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Obstetric use of misoprostol: innovations, evidence, controversy and global health perspectives

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Obstetric use of misoprostol: innovations, evidence, controversy and global health perspectives

G J Hofmeyr

Volume 2

Short Report

Limb reduction anomaly after failed misoprostol abortion

G J Hofmeyr, D Milos, V C Nikodem, M de Jager

Case report

A 42-year-old woman, para 5, gravida 6, was admitted to Coronation Hospital on 2 June 1997. She reported vaginal bleeding for the past month and draining of amniotic fluid for 2 days. She had had 5 normal deliveries, the last having been of twins, and her 6 children ranged in age from 8 years to 18 years. Her last menstrual period had been on 25 November 1996. She, her husband and 3 of her children had been born with an extra digit on one or both hands. The past medical history was otherwise non-contributory.

The patient gave the following history relevant to the current pregnancy. In March 1997 pregnancy had been diagnosed by a general practitioner, and she had gone to her local hospital to request termination of pregnancy in terms of the newly promulgated Act. An ultrasound scan confirmed pregnancy of about 13 weeks' duration. Termination of the pregnancy was attempted with misoprostol tablets, one inserted vaginally on 4 consecutive days. On the 4th day some vaginal bleeding occurred. One week later she was admitted to the hospital for sterilisation. A minilaparotomy was performed under general anaesthesia, and after the operation she was informed that the sterilisation had not been performed because she had been found to still be pregnant. She had decided not to make any further attempt at termination of the pregnancy.

On the patient's admission to Coronation Hospital on 2 June, her general condition was found to be good. The uterus was soft and non-tender and the symphysis-fundus measurement was 24 cm. Vaginal examination with a speculum confirmed drainage of non-offensive amniotic fluid and slight bleeding. Ultrasound examination revealed a breech presentation with measurements corresponding to 26 weeks' gestation, an estimated fetal weight of 970 g and greatly reduced amniotic fluid volume, which made detailed assessment for fetal anomalies difficult.

The patient was counselled about the risks of ruptured membranes at this gestational age, and the option of induction of labour, but she requested conservative management. She was treated with prophylactic antibiotics and steroid therapy to promote fetal lung maturity. Her condition was monitored with temperature charting, daily cardiotocography and alternate-day leucocyte counts and C-reactive protein estimations. No clinical or laboratory evidence of amnionitis was detected. Ultrasound examinations on 16 June and 24 June showed persistent severe oligohydramnios and estimated fetal weights of 1 100 and 1 135 g, respectively.

On 26 June the patient reported reduced fetal movements. Cardiotocography showed reduced fetal heart rate variability and repetitive fetal heart rate decelerations. Because of suspected fetal compromise, caesarean section was performed under spinal analgesia. A female infant was delivered as a breech, with good Apgar scores. She had an extra digit on each hand, and the right lower limb was absent below the knee (Fig. 1). Mother and infant were discharged from the hospital in good condition. The child was to return for orthopaedic care.

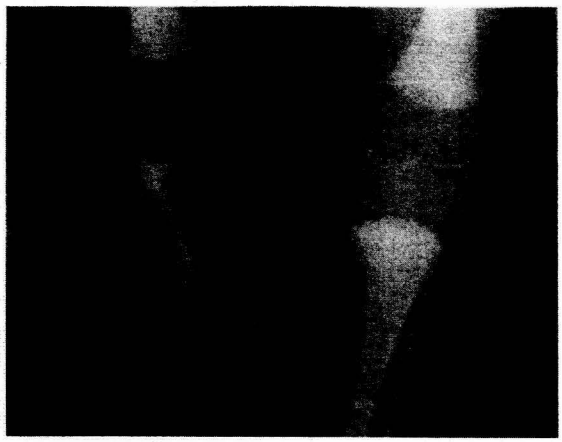

Fig. 1. Radiograph of the infant described in this report, showing below-knee limb reduction anomaly of the right leg after a failed attempt at abortion with misoprostol.

Commentary

This is to our knowledge the first reported case in South Africa of limb reduction anomaly in a surviving infant following failed abortion. Limb reduction has been well described as a teratogenic effect of misoprostol administration. Although we do not have documentation of the sequence of events in early pregnancy, which were based on the history given by the patient, the typical nature of this unusual anomaly is highly suggestive of misoprostol teratogenicity.

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 also an effective abortifacient, both alone and following pretreatment with RU-486.[1] Its widespread use in Brazil[2,3] resulted in the identification of teratogenic effects,[4] particularly limb reduction defects such as was seen in our case, following unsuccessful attempts to terminate pregnancies.

It is vital that health workers using misoprostol for termination of pregnancy be aware of these risks, and

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counsel their clients in detail about the teratogenic effects and the need to complete the termination of pregnancy once it is embarked upon.

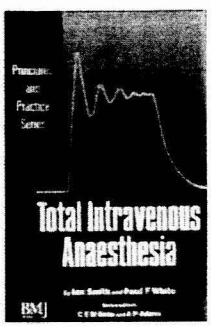
Misoprostol has become an integral part of the primary care pregnancy termination services in South Africa. There is an urgent need for the health authorities to issue guidelines on its use regarding dosage, complications and counselling, and indemnity for doctors and nurses who use it according to these guidelines for unregistered indications such as pregnancy termination.

REFERENCES

1. Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991; **338**: 1233-1236
2. Schonhofer PS. Misuse of misoprostol as an abortifacient may induce malformations. Lancet 1991; **337**: 1534-1535
3. Coelho HLL, Misago C, da Fonseca WVO, Sousa DSC, de Araujo JML. Selling abortifacients over the counter in pharmacies in Fortaleza, Brazil. Lancet 1991; **336**: 247
4. Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. Lancet 1993; **341**: 1258-1261
5. Coelho HLL, Teixeira AC, Santos AP, et al. Misoprostol and illegal abortion in Fortaleza, Brazil. Lancet 1993; **341**: 1261-1263
6. Fonseca W, Alencar AJC, Mota FSB, Coelho HLL. Misoprostol and congenital malformations. Lancet 1991; **338**: 56
7. Gonzalez CH, Vargas FR, Perez AB, et al. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. Am J Med Genet 1993; **47**: 59-64

Accepted 27 Feb 1998

Total Intravenous Anaesthesia



Ian Smith & Paul White
February 1998, paperback, 234 x 156 mm, 168 pp, R242

This is a straightforward and accessible introduction to the basic concepts of total intravenous anaesthesia, providing definitions, historical perspectives, basic principles, and an overview of the drugs, their interactions, and the equipment used.

Amply illustrated with clear black and white line diagrams and photographs, this text shows the applications of intravenous anaesthesia in a variety of situations. Subjects covered include: types of intravenous anaesthesia, pharmacokinetics and pharmacodynamics of drugs used in total intravenous anaesthesia, use of intravenous anaesthesia techniques in special patient populations, and the future of intravenous anaesthesia.

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STUDENT PAPER

A peripheral hospital can be fulfilling — for staff and patients alike

Teboho Lekhanya

S S Gida Hospital, Keiskammahoek, Eastern Cape, is a modern 220-bed hospital. It serves a map radius of 7 km and about 120 000 people. There are currently 5 doctors who, in addition to outpatient department (OPD), ward and theatre duties, make monthly visits to the hospital's 20 community clinics.

The OPD serves an average of 76 patients per weekday (range 33 - 112 for 19 February to 6 March 1996). The patients are seen by nursing sisters, UCT student interns and the doctors. Over the past few years, all of the doctors and most of the UCT students have been non-Xhosa speakers.

Aim of the survey

S S Gida is, in many respects, strategically placed to meet the South African government's primary health care initiative. However, because of its very remote location it is shunned by South African doctors. The aim of the survey was: (*i*) to explore patients' perceptions of the service being offered at S S Gida and the factors that contribute thereto; (*ii*) to determine the extent to which S S Gida is treating patients holistically, based on the patients' own opinions; and (*iii*) to make recommendations on how S S Gida (and other peripheral hospitals) can improve services so as to meet the primary health care initiative.

Methodology

A total of 30 adult patients seen in the OPD over 2 successive days were interviewed according to a questionnaire (Table I) via an interpreter who had rehearsed the questionnaire with the researchers.

Findings and discussion

Although the sample of patients was very small for statistical significance, certain points on the patient profile are worth commenting on:

1. There is a predominance of female patients. This is consistent with a survey done in the Western Cape by

Department of Medicine, University of Cape Town

Teboho Lekhanya as: *6th-year medical student*

This is a report of a survey conducted at S S Gida Hospital, Keiskammahoek, Eastern Cape, by T Lekhanya, F Mohideen and S Mullajee — all 6th-year medical students at UCT at the time.

Trends in maternal deaths from Obstetric Haemorrhage in South Africa 2008-2010

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Abstract

The most recent report on Maternal deaths in South Africa for 2008-2010 shows that there has been a significant increase in the number of maternal deaths (32.4%) due to obstetric haemorrhage and the Institutional Haemorrhage Maternal Mortality Ratio has increased from 18.8/100000 live births in 2005-2007 to 24.9/100000 live births in 2008-2010. This article is an abridged version of the chapter on the 688 maternal deaths from obstetric haemorrhage mentioned in the above report.

The chapter identifies priority provinces (Mpumulanga, Limpopo, Free State and North West) and priority problems (bleeding associated with caesarean section, abruptio placentae and ruptured uterus) for particular attention. Bleeding during and after caesarean section accounted for 26.2% of deaths due to obstetric haemorrhage, occurring most commonly in public hospitals particularly district and regional. Obstetric haemorrhage continues to be the most common avoidable cause of maternal death; 81% of the deaths having been assessed as avoidable. Resuscitation was sub-optimal in 22.3% of cases where it was attempted and the cases had sufficient information to assess.

Vignettes are presented to illustrate the numerous administrative problems and examples of poor quality of care. Interventions at different levels of care and by different stakeholders are discussed.

Introduction

During the triennium 2008-2010, 688 deaths from obstetric haemorrhage were reported to the National Committee for Confidential Enquiry into Maternal Deaths (NCCEMD), making obstetric haemorrhage the third most common cause of death accounting for 141 % of total deaths.' This proportion shows little change from 12.4% during 2005-2007. If denominator data for live birth estimates from DHIS data are used then the obstetric haemorrhage related maternal mortality ratio (MMR) for the current triennium (2008-2010) was 24.9 deaths per 100, 000 live births compared to 18.8 for the previous (2005-2007). It is very disappointing that it has increased, especially since the NCCEMD has focussed on this as a problem.

Globally obstetric haemorrhage remains a major cause of direct maternal death especially in poorly resourced settings.[1] It is an obstetric complication which particularly tests the accessibility and functioning of the health system because it's severity deteriorates so rapidly and prompt effective action can be life saving. Obstetric haemorrhage cannot always be prevented but antenatal and intrapartum assessment which enables women at risk to be transferred from clinic to hospital should allow delivery to take place in a hospital with more opportunities for resuscitation and arresting haemorrhage. Also antenatal detection and treatment of anaemia and chronic illnesses such as HIV can improve maternal health before the onset of labour. In addition active management of the third stage of labour contributes to a reduced risk of PPH. The two pillars of management of severe obstetric haemorrhage are aggressive resuscitation and various treatment modalities to arrest the haemorrhage. There are well known medical and surgical treatments for the different causes of obstetric haemorrhage, which can be implemented at each level of care. These are described in detail in the PPH monograph produced by the NCCEMD in 201[0.3] Support by a regionalised tiered maternity system with good transport systems for referrals of women with severe haemorrhage is also essential.

The 688 maternal deaths from obstetric haemorrhage were all assessed in detail by the provincial assessor teams composed of obstetricians, midwives and anaesthetists; and also reviewed by the NCCEMD members responsible for writing the haemorrhage chapter of the National Saving Mothers report for 2008-2010. These deaths will now be described in more detail and the data compared with the previous triermium.

Maternal Mortality ratio related to haemorrhage

Overall Maternal Mortality Ratio (MMR)

In the current triennium, the number of maternal deaths from obstetric haemorrhage and the MMR from haemorrhage are higher than in any other triennium with 688 deaths and an institutional MMR of 24.9 deaths per 100,000 live births.

Table 2b compares the IvIMR from each causal subcategory in 2008-2010, with MMRs for 2005-2007,

Table 2b: Comparison of causes with previous triennium

	2008-2010		2005-2007	
	No	MMR	No	MMR
Trauma (90% due to Bleeding at/after Csection)	200	7.2	141	5.5
Abruptio placenta	110	4.0	48	1.9
Ruptured uterus	108	3.9	80	3.1
"Other PPH"	103	3.7	n/a	
Retained/adherent placenta	81	2.9	88	3.4
Atonic uterus	44	1.6	67	2.6
"OtherAPH"	25	0.9	18	0.7
Placenta praevia	13	0.5	13	0.5
Inverted uterus	4	0.1	7	0.2
TOTAL	**688**	**24.9**	491	**18.8**

The proportions of deaths and MMRs due to uterine atony and retained placenta have decreased when compared to the previous triennia. The decrease in uterine atony needs to be interrogated further. It could be that some previously categorised in this group are now put into the 'PPH-non bleeding associated with CS. This was a marked increase from the 2002-2004 triennium where 'other uterine trauma' accounted for 17.6% of haemorrhage deaths. The current 2008-2010 report shows that 29.1% of deaths were due to 'other uterine trauma' (ie cervical, vaginal and CS associated) but is able to disaggregate the data more accurately and it is now clear that the predominant problem is 'bleeding after caesarean section'. Most of these women had inadequate surgical haemostasis during the CS either due to uterine atony, lower segment tears, or bleeding from the placental site. They then bled postoperatively, either as a revealed PPH or intra abdominally. A preliminary folder analysis of the women who died from CS associated bleeding indicates that many of the CS were performed for appropriate indications such as cephalopeivic disproportion and two previous CS. Fequentl y the CS was done too late when labour had become obstructed and *I* or where the second stage had proceeded for too long. However there were several CS done where they may have been unnecessary such as for 'fetal distress' when only early decelerations were recorded

The final cause of death for women who died from haemorrhage was hypovolaemic shock (88.7%) and disseminated intravascular coagulopathy (24.9%). These women bled to death,

Utilisation of antenatal care

Table 3 shows that 80.1% of women attended for antenatal care. Of note, 93.4% and 90% of women who died from uterine n.rnture

Um7ga	77	*172*	*368*
h West	78	11 3	459
Northe;m Cape	13	1.9	21 0
		ZA	
Total	**688**	100.0	24.91

MMR=number maternal deaths per 100,000 live births

Table 1b Provincial comparisons of haemorrhage related L!MR between triennia

Province	*MMR haem* 2008-2010	*MMR haem* 2005-2007
Eastern Cape	28.4	*22.4*
Free State	41.7	42.3
Gauteng	22.4	18.3
KwaZulu-Natal	17.1	14.7
Limpopo	29.2	20.9
Mpumalanga	38.3	18.1
North West	45.9	14.1
Northern Cape	21	23.8
Western Cape	73	9.5
Total	24.9	**18.8**

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***reflecting* msufflcient *attempts* to *ascertain* the** *cause.*

Table 2a shows the causal subcategories of haemorrhage

Table 2a: Distribution of sub-categories of maternal deat!'.s **from obstetric haemorrhage**

Obstetric Haemorrhage	*2008-2010* N=688	*2008-2010* %	*2005-2007* N=491	
bruption with hypertension	47	6.8	13	
- Abruption without hypertension	63	9.2	35	
- Placenta praeia	13	1.9	13	
Other API-I not specified	25	3.6	18	3.7
- Ruptured uterus with previous c/'8	4T	d	sr	? 5
- Ruptured uterus without previous c/s	61	8.9	43	8.8
- Retained placenta	62	9.0	74	15.1
- Morbidly adherent placenta	19	2.8	14	2.9
- Uterine atony	44	6.4	67	13.6
- Vaginal trauma	9	1.3		
- Cervical trauma	11	1.6	141	28.7
- Bleeding during Caesarean section	30	4.4		
- Bleeding after Caesarean section	150	21.8		
- Inverted uterus	4	0.6	7	1.4
- other PPH-non specified	103	15	n/a	

women; mostly due to abruptio placentae, ruptured uterus and prolonged labour. This means that, in half the cases, the family experienced a double bereavement; that of the mother and the baby.

