery or wait [20-22]. Twenty women with early failed pregnancy were allocated randomly to receive either 400 or 800 μ gm of vaginal misoprostol. The rate of complete expulsion was significantly higher in 800 μ gm group [20]. Thus 800 μ gm of misoprostol given vaginally is effective in evacuating the uterus in cases of early failed pregnancy.

Inevitable and incomplete miscarriage

Misoprostol was also studied in completing inevitable or incomplete miscarriage. The first report was for incomplete miscarriage. Twenty-four women received 400 μ gm of misoprostol orally, 95% of them had a complete expulsion [23]. However a study of 50 women who were either given single dose of 400 μ gm of misoprostol orally, or under went immediate surgical evacuation showed that surgery was markedly more successful than misoprostol. On the basis of these findings misoprostol is currently not recommended for the treatment of inevitable or incomplete miscarriage [24].

Cervical ripening before surgical evacuation

Ripening is the softening, effacement and gradual dilatation of the cervix. It reduces the incidence of lacerations and uterine perforation [25, 26]. It can be accomplished with hydrophilic dilatators (e.g Hypan), or biochemically with prostaglandins. Misoprostol is cheaper, easily stored, has fewer side effects and equally successful [27]. Vaginal misoprostol causes faster dilatation than the same dose of oral misoprostol [28]. According to randomized study of 120 women that compared 200,400,600,800 μ gm of vaginal

misoprostol. 600 and 800 μ gm doses caused significant side effects than 400 μ gm dose; the recommended dose for cervical ripening is 400 μ gm [29]. Other studies have attempted the ideal length of time for cervical ripening of 50 women given 200 μ gm of vaginal misoprostol six hours before curettage, 74% had cervical dilatation of at least 8 mm [30]. In another randomized trial women given 400 μ gm of misoprostol three hours before surgery had significantly greater dilatation than women given 600 μ gm or 800 μ gm two hours before surgery [31]. This suggests that the best regimen for cervical ripening in the first trimester is 400 μ gm of vaginal misoprostol three hours before curettage.

Misoprostol in the Second Trimester of Pregnancy

Procedures performed during the second trimester require cervical dilatation and extraction of the fetus or induction of labour. Misoprostol ripens the cervix and can induce labour. Jain et al. compared of the effectiveness of intravaginal misoprostol 6 hourly versus 12 hourly for termination of second-trimester pregnancies in one hundred pregnant women using 200 µg dose. The mean abortion interval was 13.8 and 14 hours in the 6 and 12-hours groups respectively. They concluded that shortening the dosing interval from 6-12 hours produced no significant benefit [32]. Jain et al. also compared misoprostol with prostaglandin in 120 women, expulsion rate was 43% and 32% in misoprostol and prostaglandin groups respectively. These results showed the effectiveness of misoprostol on prostaglandin ([33]. Jain and Mishell compared misoprostol in fetal death in 68 women with the use of laminaria tents. The rate of abortion was 69.7% and 68.6% in misoprostol and misoprostol with laminaria tents groups respectively. It was concluded that sole misoprostol is an effective in second trimester abortion [34]. Several studies have evaluated the use of misoprostol for induction of labour in the second trimester. Wong et al. conducted a trial in 140 women to compare the efficacy of vaginal gemeprost with misoprostol in termination of second trimester pregnancy, in Contraception 1998. The results showed that termination of pregnancy within 24 hours was 80% and 19.5% hours in misoprostol and gemeprost groups respectively. They concluded that vaginal misoprostol is more effective than gemeprost in second trimester pregnancy termination. [35] Nuutila et al. conducted a comparison between two doses of intravaginal misoprostol and gemeprost for induction of second-trimester abortion including 81 pregnant women. Their results showed that, pain and blood loss were less in misoprostol group. Induction delivery interval was equal between the two groups [36]. Herabutya and Prasertsawat investigated the efficacy of 200,400 and 600 µg doses of misoprostol in the second trimester including 150 women. The 48 hours successful abortion rate was 70.6%, 82% and 96% respectively. They concluded that the 600 µg dose is more effective as an inducing argent for second trimester pregnancy [37] . Bugalho et al. studied 132 pregnant women with average gestational age of 14 weeks using 800µg of misoprostol to terminate pregnancy. Nonsurgical expulsion of the fetus was successful in 88.6% of them. They conclude that vaginal administration of misoprostol is remarkably effective in achieving safe termination of pregnancy without any significant complications [38]. It was observed that, in all these studies side effects as nausea, vomiting, diarrhea and temperature elevation were mild and insignificant and did not warrant any specific treatment. As the uterus becomes more sensitive with increasing gestational age, comparison between studies in misoprostol is difficult because of widely varying duration of pregnancy. Thus a dose given early in the second trimester may not be as effective as a dose given late in the second trimester. In addition women carrying a dead fetus may be induced more rapidly than those with a viable one [32-) [34].

