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MISOPROSTOL: THEORY AND PRACTICE

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INTRODUCTION

Prostaglandins have revolutionalized obstetric practice. In particular, the advent of misoprostol has precipitated an enormous amount of innovative research as well as controversy. At present, misoprostol is being investigated for its role in the management of postpartum hemorrhage, induction of labor, cervical ripening and termination of pregnancy. Initially, this drug was approved by the US Food and Drug Administration (FDA) in 1988 for oral administration for the prevention and treatment of peptic ulcers associated with the use of non-steroidal anti-inflammatory drugs. Since the early 1990s, however, misoprostol has been viewed with increasing interest by obstetricians and gynecologists because of its uterotonic and cervical ripening activity. The multiple off-label uses for misoprostol underlie its description as 'one of the most important medications in obstetrical practice'[1]. Even in 2005, misoprostol was not approved by the FDA for use in pregnant women, a stand strangely and strongly supported by its manufacturer[2].

MISOPROSTOL

Misoprostol is a synthetic PGE_1 analog. Naturally occurring PGE_1 is not orally sustainable, as it is unstable in acid media and is also not suitable for parenteral use because of its rapid degradation in the blood. Misoprostol, the synthetic PGE_1 analog, is produced by bringing about an alteration in the chemical structure of the naturally occurring compound, thereby making it orally stable and clinically useful. Misoprostol is otherwise called alprostadil and its chemical formula is $C_{22}H_{38}O_5$ ((±)–methyl (13E)-11,16-dihydroxy-16-methyl-9-oxo-prost -13-enoate), as shown in Figure 1[3].

Misoprostol is manufactured as oral tablets of 200 µg scored and 100 µg unscored. It has several advantages – stability in ambient temperature, long shelf-life and low cost – that have made it a central focus of research in obstetrics and gynecology for 25 years[4]. Misoprostol is rapidly absorbed via the oral route and, although not formulated for parenteral use, can also be administered sublingually (buccally), rectally and vaginally[5–7].

Pharmacokinetics, physiology and teratogenicity profile

Misoprostol is extensively absorbed and undergoes rapid de-esterification to misoprostol acid; this compound is responsible for its clinical activity and, unlike the parent compound, it is detectable in plasma. After oral administration, the peak level of misoprostol acid is reached within 12 ± 3 min, with a terminal half-life of 20–40 min. Plasma levels of misoprostol acid vary considerably between and within studies, but mean values after single doses show a linear relationship with the dose over the range of 200–400 µg. No accumulation of misoprostol acid was noted in multiple dose studies and a

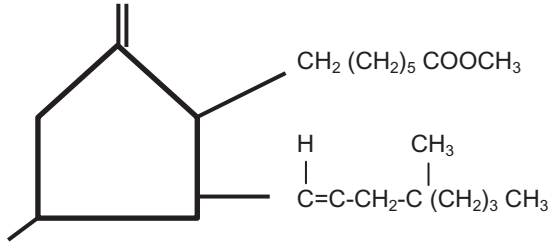

Figure 1 Chemical structure of misoprostol[3]

plasma steady state was achieved within 2 days. The bioavailability of misoprostol is decreased when administered with food or antacids[8].

Misoprostol is primarily metabolized in the liver and less than 1% of its active metabolite is excreted in the urine[9]. Patients with hepatic disease should receive decreased doses, whereas dose adjustment is not necessary for patients with renal disease who do not require dialysis. Misoprostol has no known drug interactions and does not induce the hepatic enzyme systems[9].

Pharmacokinetic studies in pregnant women show that sublingual and oral misoprostol used for first-trimester termination of pregnancy produce earlier and higher peak plasma concentrations than vaginal or rectal misoprostol, resulting in earlier, more pronounced uterine tonus (oral misoprostol 7.8 ± 3.0 min vs. vaginal misoprostol 20.9 ± 5.3 min)[6,7,10]. These findings have very recently been validated in women after delivery[11]. The effects of misoprostol on the reproductive tract are increased and gastrointestinal adverse effects are decreased when it is administered vaginally[10,12,13]. When misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentrations of misoprostol acid peak in 1–2 h and then decline slowly (Figure 2)[5]. Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than does oral administration, but overall exposure to the drug is increased (indicated by the increased area under the curve in Figure 2)[5]. The peak plasma levels of misoprostol are sustained for up to 4 h after vaginal administration[5] (Figure 2).

