Clinical Uses of Misoprostol in Obstetrics and Gynaecology

Dr. Suk-wai Ngai MBBS, MRCOG, MD
Associate Professor
Department of Obstetrics & Gynaecology, The University of Hong Kong

Introduction

Misoprostol is a synthetic prostaglandin E1 analogue approved by the Food and Drug Administration (FDA) for the prevention and treatment of gastroduodenal ulcers. Norman et al. first demonstrated its uterinecontractive abortifacient properties in 1991. This publication generated great interest in the search for the potential uses of misoprostol in Obstetrics and Gynecology. Misoprostol has since been proven to be an effective agent for cervical priming prior to surgical abortion, medical abortion, induction of labour and prevention of postpartum haemorrhage. In contrast to other synthetic prostaglandin analogues, it is substantially less expensive. It does not require refrigeration and can be administered orally, rectally, vaginally, as well as by the sublingual route. The purpose of this chapter is to summarise the evidences of its efficacy in clinical use.

Cervical Priming Prior to Surgical Abortion

Cervical preparation is critical to the success of surgical abortion. It reduces the need for rapid mechanical dilatation of the cervix which carries a significant risk of cervical laceration with immediate morbidity, and the possibility of remote complications such as cervical incompetence. Misoprostol was extensively investigated as a cervical priming agent before surgical abortion. Bulgalho et al. compared the use of vaginal misoprostol versus placebo in 1994. Our group subsequently published a series of studies to investigate its efficacy when used as a cervical priming agent by the oral route. We showed that when given orally 12 h prior to vacuum aspiration, 400 ug misoprostol was more effective than placebo and gemeprost, and as effective as mifepristone for cervical priming. Dose finding studies have determined that 400 ug vaginal misoprostol, given 3-4 hours prior to the procedure, is probably the optimal treatment for achieving adequate dilation in over 95% of women prior to suction evacuation.

First Trimester Medical Abortion

Medical abortion has become an alternative method of first trimester pregnancy termination with the availability of prostaglandins in the early 1970s and anti-progesterones in the 1980s. Studies on the use of misoprostol alone for first trimester medical abortion have largely been unsatisfactory. Repeated doses were required and it took a few days for the effect to complete. The overall successful rate ranged from 40-90%. The results were difficult to compare because different studies adopted different dosing regimens. In most of the studies, the daily doses of misoprostol vary from 600-1000 ug. The success rate of abortion was also not uniformly defined. In contrast, the combination regimen of mifepristone and misoprostol gave much more promising results. Jain et al. compared women who received misoprostol alone to women who had received 600 mg mifepristone and 400 ug oral misoprostol. Successful abortion occurred in 88% with misoprostol alone and in 94% with the combination regimen. A subsequent randomised controlled trial compared misoprostol alone to 200 mg mifepristone combined with 800 ug vaginal misoprostol, and found a success rate for the single drug of 88%; versus 95.7% for the combination. Misoprostol is currently the prostaglandin used most commonly in combination with mifepristone. In standard regimens approved by national regulatory agencies, mifepristone 600 mg orally is followed by approximately 48h later by 400 ug oral misoprostol given in the clinic for first trimester medical abortion.

However, mifepristone is not widely available. The use of the misoprostol-alone regimen remains attractive in many countries. Our group performed a pilot study on the use of sublingual misoprostol for medical abortion. We achieved 95% complete abortion rate by using 400 ug misoprostol every 4 hours for a maximal of five doses. Our finding suggested that large scale prospective randomised trials should be conducted to work out the optimal dosing regimen.

Second Trimester Medical Abortion

Abortion-related mortality and morbidity increase significantly as gestation increases. Induction of abortion after 14 weeks of gestation is associated with a sharp rise in the rates of complications and in the consequent medical costs. Such abortions constitute only 10-15% of all induced abortions but they are responsible for two-thirds of all major complications and 50% of all abortion-related maternal deaths. Different management protocols are continuously revised, aiming to achieve improved success rates and reduced discomfort to the patients. Medical abortion using prostaglandin analogues alone or in combination with mifepristone has been proven to be effective for second trimester abortion and the termination of pregnancy with intrauterine death.
Most of the misoprostol-only regimens used in second trimester abortion involved vaginal administration. In the literature, the dosage of misoprostol used in the studies involving misoprostol alone varied from 100-200 ug and the dosing interval ranged from 3 to 12 hours. Misoprostol at a dose of 100-200 ug every 6-12 hours gives a lower abortion rate at 48 hours and a longer induction-to-abortion interval than gemeprost. The induction-to-abortion interval was still long even if the dosage of misoprostol was increased to 400-600 ug every 12 hours. A randomised study demonstrated that misoprostol 400 ug given vaginally every 3 hours was probably the optimal regimen for second trimester abortion. The complete abortion rate and induction-to-abortion interval were compromised if the dosing interval extends to 6 hours. This regimen of misoprostol had been shown by a randomised study to be more effective when compared with the standard regimen of gemeprost. Recently, sublingual administration of misoprostol has been investigated. One pilot study using 400 ug misoprostol every 3 hours for a maximum of five doses achieved 100 percent second trimester abortion with a median induction-to-abortion interval of 11.6 hours. In addition, the majority of women preferred the oral route to the vaginal route because the former is more convenient and offers more privacy.

