TITRATED ORAL MISOPROSTOL SOLUTION — A NEW METHOD OF LABOUR INDUCTION

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Background. Misoprostol, a cheap, stable, orally active prostaglandin analogue, is effective for labour induction when administered either vaginally or orally, but uterine hyperstimulation and rupture have been reported. Previous studies of oral misoprostol for labour induction have used fixed dosages 3 - 6-hourly.

Objectives. To develop a new method of misoprostol use for labour induction using very small, frequent, titrated oral dosages, and to pilot effectiveness.

Study design. Open clinical pilot study.

Setting. Coronation Hospital, an academic hospital in Johannesburg, South Africa.

Methods. We developed a method using 2-hourly titrated misoprostol doses commencing with 20 µg, increased after three doses to 40 µg. To administer such small doses we dissolved one misoprostol tablet in 200 ml water. A pilot study of this method was undertaken in 25 women with various indications for induction of labour.

Results. Eighteen women (72%) delivered vaginally within 32 hours of induction and two women developed uterine hyperstimulation. The caesarean section rate was 20%.

Conclusions. Women may respond to much smaller dosages of misoprostol than are currently in use. A multicentre randomised trial of this method is underway. We emphasise the dangers inherent in the current unregistered use of misoprostol in clinical practice.

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Three years ago we drew attention in this *Journal* to the dangers of misoprostol use in the third trimester of pregnancy.[1] However, we continue to admit women with complications of misoprostol overdosage, including uterine rupture, to academic hospitals in Johannesburg.

Induction of labour in the third trimester of pregnancy may be considered beneficial in many clinical circumstances. The risks include ineffective labour (failed induction), or excessive uterine activity which may cause fetal distress or uterine rupture. Either problem may lead to an increased risk of caesarean section. Unsuccessful labour induction is most likely when the cervix is unfavourable, and in this circumstance prostaglandin preparations have proved to be beneficial.[2] Those prostaglandins, which have been registered for cervical ripening and labour induction, are expensive and unstable and require refrigerated storage.

Misoprostol (Cytotec, Searle) is a methyl ester of prostaglandin E1 registered for use in the prevention and treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. It is inexpensive, easily stored at room temperature and has few systemic side-effects.

Current experience with misoprostol used for labour induction has been reviewed recently.[3,4] Although in most studies misoprostol seemed to be at least as effective as conventional methods, widely varying dosage regimens and small numbers of women studied do not allow for adequate assessment of safety. The widespread use of misoprostol in clinical practice in this country and elsewhere, using arbitrary dosages and without registration or proper surveillance for adverse events, is cause for grave concern,[5] as are reports of complications such as uterine rupture.

Although most researchers and clinicians have chosen the vaginal route for misoprostol administration, oral administration may have several advantages. Administration is easier and may be more acceptable to women. Absorption is more rapid and possibly more predictable. The reported mean peak serum misoprostol acid level following oral administration was 227 pg/ml after 34 minutes compared with 165 pg/ml after 80 minutes for the vaginal route. Vaginally absorbed serum levels are more prolonged.[6] The shorter half-life when given orally may be advantageous in the event of uterine hyperstimulation. On the other hand, the direct local effect of vaginal misoprostol on cervical softening may be advantageous.

Randomised trials of oral misoprostol reviewed to date have used fixed misoprostol regimens with a wide range of dosages, from 50 µg 4-hourly to 200 µg every 6 hours.[4]

Based on the knowledge that uterine sensitivity is extremely variable between individuals, and in the same person over time, we adopted the principle that misoprostol should be administered orally in small, frequent dosages, titrated against the uterine response. This is analogous to the conventional

titrated use of oxytocin. To overcome the difficulty of breaking the misoprostol tablets accurately into small fragments, we decided to use one misoprostol tablet (200 µg) dissolved in a medicine bottle with 200 ml water (1 µg per ml solution). The bottle was shaken well before each administration.

METHODS

We conducted a pilot study at Coronation Hospital, Johannesburg, to assess the effectiveness of this novel approach in pregnant women with singleton, cephalic presentation requiring labour induction at term. The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand, and informed consent was signed by all participants. The initial commencing dosage chosen was 40 µg 2-hourly, but uterine hyperstimulation was observed in the first woman studied. A revised protocol was applied to all women irrespective of parity, cervical score or membrane status (intact or ruptured). Labour was induced with 2-hourly oral misoprostol solution, 20 µg for the first three doses, then increased to 40 µg repeated 2-hourly until adequate contractions were achieved. Once uterine activity became adequate no further misoprostol was given. If contractions subsequently became inadequate, labour augmentation with hourly misoprostol solution was to be started at 5 µg, increasing to 10 and then 20 µg, and repeated until adequate uterine contractions occurred.

RESULTS

The pilot study using the above dosages included 25 women due for labour induction for hypertension (7), post-term pregnancy (8), impaired fetal growth (4), prelabour rupture of membranes (4), rhesus disease (1) and pruritus (1). The cervical score was < 7 in 18 women. The results are shown in Table I. The median dosage of misoprostol used was 150 µg (range 50 - 400 µg). Once labour was established, augmentation was not required in any case. The method was favourably received by the women and staff.

Table I. Results of labour induction with titrated oral misoprostol solution

Outcome	Number of women (N = 25)	% (95% CI)
Active labour within 12 hours	12	48 (28 - 69)
Active labour within 24 hours	23	92 (74 - 99)
Vaginal delivery within 24 hours	14	56 (35 - 76)
Vaginal delivery within 32 hours	18	72 (51 - 88)
Caesarean section	5	20 (7 - 41)
Uterine hyperstimulation	2	8 (1 - 26)

DISCUSSION

The results of this small pilot study have confirmed the wide range of individual responsiveness to misoprostol, supporting the principle of using small, frequent doses titrated against uterine contractions. The regimen chosen appeared to represent a reasonable balance between achieving effectiveness and avoiding excessive hyperstimulation.

On the basis of these results we are conducting a large randomised multicentre trial to assess the effectiveness and safety of this regimen compared with conventional dinoprostone vaginal gel, and at one centre with extra-amniotic Foley catheter bulb placement. Depending on the results, a further avenue of investigation may be the use of a single small dose of misoprostol vaginally for locally mediated effects on the cervix, followed by titrated oral misoprostol solution for fine-tuning of uterine contractions.

The importance of this report is that it shows that women usually respond to much smaller doses of misoprostol than are currently in common use, and to call again for caution in the use of misoprostol in the third trimester.

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