Induction of labour with intravaginal misoprostol in the second and third trimesters of pregnancy

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Objective. To confirm the effectiveness of misoprostol as a labour-induction agent.

Design and setting. One hundred and ten consecutive second- and third-trimester hospital patients. Patients with intra-uterine deaths (group A) received 100 µg misoprostol 4-hourly and those with live fetuses (group B) 50 µg misoprostol 4-hourly until labour commenced.

Subjects. Forty-eight patients in group A (group A1 second trimester 27, group A2 third trimester 21); 62 mainly hypertensive patients in group B.

Outcome measures. These were the amount of misoprostol required to induce labour; duration of induction and labour; success and completeness of vaginal delivery; neonatal outcome; and cost.

Results. In group A1, labour was successfully induced in 21/27 (77,8%) patients with 157,4 µg misoprostol; and in 19/21 (90,5%) patients in group A2 with 128,9 µg misoprostol. Cost per successful induction was R0,55 and R0,44 respectively. Mean induction times were 13,2 hours and 13,4 hours respectively. All patients delivered vaginally but incompletely in 7/21 group A1 and 1/19 group A2 patients. In group A2, the mean duration of labour was 5,97 hours. In group B induction was successful in 51/62 (82%) with 95,1 µg of misoprostol; the mean cost was R0,32. Twelve out of 51 (23%) received oxytocin and 44/51 delivered vaginally. Mean duration of induction was 11,4 hours and of labour 5,4 hours. Two babies had low Apgar scores. There were two stillbirths (perinatal mortality rate 39,2/1 000), both apparently unrelated to misoprostol.

Conclusions. Misoprostol is an effective, easy to use, apparently safe and cheap drug for the induction of labour.

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Misoprostol is a methyl analogue of prostaglandin E_1 and was introduced to protect the intestinal mucosa from peptic ulceration induced by non-steroidal anti-inflammatory drugs. It has also been used for the induction of abortions but there are few reports of its use in obstetrics. In 1987, Mariano-Neto *et al.*[1] reported successful induction of labour with oral misoprostol in cases of second- and third-trimester intra-uterine death. Other reports on the intravaginal route for induction of labour have shown that misoprostol alone is at least as good as prostaglandin preparations, either on their own or in combination with oxytocin.[2-4] Although hyperstimulation occurs more commonly, it does not seem to result in an increase in fetal distress.[3] All authors note how cheap misoprostol is. In South Africa, misoprostol has not yet been registered for use in obstetrics.

Patients and methods

This paper reports our experience of 110 consecutive inductions of labour with misoprostol. Group A comprised 27 patients with second-trimester (group A1) and 21 patients with third-trimester (group A2) intra-uterine deaths (IUDs). Group B included 62 patients in the third trimester with a variety of obstetric complications, mainly hypertension (Table I). In South Africa, misoprostol is available as a scored 200 µg tablet. Initially we had intended to use 100 µg for patients in group A and 50 µg for patients in group B. The restricted availability of the drug at one stage and the difficulty with division of the tablet into quarters meant that this policy was not strictly followed. The misoprostol was placed in the upper vagina, regardless of the ripeness of the cervix. If labour had not started within 4 hours the misoprostol was repeated to a maximum of four doses. At the discretion of the labour ward staff, oxytocin was used to augment labour. Otherwise, an intravenous drip was not routinely inserted. If the patient was not in labour within 12 hours of receiving the last dose of misoprostol, the treatment was considered a failure.

Table I. Group B — indications for induction

Hypertension	41
IUGR — no hypertension	2
Rupture of membranes	8
Diabetes	5
Antepartum haemorrhage	2
Postdates	1
Spurious labour	1
Non-reactive non-stress test	1
Thyroid cancer with stridor	1

IUGR = intra-uterine growth retardation.

Results

Labour was successfully induced in 21/27 (77,8%) of the group A1 patients and 19/21 (90,5%) of the group A2 patients (Table II). All successful inductions were achieved with two doses of misoprostol. None of the patients who received more than two doses went into labour. The mean induction time from the first tablet to delivery was just over 13 hours in both groups. The patients with second-trimester IUD were delivered in the general gynaecology ward and exact figures for the duration of labour were not available. In group A2 the mean duration of labour was just under 6

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hours. All group A patients aborted vaginally, but incompletely in 7/21 of group A1 and 1/19 of group A2.

In group B labour was successfully induced in 51/62 (82%). Twelve out of these 51 (23%) also received oxytocin and 44/51 (86%) delivered vaginally. The mean duration of induction was 11,4 hours and of labour 5,4 hours. Caesarean sections were performed in 7/51 (14%). The indications were cephalopelvic disproportion in 3, fetal distress in 2, and antepartum haemorrhage in 2. Two babies were delivered with 1-minute Apgar scores of 3 and 4. Both were easily resuscitated and discharged from the hospital in good condition. There were two stillbirths (perinatal mortality rate 39,2/1 000). The first patient was a 20-year-old primigravida at 34 weeks' gestation who was induced for hypertension. She received four doses of misoprostol. After 9 hours of labour an oxytocin infusion was started because of slow progress. After a further 9 hours fetal bradycardia was noted and the fetus died 1 hour later. She was delivered of a stillborn infant weighing 1 950 g. The second patient was a 23-year-old primigravida with hypertension at 35 weeks. She received two doses of misoprostol and after a $7^1/_2$-hour labour was delivered of a stillborn infant weighing 2 200 g with the umbilical cord wound tightly around the neck. The fetal heart had been heard just before the onset of the second stage but was not monitored during the delivery.