In the third trimester, doses in the range of 25 to 50 μ gm induce labour. The optimal dose of vaginal misoprostol for induction of labour in the second trimester probably varies between 50 -800 μ gm. The authors conducted a controlled randomized study including 150 women who were randomly allocated to have 100 μ gm of misoprostol either vaginally, orally or sublingually. Higher success rate was observed in women who received sublingual misoprostol. Vaginal misoprostol was also successful by the evidence of their experience [39]. Higher doses may be needed to induce expulsion early in the second trimester. The usual regimen for induction of labour in the second trimester is 200 μ gm of vaginal misoprostol. Increasing

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the frequency of misoprostol administration may increase efficacy, but in one randomized study of 100 women, 200 μ gm of vaginal misoprostol every 6 hours was not more effective than the same dose given every 12 hours [34]. Administration of 400 μ gm misoprostol every three hours resulted in complete expulsion in 91% of women undergoing induction [35]. Vaginal doses of 200, 400,600 μ gm given every 12 hours resulted in expulsion in 71%, 82%, 96%, respectively [37]. The higher dose was associated with higher rates of adverse effects including rising temperature, nausea, vomiting and diarrhea [37]. Uterine rupture was reported in two women under going induction by misoprostol in the second trimester. One of them had two caesarian deliveries; the second was not [40-41]. Almost all trials for induction of labour in the second trimester have excluded women with uterine scars. Although the optimal regimen has not been determined, it appears that 200 - 600 μ gm of misoprostol given vaginally every 12 hours, or 400 μ gm every 3 hours successfully induces labour in the second trimester.

Misoprostol in the Third Trimester of Pregnancy

Induction of labour with a viable fetus

Many clinical trials have compared misoprostol with placebo,[42-43] oxytocin,[44-46] and prostaglandins, primarily denoprostone (Prostaglandin$_{E2}$ gel)[47- 53] for induction of labour at term. Misoprostol given vaginally,[42] or orally [43] is superior to placebo for cervical ripening before induction of labour with oxytocin. Misoprostol itself is effective in induction of labour. In 1997 a meta-analysis of randomized controlled trials focusing in induction of labour in a total of 488 women who received misoprostol and 478 controls (Most of them received prostaglandin $_{E2}$ gel). The induction delivery interval was 4.6 hours shorter, and the rate of caesarean section was lower in the misoprostol group [54]. The Cochrane Pregnancy and Child Birth Group reviewed 26 randomized trials comparing misoprostol with oxytocin and prostaglandin$_{E2}$ for induction of labour with a viable fetus [55]. Some of these trials compared oral with vaginal misoprostol, and others compared different misoprostol regimens [55, 56]. The primary outcomes were vaginal delivery, caesarean section and adverse effects [55, 56]. Vaginal misoprostol (25-100 μ gm) was more effective than oxytocin or prostaglandin$_{E2}$ for inducing vaginal delivery. Uterine hyper stimulation rate was more common in women who received misoprostol [56]. There was no difference in the rates of caesarean delivery, serious maternal or neonatal morbidity or mortality between women who received misoprostol and those who received oxytocin or prostaglandin$_{E2}$.[55, 56] The relative risk of rare adverse outcomes with the use of misoprostol for induction of labour remains unknown.

Recent studies have focused on low dose misoprostol. In a study of 522 women given 25 μ gm of vaginal misoprostol every 3 hours or 25 μ gm every 6 hours, the regimen with the longer interval between the doses resulted in a longer time to deliver, and greater need for oxytocin. However the two regimens did not differ in rates of hyper stimulation, muconium passage, caesarean delivery, neonatal admission to intensive care unit or Apgar scores [57]. In a study of 200 women given 25 μ gm of vaginal misoprostol or denoprostone insert. Induction to delivery interval, the rate of cesarean delivery and indexes of neonatal effects were similar in the two groups [58]. The available data suggest that the best dose of misoprostol for induction of labour is probably 25-50 μ gm given every 4-6 hours.