Among women who were 9–11 weeks pregnant and given misoprostol before a surgical termination of pregnancy, intrauterine pressure began to increase an average of 8 min after oral administration and 21 min after vaginal

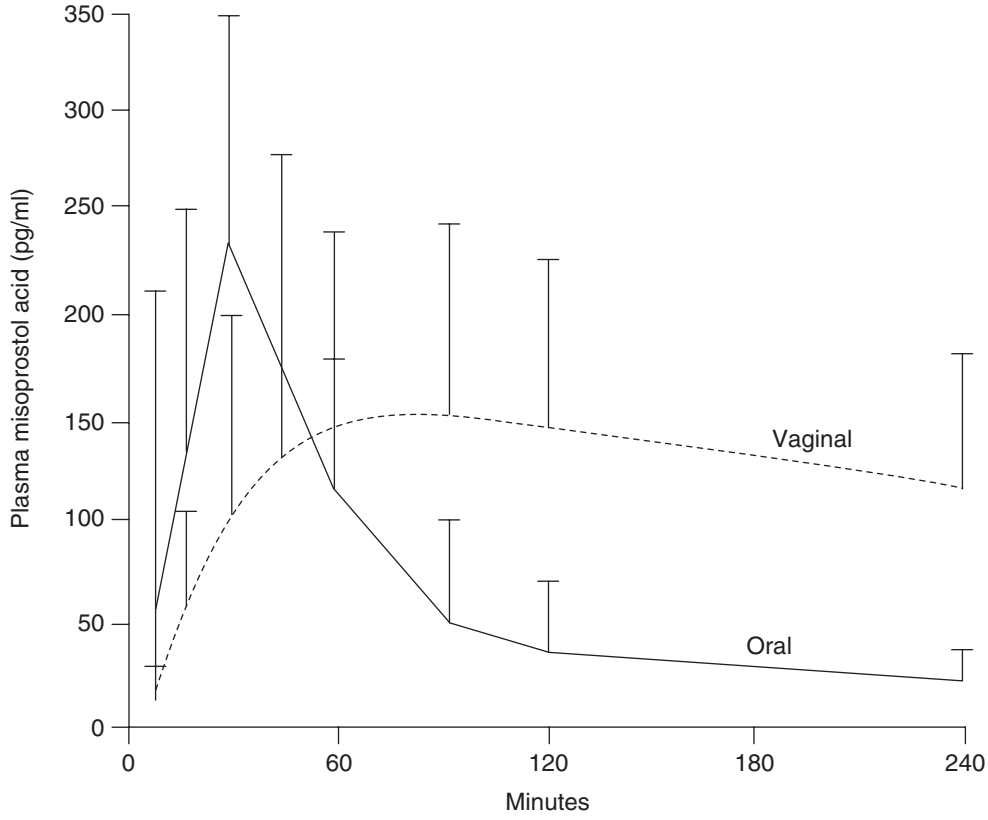

Figure 2 Mean (standard deviation) plasma concentrations of misoprostol acid after oral and vaginal administration of misoprostol in 20 women. Reprinted from Zieman M, *et al.*[5]

administration; it was maximal 25 min after oral administration and 46 min after vaginal administration, respectively. Uterine contractility initially increased and then reached a plateau 1 h after oral administration, whereas uterine contractility increased continuously for 4 h after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration[10]. The maximum serum concentration was achieved 23 min later in rectal administration and the peak levels were lower compared to oral administration of misoprostol[7] (Figure 2).

In the pharmacokinetic study by Tang and colleagues[6], the peak plasma level of misoprostol acid was highest and earliest after administration of misoprostol by the sublingual route. Misoprostol tablets dissolved in water and taken orally have also been shown to produce a faster onset and stronger uterotonic effect than either oral tablet or rectal administration[14,15]. However, there was no significant difference when misoprostol was used in the form of moistened tablets compared to dry tablets for first-trimester termination of pregnancy[16].