The only other complication in group B was a patient with puerperal psychosis requiring prolonged psychiatric treatment.

Discussion

Although misoprostol is not registered for use in obstetrics in South Africa the reports in international journals of its success and its nominal cost made us take an interest in the drug. We feel that the latter is particularly important in view of the increased need for cost-saving on drugs. Our previous approach to IUD in the second and third trimesters had been to use extra-amniotic prostaglandin $F_2\alpha$ followed by intravenous oxytocin. For the induction of labour in the third trimester with a live fetus we had previously used intravaginal dinoprostone tablets 1 mg 4-hourly or intracervical dinoprostone gel, depending on availability. Misoprostol required no elaborate storage, being stable at room temperature, even after the tablets were broken. This meant that one tablet could be shared between several patients. Some difficulty was experienced with the division of the 200 µg misoprostol tablet into quarters. It would be helpful if the drug could be prepared as either a 50 µg or a scored 100 µg tablet to overcome this problem. The misoprostol fragment was easy to insert with a finger and the exact placement of the drug in the vagina appeared to be unimportant. It was noted in several patients that at the time of subsequent insertions the piece of tablet previously inserted seemed not to have changed at all. Presumably the active prostaglandin is absorbed without the base having to be dissolved first. Misoprostol effectively induced labour with an overall success rate of 80%, irrespective of the ripeness of the cervix. We experienced very few problems with the drug and it was apparently safe. Sanchez-Ramos *et al.*[3] reported hyperstimulation of the uterus and advised that in such cases the drug be removed from the vagina and

Table II. Results

	Group A (IUD)				Group B (alive)	
	A1 — 2nd trimester		A2 — 3rd trimester			
	All	Induced	All	Induced	All	Induced
No. of patients	27	21 (77,8%)	21	19 (90,5%)	62	51 (82%)
Gestation (wks)	14 - 27		28 - 39		33 - 43	
Parity	0 - 6		0 - 6		0 - 8	
Misoprostol (µg)						
(mean ± SD)	170,4 ± 62,4	157,4 ± 59,6	145,2 ± 80	128,9 ± 56,9	102,4 ± 49,5	95,1 ± 43,4
Range (µg)	50 - 300	50 - 200	50 - 400	50 - 200	50 - 250	50 - 250
Doses	x 1 - 3	x 1 (8 patients) x 2 (13 patients)	x 1 - 4	x 1 (11 patients) x 2 (8 patients)	x 1 - 4	x 1 (25 patients) x 2 (24 patients) x 3 (1 patient) x 4 (1 patient)
First dose to delivery (h)						
Mean ± SD		13,2 ± 9,3		13,4 ± 8,9		11,4 ± 7,5
Range		0,9 - 40,6		1,5 - 32		1,1 - 39,9
Labour (h)						
Mean ± SD		—		5,97 ± 3,2		5,4 ± 2,9
Range		—		1,5 - 13,5		1,0 - 32
Cost (SA rand) per induction		0,55		0,44		0,32

IUD = intra-uterine death; — = no figures available.

uterine relaxants given. Even with the small doses of misoprostol that we used, there was often rapid onset of contractions. Two patients in group A and one in group B had induction-delivery intervals of less than 2 hours. As is the case with other uterine stimulants, we feel that this suggests an unpredictable sensitivity to misoprostol and that even 50 µg might be too large a starting dose. Perhaps 25 µg would be a more appropriate dosage but it would be difficult to obtain from the current 200 µg tablet. Fletcher *et al.*[4] used a single dose of 100 µg misoprostol but their induction success rate appears to be lower than ours. It is possible that a regimen of repeated smaller doses of misoprostol is more effective. Sanchez-Ramos *et al.*[3] recommended giving up to 12 repeat doses to a maximum of 600 µg of misoprostol. However, our experience suggests that if labour is not induced with two applications there may be little point in continuing with the drug. Some patients seem to be resistant to misoprostol.

Although we ascribe the two stillbirths to poor intrapartum monitoring and not to the drug, we feel that the fetal safety of misoprostol has not been conclusively proved by this small study. We urge caution and the use of frequent fetal monitoring during the induction and particularly at the commencement of the second stage of labour. We do not consider the caesarean section rate of 14% high for a group with such obstetric complications.

The potential cost-savings associated with a change to misoprostol are considerable. The cost per induction for the 110 patients in this report was only 43 cents. For the cost of one induction of labour by our previous regimen, we could induce 120 patients with misoprostol. Even the cost of induction of labour with a 5 U oxytocin drip was 30 times more expensive. These cost comparisons are for government hospital contract prices and the comparison with prices in private hospitals is even more favourable to misoprostol.

Misoprostol is clearly a powerful drug; it produces contractions in early and later pregnancy and, as we had the impression that the amount of blood lost at delivery was less than normal, during the puerperium as well. We suggest that research into the uses of misoprostol might be extended to assess its value in the augmentation of labour, the management of the third and fourth stages of labour and postpartum haemorrhage.

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