Table 4: Perinatal outcome for women who died from obstetric haemorrhage

Per/natal outcome	*N*	*%*
Survivors	337	49.0
Stillbirths	246	35.8
NND	19	2.8
Miscarriage and ectopic	14	2.0
Undelivered	72	10.5

Level of care where haemorrhage related deaths occurred

The majority of haemorrhage deaths (94.2%) occurred at public hospitals; 37.8% at level one (district), 36.2% at level two (regional) and 20.2% at level 3 (tertiary) hospitals. Private hospitals accounted for 1.6% of haemorrhage maternal deaths and primary care clinics for 3.6%. District Health Information System (DHIS) data for South Africa shows that 20.1% of all deliveries occur at CHCs, 41% at level one hospitals, 27.5% at level 2 hospitals and 11.6% at level 3 hospitals. This shows that there is some referral upwards of such patients but the majority of haemorrhage deaths occur at district and regional public hospitals, where the workload is greatest.

The deaths associated with haemorrhage at CS occurred as follows: Level one hospital - 60 (33.3%)%; Level two - 73 (41%); Level three - 40(22.2%). This is similar to the proportions, shown from DHIS statistics, of total CS done at each level of care i.e. Level one - 35.9%; Level two - 42.9%; Level three -21.2%. This suggests that women who die from haemorrhage associated with CS die at the same level at which the CS was performed.

Considering proportions of deaths from different subcategories within each level of care, it was found that for CHCs (n25), PPH non-specified (48% of deaths at this level of care), retained placenta (16%) and uterine rupture without previous CS (12%) were the most frequent causes of haemorrhage death. For all levels of hospital and private sector hospitals, bleeding after CS **was** the most frequent cause of death for that level of care followed by abruptio placentae (all hospitals) and ruptured uterus (public hospitals). District hospitals had a larger proportion of deaths from retained placenta and PPH - non specified, than level two or three hospitals.

Avoidable factors for maternal deaths due to obstetric haemorrhage

The provincial assessor teams assessed the maternal deaths due to haemorrhage and Table 5 shows the distribution of avoidable factors for assessable maternal deaths.

At patient/community level there were 33.6% of assessable cases with avoidable factors, and at administrative level there were 55.3%. For health worker related care there were avoidable factors in 52.2% of assessable cases at district health facilities, 51.5% at regional hospitals and 25.7% at tertiary hospitals - In addition, there were problems with resuscitation in 47.5%. These statistics cannot be directly compared with those of 2005 - 2007 because for that year APH and PPH were assessed separately. Nevertheless it appears that the overall proportion of cases with avoidable factors has not changed since the previous report.

Table 5: Distribution of avoidable factors, missed opportunities and sub-standard care for deaths from obstetric haemorrhage

Category	*Assessable cases (n)*	*% of avoidable factors in assessable cases*
Patient orientated	648	33.6
Administrative factors	665	55.3
Health worker related emergency management problems		
Primary level	644	52.2
Secondary level	363	51.5
Tertiary level	331	25.7
Resuscitation	621	47.5

Patient related factors (Table 6)

These are factors operating at the level of the patient, her community and the socio - political context in which she lives. There were a few women who delivered at home, had a retained placenta and then had considerable delays in getting to a health facility. Since the Confidential Enquiry is predominantly institutional, these factors are the least investigated or understood. In the absence of detailed community inquiry, it is conjectural to explore reasons for non booking (11.6%) and delayed presentation (14.8%), which are the most frequent avoidable factors in this category. Presumably poverty, long distances, lack of knowledge, lack of community support structures and income generating responsibilities are all factors that could be contributory. There were two women from the Jehovah's Witness faith with abruptio placenta who declined blood transfusion.

Table 6: Distribution of patient orientated avoidable factors for haemorrhage deaths

Descntion	*Number*	*Percentage of assessable deaths*
Lack of information	44	
No avoidable factor	430	66.4
No antenatal care	75	11.6
Infrequent antenatal care	35	5.4
Delay in accessing medical help	96	14.8
Declined medication/surgery/advice	20	3.1
Family problem	1	0.2
Community problem	2	0.3
Unsafe abortion	1	0.2
Other	19	2.9

Administrative related avoidable factors (Table 7)

Table 7: Distribution of administrative related avoidable factors for haemorrhage deaths

Description	*Number*	*Percentage of assessable deaths*
Lack of information	30	
No avoidable factor	297	44.7
Transport problem: Home to institution	16	2.4
Transport problem: Institution to institution	73	11.0
Lack of accessibility: Bafflers to entry	5	0.8
Lack of accessibility: Other	3	0.5
Delay initiating critical care (Overburdened service)	39	5.9
Lack of health care facilities: IOU	41	6.2
Lack of health care facilities: Blood/blood products	88	13.2
Lack of health care facilities: Other	18	2.7
Lack of appropriately trained staff: Doctors	130	19.5
Lack of appropriately trained staff: Nurses	71	10.7
Communication problems: Technical	5	0.8
Communication problems: Interpersonal	14	2.1
Other	58	8.7

Administrative related avoidable factors were more frequently documented than patient related factors; the most frequently cited problems were:

- Transport problems between institutions (11%); this was documented less than in the previous triennium. However it remains an important limiting factor with many district hospitals not having on site emergency transport.

many of the district hospitals where these women died.

This CS was probably unnecessary; the 4 hour delay in performing it meant that it became a difficult second stage procedure. As ifiustrated also in case 4, the patient should not have been sent to the ward with such a low BP and still bleeding, but there was no nurse in the recovery area to monitor her.

Case 2. Insufficient nursing staff and non-availability of doctors

14yr old primigravida - Arrived at maternity ward *of* a level one hospital two days after booking for antenatal care. She was in active labour with absent fetal hearts and an undiagnosed multiple pregnancy. At the time of her admission there was one midwife who, in addition to her, was attending to seven other referrals from the clinics.

Three hours later, she delivered twin stillbirths, 3 minutes apart. Severe vaginal bleeding noted. All three doctors called could not come for various reasons, one was a private doctor and was busy in OPD, the second indicated she was not the one on call, the third was on call but was far away from the hospital

The nurse resuscitated the patient with iv fluids and one unit of emergency blood but the patient demised 2 hours later; the private doctor having arrived 15 minutes before she died.

Comment: There were insufficient midwives to deal with the workload; the midwife was not confident in adult resuscitation.

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proportion of deaths from retained placenta ana'FFff- non

ZWoidable (actors fox maternal deaths due to obstetric haemorrhage

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Delay in accessing medical help	96	14.8
Declined medication/surgery/advice	20	3.1
Family problem	1	0.2
Community problem	2	0.3
Unsafe abortion	1	0.2
Other	19	2.9

Comment: Consideration should be given to making MROP part of the competencies of midwives especially retrieving it from the cervical os once separated. The district hospital should have had a functional theatre for Manual Removal of Placenta (MROP) so that the patient did not need to be referred. The junior doctor doing the MROP was not confident or skilled with this procedure and should have called for specialist help. After the MROR there was ongoing bleeding and the patient should have been returned to theatre for balloon tamponade to reduce placental site bleeding or laparotomy.

Health worker related avoidable factors (Tables 8 and *9)*

The pattern and ftquency of avoidable factors at different levels of care is shown in Table 8; It is similar to the previous triennium and occurred in a lower proportion of level three facility deaths than level two or one.

Substandard care was the most frequently cited problem occurring in 24.4% of assessable cases at level one, 32.2% at level two and 17.8% at level three. Problems with recognition of severity or making a diagnosis were more common at level one (20%) and level two (19.8%) than level three (7.6%). In particular the diagnosis of uterine rupture was often missed, even at caesarean section where posterior ruptures were not detected. Delay in referring patients and managing them at an inappropriate level was a problem occurring at level one in 16.6% and 12.3% of cases respectively. This occurred particularly with cases of abruptio placentae. Incorrect management referred to several patients with abrupfio placenta and an PhD who were taken for C Section and bled severely during the CS, and incorrect use of misoprostol for labour induction which will be discussed later.

Many of the women who died from CS associated bleeding had bled during the CS and there was inadequate control of haemostasis; in some further uterotonics were needed; in others especially those with atonic uterus following obstructed labour or with abruptio placenta - a B Lynch suture could have been inserted. Of great concern is the very suboptimal post CS monitoring observed for most of the deaths as illustrated in the following case. Guidelines for post CS monitoring were recently published by the NCCEMD in the South African Medical journal.'

Case 4. Inadequate Post CS monitoring

28 P2 G3 admitted with eclampsia to district hospital.

2100: C section performed by medical officer

2200: In Recovery area - BP 89/56, pulse 110. PV bleeding noted, Sent to ward

2300: Arrived in ward BP 86/49, P110. Still bleeding vaginally. Observation chart completed with plan for next observations to be done at 0600.

0500: Found gasping; in pool of blood: died.

Comment: The patient was unstable in recovery and should not have been sent to the ward. The attendant did not recognise signs of shock and call a doctor and the planned schedule of observations was too infrequnt. A doctor should have been called to assess the patient and decide about further uterotonics or relook laparotomy

When signs of hypovolaemic shock and anaemia were detected, there were several cases where no doctor came to assess the patient but gave verbal instruction over the phone for administration of fluids/ blood rather than instructing or implementing interventions to look for the cause and arrest the bleeding. In particular, concealed intra abdominal bleeding was frequently not detected post CS; pads were checked but not the abdomen. This is illustrated by the following case.

Case 5. Inadequate response to bleeding after CS

17 POG 1 with prolonged second stage at district hospital

Failed forceps; NO theatre facility available

Tiansferred by ambulance to another district hospital. Pre-op haemoglobin 1 lgms/dl

Difficult C Section. Blood loss of 1 litre recorded. Poor documentation

Mother sent to postnatal ward; baby had hypoxic encephalopathy and was sent to nursery

1 hr post CS ; pale & tachycardic - given emergency blood as per doctor's telephonic advice

5hrs post CS ; Hb 4gms.BP 80/40. Pulse a30/min. Patient very pale . More blood given as directed telephonically by doctor.

7 hours post CS; Died.

Comment.' District hospitals that perform assisted vaginal deliveries should have functional theatres. The doctor should have come to assess this patient with ongoing intra abdominal bleeding and arranged to do a re-look laparotomy.

In terms of treatment of uterine atony, there still appears to be reluctance by midwives, doctors and anaesthetists to use either syritometrine or ergomethne. Oxytocin infusion and 600mcgrns rectal misoprostol appear to be the main uterotonics given. The

Table 8: Distribution of health worker related avoidable factors missed opportunities and sub-standard care

Medical management problems	*1° Level*		*2° Level*		*3° Level*	
	N	*%*	*N*		*N*	*%*
Initial assessment	44	6.8	23	6.3	4	1.2
Problem with recognition / diagnosis	129	20.0	72	19.8	25	7.6
Delay in referring the patient	107	16.6	18	5.0	0	0.0
Managed at inappropriate level	79	12.3	10	2.8	0	0.0
Incorrect management (Incorrect diagnosis)	42	6.5	17	4.7	8	2.4
Sub-standard management (Correct diagnosis)	157	24.4	117	32.2	59	17.8
Not monitored / Infrequently monitored	39	6.1	26	7.2	11	3.3
Prolonged abnormal monitoring with no action taken	52	8.1	30	8.3	14	4.2
Assessable cases	644		363		331	

latter in particular is inferior to ergometrine in reducing bleeding and should preferably be given sublingually in a dose of 400mcgms to minimize side effects. Management algorithms clearly indicate that ergometrine should be the second line agent unless the woman is hypertensive or cardiac. This protocol is frequently not followed, resulting in many women having insufficient uterotomc therapy especially at Cs.

Case 6. No diagnosis of cause of PPH and no treatment to stop bleeding

23y1s, para 0. On AZT, anaemic during pregnancy (Hb 8grris/dl).

Normal vaginal delivery at district hospital with 1 Ounits oxytocin given im for third stage

PPH. Treated with 20units oxytocin infusion and 600mcmgs rectal misoprostol. One unit emergency blood.

Died en route to regional hospital

Comment: Attempts should have been made to find the cause of the PH-I and stop it before transferring. No ergometrine was given. The patient should have had an EUA to inspect for retained products and cervical tears and further measures such as balloon tamponade or laparotomy with uterine compression sutures to stop the bleeding. Telephonic advice from the regional hospital to the district could have given better advice before transfer.

Several of the women who died from ruptured uterus with no history of prior CS, had been induced for an Intrauterine demise (1131)) with misoprostol. In some cases excessive doses, such as 400mcgms, were given in the third trimester and in others repeat doses were given despite contractions. In women with an IUD, monitoring is often less frequent and no cardiotocograins (CTG5) used because there is no live fetus to monitor. However this reduced vigilance of monitoring sometimes means that signs of hyperstimulation and subsequent rupture are missed. The following case illustrates this:

Case Y. Excessive dose of misoprostol causing uterine rupture

40yrs, para 4 with IUD at 39weeks, breech. IOL with 1 Oomcgms misoprostol pv. at 1 700hrs

Infrequent monitoring,

Contracting at 1900.

Found dead at 0200. Post Mortem showed ruptured uterus.

Comment: The dose of misoprostol administered was four times too high and vaginal. In addition there was very inadequate monitoring of this mother so the uterine rupture was not detected prior to her death.

In addition some women with viable pregnancies were induced with inappropriately high doses of misprostol and/or given repeat doses when contractions had already started.

Review of the deaths from uterine rupture suggest extreme caution must be observed for induction using misoprostol with strict adherence to low dosage regimens and dosing schedules. Non pharmacological methods of cervical ripening and induction such as intracervical Foley's catheter procedures should be promoted, especially where frequent surveillance can not be performed.