Adverse effects

Common side-effects of misoprostol include diarrhea and abdominal pain. Less common side-effects include headache, abdominal cramps, nausea and flatulence, chills, shivering, and fever, all of which are dose-dependent. It is interesting to note that, before its use in pregnant women, chills, shivering and fever were not commonly reported side-effects, suggesting that these are dose-dependent.

Package warnings are very clear that misoprostol is not to be taken by pregnant women, and non-pregnant women should use contraceptives while taking misoprostol and should be warned about the effects of misoprostol if taken by pregnant women. Misoprostol should also be avoided in nursing mothers because of concern over causing diarrhea in the baby[8,11].

Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol for termination of pregnancy, but the drug's teratogenic mechanism has not been elucidated[17,18]. Several reports associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations (Mobius syndrome), and limb defects[19]. Misoprostol is listed as a pregnancy category X drug.

Toxic doses of misoprostol have not been determined; however, pregnant women have tolerated cumulative doses up to 2200 μg administered over a period of 12 h without

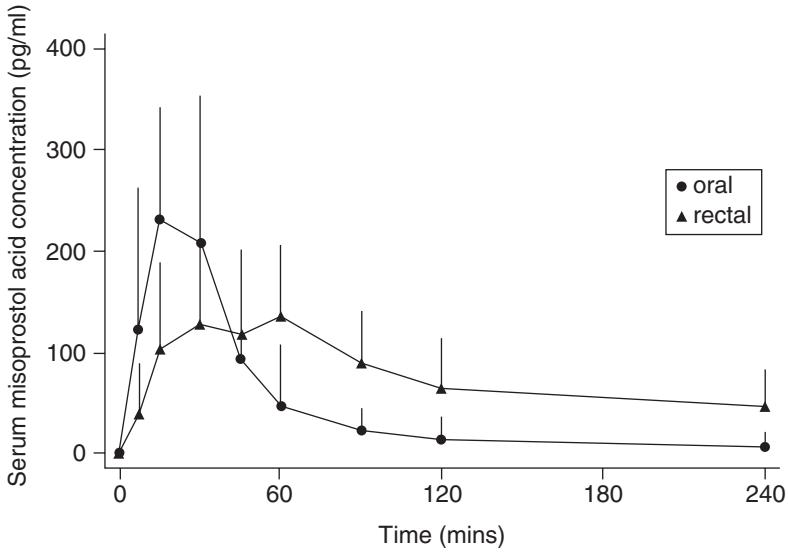

Figure 3 Mean serum concentration of misoprostol acid over time with oral and rectal administration. Error bars represent one standard deviation[7]

any serious adverse effects[20]. A dose of 6000 μg of misoprostol, taken orally to induce termination of pregnancy (with trifluoperazine), resulted in abortion, hyperthermia, rhabdomyolysis, hypoxemia and a complex acid–base disorder[21].

MISOPROSTOL IN THE FIRST TRIMESTER

For first-trimester medical termination of pregnancy, misoprostol is used most extensively in conjunction with either mifepristone or methotrexate. Both regimens are effective. In the initial studies of mifepristone and misoprostol for medical termination of pregnancy, both drugs were given orally. Only regimens of mifepristone in combination with oral misoprostol have been licensed for abortion in any country. Administration of 600 mg of oral mifeprostone followed 48 h later by 400 μg of oral misoprostol resulted in 91–97% complete abortion in women who were no more than 49 days pregnant, compared to 83–95% of women who were no more than 56 days pregnant[22–25]. Lowering the dose of mifepristone to 200 mg and increasing the dose of oral misoprostol to 600 μg increases the efficacy, with abortion rates of 96–97% among women no more than 49 days pregnant and 89–93% among women 50–63 days pregnant[26,27]. A combined regimen of mifepristone and misoprostol can result in complete abortion in 94–95% for medical abortion to women of 9–13 weeks pregnancy but is associated with high incidence of heavy bleeding[28,29]. The timing of administration of misoprostol after mifeprostone for medical termination of pregnancy ranges from 6 to 48 h. The complete abortion rates improve with one or two additional doses of misoprostol.