Intrauterine Death

Induction of labour for intrauterine death can be difficult particularly when the cervix is unripe. The success rates of misoprostol alone regimen range from 67% to 100%. Most of the published regimens have recommended the vaginal route. More recently, mifepristone has also been successfully used in this aspect. Fletcher et al. reported successful induction of labour using mifepristone 200 mg 12 hourly for two days, and subsequently a prospective double blind trial confirmed that mifepristone can be useful in the management of intrauterine death. In the latter study 43 women with a silent miscarriage or stillbirth received mifepristone 200 mg three times a day for two days resulting in 63% of them delivering within 72 hours of commencing treatment compared with only 17% in the placebo group. Wahaarachchi et al. first reported a combination of vaginal and oral route. Women received a single dose of 200 mg mifepristone and subsequently a 25-ug dose was associated with lower incidence of tachysystole and uterine hyperstimulation. The lower-dose regimen achieved a comparable induction-delivery interval when compared with the high dose regimen. Doses higher than 50 ug should not be given because it has been associated with an increased risk of serious complications.

Induction of labour with previous uterine scar is always challenged. No matter what method is used, there are higher risks of uterine rupture than those without a scar. The first randomised controlled trial of 25 ug vaginal misoprostol for induction of labour in women with one prior caesarean section was terminated after two women in the misoprostol group had disruption of their uterine scar. No further prospective trials in this area has been published. Plaut et al. reported a 5.5% rate of scar rupture associated with the use of misoprostol compared with 0.2% in patients attempting vaginal birth after caesarean section with no stimulation in a retrospective study. With the rising caesarean section rate, there will be an increasing number of women undergoing termination of pregnancy or labour induction with a previous uterine scar. Current evidence would suggest that they are at an increased risk of scar rupture. Women should be appropriately counselled about the risks and consequences.

Prevention for Postpartum Haemorrhage

Postpartum haemorrhage (PPH) continues to be a leading cause of maternal morbidity and mortality worldwide. Uterotonics agents administered during the third stage of labour have been shown to reduce the incidence of PPH by 40%. Misoprostol administered by oral, vaginal and rectal routes had been investigated. The World Health Organization (WHO) conducted the largest scale study involving nine countries with altogether 20,000 women were recruited. This trial was to compare the use of oral misoprostol (600 ug) to 10 IU of oxytocin. The sample size was of adequate power to measure two outcomes: blood...
loss of 1000 ml or more and the use of additional uterotonics for agents. Unfortunately, the trial had several problems: 1. it was unclear whether the women received intravenous or intramuscular oxytocin; 2. there was an unexplained statistical heterogeneity between the individual centres for the primary outcome of measured blood loss. The finding of this large trial is often quoted as a 1% difference between oral misoprostol and oxytocin. The WHO trial, however, proved the safety of misoprostol administered orally at doses up to 600 μg. The alternative administered route including vaginal and rectal route has been investigated. The pilot study by O’Brien et al reported that misoprostol 1000 μg given rectally is an effective intervention in women with PPH who are unresponsive to standard uterotonic agents.38

Side Effects and Complications

Minor side effects including nausea, vomiting, and diarrhoea, are characteristics of prostaglandin administration and are due to prostaglandin’s stimulatory effect on the gastrointestinal tract. Serious complications including uterine rupture, major haemorrhage and cervical tear are rare.25 Cases of uterine rupture were reported to occur with both misoprostol and gemeprost, with our without priming by misoprostol.26,27 Risk factors of uterine rupture include previous caesarean section, grand multipara, advance gestation, prolonged prostaglandin therapy and use of oxytocin in addition to prostaglandins. Cardiovascular complications are uncommon. Long term complications associated with medical abortion in the second trimester using misoprostol with or without misoprostol are rarely reported.

Conclusions

Misoprostol is an important medication for Obstetrics and Gynaecology practice. It is effective for medical abortion in combination with misoprostol. There is solid evidence supporting the use of misoprostol for cervical ripening prior to first trimester suction evacuation. It is also an effective labour inducing agent. It was proven to be safe when used in third stage to prevent postpartum haemorrhage. However, the use in women with previous scar should be cautious.

References