The problem of "Too Little Too Late" was illustrated by many cases in which additional surgical measures such as uterine balloon tamponade, uterine compression sutures and uterine artery ligation were not performed. Hysterectomy is the last resort measure for saving lives due to obstetric haemorrhage. was performed in 17.9% of these women; often done too late. Earlier recourse to hysterectomy may have saved many of thesE women's lives. Junior doctors faced with severe bleeding associated with C section who are not confident to do a hysterectomy and in whom other modalities have failed, can try applying a uterine tourniquet such as a rubber foleys catheter tied around the lower part of the body of the uterus (as is done at myomectomy); this can reduce bleeding during subsequent transfer to higher level of care. Research is needed on this procedure which currently is being reported in South Africa with some success.

The above vignettes, together with Table 8, indicate that much work still needs to be done in improving the quality of care and effectiveness of care provided by health workers across the levels of care but particularly in level one and two facilities,

Table 9 indicates that there were avoidable factors related tc the resuscitation in nearly half (47.5%) of cases where resuscitation was attempted. In 74.1% of this group the problem was with the circulation, ie inadequate fluid and/or blood resuscitation. it is concerning that for 92 women (13.3%) resuscitation was not attempted. This suggests arrival at a facility too late for any attempt at resuscitation or, patients being discovered 'dead in their beds' having had a major bleed that was unrecognized due to inadequate monitoring.

Table 9: Distribution of problems with resuscitation in obstetric haemorrhage deaths

Resuscitation problems	*Number*	*% where resuscitation attempted*	*Distfibudon of problems in resuscitation*
Lack of information	70		
No avoidable factor	276	52,5	
Airway problems	6		2.1
Breathing problems	16		5.5
Circulation problems	215		74.1
Drug problems	6		2.1
Investigation problems	12		4.1
Monitoring problems	35		12.1
Resuscitation not attempted	92		

Table 10 shows the overall avoidability of deaths from haemorrhage when administrative and health worker related factors are combined; ie only health system factors are considered .There was suboptimal care in 85.6% of deaths; 28.5% were possibly avoidable and a large number of 52.2% were probably avoidable (i.e. different care would reasonably have expected to make a difference to the outcome). This way of classifying health system avoidable factors differs from the previous report where a categorisation of 'clearly avoidable' was used. If a composite of possibly and probably avoidable factors in the current report is seen as equivalent to 'clearly avoidable' in the previous report then, for 2008-2010 the proportion was 80.7 % compared to over 80% 'clearly avoidable' for 2005 - 2007. Thus haemorrhage deaths remain, after anaesthesia, the deaths most frequently assessed to be

avoidable by assessors. This means that addressing health system failures which contribute to deaths from haemorrhage must be an absolute priority for policy makers, health managers and health workers.

Table 10: Distribution of avoidability for maternal deaths from obstetric haemorrhage

Percent per disease category	*N*	%
No suboptimal care	99	14.4
Suboptimal care, different management would have made no difference to the outcome	34	4.9
Suboptimal care, different management might have made a difference to the outcome	196	28.5
Suboptimal care, different management would reasonably have been expected to have made a difference to the outcome	359	52.2

Discussion

It is very disappointing that the MIvIR due to obstetric haemorrhage has increased, despite it being highlighted as a major problem in the previous report. Important interventions initiated by the NCCEIvID with the Department of Health to address this problem include: ESMOE training (2009), posters on PPH management for labour wards and theatre (2010), and the PPH monograph (2010). This was distributed through much of the country with training at the end of 2010. The latter initiatives would not yet have been expected to have had an



Review of the deaths from uterine rupture suggest extreme caution must be observed for induction using misoprostol with snot adherence to low dosage regimens and dosing schedules.

pharmacological methods of cervical ripening and ±ction such as intracervical Foley's catheter procedures sb:uld be promoted, especially where frequent surveillance car be performed.

:e problem of "Too Little Too Late" was illustrated by many n which additional surgical measures such as uterine

workers prescribing excessive doses of misoprostol for IOL, especially of IUDs, in the third trimester; and the women with abruptio placenta and IUD who are taken for C section instead of allowing vaginal delivery. The large number of women dying after C section is due to a combination of poor attempts to secure haemostasis at the CS; poor use of uterine compression sutures, and very infrequent monitoring with failure to act on deteriorating vital signs. There appeared to be a reluctance of doctors when phoned to actually come and assess such patients and reluctance to take them back to theatre. it is not possible from the folders to ascertain whether non availability of doctors was due to short staffing or lack of professionalism.

There are many useful published guidelines for the stepwise management of severe obstetric haemorrhage. References for the WHO guidelines, RCOG guidelines and Canadian Society Obs/GYN guidelines are given below [56]. In South Africa there are also Comprehensive Guidelines for management of obstetric haemorrhage can be found in the PPH monograph produced by the NCCEMD in 2010. The challenge is to implement them. This requires actions from a variety of role players at different levels of care and in different fields of expertise as indicated in the following section.

Interventions required at different levels to reduce deaths from haemorrhage

In addition to a focus on priority provinces and priority conditions, the assessment of avoidable factors leads to the following recommendations for actions by different role players.

Patient level! community: Community health workers need

have expected to make a difference to the outcome). This way of classifying health system avoidable factors differs from the previous report where a categorisation of 'clearly avoidable' was used. If a composite of possibly and probably avoidable factors in the current report is seen as equivalent to 'clearly avoidable' in the previous report then, for 2008-2010 the proportion was 80,7 % compared to over 80% 'clearly avoidable' for 2005 - 2007. Thus haemorrhage deaths remain, after anaesthesia, the deaths most frequently assessed to be

District maternal and child health teams: Provincial and district maternal and child health teams which ideally include an obstetrician, advanced midwife, family physician and primary care nurse should actively engage in outreach and participate in audit meetings. They must provide ESMOE training and scenario training ('drills') for haemorrhage, particularly at CHCs, MOUs and level one hospitals. Ongoing skills training in resuscitation, caesarean section and procedures to arrest haemorrhage must be provided to all doctors to ensure competence. Purpose designed monitoring charts for monitoring vital signs and blood loss after delivery but particularly after CS need to be designed and introduced with early warning signs colour coded. This has been done with good effect in the UK.[9]

Medical and Nursing Training schools; ESMOE training to be continued. Resuscitation skills and Emergency management of obstetric haemorrhage all need to be seen as core competencies for the student to achieve before qualifications. The new proposed scope of practice for midwives, which is still under discussion with South African Nursing Council, prescribes manual removal of placenta and adult resuscitation as a core competency,this needs further discussion for practicality feasibility and implementation.

Relevant research by academic centres into newer solutions such as: use of uterine tourniquet as a temporising method, use of prophylactic ergometrine at CS'° and tranexanñc acid for ongoing bleeding at CS", would inform policy and protocols.

Health workers: The PPH monograph' and algorithms for PPH after vaginal delivery, and after CS must be available for adequately staffed labour wards.

3. Emergency transport to be onsite for transfers from distric hospitals.
4. Clinical managers to ensure implementation of PPH monograph, ESMOE skills training, PPH drills and early warning monitoring charts. A particular focus on skills to perform C section safely is required.
5. Facility auditing of severe PPH and display of trends by graphs/charts in labour wards and theatres.
6. Use of misoprostol for induction of labour to be closely monitored and all health care providers to be trained on correct use so as to prevent uterine rupture. Foley catheter induction to be promoted as a safer method.
7. Avoid performing CS for abruptio placentae with an intra-uterine death, and without appropriate indications.
8. Syntometrmne or ergomeirine to be used as second line treatment for uterine atony in preference to misoprostol, unless contraindicated; and to be considered for prophylaxis at CS.
9. Monitoring after C section, complicated NVD, and manual removal of placenta to be improved in terms of frequency of observations and action on abnormal observations; this to be facilitated with early warning monitoring charts. At risk women to be monitored in a special care area.
10. All women with blood loss in excess of i000mIs need to be immediately assessed by a doctor.

References

Saving Mothers 2008-2010. The fifth report of the National Committee for Confidential Enquiry into Maternal Deaths in South

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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, selectively binding to EP-2/EP-3 prostanoid receptors.

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 resulted in the identification of teratogenic effects, particularly limb reduction defects, 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 800 women admitted to hospital with abortion complications in Rio de Janeiro, 456 reported using misoprostol.[2] 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*[3] described uterine tachysystole (excessive uterine activity with misoprostol use at term), which appeared unrelated to dosage.

In this journal, Merei *et al*[4] reported a series of 60 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 they described 345 inductions with live fetuses and 66 with intra-uterine death. There was 1 unexplained maternal death, 2 uterine ruptures (1 of these patients had had a previous caesarean section), 6 caesarean sections for fetal distress and 1 for uterine hyperstimulation, and 10 perinatal deaths.

The conclusion from a recent meta-analysis[5] 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 1.60 – 4.04). More recently, we have reviewed 21 reported randomised trials of vaginal misoprostol for induction of labour.[6] 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,[7] 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[8] and 50 µg 4-hourly for induction of labour[9] 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.[10] 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 urgent, needed coupled with indemnity against complications which may be associated with its use within these guidelines.

Support from the South African Medical Research Council is acknowledged.

G J Hofmeyr

Debate

Heart scanner — who's between a rock and a hard place?

I am a radiologist with a minor shareholding in the electron beam computed tomography (EBCT) scanner discussed by Ina van der Linde,[1] and feel compelled to comment on its implied imminent demise.

Officialdom throughout the world demonstrates certain traits. Words such as self-righteous, retention of control and red tape spring to mind. They make endless rules which, when analysed, translate into self-empowerment and protection of their domain. South Africa in particular personified this in its apartheid system. I believe that a similar dynamic is at work in regard to the fate of EBCT.

The expensive EBCT scanner was imported after assurance was received from the Radiology Society of South Africa (RSSA) that conventional CT radiology codes could be used for EBCT studies. At that time everyone including the RSSA said that as EBCT was the only machine capable of detecting and measuring coronary artery calcification a new code specific to this facet should be applied for. This was done, and the EBCT machine was ordered and subsequently installed in the Pretoria Heart Hospital in mid-1997. Events orchestrated by officialdom resulted in the August 1997 *Guide to Fees* printing code 3598 for 'EBCT assessment of coronary artery calcification' with *no* unit and *no* rand values. The days of old-fashioned non-transparent *kragdadigheid* tactics are seriously challenged when new official sleight-of-hand reaches such heights. Not only are there no rand values, but hey presto, the 311,60 units given to code 3598 by MASA in June 1997 have also disappeared. A barrage of warnings has also emanated from the same officials, namely that code 3598 must be used for tracking purposes only, and I thought the pass laws were scrapped! So that procedures using this technology cannot be charged under existing codes. Hence Ina van der Linde's article heading 'Heart scanner miracle?' and her comment 'does all this leave the HeartScan S4 team between a rock and a hard place?'

To throw more light on the subject I will provide some background information. EBCT can perform conventional CT examinations. However its ability to perform CT scans approximately 10 times faster than conventional scanners gives EBCT unparalleled advantages where rapid image acquisition is necessary, such as after trauma and in paediatric patients. For example, a brain scan can be performed in 3 seconds, avoiding the necessity of sedating or anaesthetising a child for a diagnostic procedure. CT angiography and organ perfusion analyses are examples where the extremely rapid acquisition time of EBCT, together with the use of less contrast medium, is distinctly advantageous. Does RAMS realise this? They seem determined to throw the EBCT baby, but with the bathwater.

At present the abilities of EBCT are undoubtedly misused in cardiac analysis, where prior to EBCT implementation planning needed non-invasive cardiac imaging. EBCT's high exposure time with and without intravenous

TITRATED ORAL MISOPROSTOL SOLUTION — A NEW METHOD OF LABOUR INDUCTION

G Justus Hofmeyr, Baron B Matonhodze, Zarko Alfirevic, Elizabeth Campbell, Marinda de Jager, Cheryl Nikodem

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.

S Afr Med J 2001; 91: 775-776.

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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.

We acknowledge support from the University of the Witwatersrand, the South African Medical Research Council and Liverpool University, UK.

References

1. Hofmeyr GJ. Misoprostol in obstetrics and gynaecology — unregistered, dangerous and essential. *S Afr Med J* 1998; 88: 535-536.
2. Keirse MJNC. Prostaglandins in preinduction cervical ripening: Meta-analysis of worldwide clinical experience. *J Reprod Med* 1993; 38: 1 suppl, 89-98.
3. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). In: The Cochrane Library, Issue 2, 2001. Oxford: Update Software.
4. Alfirevic Z, Howarth G, Gausmann A. Oral misoprostol for induction of labour with a viable fetus (Cochrane Review). In: The Cochrane Library, Issue 2, 2001. Oxford: Update Software.
5. Wagner M. Misoprostol (Cytotec) for labor induction: a cautionary tale. *Midwifery Today* 2001; 49: 31-33.
6. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; 90: 88-92.

Accepted 27 December 2000

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British Journal of Obstetrics and Gynaecology
September 2001, Vol. 108, pp. 952–959

Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial

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Objectives To determine the effects of titrated oral misoprostol solution, compared with vaginal dinoprostone.

Study design Open, randomised clinical trial.

Setting Academic hospitals in South Africa and Liverpool, UK.

Methods Women undergoing induction of labour after 34 weeks of pregnancy were allocated by randomised, sealed opaque envelopes, to induction of labour with titrated oral misoprostol solution, or two doses of vaginal dinoprostone (2mg) administered six hours apart. Failure to deliver within 24 hours of randomisation was the primary outcome on which the sample size was based. The data were analysed by intention-to-treat.

Results Six hundred and ninety-five women were randomly allocated: 346 to oral misoprostol and 349 to vaginal dinoprostone. There were no significant differences in substantive outcomes. Vaginal delivery within 24 hours was not achieved in 38% of women in the oral misoprostol group and 36% in the vaginal dinoprostone group (RR 1.08; 95% CI 0.89-1.31). The caesarean section rates were 16% and 20%, respectively (RR 0.80; 95% CI 0.58-1.11). Hyperstimulation with fetal heart rate changes occurred in 4% of women in the oral misoprostol group and 3% after vaginal dinoprostone (RR 1.32, 95% CI 0.59–2.98). The response to induction of labour in women with unfavourable cervices was somewhat slower with misoprostol when membranes were intact, and with dinoprostone when membranes were ruptured. There were no differences in neonatal outcome between the two groups.

Conclusions This new approach to oral misoprostol administration was successful in minimising the risk of uterine hyperstimulation, which has been a feature of misoprostol use for induction of labour, at the expense of a somewhat slower response in women with intact membranes and unfavourable cervices. Misoprostol is not registered for use in pregnant women, and further research is needed to confirm optimal and safe dosages.

INTRODUCTION

Induction of labour is a common intervention during pregnancy in both developing and developed countries. In the UK in 1994/1995, 19.5% of women had labour induced[1], which corresponds to approximately 130,000 women each year. Licensed pharmacological methods used for induction of labour, mostly vaginal prostaglandins, are expensive and require cold storage making them unsuitable for resource poor settings. Cheaper alternatives which are stable at room temperature may have the potential to produce substantial cost savings in developed countries and allow safe induction of labour in those countries which currently cannot provide pharmacological induction of labour.