Vaginal administration of misoprostol was more effective and better tolerated than oral administration for the induction of first-trimester abortion[30,31]. However, some studies concluded that both oral and vaginal misoprostol were of similar efficacy. Sublingual administration of misoprostol had a success rate of 92%[32].

A single dose of intramuscular or oral methotrexate (50 mg per square meter of body-surface area) followed 5–7 days later by 800 μg of vaginal misoprostol resulted in complete abortion in 88–100% of women provided this regimen; 53–60% of women aborted within 24 h after one dose of misoprostol was administered[33–39]. If complete abortion did not occur within that interval, repeating the misoprostol dose resulted in complete termination of pregnancy in 19–32% of women within 24 h after the second dose[33,34]. The remaining 10–30% of women who aborted successfully had a delayed response, with the abortion completed over an average period of 24–28 days[33,34].

Misoprostol has also been used alone for medical termination of pregnancy, with variable efficacy. The earliest studies of misoprostol-induced termination of pregnancy in the first trimester reported complete abortion rates of 5–11% among women given a total dose of 400 μg of oral misoprostol[40,41]. Up to three 800-μg doses of vaginal misoprostol given every 48 h resulted in complete termination of pregnancy in up to 96% of women who were no more than 63 days pregnant[42]. However, in a randomized trial comparing methotrexate plus vaginal misoprostol with vaginal misoprostol alone, only 47% of the women given misoprostol alone had complete termination of pregnancy, as compared with 90% of the women given methotrexate plus misoprostol ($p < 0.001$)[43].

With regard to the use of misoprostol as a cervical-priming agent before vacuum aspiration of the uterus, numerous randomized, controlled studies have shown that misoprostol is more effective than placebo and vaginal PGE_2 in terms of the degree of cervical dilatation achieved[44,45]. As cervical priming facilitates surgical vacuum aspiration, the risks of dilatation and evacuation of the uterus are therefore minimized. These results were replicated by numerous other randomized, controlled trials involving a large number of participants. The best regimen for cervical ripening in the first trimester is 400 μg of vaginal misoprostol given 3–4 h before suction curettage[44,46,47]. In one study, misoprostol, when administered with mifeprostone for termination of early pregnancy in scarred uteri, was safe and effective, but further randomized trials are essential to confirm this[48].

Sublingual misoprostol was effective in facilitating cervical dilatation before surgical abortion, and its use significantly decreased the time

of surgical evacuation and minimized blood loss during the procedure[49,50].

MISOPROSTOL IN EARLY PREGNANCY FAILURE

Single or repeated doses of misoprostol result in complete expulsions with minimal side-effects and complications in evacuation of first-trimester missed abortions[51,52]. Vaginal misoprostol is more effective then oral administration[53]. Misoprostol is also effective in incomplete termination of pregnancy, and it is safer than the surgical method[54,55].

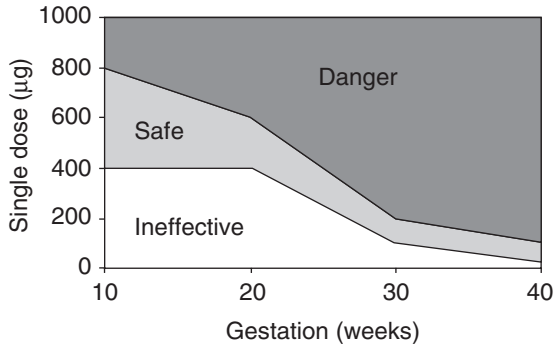

Figure 4 Safe single doses of misoprostol for producing uterine contractions at various gestations[63]

MISOPROSTOL IN THE SECOND TRIMESTER

Indications for termination of pregnancy in the second trimester include chromosomal and structural fetal abnormalities as well as social reasons. Surgical evacuation of the uterus, still being practiced in some centers, is associated with greater morbidity, mortality and complications. Intra-amniotic hypertonic saline/urea instillation, intra-amniotic PGF_2 infusion, extra-amniotic ethacridine lactate, oxytocin infusion and vaginal PGE_2 were practiced before the introduction of misoprostol.

