

The continuing problem with misoprostol

An article in this edition describes two cases of serious genital tract injury that occurred with standard doses of misoprostol, commonly sold as Cytotec, when used to achieve evacuation of the uterus in the second trimester.

Misoprostol is the only prostaglandin E_1 analogue uterine stimulant that is currently commercially available in obstetrics and gynaecology; all other prostaglandin preparations, commercially known as Prostin, Prandin, Prepidil, and by many other names, are prostaglandin E_2 analogues, and long preceded the use of misoprostol.

Misoprostol was originally synthesised for use in peptic ulceration, but early in its genesis its use as a uterine stimulant began. It is not unusual for a drug to have a use different to the one for which it was originally devised; chlorpromazine, or Largactil, for example, was originally a premedicating agent for anaesthesia. Now, owing to a discovered additional benefit, it is predominantly a psychotropic agent for the treatment of psychotic delusions in schizophrenia.

Misoprostol can be used in low doses to soften the cervix to allow instrumentation for suction evacuation of the uterus in termination or incomplete miscarriage, or to soften the cervix prior to instrumentation in, for example, hysteroscopy. But it is in its use as an abortifacient or as an agent for inducing labour that greater problems may occur. A further use is for contracting the atonic uterus in primary postpartum haemorrhage, for which it remains recommended primarily when other agents are not available and where medical supervision is limited.

As an abortifacient in the first trimester, misoprostol may be used alone or in combination with mifepristone or methotrexate.

The side-effects of misoprostol vary from the relatively minor to the very serious. It may cause shivering, or a mild pyrexia with repeated doses, and, particularly if taken orally, it may cause gastrointestinal upset, especially diarrhoea (in a dehydrated patient, this may not be a minor complication).

But the greatest concern regarding misoprostol is an idiosyncratic, excessive uterotonic response at what are considered reasonable therapeutic doses. Idiosyncratic means particular to the individual – that the response may far exceed the response in many others, and that it may far exceed the average response. This unusual response cannot be predicted.

An individual given reasonable doses of misoprostol may, therefore, develop excessive uterine contractions leading to, as in the two cases reported here, tearing of the undilated cervix with excessive pressure from above. Tearing of the undilated cervix more usually occurs when the cervix is fibrosed from previous traumatic instrumentation and is therefore resistant to dilatation. In the two cases reported here, no such history existed (information in a history may, of course, be withheld).

In induction of labour, misoprostol may be hazardous. Induction of labour is designed to mimic the natural evolution of contractions leading to dilation of the cervix and descent of the presenting part. At times, the induction agent alone is necessary to sustain labour and effect delivery, but at times, oxytocin, after an appropriate interval, is required.

Overstimulation or hyperstimulation is well recognised with prostaglandin E_2 analogues, as with E_1 analogues, and for this reason

delivery systems for E_2 analogues that do not completely dissolve and can be removed from the vagina were developed. With E_2 , as with E_1 analogues, an excessive response cannot be predicted.

The consequence of overstimulation can be grave: fetal distress may lead to the passage of meconium, with the attendant risk of aspiration. Acidosis may lead to fetal and neonatal asphyxia, and cerebral palsy or death. In very excessive responses, the uterus may rupture, resulting in fetal and even maternal death, or the undilated cervix may tear (as occurred in the cases reported here), resulting in life-threatening haemorrhage.

Are any of these complications greater with misoprostol than with the previously developed E_2 analogues? How can such complications be avoided?

It is not known whether serious complications with misoprostol exceed those with E_2 analogues. Many studies have looked at case series of misoprostol and the question remains unanswered. Sizeable comparative data are absent. And there is concern that harmful effects of uterine stimulants may go unreported – such reports may reflect badly on institutions if, on review, preventive and corrective measures are deemed inadequate, and in an era of litigation, a culture of silence is inevitable.

In induction of labour, monitoring should commence by cardiotocogram (CTG) once contractions are established. This is especially the case when tachysystole (six contractions or more in two 10-minute episodes) is suspected, or prolonged or coupled contractions are suspected that may prevent fetal recovery. A midwife cannot observe a patient undergoing induction of labour throughout the many hours it may take, and so all patients undergoing induction must be asked to inform supervising staff when regular contractions occur and assessment can begin. While baseline changes and late decelerations can be detected by intermittent auscultation, baseline variability cannot, and, for many, assessment by CTG would be an essential prerequisite for induction, and for the high-risk labour that follows. Teaching of correct CTG interpretation is essential. In the developing world, CTG machines may not be available.

Induction of labour should be avoided in cases where uteroplacental insufficiency is suspected or present. In the developing world, sonar machines may not always be available, and clinical judgement of poor growth and oligohydramnios is unreliable. However, excessive uterine contractions may exceed the reserve even of the fetus in whom liquor levels, doppler investigations (where available) and growth are normal.

Excessive response to misoprostol as an abortifacient may perhaps be limited, as in induction of labour, by withholding further doses once a response is established. The importance of adequate medical assessment cannot be overemphasised: assessment cannot prevent an excessive response, but patients being administered misoprostol in repeated doses should not be ignored in side-rooms or a corner of the ward, but observed and assessed by an enquiry into contractions and palpation.

Misoprostol is popular because of its efficiency at achieving delivery/evacuation, and because it is inexpensive. This latter benefit may contribute to its distribution outside hospitals, clinics and pharmacies. Away from medical supervision, dose control may be

non-existent. Patients may also arrive in maternity and gynaecology admission areas seemingly undergoing spontaneous labour or miscarriage, and suffer the dire consequences of excessive doses of misoprostol, the administration of which is never confessed.

It is possible that such patients may be given further doses when in hospital, thereby exaggerating the total dose given. The pharmacodynamics of possible previous and undeclared doses of the drug are not uniform across a population, and for a few, the effects of previously administered doses may persist.

The inhibition of excessive misoprostol contractions by tocolytic agents, as with the inhibition of any uterine stimulant, may be effective. Sustained inhibition protocols and the safety of repeated tocolytic doses are less well known.

Wherever misoprostol is used, rapid recourse to a safe operating theatre is an essential requirement. The absence of such can only magnify any complications that occur.

Is misoprostol safe for all who use it? No, it is not. The risks for the few that react excessively to its stimulus are great. Vigilance and anticipation of idiosyncratic responses are essential. Thorough

reporting of complications may lead others to question its suitability, as has the National Institute for Health and Care Excellence (NICE)^[1] in the UK, which has stated that its use in induction of labour should be confined to induction of labour or evacuation in the presence of intrauterine fetal death (as in the cases reported here, though they were in the second trimester), or in the context exclusively of formal clinical trials. While this opinion is not universally held, it was informed by more than a casual concern for potentially very serious, harmful effects.



Will Edridge
Editor

1. National Institute for Health and Care Excellence. Clinical Guidance: Inducing Labour. London: NICE, 2008. <https://www.nice.org.uk/guidance/cg70> (accessed 30 August 2017).