Misoprostol is a unique prostaglandin E_1 analogue which is rapidly absorbed orally. Tablets, marketed for anti-inflammatory drug-induced gastric ulceration, are stable and inexpensive. The use of misoprostol in pregnancy has been reviewed recently[2]. Several randomised trials of induction of labour with misoprostol have been undertaken[4–10]. In most trials, the vaginal route has been chosen, presumably because this route has been most successful for other prostaglandins and because misoprostol has a far longer half-life when administered vaginally than orally[3]. However, the short half-life of oral misoprostol may be an advantage in induction of labour, given the varying responses of women to prostaglandins and the danger of uterine hyperstimulation.

Previous randomised trials of oral misoprostol have used a fixed dosage regimen administered four to six hourly[4–8], 100-200μg three-hourly[9], or 100μg vaginally followed by 100μg orally two-hourly[10]. In November 1999 the American College of Obstetricians and Gynecologists provided guidelines to their members on the use of misoprostol for cervical ripening and induction of labour[11]. The manufacturers have acknowledged the

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PII: S0306-5456(01)00231-5

role of doctors in prescribing an approved pharmaceutical product for use outside its approved indication[12]. The Cochrane Review[13] on the topic remains inconclusive because widely varying dosage regimens have been used and the studies to date have been far too small to address the issue of safety. We have emphasised the dangers of misoprostol, particularly in larger dosages, and the need for large studies to confirm safety. Our review in this journal[14] has attracted criticism because of our view that misoprostol should not be recommended for widespread use before more controlled evidence of safety is available[15].

In this study, in order to allow for individual sensitivity and the short half-life of oral misoprostol, we planned to use small doses at frequent intervals, increasing the dosage when necessary. Following completion of a small dose-finding pilot study[16], we carried out a randomised controlled trial of the effectiveness of titrated oral misoprostol solution and dinoprostone for induction of labour in the third trimester of pregnancy.

METHODS

Women due for induction of labour with a singleton pregnancy and cephalic presentation were asked to participate. The exclusion criteria were: gestation less than 34 weeks, significant antepartum haemorrhage, previous caesarean section, uncontrolled diabetes mellitus, severe pre-eclampsia or eclampsia and fetal distress. All eligible women were asked to sign a written consent form. The local research ethics committees approved the study protocol.

To allocate treatment, the next in a series of sealed, consecutively numbered opaque envelopes was taken from one of four dispensers, depending on whether the membranes were ruptured and whether the cervix was favourable (modified Bishop score >6)[17]:

1. membranes intact/cervix unfavourable;
2. membranes intact/cervix favourable;
3. membranes ruptured/cervix unfavourable;
4. membranes ruptured/cervix favourable.

The envelopes were prepared remote from the study sites by one author (P.B.), using a computer-generated list of allocations. Allocations were balanced between groups using random block sizes (between two and six). Each envelope was numbered sequentially and contained the appropriate management protocol. During the analysis the allocation recorded on the data form was cross checked with the lists held at Oxford. The woman's name was entered in a register with the number of the envelope before opening the envelope. The management protocol included in the envelope was followed unless clinical imperatives dictated otherwise. When labour commenced, electronic fetal heart rate monitoring was used whenever feasible. The study was not placebo controlled, therefore women and clinicians were aware of the allocated treatment. The treatment protocols were as follows:

1. Misoprostol

The smallest preparation of misoprostol available in trial countries was a 200μg tablet. For induction of labour a starting dose of 20μg was required. To overcome the problem of breaking the 200μg tablet into small fragments, we dissolved the tablet in 200ml water (1μg per mL), shaking the solution well before each administration. At the South African sites, tap water was used, and the same bottle used till finished (maximum 12 hours). At the Liverpool site, sterile water was used and the solution made up freshly for each administration. The solution was administered orally every two hours until adequate uterine contractions occurred (three per 10 minutes lasting 30 seconds) and then stopped. The initial dosage of 20mL (20μg) was increased to 40μg after two (Liverpool) or three doses (South African sites). The timing and strength of contractions was assessed by regular abdominal palpation. If the contractions became inadequate, augmentation of the active phase of labour was attempted with hourly titrated oral misoprostol (1μg/mL solution) escalating the dose from 5ml to 10ml and, 20ml (maximum). If uterine contractions were judged to be adequate, the next dose of misoprostol was omitted.

2. Conventional method

Dinoprostone (Prandin, prostin gel) 2mg was inserted into the posterior vaginal fornix and repeated after six hours if the contractions were not adequate. If labour was not established after a further 12 hours, or contractions became inadequate, an oxytocin infusion was commenced with syntocinon at 2miu per minute, increasing if necessary to 4miu, 8miu, 16miu or 32miu per minute.

At the South African sites, women with intact membranes were randomly allocated to three groups, the third being for induction of labour with an extra-amniotic Foley catheter bulb. The results of this comparison will be reported separately.

Artificial rupture of the membranes was performed at the discretion of the person attending the woman. The South African centres followed a conservative policy because of the high prevalence of HIV infection.

Tachysystole (>5 contractions per 10 minutes for at least 20 minutes) or hypersystole (a contraction lasting at least two minutes) were initially diagnosed by combination of abdominal palpation and cardiotocography. These conditions were managed conservatively with the woman being placed in the left lateral position with continuous

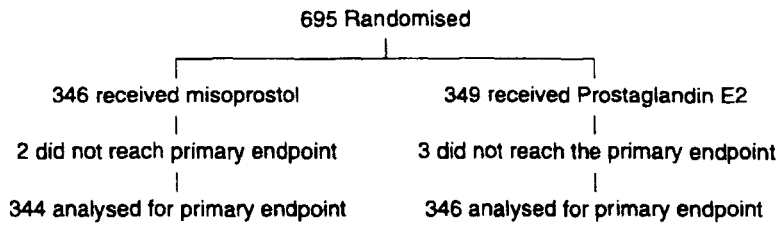


Fig. 1. Trial profile.

fetal heart rate and contraction monitoring. Artificial rupture of the membranes was avoided if possible.

Hyperstimulation syndrome (tachysystole or hypersystole with fetal heart rate abnormality) was managed by changing to the left lateral position, oxygen administration by face mask and if considered necessary, tocolysis (intravenous hexoprenaline or ritodrine).

Statistical considerations

The sample size calculation was based on the incidence of the primary outcome — failed vaginal delivery — within 24 hours, of 58% in the dinoprostone groups reported in randomised trials of vaginal misoprostol compared with dinoprostone[14]. To detect a reduction to 45% with 95% certainty and 90% power would require 324 women in each group.

Data were entered into Epi-info 6 or Excel at the recruiting sites and analysed independently using SPSS. Differences between groups were expressed as relative risks with 95% confidence intervals. Pre-specified subgroups for analysis were by membrane status, cervical status and country. Comparison by country was considered necessary because of anticipated differences in patient populations (more high risk women at the South African sites), and management (more conservative policy to membrane rupture at the South African sites), and because of minor differences in the misoprostol induction regimen (see above).

RESULTS

The number of women randomised was 695. The trial Profile is shown in Fig. 1. Data were not kept on women excluded from participation. The characteristics of women at trial entry are shown in Table 1. Post-term pregnancy (41%), prelabour rupture of membranes (17%) and hypertension (16%) were the most common indications for induction of labour at all three sites. Most women had intact membranes and an unfavourable cervix at the time of trial entry ($n = 443$, 64%) of whom 48%

Table 1. Characteristics of women at trial entry expressed as n (%), mean [SD] or median [interquartile range]. IOL = induction of labour; POH = past obstetric history; PROM = premature rupture of the membranes. Denominators are given when data are missing.

	South Africa		Liverpool		Combined	
	Misoprostol	**Dinoprostone**	**Misoprostol**	**Dinoprostone**	**Misoprostol**	**Dinoprostone**
No. randomised	211	220	135	129	346	349
Age (years)	27.7 [6.4]	27.1 [6.1]	26.4 [6.4]	27.3 [5.7]	27.2 [6.4]	27.2 [5.9]
Missing	1	3			1	3
Gestation (weeks)	39.4 [2.2]	39.2 [2.5]	40.2 [1.8]	40.2 [2.0]	39.7 [2.1]	39.6 [2.4]
Missing	1	3			1	3
Previous pregnancy ≥24 weeks	132/210 (63)	134/217 (62)	45 (33)	48 (37)	177/345 (51)	182/346 (53)
Primary indication for IOL						
Impaired growth	17 (8)	22 (10)	4 (3)	10 (8)	21 (6)	32 (9)
Post-term	88 (42)	97 (44)	55 (41)	48 (37)	143 (41)	145 (42)
Hypertension	48 (23)	39 (18)	14 (10)	9 (7)	62 (18)	48 (14)
POH	12 (6)	10 (5)	4 (3)	3 (2)	16 (5)	13 (4)
PROM	36 (17)	41 (19)	20 (15)	22 (17)	56 (16)	63 (18)
Other	9 (4)	9 (4)	38 (28)	37 (29)	47 (14)	46 (13)
Not known	1 (0)	2 (1)	0 (0)	0 (0)	1 (0)	2 (1)
Cervical score (Bishops)						
<7	145 (69)	146 (66)	125 (93)	123 (95)	270 (78)	269 (77)
Median	5 [4-7]	5 [4-7]	4 [3-5]	4 [3-5]	5 [4-6]	5 [4-6]
Missing	1	3			1	3
Membranes ruptured	36 (17)	41 (19)	24 (18)	24 (19)	60 (17)	65 (19)
Not known	3 (1)	5 (2)	1 (1)	0 (0)	4 (1)	5 (1)

Table 2. Outcomes expressed as *n* (%), mean [SD] or median [interquartile range]. FHR = fetal heart rate; CS = caesarean section.

	South Africa		Liverpool		Combined		Combined RR (95% CI) or Mean difference (95%CI)
	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	
No. randomised	211	220	135	129	346	349	
Primary outcome							
Vaginal delivery not achieved <24h	78 (37)	77/217 (35)	55 (41)	46 (36)	133 (38)	123/346 (36)	1.08 (0.89-1.31)
Secondary outcomes							
1. Labour:							
Cervical score unchanged after 12h[a]			17/105 (16)	12/84 (14)	17/105 (16)	12/84 (14)	1.13 (0.57-2.24)
Randomisation to labour							
Interval (min)	819 [524]	547 [470]	784 [533]	782 [1599]	805 [527]	636 [1053]	169 (44-294)
Missing	4	7			4	7	
Amniotomy	44/210 (21)	37/217 (17)	59 (44)	76 (59)	103/345 (30)	113/346 (33)	0.91 (0.73-1.14)
Oxytocin augmentation	13/210 (6)	47/217 (22)	37 (27)	67 (52)	50/345 (14)	114/346 (33)	0.44 (0.33-0.59)
Misoprostol augmentation	22/210 (10)	0	36 (27)	1 (1)	58/345 (17)	1/346 (0)	58.2 (8.1-417.6)
Fetal blood sampling	2/210 (1)	0	15 (11)	17 (13)	17/345 (5)	17/346 (5)	1.00 (0.52-1.93)
Vaginal bleeding	5/210 (2)	6/217 (3)	14 (10)	16 (12)	19/345 (6)	22/346 (6)	0.87 (0.48-1.57)
Uterine activity							
Tachysystole	14/193 (7)	14/205 (7)	9 (7)	4 (3)	23/328 (7)	18/334 (5)	1.30 (0.72-2.37)
Hypersystole	1/193 (1)	1/205 (0)	1 (1)	0 (0)	2/328 (1)	1/334 (0)	2.04 (0.19–22.4)
Hyperstimulation with FHR changes	10/193 (5)	9/205 (4)	3 (2)	1 (1)	13/328 (4)	10/334 (3)	1.32 (0.59-2.98)
Epidural or opioid	57/210 (27)	67/217 (31)	117 (87)	113 (88)	174/345 (50)	180/346 (52)	0.97 (0.84-1.12)
2. Delivery							
Mode of delivery							
CS	29/210 (14)	46/218 (21)	25 (19)	22 (17)	54/345 (16)	68/347 (20)	0.80 (0.58-1.11)
Instrumental delivery	5/210 (2)	6/218 (3)	19 (14)	22 (17)	24/345 (7)	28/347 (8)	0.86 (0.51-1.46)
Indication for operative delivery							
Delay	14/210 (7)	28/217 (13)	17 (13)	15 (12)	31/345 (9)	43/346 (12)	0.72 (0.47-1.12)
Fetal distress	15/210 (7)	20/217 (9)	17 (13)	20 (16)	32/345 (9)	40/346 (12)	0.80 (0.52-1.25)
Other	5/210 (2)	3/217 (1)	11 (8)	9 (7)	16/345 (5)	12/346 (3)	1.34 (0.64-2.78)
Randomisation to delivery interval	980 [618-1634]	825 [450-1498]	1125 [734-1680]	954 [589-1448]	1030 [673-1646]	855 [505-1466]	115 (-26.8-257)
Missing	1	3	0	0	1	3	

[a] These data collected in Liverpool only.

Table 3. Maternal side effects and complications expressed as *n* (%), mean [SD] or median (interquartile range).

	South Africa		Liverpool		Combined		Combined RR (95% CI) or
	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	Mean difference (95%CI)
No. randomised	211	220	135	129	346	349	
Side effects							
Mild shivering	76/210 (36)	74/217 (34)	4 (3)	0 (0)	80/345 (23)	74/346 (21)	1.08 (0.82–1.43)
Severe shivering	2/210 (1)	3/217 (1)	0 (0)	1 (1)	2/345 (1)	4/346 (1)	0.50 (0.09–2.72)
Vomiting	35/210 (17)	32/217 (15)	7 (5)	2 (2)	42/345 (12)	34/346 (10)	1.24 (0.81–1.90)
Any side effects	94/210 (45)	97/217 (45)	20 (15)	4 (3)	114/345 (33)	101/346 (29)	1.13 (0.91–1.41)
Blood loss at delivery >500ml	51/210 (24)	51/218 (23)	18 (13)	20 (16)	69/345 (20)	71/347 (20)	0.98 (0.73–1.31)
Maternal complications							
Ruptured uterus	0	0	0	0	0	0	
Sepsis	0	0	0	0	0	0	
Pyrexia >38C	1/210 (0)	2/218 (1)	7 (5)	1 (1)	8/345 (2)	3/347 (1)	2.68 (0.72–10.03)
Retained placenta	1/210 (0)	2/218 (1)	5 (4)	0	6/345 (2)	2/347 (1)	3.02 (0.61–14.85)
Other	6/210 (3)	9/218 (4)	8 (6)	4 (3)	14/345 (4)	13/347 (4)	1.08 (0.52–2.27)
Hospital stay >5 days	2/210 (1)	1/218 (0)	16 (12)	13 (10)	18/345 (5)	14/347 (4)	1.29 (0.65–2.56)

were primiparous. Eighteen percent of women had intact membranes and a favourable cervix (55 primiparous and 71 multiparous women); 9% of women had ruptured membranes and an unfavourable cervix (40 primiparous and 22 multiparous women) while 9% of women had ruptured membranes and a favourable cervix (24 primiparous and 38 multiparous women). All demographic and other characteristics at trial entry were balanced between the groups and between the sites.