Intravaginal misoprostol in the dose of 400 μg is effective and associated with fewer side-effects[56]. Vaginal misoprostol was found to be as effective as or more effective than PGE_2. Misoprostol was equally effective as extra-amniotic prostaglandins[57–60]. Misoprostol in the dose of 400 μg every 3 h was more effective in terms of a significantly shorter drug administration-to-abortion interval and a higher percentage of successful abortion within 48 h compared to misoprostol 400 μg every 6 h, and the incidence of side-effects was similar in both groups except for that of fever. However, the fever returned to normal within 24 h after the last dose of misoprostol[61].

Vaginal misoprostol was significantly more effective as judged by drug administration-to-abortion interval and the need to augment the therapy with oxytocin infusion when compared to oral misoprostol[62].

It is somewhat paradoxical that a greater dose (800 μg) of vaginal misoprostol is essential for abortion in the first trimester, whereas doses in the range of 25–50 μg induce labor in the third trimester. The optimal dose of vaginal misoprostol for induction of labor in the second trimester probably lies somewhere between 50 and 800 μg. Within this range, higher doses may be needed to cause termination of pregnancy early in the second trimester, whereas lower doses may be sufficient later in the second trimester. Higher and more frequent doses are associated with shorter drug administration-to-abortion interval compared to lower and less frequent doses[1,63] (Figure 4).

MISOPROSTOL IN THE THIRD TRIMESTER

Induction of labor

This is one of the common obstetric interventions primarily performed with the aim of reducing maternal and perinatal morbidity and mortality. The success of induction of labor not only lies with replication of physiological mechanisms, but also depends upon the cervical status. An unfavorable cervix presents the greatest challenge to successful induction. The development of effective, safe (to both mother and fetus) and less expensive pharmacological agents to accomplish this task has been the focus of much clinical research.

The results of the first study (1993) suggested that misoprostol is a cost-effective and safe alternative for induction of labor at term. Many later studies, including randomized trials,

not only confirmed this finding, but also have shown that misoprostol is more effective than a placebo or other prostaglandins; moreover, it is associated with a higher rate of vaginal delivery within 24 h, a shorter induction-to-delivery interval and significantly lower Cesarean section rates than pooled figures for the control groups[64–67].

Studies of different routes of misoprostol administration were conducted for induction of labor, including oral, vaginal, intracervical and sublingual[68–73]. Although all routes were successful, vaginal misoprostol is associated with a shorter induction-to-delivery interval, lower number of doses and diminished oxytocin use[68,70]. Misoprostol gel is associated with fewer uterine contraction abnormalities and longer induction-to-labor and delivery interval when compared to misoprostol tablets[71].

The safety of misoprostol is crucial, as some studies have shown a high frequency of uterine tachysystole and hyperstimulation, including some reports of uterine rupture during the induction of the labor with misoprostol[74–76]. A vaginal dose of 25 μg is often recommended as the more prudent dose, as it is associated with lower incidence of uterine hyperstimulation and it is comparable to the 50 μg dose in achieving delivery within 24 h[64,77–81]. Doses higher than 50 μg have been associated with increased risk of complications. The interval of administration of misoprostol ranges from every 3 to 6 h. It is better to use 6-h dosing intervals to avoid the possible risk of tachysystole[82]. Misoprostol is also effective as a cervical ripening agent for prelabor rupture of the membranes[83]. Oral misoprostol not only induced labor but also resulted in delivery within 24 h without increasing maternal or neonatal complications[66,84].

