SAMJ
Commentary and Debate

Editorial

Misoprostol in obstetrics and gynaecology — unregistered, dangerous and essential

Misoprostol (Cytotec; Searle) is a methyl ester of prostaglandin E_1 and is marketed for use in the prevention and/or treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. It is inexpensive, easily stored at room temperature and rapidly absorbed orally, and has few side-effects. Several studies have shown it to be an effective myometrial stimulant of the pregnant uterus,[1] selectively binding to EP-2/EP-3 prostanoid receptors.[2]

The well-documented effectiveness of misoprostol in several gynaecological and obstetric applications has resulted in an enthusiasm for its use which has overtaken the need for careful documentation of potential risks. The purpose of this editorial is to highlight some of these risks.

First-trimester termination of pregnancy. Misoprostol is an effective abortifacient, both alone and following pretreatment with RU-486.1 Its widespread use in Brazil[3-6] resulted in the identification of teratogenic effects,[7] particularly limb reduction defects[8] following unsuccessful termination of pregnancy, such as in the case reported in this issue (p. 566).

It is vital that health workers using misoprostol for termination of pregnancy are aware of these risks, and that they counsel their patients in detail about the teratogenic effects and the need to complete the termination of pregnancy once it is embarked upon. It is also important for health workers prescribing misoprostol for the usual indications for women of childbearing age to emphasise the need to discontinue treatment if pregnancy is planned or suspected.

Second-trimester termination of pregnancy. Use of misoprostol for second-trimester termination of pregnancy has been associated with uterine rupture, particularly when combined with oxytocin infusion. In a report of 803 women admitted to hospital with abortion complications in Rio de Janeiro, 458 reported using misoprostol.[5] There were 3 deaths, 2 from sepsis and one from uterine rupture at 16 weeks' gestation following self-medication with misoprostol.

The misoprostol dosage used in the second trimester needs to be limited, and oxytocin infusion should not commence within 6 hours of administering misoprostol.

Third-trimester induction of labour. In 1988 Neto *et al.*[9] described uterine tachysystole (excessive uterine activity) with misoprostol use at term, which appeared unrelated to dosage.

In this journal, Merell *et al.*[10] reported a series of 62 misoprostol inductions. Among this number there were 2 stillbirths, one apparently due to a tight nuchal cord, and one unexplained. The authors commented on rapid onset of contractions and on one woman with an induction-to-delivery interval of 2 hours. They urged caution and the frequent use of fetal monitoring. In a subsequent abstract[11] they described 345 inductions with live fetuses and 86 with intra-uterine death. There was 1 unexplained maternal death, 2 uterine ruptures (1 of these patients had had a previous caesarean section), 8 caesarean sections for fetal distress and 1 for uterine hyperstimulation, and 10 perinatal deaths.

The conclusion from a recent meta-analysis[12] was that published data confirmed the safety of intravaginal misoprostol for cervical ripening and labour induction, despite data showing an increased incidence of tachysystole (odds ratio 2.70, 95% confidence interval 1.80 - 4.04). More recently, we have reviewed 21 reported randomised trials of vaginal misoprostol for induction of labour.[13] The range of dosages used was enormous (25 µg 6-hourly to 100 µg 2-hourly). Vaginal dosages as low as 25 µg (one-eighth of a tablet) 3-hourly were more effective than either oxytocin or dinoprostone for the induction of labour, but were associated with increased uterine hyperstimulation, fetal heart rate changes and increased meconium passage. In one trial using 25 µg 4-hourly,[14] the rate of uterine hyperstimulation appeared not to be increased, and this dosage was not more effective than dinoprostone.

Recently the use of oral misoprostol 200 µg for cervical priming for prelabour rupture of membranes at term,[15] and 50 µg 4-hourly for induction of labour,[16] have been reported, without an obvious increase in the incidence of uterine tachysystole.

Despite some enthusiastic publications, we maintain that at present the use of misoprostol for induction of labour at term should be limited to carefully controlled studies to determine safety and optimal route of administration and dosage.

Prevention of postpartum haemorrhage. The possibility that an inexpensive, stable oral preparation may reduce the risk of postpartum haemorrhage has enormous implications for the safety of childbirth, particularly for women in developing countries.[17-21] To date, the effectiveness of misoprostol in the third stage of labour has not been established. Its use should await the results of further trials, particularly the large, multicentre World Health Organisation sponsored trial currently in progress.

In conclusion, misoprostol has the potential to be an extraordinarily useful drug in obstetric and gynaecological practice, particularly in developing countries where conventional prostaglandin preparations are unaffordable. As its commercial registration for use in pregnancy appears unlikely, clear guidelines from the health authorities regarding its use are urgently needed, coupled with indemnity against complications which may be associated with its use within these guidelines.

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