Of the women in the oral misoprostol group, 38% did not achieve vaginal delivery within 24 hour compared with 36% after vaginal dinoprostone (RR 1.08; 95% CI 0.89-1.31) (Table 2). There were fewer caesarean sections, a longer time to delivery and a greater incidence of uterine tachysystole with misoprostol, but differences were not statistically significant. There were no differences in clinically important uterine hyperstimulation, maternal complications (Table 3) or neonatal outcomes (Table 4). In particular there was no increased incidence of shivering with the doses of misoprostol used in this trial. The main outcomes by membrane and cervical status are shown in Table 5.

Kaplan Meier survival curves showing time from trial entry to delivery in the pre-specified subgroups show a statistically significant earlier delivery in the dinoprostone group for women with an unfavourable cervix and intact membranes (Fig. 2). For women with an unfavourable cervix and ruptured membranes, delivery occurred earlier in the misoprostol group (Fig. 3), although this may have been due to a greater number of caesarean sections (Table 5). When the cervix was favourable there was no statistically significant difference between misoprostol and dinoprostone in time to delivery, regardless of membrane status (Figs. 4 and 5).

DISCUSSION

Small, frequent, titrated oral doses of misoprostol were successful in avoiding the significant increase in uterine

Table 4. Neonatal outcomes expressed as *n* (%), mean [SD].

	South Africa		Liverpool		Combined		Combined RR (95% CI) or mean difference (95%CI)
	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	
No. randomised	211	220	135	129	346	349	
Birthweight	3101 [499]	3045 [547]	3470 [563]	3440 [659]	3246 [554]	3192 [620]	54 (-33.8–142)
Missing	1	3			1	3	
Apgar <7 at 5 mins	7 (3)	13 (6)	4 (3)	2 (2)	11 (3)	15 (4)	0.74 (0.34–1.58)
Not known	1 (0)	2 (1)	0 (0)	0 (0)	1 (0)	3 (1)	
NICU admission	4/210 (2)	6/217 (3)	5 (4)	8 (6)	9/345 (3)	14/346 (4)	0.64 (0.28–1.47)
Neonatal complications							
Perinatal death	1/210 (0)	1/218 (0)	0	0	1/345 (0)*	1/346 (0)	1.00 (0.06–15.97)
Seizures	1/210 (0)	0	0	0	1/345 (0)	0	
Sepsis	0	0	1 (1)	0	1/345 (0)	0	
Others	8/210 (4)	6/218 (3)	10 (7)	9 (7)	18/345 (5)	15/346 (4)	1.20 (0.62–2.35)

Table 5. Subgroup analysis by membrane and cervical status expressed as *n* (%) and relative risks (RR) and 99% CI.

	Membranes intact, cervix unfavourable			Membranes intact, cervix favourable			Membranes ruptured, cervix unfavourable			Membranes ruptured, cervix favourable		
	Misoprostol	Dinoprostone	RR (99% CI)	Misoprostol	Dinoprostone	RR (99% CI)	Misoprostol	Dinoprostone	RR (99% CI)	Misoprostol	Dinoprostone	RR (99% CI)
No. Randomised	223	220		62	66		29	33		32	30	
Vaginal delivery not achieved < 24h	104 (47)	90/219 (41)	1.13 (0.86–1.5)	15 (24)	17/64 (27)	0.91 (0.41–2.01)	11 (38)	11 (33)	1.14 (0.47–2.75)	3 (9)	5 (17)	0.56 (0.10–3.29)
CS	37 (17)	48 (22)	0.76 (0.46–1.26)	6 (10)	14/64 (22)	0.44 (0.14–1.43)	9 (31)	3 (9)	3.41 (0.70–16.7)	2/31 (6)	3 (10)	0.65 (0.07–6.19)
Uterine hyperstimulation with FHR changes	6/211 (3)	9/212 (4)	0.67 (0.18–2.55)	4/59 (7)	0		1 (3)	0		2/29 (7)	1/29 (3)	2.0 (0.09–43.8)

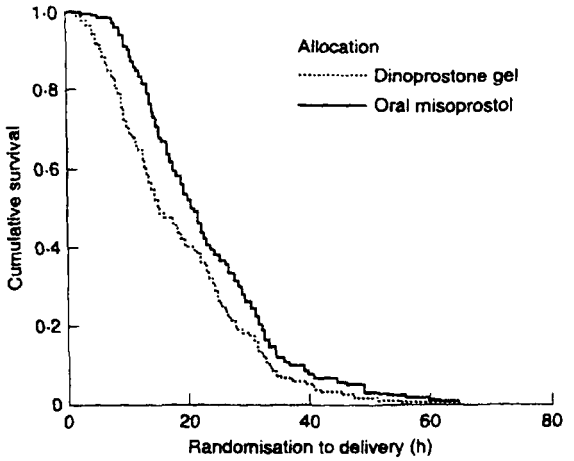


Fig. 2. Kaplan-Meier plot of time to delivery: membranes intact, unfavourable cervix (log rank test, $P = 0.001$).

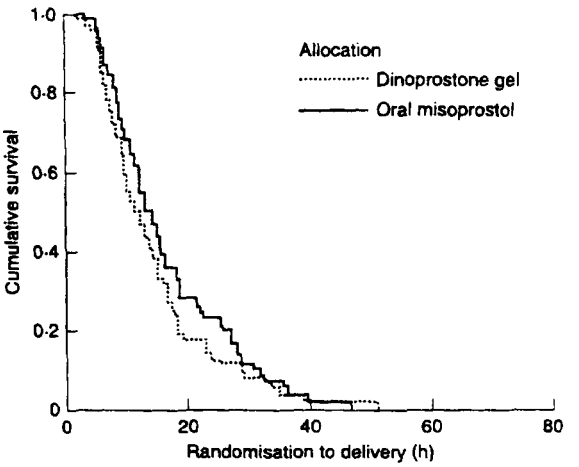


Fig. 4. Kaplan-Meier plot of time to delivery: membranes intact, cervix favourable (log rank test, $P = 0.270$).

hyperstimulation reported in previous studies, at the expense of a somewhat slower response in women with intact membranes and unfavourable cervices. A possible reason for the slower response in these women is the lack of a local effect on the cervix when misoprostol is administered orally rather than vaginally. However, there is a fine balance between the rapid response of vaginally administered misoprostol and the increased risk of uterine hyperstimulation in dosages exceeding 25μg four-hourly. More 'aggressive' regimens will undoubtedly result in shorter labours. This may appeal to women and clinicians only if safety for the mother and the baby is not compromised.

The external validity of our findings is enhanced by the fact that sites with different patient profiles were included and the results were similar between sites; and the fact that the great majority of women who met the entry criteria agreed to participate (exact numbers not recorded).

In our study women and clinicians were not blind to the allocated treatment. Therefore, events such as diagnosis of excessive uterine activity, decision to start syntocinon or to perform caesarean section were susceptible to bias. Such bias might operate in either direction, for example, early recourse to caesarean section because of anxiety about an experimental therapy, or delayed caesarean section because of enthusiasm for the new therapy.

The possibility of uterine rupture as a rare complication of induction of labour with misoprostol must be considered. A case of uterine rupture in a nulliparous woman following a single 100μg vaginal dose of misoprostol has been reported[18]. One trial of vaginal misoprostol for induction of labour in women with a

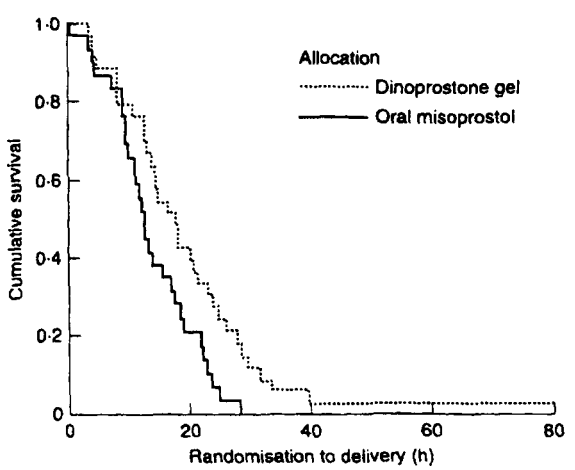


Fig. 3. Kaplan-Meier plot of time to delivery: ruptured membranes, unfavourable cervix (log rank test, $P = 0.015$).

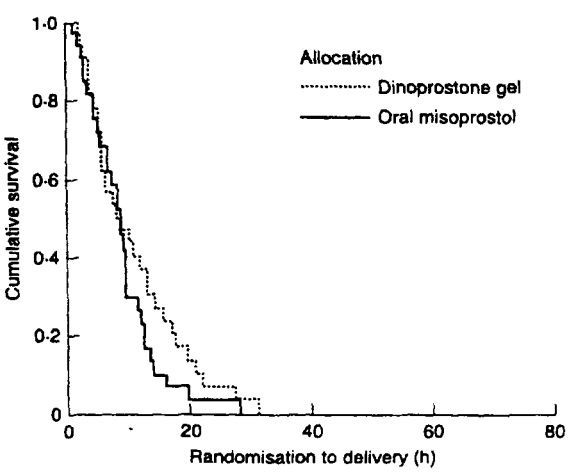


Fig. 5. Kaplan-Meier plot of time to delivery: ruptured membranes, favourable cervix (log rank test, $P = 0.217$).

previous caesarean section has been stopped prematurely because of dehiscence of the uterine incision in two of the first 17 misoprostol treated women[19]. The dosage of vaginal misoprostol used was conservative (25μg 6-hourly to a maximum of four doses). Two and three doses were used, respectively.

A possible solution to the problem of hyperstimulation is the use of a single, small vaginal dose to achieve the local effect in women with unfavourable cervices, followed by frequent, small titrated oral doses to 'fine-tune' the uterine response and minimise the risk of hyperstimulation. The titrated oral regimen used in this study was tolerated well by women and staff. However, a requirement by pharmacists to provide fresh solution every two hours at the Liverpool site proved to be cumbersome and time-consuming. Currently unavailable small dose tablets would make such a regimen much more appealing.

Whatever misoprostol regimen is tested in the future it should be assessed rigorously before it can be recommended for routine clinical practice. We believe that more randomised trials of various misoprostol regimens are needed. Ideally, they should be double-blinded. The real challenge ahead is to design sufficiently large induction of labour trials which will be acceptable to women and clinicians and will have the power to address the issues of safety, as well as effectiveness, in an unbiased fashion.

Acknowledgements

The authors would like to thank the nursing staff, midwives and women of Coronation, Chris Hani Baragwanath and Liverpool Women's Hospitals, and Professor C. J. van Gelderen of the Chris Hani Baragwanath Hospital. Ms S. Ayers provided statistical support. Elizabeth Campbell was funded by University of Liverpool and Liverpool Women's Hospital NHS Trust.

References

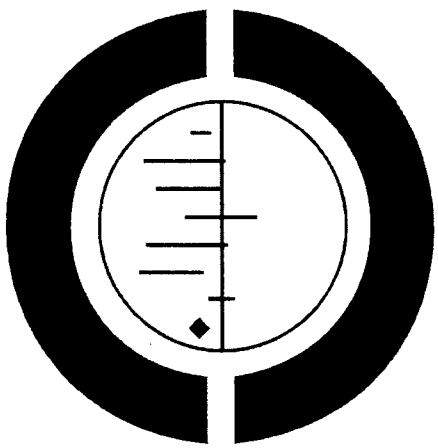
1. Department of Health. *NHS Maternity Statistics, England: 1989-90 to 1994-5*. London: HMSO. Statistics bulletin 1997/28, 1997:1–44.
2. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. *N Engl J Med* 2001;**344**:38–47.
3. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997;**90**:88–92.
4. Tessier F, Dansereau J. A double-blind randomised controlled trial comparing oral misoprostol to vaginal prostaglandin E2 gel for the induction of labour at or near term. *Am J Obstet Gynecol* 1997;**176**:S111.
5. Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. *Obstet Gynecol* 1997;**89**:392–397.
6. Adair CD, Weeks JW, Barrilleaux PS, Philibert L, Edwards MS, Lewis DF. Labor induction with oral versus vaginal misoprostol: a randomised, double-blind trial. *Am J Obstet Gynecol* 1998;**178**:S93.
7. Kwon JS, Davies GA, MacKenzie VP. A comparison of oral and vaginal misoprostol for induction of labour at term: a randomised trial. *Br J Obstet Gynaecol* 2001;**108**:23–26.
8. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labor induction. *Am J Obstet Gynecol* 1999;**180**:1155–1160.
9. Toppozada MK, Anwar MYM, Hassan HA, El-Gazaerly WS. Oral or vaginal misoprostol for induction of labour. *Int J Gynecol Obstet* 1997;**56**:135–139.
10. Kadanali S, Kucukozkan T, Zor N, Kumtepe Y. Comparison of labor induction with misoprostol vs. oxytocin/prostaglandin E2 in term pregnancy. *Int J Gynaecol Obstet* 1996;**55**:99–104.
11. Hale RW, Zinberg S. Misoprostol and pregnancy. *N Engl J Med* 2001;**344**:59–60.
12. Friedman MA. Manufacturer's warning regarding unapproved uses of misoprostol. *N Engl J Med* 2001;**344**:61.
13. Alfirevic Z, Howarth G, Gausmann A. Oral misoprostol for induction of labour with a viable fetus. In: The Cochrane Library, Issue 3. Oxford: Update Software, 1999.
14. Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review. *Br J Obstet Gynaecol* 1999;**106**:798–803.
15. Day L, Tailor A, Howard R, Burrell S. Misoprostol for induction of labour at term: Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Author's reply. *Br J Obstet Gynaecol* 2000;**107**:576–577.
16. Hofmeyr GJ, Matonhodze BB, Alfirevic Z, Campbell E, de Jager M, Nikodem C. Titrated oral misoprostol solution: a new method of induction of labour. *S Afr Med J* 2001. In press.
17. Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol* 1964;**24**:266–268.
18. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour in late pregnancy. In The Cochrane Library, Issue 2. Oxford: Update Software, 2001.
19. Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with previous cesarean delivery. *Obstet Gynecol* 1998;**91**:828–830.

Accepted 6 June 2001

6.

Methods for cervical ripening and labour induction in late pregnancy: generic protocol (Protocol)

Hofmeyr GJ, Alfirevic Z, Kelly AJ, Kavanagh J, Thomas J, Neilson JP, Dowswell T



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[Intervention Protocol]

Methods for cervical ripening and labour induction in late pregnancy: generic protocol

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: Amended to reflect a change in scope (see 'What's new'), published in Issue 3, 2009.

Citation: Hofmeyr GJ, Alfirevic Z, Kelly AJ, Kavanagh J, Thomas J, Neilson JP, Dowswell T. Methods for cervical ripening and labour induction in late pregnancy: generic protocol. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD002074. DOI: 10.1002/14651858.CD002074.pub2.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine, from the best available evidence, the effectiveness and safety of induction agents or procedures for third trimester cervical ripening and induction of labour.

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BACKGROUND

Induction of labour

Induction of labour may be considered beneficial in many clinical circumstances. These include fetal growth restriction (or other states of potential fetal compromise), spontaneous rupture of membranes, pre-eclampsia, and post-term pregnancy. The effects of induction of labour in some specific clinical situations are assessed in other Cochrane reviews (e.g. Boulvain 2001a; Gülmezoglu 2006; Irion 1999).