Misoprostol is not recommended for induction in cases of previous Cesarean section, as it is associated with higher frequency of disruption of prior uterine incision compared with use of PGE_2 or oxytocin. Misoprostol use is associated with a 5.6% rupture of uterine scars compared to 0.2% in patients attempting vaginal birth after Cesarean delivery without stimulation, as shown by meta-analysis[85]. Misoprostol use in grand multipara is not associated with adverse maternal or neonatal outcome. However, its use in such patients warrants strict vigilance[86,87]. The use of prostaglandins including misoprostol increases the uteroplacental resistance but does not affect the umbilical blood flow in a Doppler velocimetry study of umbilical, uterine and arcuate arteries immediately before and 2–3 h after the administration of vaginal misoprostol or cervical PGE_2, thus suggesting misoprostol is as safe as PGE_2 gel[88]. Available data suggest that vaginal misoprostol in a dose of 25 μg every 6 h is as safe as PGE_2 in patients with a live fetus for induction of labor.

Induction of labor after fetal death

Misoprostol is ideally suited agent for induction of labor after fetal death as there is no concern about the adverse effects of uterine hyperstimulation on the fetus. For fetal death at term, a dose as low as 50 μg every 12 h may be adequate for induction of labor, whereas higher doses are necessary in patients with fetal death in the second trimester and early in the third trimester[89,90].

THIRD STAGE OF LABOR

Postpartum hemorrhage is a major cause of maternal morbidity and mortality. It is sudden, dramatic and unpredictable. In developing countries, over 125 000 or approximately 28% of total maternal deaths are caused by postpartum hemorrhage each year. According to one estimate, the risk is approximately 1 in 1000 deliveries[91].

Based on misoprostol's uterotonic effects, this drug has been evaluated for both prevention and treatment of postpartum hemorrhage (see Chapters 4 and 16–19). The WHO misoprostol multicenter trial concluded that use of an oral tablet of 600 μg was associated with a higher risk of severe postpartum hemorrhage, the need for additional uterotonic agents, shivering and pyrexia compared with intramuscular or intravenous oxytocin[92]. However, the dose of misoprostol used in these trials varied from 400 to 600 μg (orally and rectally). Moreover, the frequency of postpartum hemorrhage (blood loss > 1000 ml) was not lower in the misoprostol group than in the control group in any of the trials. None the less, there was higher

use of oxytocin in the control groups. In many reports, misoprostol 600 μg oral or 400 μg rectal is significantly less effective than injectable uterotonics in preventing postpartum hemorrhage[92–103]. Misoprostol at the dose of 400–600 μg is associated with risk of shivering, and doses more than 400 μg also significantly increase the risk of pyrexia. At present, oral or rectal misoprostol is not as effective as conventional injectable uterotonic agents, and the high rates of shivering and fever associated with its use make it undesirable for routine use to prevent postpartum hemorrhage, especially for low-risk women. Thus, there is insufficient evidence to date to support the routine use of misoprostol when oxytocin or methylergometirne is available. There is some evidence of increased uterotonic effect with the administration of misoprostol, either by the sublingual route or as an oral solution[6,14,15]. Use of buccal misoprostol in a placebo-controlled trial to prevent hemorrhage at Cesarean delivery was not associated with a significant difference between the two groups, both in the incidence of postpartum hemorrhage and a difference in pre- and postoperative hemoglobin level. However, misoprostol reduced the need for additional uterotonic agents during Cesarean delivery[104]. In all of these studies, it is important to note that misoprostol was compared to conventional uterotonics. It is tragic but true, however, that these latter drugs are not available in many parts of the world where women deliver with no medical assistance whatsoever.

Despite the lesser efficacy of misoprostol compared with conventional injectable oxytocics and the potential to cause side-effects, several factors – ease of use, stability in field conditions, longer shelf-life, and less expense – underlie its continued evaluation as a uterotonic agent. It remains of great interest, especially for use in home deliveries by traditional birth attendants and minimally qualified nurse midwives in less developed areas where administration of injectable uterotonics may not be feasible or may not be available. Here, it offers a plausible preventive strategy in such areas for reducing maternal mortality related to postpartum hemorrhage[105–107]. The results of an ongoing National Institute of Child Health and Human Development (NICHD) sponsored Global Network for Women's and Children's Health Research randomized, placebo-controlled trial of misoprostol in home delivery settings in rural India will perhaps answer the question regarding the benefit of oral misoprostol in the prevention of postpartum hemorrhage[108] (see also Chapter 8).