Among these data, author of this review and his colleagues have compared- in randomized controlled trial - 100 μ gm vaginally vs. oxytocin. The results were; higher efficacy of misoprostol versus oxytocin [59]. Their second report was a randomized controlled trial enrolling 120 women with unripe cervices. Sixty of them received vaginal misoprostol (100 μ gm) and 60 received denoprostone (3mg). Insertion delivery interval, use of oxytocin infusion, and rate of cesarean section were less in misoprostol group [60]. The third study compared oral vs. vaginal misoprostol in a dose of 50 μ gm. in induction of labour, 40 women in each group. Similar results were obtained in vaginal misoprostol group [61]. The fourth study was conducted in induction of labour with 25 μ gm. vs. 50 μ gm vaginally. 50 μ gm group showed better results in terms of insertion delivery interval, oxytocin infusion and rate of caesarean section. The fetal indexes were the same in each group [62]. The fifths study was also a randomized trial including 150

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women divided in 3 groups, 50 women in each to receive either vaginal, oral or sublingual 50 μ gm of misoprostol. The vaginal misoprostol group had the shorter insertion delivery interval, had less use of oxytocin infusion, and rate of caesarean section was less [63]. It was observed that sublingual misoprostol acts faster than the vaginal misoprostol. It was not stated if there were fetal heart rate changes or not, neither associated with hyper-stimulation of the uterus as rare relative risks of misoprostol. It should be noted that, use of sublingual misoprostol is not a common practice worldwide. However, some reported are there comparing sublingual misoprostol in 50 μ gm dose with artificial rupture of the membranes and oxytocin, 50 women in each group. It concluded that the well accepted sublingual misoprostol by women is less effective in a achieving delivery within 24 hours [64]. Thus, further studies on sublingual misoprostol are urgently needed. Late on we published a randomized, controlled trial comparing sublingual, vaginal and oral misoprostol in a dose of 100 μ gm in delayed miscarriage. Our results showed that, sublingual misoprostol is associated with a shorter intake expulsion interval, less use of oxytocin, rate of surgical evacuation, blood transfusion, and hospital stay[39].

It is observed that our studies in the second trimester of pregnancy were conducted with relatively low doses of misoprostol. However they are few and small in sample size, and we were interested in cervical ripening and dilatation rather than to complete the expulsion non-surgically. Probably we may have had more surgical evacuations of products of conception.

Induction of Labour after fetal death

Up-to-date, misoprostol is ideal method for Induction of labour after fetal death in the third trimester because there is no concern about adverse effects on the fetus. A dose of 100 μ gm of misoprostol given every 12 hours results in success rate approaching 100%[65][66]. A higher a dose of misoprostol 200 μ mg given vaginally every 12 hours may be required in early third trimester fetal death. For fetal death at term 50 μ gm may be adequate for induction of labour.

Induction of labour with uterine scar

In women with uterine scar, misoprostol should not be used for induction of labour. It is not proved to be safe. Studies showed uterine rupture in its use [67-69].

Misoprostol in Postpartum Haemorrhage

Misoprostol has been evaluated for both prevention and treatment of postpartum haemorrhage. In a prospective observational study 237 women were given oral 600 μ gm of misoprostol just after clamping of the cord. Blood loss of 500ml or more was observed in only 6% of them. None had a blood loss of more than 1000 ml [70]. Three randomized trials involving 1115 women evaluated 400 μ gm of misoprostol given rectally or a dose of 400 to 600 μ gm given orally [71-73]. The frequency of postpartum haemorrhage (blood loose > 1000 ml) was not lower in the misoprostol group than the control group in any of these trials. In all three trials oxytocin was given more in the control groups [71-73]. Thus there is currently insufficient evidence to support the routine use of misoprostol to prevent postpartum haemorrhage when oxytocin or ergometrine is available. Misoprostol has been reported to control postpartum haemorrhage that is unresponsive to oxytocin and ergometrine [74]. In one series of 14 women who received 1000 μ gm of rectal misoprostol after oxytocin and ergometrine bleeding stopped within 3 minutes. However the lack of the control group makes it impossible to know whether misoprostol was responsible for the control of bleeding.

Conclusion

Misoprostol is one of the most important medications in obstetrical practice. Yet its use in pregnancy remains unapproved by the FDA. The non-experimental, off-label use of the drug requires sound scientific evidence. Data from clinical trials provide strong and consistent support for the use of misoprostol. There is also a strong and consistent evidence to support the use of misoprostol for cervical ripening before surgical evacuation in the first trimester, induction of labour in the second and third trimester. Misoprostol may also prevent postpartum haemorrhage when parentral medications are not available. Possibly in rural and remote areas where health settings are out of reach. The distribution of misoprostol among midwives

conducting home delivery to be used after delivery may reduce the incidence of primary postpartum Haemorrhage, long distance referral and maternal mortality.

Although there are no published estimates of the extent to which misoprostol is used for obstetrical and gynecological indications, over 200 studies involving 1600 women have evaluated effectiveness and safety as a robust and versatile drug in pregnancy and the results support its continued use.

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