A review of the evidence-base for labour induction indications found that recommendations for induction of labour for post-term gestation, premature rupture of membranes at term, and premature rupture of membranes near term with pulmonary maturity are supported by evidence; induction for fetal growth impairment before term reduces intrauterine fetal death, but increases caesarean deliveries and neonatal deaths; evidence is insufficient to support induction for women with insulin-requiring diabetes, twin gestation, fetal macrosomia, oligohydramnios, cholestasis of pregnancy, maternal cardiac disease and fetal gastroschisis (Mozurkewich 2009). On the other hand, risk-guided preventive labour induction is claimed to improve birth outcomes (Nicholson 2009). Labour induction, for clinical indications, if performed, usually takes place during the third trimester of pregnancy (after 28 weeks).

Labour may also be induced for social reasons, e.g., to coincide with planned leave from work by the woman or her partner (Crosby 2008). Labour induction tends to be more common in women who live far from obstetric services (Kornelsen 2009).

Recently, emphasis has been placed on the value of avoiding elective delivery before 39 weeks' gestation due to increased rates of neonatal high care admissions (Clark 2009). A specific program to reduce early term elective deliveries has been found to be effective (Oshiro 2009), as has labour induction guidelines backed by medical staff education (Fisch 2009).

Labour induction in the evening (for example, at about 2100 hours) has been found to be associated with similar labour duration and improved neonatal outcome than that commenced in the morning (Bakker 2009).

Methods for inducing labour

When a woman and her caregivers agree that labour induction is necessary (or desirable), the best method of induction needs to be chosen. The main problems experienced during induction of labour are an inability to achieve effective labour, or the production of excessively strong uterine contractions. The latter may cause both maternal and fetal distress, and both problems may lead to an increased risk of caesarean section. Excessive uterine activity, through inappropriate use of uterine stimulants, may occasionally lead to the very serious complication of uterine rupture (and fetal death).

There is considerable variation in how women perceive induction of labour. At one end of the continuum are women who dislike the idea of induction intensely. At the other end of the continuum are women who welcome interventions to bring the birth of their baby forward. Whilst there are legitimate reasons to debate what is a desirable rate of induction of labour in any population of pregnant women, and whether in some settings this rate is much higher than it should be, that is not the objective of this protocol and its daughter reviews. These focus specifically on methods, not use and abuse.

There are several clinical factors which may influence the choice of induction method. These include parity, the condition of the cervix, membrane status, and presence or absence of a uterine scar (usually from a previous caesarean section).

Parity is important because women tend to be more sensitive (and sometimes much more sensitive) to stimulatory drugs if they have had a baby (or babies) previously. In a recent observational study, nulliparous women with an undilated cervix whose labours were electively induced had a 50% caesarean section rate (Clark 2009).

The state of the woman's cervix can be assessed by vaginal examination and 'scored' (Bishop 1964) to make a semi-quantitative prediction of 'favourability' for labour induction. Induction tends to be easier if the cervix is soft, dilated, and short (favourable/high cervical score) and more difficult if firm, closed and long (unfavourable/low cervical score). When the cervix is unfavourable, prostaglandin preparations are often used (Keirse 1993; MacKenzie 1997) although these may be particularly associated with uterine hyperstimulation (Egarter 1990). More recently, ultrasound measurements of cervical length and distance from the perineum to the baby's head have been suggested as additional parameters for assessment of cervical readiness (Eggebø 2009). Ultrasound measurement of cervical length and body mass index were found to be better predictors of caesarean section than the clinical cervical score (Uyar 2009).

Women whose membranes have already ruptured may respond differently to stimulatory drugs than those whose membranes are still intact at the time of labour induction. The drainage of amniotic fluid through the vagina may also flush out locally applied medication. The presence of a uterine scar carries a risk of dehiscence during labour, especially if uterine activity is excessive. Though uncommon, this is potentially a very serious complication that can pose a threat to the lives of both baby and mother.

There are many methods of labour induction that include administration of oxytocin; prostaglandins; prostaglandin analogues and smooth muscle stimulants, such as herbs or castor oil; or mechanical methods, such as digital stretching of the cervix and sweeping of the membranes; hygroscopic cervical dilators; extra-amniotic balloon catheters; artificial rupture of the membranes; and nipple stimulation. Acupuncture and homeopathy have also been used.

Because of the scale of this topic and the multiplicity of trials

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comparing one method with others and the potential for duplication of effort, members of the Cochrane Pregnancy and Childbirth Group decided to address this subject strategically. We developed a common methodology and panel of outcome measures for all labour induction reviews. In addition, we devised a strategy whereby each comparison has a single 'home' review (e.g., comparison of mifepristone versus vaginal misoprostol would appear only in the mifepristone review - *see* Data collection and analysis). We decided to combine techniques that aim to ripen the cervix (make it more soft, short and open) and those that aim to induce labour. As mentioned above, prostaglandins are frequently used to ripen the cervix when it is 'unfavourable' but this commonly causes labour to start. We therefore felt that the distinction between ripening and labour induction is, in practice, artificial.

This protocol forms the basis of a series of reviews of methods of labour induction - *see* Methods for more detailed information. It differs from other protocols published in *The Cochrane Library* because it will be retained permanently as a protocol to describe the methods that shaped the production of all labour induction reviews, unlike other Cochrane protocols which usually develop into full reviews. In addition to the general background in this generic protocol, each of the individual induction of labour reviews will include its own method-specific background information.

OBJECTIVES

To determine, from the best available evidence, the effectiveness and safety of induction agents or procedures for third trimester cervical ripening and induction of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials comparing any method of third trimester cervical ripening or labour induction, with placebo/no treatment or other methods; the trials should include some form of random allocation to either group; and they should report one or more of the prestated outcomes.

Types of participants

Pregnant women due for third trimester induction of labour, carrying a viable fetus.

Types of interventions

All methods of third trimester cervical ripening or labour induction compared with placebo/no treatment or any other method.

Types of outcome measures

Clinically relevant outcomes for trials of methods of cervical ripening/labour induction have been prespecified by two authors of labour induction reviews (Justus Hofmeyr and Zarko Alfirevic). We settled differences by discussion.

Primary outcomes

Five primary outcomes were chosen as being most representative of the clinically important measures of effectiveness and complications:

(1) vaginal delivery not achieved within 24 hours (or period specified by trial authors);

(2) uterine hyperstimulation with fetal heart rate (FHR) changes;

(3) caesarean section;

(4) serious neonatal morbidity or perinatal death (e.g., seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);

(5) serious maternal morbidity or death (e.g., uterine rupture, admission to intensive care unit, septicaemia).

Perinatal and maternal morbidity and mortality are composite outcomes. This is not an ideal solution because some components are clearly less severe than others. It is possible for one intervention to cause more deaths but less severe morbidity. However, in the context of labour induction at term this is unlikely. All of these events will be rare, and a modest change in their incidence will be easier to detect if composite outcomes are presented. The incidence of individual components will be explored as secondary outcomes (*see* below).

Secondary outcomes

Secondary outcomes relate to measures of effectiveness, complications and satisfaction.

Measures of effectiveness

(6) cervix unfavourable/unchanged after 12 to 24 hours;

(7) oxytocin augmentation.

Complications

(8) uterine hyperstimulation without FHR changes;

(9) uterine rupture;

(10) epidural analgesia;

(11) instrumental vaginal delivery;

(12) meconium-stained liquor;

(13) Apgar score less than seven at five minutes;

(14) neonatal intensive care unit admission;

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(15) neonatal encephalopathy;
(16) perinatal death;
(17) disability in childhood;
(18) maternal side-effects (all);
(19) maternal nausea;
(20) maternal vomiting;
(21) maternal diarrhoea;
(22) other maternal side-effects;
(23) postpartum haemorrhage (as defined by the trial authors);
(24) serious maternal complications (e.g., intensive care unit admission, septicaemia but excluding uterine rupture);
(25) maternal death.

Measures of satisfaction

(26) woman not satisfied;
(27) caregiver not satisfied.

'Uterine rupture' will include all clinically significant ruptures of unscarred or scarred uteri. Trivial scar dehiscence noted incidentally at the time of surgery will be excluded.

Additional outcomes may appear in individual reviews.

While all the above outcomes will be sought, only those with data will appear in the analysis tables.

The terminology of uterine hyperstimulation is problematic (Curtis 1987). In the reviews we will use the term 'uterine hyperstimulation without FHR changes' to include uterine tachysystole (more than five contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and 'uterine hyperstimulation with FHR changes' to denote uterine hyperstimulation syndrome (tachysystole or hypersystole with fetal heart rate changes such as persistent decelerations, tachycardia or decreased short term variability).

Outcomes will be included in the analysis: if reasonable measures were taken to minimise observer bias; and data were available for analysis according to original allocation.

In more recent reviews and updates the following outcomes have been added:(28) neonatal infection;
(29) neonatal antibiotics;
(30) chorioamnionitis;
(31) endometritis;
(32) maternal antibiotics.

Search methods for identification of studies

The search methods for identification of studies will be set out in each review.

Data collection and analysis

To avoid duplication of data the labour induction methods have been listed in a specific order, from one to 27. Each review includes comparisons between one of the methods (from two to 27) with only those methods above it on the list. Thus, the review of intravenous oxytocin (4) will include only comparisons with intracervical prostaglandins (3), vaginal prostaglandins (2) or placebo (1). Methods identified in the future will be added to the end of the list. The current list is as follows:

1. placebo/no treatment;
2. vaginal prostaglandins (Kelly 2003);
3. intracervical prostaglandins (Boulvain 2008);
4. intravenous oxytocin (Kelly 2001c);
5. amniotomy (Bricker 2000);
6. intravenous oxytocin with amniotomy (Howarth 2001);
7. vaginal misoprostol (Hofmeyr 2003);
8. oral misoprostol (Alfirevic 2006);
9. mechanical methods including extra-amniotic Foley catheter (Boulvain 2001b);
10. membrane sweeping (Boulvain 2005);
11. extra-amniotic prostaglandins (Hutton 2001);
12. intravenous prostaglandins (Luckas 2000);
13. oral prostaglandins (French 2001);
14. mifepristone (Neilson 2000);
15. estrogens (Thomas 2001);
16. corticosteroids (Kavanagh 2006a);
17. relaxin (Kelly 2001a);
18. hyaluronidase (Kavanagh 2006b);
19. castor oil, bath, and/or enema (Kelly 2001b);
20. acupuncture (Smith 2004);
21. breast stimulation (Kavanagh 2005);
22. sexual intercourse (Kavanagh 2001);
23. homoeopathic methods (Smith 2003);
24. nitric oxide (Kelly 2008)
25. buccal or sublingual misoprostol (Muzonzini 2004);
26. hypnosis;
27. other methods for induction of labour.

The reviews will be analysed by the following clinical categories of participants:

1. previous caesarean section or not;
2. nulliparity or multiparity;
3. membranes intact or ruptured;
4. cervix favourable, unfavourable or undefined.

For most reviews, the initial data extraction process was conducted centrally. This was co-ordinated from the Clinical Effectiveness Support Unit (CESU) at the Royal College of Obstetricians and Gynaecologists, UK, in co-operation with the Pregnancy and Childbirth Group of the Cochrane Collaboration. This process allowed the data extraction process to be standardised across all the reviews. From 2001, the data extraction was no longer conducted centrally.

The trials were initially reviewed on eligibility criteria, using a standardised form and the basic selection criteria specified above. Following this, a standardised data extraction form was developed and then piloted for consistency and completeness. This pilot

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process involved the researchers at the CESU and previous review authors in the area of induction of labour. For a description of the methods used to carry out the initial reviews, *see* Appendix 1 and Appendix 2.

In 2008 the methods and software for carrying out reviews were updated, as a result of which new reviews and updates, where appropriate, will use these new methods (Higgins 2008; RevMan 2008), which will be described in the Methods section of all the individual new and updated reviews.

ACKNOWLEDGEMENTS

Leanne Bricker, Linda French, Philippa Middleton, Brenda Tan.

Thanks to Peter Brocklehurst for his contribution to previous versions of this generic protocol.

REFERENCES

Additional references

Alfirevic 2006
Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD001338.pub2]

Bakker 2009
Bakker JJ, De Vos R, Pel M, Wisman C, Van Lith JM, Mol BW, et al.Start of induction of labour with oxytocin in the morning or in the evening. A randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2009;**116**(4):562–8.

Bishop 1964
Bishop EH. Pelvic scoring for elective induction. *Obstetrics & Gynecology* 1964;**24**:266–8.

Boulvain 2001a
Boulvain M, Stan CM, Irion O. Elective delivery in diabetic pregnant women. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD001997]

Boulvain 2001b
Boulvain M, Kelly A, Lohse C, Stan C, Irion O. Mechanical methods for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD001233]

Boulvain 2005
Boulvain M, Stan C, Irion O. Membrane sweeping for induction of labour. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD000451.pub2]

Boulvain 2008
Boulvain M, Kelly AJ, Irion O. Intracervical prostaglandins for induction of labour. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD006971]

Bricker 2000
Bricker L, Luckas M. Amniotomy alone for induction of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002862]

Clark 2009
Clark SL, Miller DD, Belfort MA, Dildy GA, Frye DK, Meyers JA. Neonatal and maternal outcomes associated with elective term delivery. *American Journal of Obstetrics and Gynecology* 2009;**200**(2):156.

Clarke 2002
Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1.5 [Updated April 2002]. In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software. Updated quarterly.

Crosby 2008
Crosby W. Elective induction of labor: part 2. *Journal of the Oklahoma State Medical Association* 2008;**101**(12):369–73.

Curtis 1987
Curtis P, Evans S, Resnick J. Uterine hyperstimulation. The need for standard terminology. *Journal of Reproductive Medicine* 1987;**32**:91–5.

Egarter 1990
Egarter CH, Husslein PW, Rayburne WF. Uterine hyperstimulation after low-dose prostaglandin E2 therapy: tocolytic treatment in 181 cases. *American Journal of Obstetrics and Gynecology* 1990;**163**:794–6.

Eggebø 2009
Eggebø TM, Økland I, Heien C, Gjessing LK, Romundstad P, Salvesen KA. Can ultrasound measurements replace digitally assessed elements of the Bishop score?. *Acta Obstetricia et Gynecologica Scandinavica* 2009;**88**(3):325–31.

Fisch 2009
Fisch JM, English D, Pedaline S, Brooks K, Simhan HN. Labor induction process improvement: a patient quality-of-care initiative. *Obstetrics & Gynecology* 2009;**113**(4):797–803.