Oral misoprostol in the dose 600 μg was associated with lower incidence of measured blood loss ≥ 500 ml and lower incidence of reduction in postpartum hemoglobin (reduction of hemoglobin ≥ 2 g/dl was 16.4% with misoprostol and 21.2% with ergometrine), but the difference were not statistically significant. Shivering was significantly more common with misoprostol, whereas vomiting was more common with ergometrine in a randomized, controlled trial with misoprostol 600 μg and ergometrine (0.5 mg, four tablets) in the home delivery settings of rural Gambia[109]. Rectal misoprostol has also been reported to control postpartum hemorrhage that is unresponsive to oxytocin and methylergometrine in the dose of 1000 μg[110].

Rectal misoprostol in the dose of 800 μg could be a useful first-line drug for the treatment of primary postpartum hemorrhage[111]. In a randomized, double-blind, placebo-controlled trial with sublingual misoprostol at a primary health center in Bissau, Guinea-Bissau, West Africa, the incidence of postpartum hemorrhage was not significantly different between the two groups. However, significantly fewer women in the misoprostol group experienced a blood loss of ≥ 1000 ml or ≥ 1500 ml. The decrease in hemoglobin concentration tended to be less in the misoprostol group, the mean difference between the two groups being 0.16 mmol/l (–0.01 to 0.32 mmol/l). From this study, it was concluded that sublingual misoprostol reduces the frequency of severe postpartum hemorrhage[112]. Further randomized, controlled trials are necessary to identify the best drug dose and route of administration for the treatment of postpartum hemorrhage[113], particularly when use of conventional agents is not possible. Such studies should differentiate the site of use for misoprostol. When there is no syringe to inject methergin or oxytocin or no refrigeration facility for these drugs, misoprostol may be the only viable option and should be compared to the

local standard practice (where there is no use of uterotonic agents).

OTHER USES

Misoprostol is used prior to procedures such as intrauterine insemination and hysteroscopy[114–116]. Its use in cervical pregnancy is documented with one case report; however, extreme caution is recommended with this approach and methotrexate is favored by many authorities[117].

CONCLUSION

Misoprostol is one of the most important medications in obstetric practice. As of the time of writing, its use in pregnant women remains unapproved by the US FDA, except in conjunction with mifeprostone (or, in some cases, methotrexate) for first-trimester medical termination of pregnancy. Despite this, the international literature is replete with favorable reports of off-label uses. For example, there is strong and consistent evidence to support the use of misoprostol for cervical ripening before surgical abortion in the first trimester and for induction of labor in the second and third trimesters. Whereas lower dose and strict vigilance are required for use of misoprostol for induction of labor with a live fetus, it is ideal for induction of labor in patients with intrauterine fetal death.

Misoprostol may also prevent postpartum hemorrhage when injectable uterotonic agents are either impractical or unavailable. On the other hand, misoprostol may not be the preferred uterotonic for prevention of postpartum hemorrhage where injectable oxytocics are readily available. Its use in the treatment of postpartum hemorrhage in regions of the world where the standard of care is delivery without uterotonic agents (i.e. delivery with no uterotonic medication) needs further evaluation. The oral route is associated with faster effect and with more side-effects. The other routes, such as vaginal and rectal, have sustained and longer effects with less side-effects. The sublingual and buccal routes and dose need further evaluation.

Finally, after considerable dialogues between the American College of Obstetricians and Gynecologists (ACOG) and Searle, the manufacturer of misoprostol, the FDA has approved a new label for the use of misoprostol during pregnancy. The new labeling revises the contraindications and the precaution that misoprostol should not be used in pregnant women by stating that the contraindication is only for pregnant women who are using the medication to reduce the risk of non-steroidal anti-inflammatory drugs. Misoprostol is now a legitimate part of the FDA-approved regimen for use with mifeprostone to induce abortion in early abortion and is also recognized for induction of labor[118].

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