French 2001
French L. Oral prostaglandin E2 for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003098]

Gülmezoglu 2006
Gülmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD004945.pub2]

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Higgins 2008
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Hofmeyr 2003
Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD000941]

Howarth 2001
Howarth GR, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD003250]

Hutton 2001
Hutton E, Mozurkewich E. Extra-amniotic prostaglandin for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003092]

Irion 1999
Irion O, Boulvain M. Induction of labour for suspected fetal macrosomia. *Cochrane Database of Systematic Reviews* 1998, Issue 2. [DOI: 10.1002/14651858.CD000938]

Kavanagh 2001
Kavanagh J, Kelly AJ, Thomas J. Sexual intercourse for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003093]

Kavanagh 2005
Kavanagh J, Kelly AJ, Thomas J. Breast stimulation for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD003392.pub2]

Kavanagh 2006a
Kavanagh J, Kelly AJ, Thomas J. Corticosteroids for induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003100.pub2]

Kavanagh 2006b
Kavanagh J, Kelly AJ, Thomas J. Hyaluronidase for cervical priming and induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003097.pub2]

Keirse 1993
Keirse MJNC. Prostaglandins in preinduction cervical ripening: meta-analysis of worldwide clinical experience. *Journal of Reproductive Medicine* 1993;**38 suppl**:89–98.

Kelly 2001a
Kelly AJ, Kavanagh J, Thomas J. Relaxin for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003103]

Kelly 2001b
Kelly AJ, Kavanagh J, Thomas J. Castor oil, bath and/or enema for cervical priming and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003099]

Kelly 2001c
Kelly AJ, Tan BP. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD003246]

Kelly 2003
Kelly AJ, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003101]

Kelly 2008
Kelly AJ, Kavanagh J. Nitric oxide donors for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD006901]

Kornelsen 2009
Kornelsen J, Moola S, Grzybowski S. Does distance matter? Increased induction rates for rural women who have to travel for intrapartum care. *Journal of Obstetrics and Gynaecology Canada* 2009;**31**(1):21–7.

Luckas 2000
Luckas M, Bricker L. Intravenous prostaglandin for induction of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002864]

MacKenzie 1997
MacKenzie IZ, Burns E. Randomised trial of one versus two doses of prostaglandin E2 for induction of labour: 1. Clinical outcome. *British Journal of Obstetrics and Gynaecology* 1997;**104**:1062–7.

Mozurkewich 2009
Mozurkewich E, Chilimigras J, Koepke E, Keeton K, King VJ. Indications for induction of labour: a best-evidence review. *BJOG: an international journal of obstetrics and gynaecology* 2009;**116**(5):626–36.

Muzonzini 2004
Muzonzini G, Hofmeyr GJ. Buccal or sublingual misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004221.pub2]

Neilson 2000
Neilson JP. Mifepristone for induction of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002865]

Nicholson 2009
Nicholson JM, Stenson MH, Kellar LC, Caughey AB, Macones GA. Active management of risk in nulliparous pregnancy at term: association between a higher preventive labor induction rate and improved birth outcomes. *American Journal of Obstetrics and Gynecology* 2009;**200**(3):254.e1–254.e13.

Oshiro 2009
Oshiro BT, Henry E, Wilson J, Branch DW, Varner MW, for the Women and Newborn Clinical Integration Program.

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Decreasing elective deliveries before 39 weeks of gestation in an integrated health care system. *Obstetrics & Gynecology* 2009;**113**(4):804–11.

RevMan 2003
The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003.

RevMan 2008
The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

Smith 2003
Smith CA. Homoeopathy for induction of labour. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003399]

Smith 2004
Smith CA, Crowther CA. Acupuncture for induction of labour. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD002962.pub2]

Thomas 2001
Thomas J, Kelly AJ, Kavanagh J. Oestrogens alone or with amniotomy for cervical ripening or induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD003393]

Uyar 2009
Uyar Y, Erbay G, Demir BC, Baytur Y. Comparison of the Bishop score, body mass index and transvaginal cervical length in predicting the success of labor induction. Archives of Gynecology and Obstetrics in press.

References to other published versions of this review

Hofmeyr 2000
Hofmeyr GJ, Alfirevic Z, Kelly AJ, Kavanagh J, Thomas J, Brocklehurst P, Neilson JP. Methods for cervical ripening and labour induction in late pregnancy: generic protocol. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Methods for cervical ripening and labour induction in late pregnancy: generic protocol. [DOI: 10.1002/14651858.CD002074CD002074; :]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Methods used in initial reviews

Information is extracted regarding the methodological quality of trials on a number of levels. This process is completed without consideration of trial results. Assessment of selection bias examines the process involved in the generation of the random sequence and the method of allocation concealment separately. These are then judged as adequate or inadequate using the criteria described in Appendix 2 for the purpose of the reviews.

Performance bias is examined with regards to whom was blinded in the trials, i.e., patient, caregiver, outcome assessor or analyst. In many trials the caregiver, assessor and analyst were the same party. Details of the feasibility and appropriateness of blinding at all levels are sought.

Predefined sub-group analyses are: previous caesarean section or not; nulliparity or multiparity; membranes intact or ruptured, and cervix unfavourable, favourable or undefined. Only those outcomes with data will appear in the analysis tables.

Individual outcome data are included in the analysis if they meet the prestated criteria in 'Types of outcome measures'. Included trial data are processed as described in the Cochrane Reviewers' Handbook (Clarke 2002). Data extracted from the trials are analysed on an intention to treat basis (when this was not done in the original report, re-analysis is performed if possible). Where data are missing, clarification is sought from the original authors. If the attrition was such that it might significantly affect the results, these data are excluded from the analysis. This decision rests with the reviewers of primary reviews and is clearly documented. Once missing data become available, they are included in the analyses.

Data are extracted from all eligible trials to examine how issues of quality influence effect size in a sensitivity analysis. In trials where reporting is poor, methodological issues are reported as unclear or clarification sought.

Due to the large number of trials, double data extraction was not feasible and agreement between the three data extractors was therefore assessed on a random sample of trials.

Once the data had been extracted, they were distributed to individual reviewers for entry onto the Review Manager computer software (RevMan 2003), checked for accuracy, and analysed as above using the RevMan software. For dichotomous data, relative risks and 95% confidence intervals are calculated, and in the absence of heterogeneity, results are pooled using a fixed effects model.

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From 2001, the data extraction is no longer conducted centrally. This means that the data extraction is now carried out by the reviewers of the primary reviews if new trials are found when the search strategy is rerun, and the reviews are updated.
The predefined criteria for sensitivity analysis includes all aspects of quality assessment as mentioned above, including aspects of selection, performance and attrition bias.
Primary analyses are limited to the prespecified outcomes and sub-group analyses. In the event of differences in unspecified outcomes or sub-groups being found, these are analysed post hoc, but clearly identified as such to avoid drawing unjustified conclusions.

Appendix 2. Methodological quality of trials

Methodological item	Adequate	Inadequate
Generation of random sequence	Computer generated sequence, random number tables, lot drawing, coin tossing, shuffling cards, throwing dice	Case number, date of birth, date of admission, alternation.
Concealment of allocation	Central randomisation, coded drug boxes, sequentially sealed opaque envelopes	Open allocation sequence, any procedure based on inadequate generation

WHAT'S NEW

Date	Event	Description
2 April 2009	New citation required and major changes	We have updated the Background and removed our original secondary objective, i.e. to prepare secondary reviews that would compare various induction of labour methods for specific clinical categories of women. We have also updated this generic protocol to take account of recent advances in the methodology of Cochrane reviews

HISTORY

Protocol first published: Issue 2, 2000

Date	Event	Description
23 October 2008	Amended	Converted to new review format.

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CONTRIBUTIONS OF AUTHORS

Justus Hofmeyr and Zarko Alfirevic conceived the idea of the generic protocol, defined the clinical outcomes, and co-authored initial drafts of the protocol. Tony Kelly was involved in initial planning of the process, led definition of review methods, and helped write the protocol. Josephine Kavanagh was also involved in initial planning of the process, helped develop review methods, and helped write the protocol. Jane Thomas helped develop review methods and provided comments on the draft version of the protocol. Peter Brocklehurst was involved in initial planning and provided comments on the draft version of the protocol. Jim Neilson refined the protocol with the assistance of feedback from many colleagues.

Therese Dowswell assisted Justus Hofmeyr and Zarko Alfirevic in updating the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Effective Care Research Unit, University of the Witwatersrand/Fort Hare, East London Hospital Complex, South Africa.
- The University of Liverpool, UK.
- Royal College of Obstetricians and Gynaecologists, UK.

External sources

- HRP - UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.

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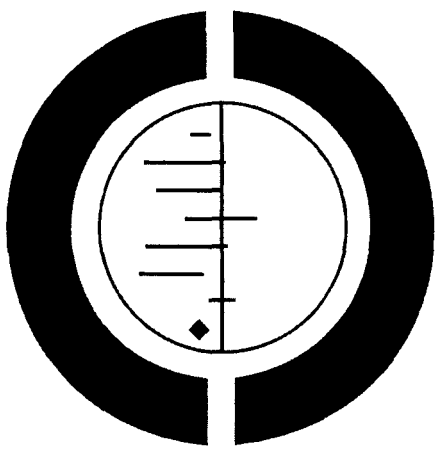
7.

Vaginal misoprostol for cervical ripening and induction of labour (Review)

Hofmeyr GJ, Gülmezoglu AM, Pileggi C



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[Intervention Review]

Vaginal misoprostol for cervical ripening and induction of labour

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2010.
Review content assessed as up-to-date: 28 May 2009.

Citation: Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.pub2.

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ABSTRACT

Background

Misoprostol (Cytotec, Searle) is a prostaglandin E1 analogue widely used for off-label indications such as induction of abortion and of labour. This is one of a series of reviews of methods of cervical ripening and labour induction using standardised methodology.

Objectives

To determine the effects of vaginal misoprostol for third trimester cervical ripening or induction of labour.

Search strategy

The Cochrane Pregnancy and Childbirth Group's Trials Register (November 2008) and bibliographies of relevant papers. We updated this search on 30 April 2010 and added the results to the awaiting classification section.

Selection criteria

Clinical trials comparing vaginal misoprostol used for third trimester cervical ripening or labour induction with placebo/no treatment or other methods listed above it on a predefined list of labour induction methods.

Data collection and analysis

We developed a strategy to deal with the large volume and complexity of trial data relating to labour induction. This involved a two-stage method of data extraction.

We used fixed-effect Mantel-Haenszel meta-analysis for combining dichotomous data.

If we identified substantial heterogeneity (I^2 greater than 50%), we used a random-effects method.

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Main results

We included 121 trials. The risk of bias must be kept in mind as only 13 trials were double blind.

Compared to placebo, misoprostol was associated with reduced failure to achieve vaginal delivery within 24 hours (average relative risk (RR) 0.51, 95% confidence interval (CI) 0.37 to 0.71). Uterine hyperstimulation, without fetal heart rate (FHR) changes, was increased (RR 3.52 95% CI 1.78 to 6.99).

Compared with vaginal prostaglandin E2, intracervical prostaglandin E2 and oxytocin, vaginal misoprostol was associated with less epidural analgesia use, fewer failures to achieve vaginal delivery within 24 hours and more uterine hyperstimulation. Compared with vaginal or intracervical prostaglandin E2, oxytocin augmentation was less common with misoprostol and meconium-stained liquor more common.

Lower doses of misoprostol compared to higher doses were associated with more need for oxytocin augmentation and less uterine hyperstimulation, with and without FHR changes.

We found no information on women's views.

Authors' conclusions

Vaginal misoprostol in doses above 25 mcg four-hourly was more effective than conventional methods of labour induction, but with more uterine hyperstimulation. Lower doses were similar to conventional methods in effectiveness and risks. The authors request information on cases of uterine rupture known to readers. The vaginal route should not be researched further as another Cochrane review has shown that the oral route of administration is preferable to the vaginal route. Professional and governmental bodies should agree guidelines for the use of misoprostol, based on the best available evidence and local circumstances.

PLAIN LANGUAGE SUMMARY

Vaginal misoprostol is effective in inducing labour but more research is needed on safety

Sometimes it is necessary to bring on labour artificially because of safety concerns for the mother or baby. Misoprostol is a hormone given by insertion through the vagina or rectum, or by mouth to ripen the cervix and bring on labour. The review of 121 trials found that larger doses of misoprostol are more effective than prostaglandin and that oxytocin is used in addition less often. However, misoprostol also increases hyperstimulation of the uterus. With smaller doses, the results are similar to other methods. The trials reviewed are too small to determine whether the risk of rupture of the uterus is increased. More research is needed into the safety and best dosages of misoprostol. Another Cochrane review has shown that the oral route of administration is preferable to the vaginal route.

BACKGROUND

Sometimes it is necessary to bring on labour artificially because of safety concerns for the mother or baby. This review is one of a series of reviews of methods of labour induction using a standardised protocol. For more detailed information on the rationale for this methodological approach, please refer to the currently published 'generic' protocol (Hofmeyr 2009). The generic protocol describes how a number of standardised reviews will be combined to compare various methods of preparing the cervix of the uterus and inducing labour.

The main problems experienced during induction of labour are ineffective labour, and excessive uterine activity which may cause fetal distress. Both problems may lead to an increased risk of caesarean section. Methods of induction of labour include administration of oxytocin, prostaglandins, prostaglandin analogues and smooth muscle stimulants such as herbs or castor oil (Mitri 1987), or mechanical methods such as digital stretching of the cervix and sweeping of the membranes, hygroscopic cervical dilators, extra-amniotic balloon catheters, artificial rupture of the membranes, and nipple stimulation.

Standardised 'scoring' of the cervix prior to labour induction has been recommended (Bishop 1964). Oxytocin has the disadvantage of a high failure rate when the cervix is unfavourable (low cervical

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score), and requiring monitored continuous intravenous infusion.

Artificial rupture of membranes is also less effective or may not be possible when the cervix is unfavourable. It may increase the risk of infection if labour does not proceed promptly. Rupture of membranes may also increase the vertical transmission of specific maternal infections such as HIV.

Unsuccessful labour induction is most likely when the cervix is unfavourable and, in this circumstance, prostaglandin preparations have proved to be beneficial (Keirse 1993; MacKenzie 1997). Those prostaglandins that have been registered for cervical ripening and labour induction are expensive and unstable, requiring refrigerated storage. Uterine hyperstimulation has been identified as a particular problem during labour induction with prostaglandins, and has been treated with tocolysis (Egarter 1990).

Misoprostol (Cytotec, Searle) is a methyl ester of prostaglandin E1 additionally methylated at C-16 and is marketed 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. It is rapidly absorbed orally and vaginally. The reported mean peak serum misoprostol acid following oral administration was 227 pg/ml versus vaginal route 165 pg/ml; the times to peak levels were 34 versus 80 minutes. Vaginally absorbed serum levels are more prolonged (Zieman 1997). Irrespective of serum levels, vaginal misoprostol may have locally mediated effects.

Misoprostol has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors (Senior 1993).

Misoprostol has been used widely for obstetric and gynaecological indications despite the fact that it has not been registered for such use. It has therefore not undergone the systematic testing for appropriate dosage and safety required for registration.

Misoprostol is an effective abortifacient, both alone and following pretreatment with mifepristone (Norman 1991). Its widespread use in Brazil (Costa 1993) resulted in the identification of teratogenic effects (Fonseca 1991).

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 with abortion complications in Rio de Janeiro, 458 reported using misoprostol (Costa 1993). There was one maternal death from uterine rupture at 16 weeks' gestation following self-medication with misoprostol.

Third trimester cervical ripening and labour induction with misoprostol have been reported using the oral, vaginal, rectal and buccal/sublingual routes. Clinical experience with misoprostol for labour induction has been reviewed by Wing (Wing 1999b).

Mariani Neto et al (Mariani Neto 1987) first reported using oral misoprostol 400 micrograms (mcg) four hourly for induction of labour following intrauterine death.

In a subsequent paper (Mariani Neto 1988), they described 'uterine tachysystole' with misoprostol use at term, which appeared unrelated to dosage. Since that time, several small studies have confirmed an increased incidence of uterine tachysystole (greater than five contractions per 10 minutes for at least 20 minutes), uterine hypersystole/hypertonus (a contraction of two minutes or more) and/or uterine hyperstimulation syndrome (uterine tachysystole or hypersystole with fetal heart rate (FHR) changes such as persistent decelerations, tachycardia or reduced short term variability). The conclusion from a meta-analysis was that published data confirmed the safety of intravaginal misoprostol for cervical ripening and labour induction. The data showed an increased incidence of uterine tachysystole (odds ratio 2.70, 95% confidence intervals 1.80 to 4.04), but there was no statistically significant increase in adverse fetal outcome (Sanchez-Ramos 1997). Wing et al (088 Wing 1995a; 044 Wing 1995b; 025 Wing 1996; 038 Wing 1997) have suggested that uterine hyperstimulation and meconium passage with vaginal misoprostol may be less frequent using a 25 microgram dose, six hourly.

Merrell and co-workers (Merrell 1995) reported a series of 62 inductions of labour with vaginal misoprostol. There were two stillbirths, one apparently due to a tight nuchal cord, and one unexplained. They commented on rapid onset of contractions and described one woman with induction to delivery interval of only two hours. In a subsequent abstract (Merrell 1996), they described labour inductions with vaginal misoprostol in 345 women with live fetuses and 86 with intrauterine deaths. There was one unexplained maternal death; two uterine ruptures, one of which followed a previous caesarean section; eight caesarean sections for fetal distress and one for uterine hyperstimulation; and 10 perinatal deaths.

There have been several reports of uterine rupture following misoprostol labour induction with and without previous caesarean section (Bennett 1997; Sciscione 1998; Blanchette 1999; Matthews 1999; Khosla 2002). One unpublished case of uterine rupture occurred in a nulliparous woman following misoprostol use (EM Smith, personal communication). At term plus 12 days she received misoprostol 100 mcg vaginally. After six hours her cervix was found to be 7 cm dilated, and she progressed to full dilatation within a further 70 minutes. Fetal distress was suspected. Ventouse application produced no descent, so delivery was effected by caesarean section. The infant showed no signs of life at birth. After resuscitation, life was sustained for a few hours only. A posterior uterine tear arising from the cervix and spiraling up the posterior aspect of the uterus was discovered and repaired. Because such uterine tears are rare in nulliparous women without prolonged labour or syntocinon use, a causal relationship with the use of misoprostol must be considered.

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One trial of misoprostol for labour induction in women with prior caesarean section has been terminated prematurely because of disruption of the uterine incision in two of the first 17 misoprostol-treated women (025 Wing 1998a). The dosage of misoprostol used was conservative (25 µg six hourly to a maximum of four doses). Two and three doses were used respectively in the two cases of ruptured uterus.

In a retrospective review, uterine rupture occurred in 5/89 (5.6%) of women with previous caesarean delivery who had labour induced with misoprostol, compared with 1/423 (0.2%) of those who did not (Plaut 1999). In another retrospective review of labour induction in 575 women with previous caesarean section, the rate of uterine rupture was 5/172 (2.9%) for prostaglandin E2 gel; 1/129 (0.76%) for intracervical Foley catheter; and 3/474 (0.74%) for induction not requiring cervical ripening; compared with 7/1544 (0.45%) for spontaneous trial of labour (Ravasia 2000). In a third retrospective review, no uterine ruptures were detected among 48 women with previous caesarean section whose labour was induced with misoprostol 50 mcg vaginally four hourly (Choy-Hee 2001).

Personal discussion with colleagues has revealed several cases of rupture of an unscarred uterus following misoprostol usage, possibly related to higher dosages than have been used in the trials reviewed. These cases are usually not reported. We call on readers to send us details of any such cases known to them, including if possible age, parity, any previous uterine surgery, dosage of misoprostol and details of the uterine rupture. This will enable us to compile a register of such problems.

This review will focus on the effectiveness and safety of misoprostol administered vaginally for cervical ripening and labour induction in the third trimester of pregnancy.

The use of oral (Alfirevic 2006) and buccal/sublingual (Muzonzini 2004) misoprostol for cervical priming and labour induction, compared with other methods including misoprostol administered vaginally, are reviewed separately.

OBJECTIVES

To determine, from the best available evidence, the effectiveness and safety of misoprostol administered vaginally for third trimester cervical ripening and induction of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials comparing misoprostol administered vaginally for cervical ripening or labour induction, with placebo/no treatment or other methods listed above it on a predefined list of methods of labour induction (*see* Methods); the trials included some form of random allocation to either group; they reported one or more of the pre-stated outcomes; reasonable measures were taken to ensure allocation concealment; and violations of allocated management were not sufficient to materially affect outcomes. We have not included quasi-randomised trials.

Types of participants

Pregnant women due for third trimester induction of labour. We have not excluded multiple pregnancies. Predefined sub-group analyses (see list below): previous caesarean section or not; nulliparity or multiparity; membranes intact or ruptured, and cervix unfavourable, favourable or undefined. Only those outcomes with data appear in the analysis tables.

Types of interventions

Vaginal administration of misoprostol compared with placebo/no treatment or any other method above it on a predefined list of methods of labour induction.

Primary comparisons

Misoprostol versus placebo/no treatment
Misoprostol versus oxytocin
Misoprostol versus vaginal prostaglandins
Misoprostol versus intracervical prostaglandins
Low dosage misoprostol regimens versus higher dosage regimens
Misoprostol gel versus tablets
In all the studies of misoprostol versus prostaglandins, the prostaglandin used was dinoprostone intravaginally as a gel, tablet or slow-release pessary, or intracervically as a gel. In most of the studies, oxytocin was used with similar protocols for both the misoprostol and the prostaglandin group, except that in one study (175 Kadanali 1996) oxytocin was started if indicated after six hours in the dinoprostone group and only after 24 hours in the misoprostol group. The effective comparison in this trial is therefore misoprostol versus dinoprostone plus early oxytocin. The results are in keeping with those of other studies.

Types of outcome measures

Two authors of labour induction reviews (Justus Hofmeyr and Zarko Alfirevic) have prespecified clinically relevant outcomes for trials of methods of cervical ripening/labour induction. We have settled differences by discussion.

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We chose five primary outcomes as being most representative of the clinically important measures of effectiveness and complications. We limited sub-group analyses to the primary outcomes:
(1) vaginal delivery not achieved within 24 hours;
(2) uterine hyperstimulation with FHR changes;
(3) caesarean section;
(4) serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);
(5) serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia).
Perinatal and maternal morbidity and mortality are composite outcomes. This is not an ideal solution because some components are clearly less severe than others. It is possible for one intervention to cause more deaths but less severe morbidity. However, in the context of labour induction at term this is unlikely. All these events will be rare, and a modest change in their incidence will be easier to detect if composite outcomes are presented. We have explored the incidence of individual components as secondary outcomes (*see* below).
Secondary outcomes relate to measures of effectiveness, complications and satisfaction.

Measures of effectiveness

(6) Cervix unfavourable/unchanged after 12 to 24 hours;
(7) oxytocin augmentation.

Complications

(8) Uterine hyperstimulation without FHR changes;
(9) uterine rupture;
(10) epidural analgesia;
(11) instrumental vaginal delivery;
(12) meconium-stained liquor;
(13) Apgar score less than seven at five minutes;
(14) neonatal intensive care unit admission;
(15) neonatal encephalopathy;
(16) perinatal death;
(17) disability in childhood;
(18) maternal side effects (all);
(19) maternal nausea;
(20) maternal vomiting;
(21) maternal diarrhoea;
(22) other maternal side effects;
(23) postpartum haemorrhage (as defined by the trial authors);
(24) serious maternal complications (e.g. intensive care unit admission, septicaemia but excluding uterine rupture);
(25) maternal death.

Measures of satisfaction

(26) Woman not satisfied;
(27) caregiver not satisfied.
'Uterine rupture' will include all clinically significant ruptures of unscarred or scarred uteri. We will exclude trivial scar dehiscence noted incidentally at the time of surgery.
While we sought all the above outcomes, we have included only those with data in the analysis tables.
The terminology of uterine hyperstimulation is problematic (Curtis 1987). In this review we have used the term 'uterine hyperstimulation without FHR changes' to include uterine tachysystole (greater than five contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and 'uterine hyperstimulation with FHR changes' to denote uterine hyperstimulation syndrome (tachysystole or hypersystole with FHR changes such as persistent decelerations, tachycardia or decreased short-term variability). However, due to varied reporting there is the possibility of subjective bias in interpretation of these outcomes. Also, it is not always clear from trials if these outcomes are reported in a mutually exclusive manner.
We included outcomes in the analysis if reasonable measures were taken to minimise observer bias; missing data were insufficient to materially influence conclusions; and data were available for analysis according to original allocation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (November 2008). We updated this search on 30 April 2010 and added the results to Studies awaiting classification for consideration in the next update.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search

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Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We hand searched the reference lists of trial reports and reviews. We screened and assessed all Chinese papers according to the review protocol by a first-language Chinese speaker (Linan Cheng) and excluded all due to serious methodological limitations. We did not apply any language restrictions.

Data collection and analysis

To avoid duplication of data, the authors of induction of labour reviews agreed a specific order for labour induction methods, from one to 27. Each primary review included comparisons between one of the methods (from two to 27) with only those methods above it on the list. Thus, this review of intravenous oxytocin (4) included only comparisons with intracervical prostaglandins (3), vaginal prostaglandins (2) or placebo/no treatment (1). The current list is as follows:

(1) placebo/no treatment;
(2) vaginal prostaglandins (Kelly 2003);
(3) intracervical prostaglandins (Boulvain 2008);
(4) intravenous oxytocin (Kelly 2001a);
(5) amniotomy (Bricker 2000);
(6) intravenous oxytocin with amniotomy (Howarth 2001);
(7) vaginal misoprostol;
(8) oral misoprostol (Alfirevic 2006);
(9) mechanical methods including extra-amniotic Foley catheter (Boulvain 2001);
(10) membrane sweeping (Boulvain 2005);
(11) extra-amniotic prostaglandins (Hutton 2001);
(12) intravenous prostaglandins (Luckas 2000);
(13) oral prostaglandins (French 2001);
(14) mifepristone (Hapangama 2009);
(15) oestrogens with or without amniotomy (Thomas 2001);
(16) corticosteroids (Kavanagh 2006a);
(17) relaxin (Kelly 2001b);
(18) hyaluronidase (Kavanagh 2006b);
(19) castor oil, bath, and/or enema (Kelly 2001c);
(20) acupuncture (Smith 2004);
(21) breast stimulation (Kavanagh 2005);
(22) sexual intercourse (Kavanagh 2001);
(23) homoeopathic methods (Smith 2003);
(24) nitric oxide donors (Kelly 2008);
(25) buccal or sublingual misoprostol (Muzonzini 2004);
(26) hypnosis;
(27) other methods for induction of labour.

The reviews were analysed by the following clinical categories of participants:

1. previous caesarean section or not;
2. nulliparity or multiparity;
3. membranes intact or ruptured;
4. cervix favourable, unfavourable or undefined.

For most reviews, the initial data extraction process was conducted centrally. This was co-ordinated from the Clinical Effectiveness Support Unit (CESU) at the Royal College of Obstetricians and Gynaecologists, UK, in co-operation with the Pregnancy and Childbirth Group of The Cochrane Collaboration. This process allowed the data extraction process to be standardised across all the reviews. From 2001, the data extraction was no longer conducted centrally.

The trials were initially reviewed on eligibility criteria, using a standardised form and the basic selection criteria specified above. Following this, a standardised data extraction form was developed and then piloted for consistency and completeness. This pilot process involved the researchers at the CESU and previous review authors in the area of induction of labour. For a description of the methods used to carry out the initial reviews, *see* Appendix 1.

Due to the large number of trials, double data extraction was not feasible and agreement between the three data extractors was therefore assessed on a random sample of trials to update in 2003. For the same reason, in the 2009 update, the data extraction was checked on around 50% of the trials in a random sample selection. In 2008, the methods and software for carrying out reviews were updated, as a result of which new reviews and updates, where appropriate, use these new methods (Higgins 2008a; RevMan 2008), which are described in the Methods section of all the individual new and updated reviews.

For this update, we used the following methods when assessing the new trials identified by the updated search.

Selection of studies

One review author (Cynthia Pileggi (CP)) assessed for inclusion all the potential studies we identified as a result of the search strategy. We discussed studies for which there was any uncertainty with a second author (Justus Hofmeyr (GJH)).

Data extraction and management

We designed a form to extract data. For eligible studies, one review author (CP) extracted the data using the agreed form. GJH independently repeated selection of studies and data extraction on a random sample of studies. We resolved discrepancies through discussion or, if required, we would have consulted the third author. We entered the data into Review Manager software (RevMan 2008) and checked them for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

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Assessment of risk of bias in included studies

One review author (CP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a).

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we would re-include missing data in the analyses. We assessed methods as:

- adequate (less than 5% loss to follow up);
- inadequate:
- unclear.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2008a). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio with 95% confidence intervals.

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Continuous data

This systematic review did not include continuous data.

Unit of analysis issues

Cluster-randomised trials

We would include cluster-randomised trials in the analyses along with individually randomised trials. We would adjust their sample sizes using the methods described in the *Handbook* (Higgins 2008b) using an estimate of the intra cluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used,we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify cluster-randomised trials in addition to the individually-randomised trials, we plan to synthesise the relevant information. We would consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We also planned to acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Dealing with missing data

For included studies, we have noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (I^2 greater than 50%), we explored it by pre-specified subgroup analysis.

Assessment of reporting biases

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect Mantel-Haenszel meta-analysis for combining dichotomous data where trials were examining the same intervention, and we judged the trials' populations and methods sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used a random-effects meta-analysis.

If we identified substantial heterogeneity, we noted this and performed the analysis using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses:

1. previous caesarean section or not;
2. nulliparity or multiparity;
3. membranes intact or ruptured;
4. cervix favourable, unfavourable or undefined.

We used primary outcomes only in subgroup analysis.

For fixed-effect meta-analyses we conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We plan to carry out sensitivity analysis by excluding trials with greater risk of bias, particularly with respect to allocation concealment, in a future update of this review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Included studies

We have included 121 studies in this review. *See* table of Characteristics of included studies for details. Because a wide range of misoprostol dosages has been used, we have coded the included studies with a prefix to reflect roughly the dosage of vaginal misoprostol received in the first six hours, calculated as follows: initial

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dose + (s x (6 - i)/4), where 's' is a subsequent dose within six hours, and 'i' is the interval in hours. This is based on the approximation that vaginal misoprostol is absorbed uniformly over a four-hour period. Where a subsequent oral dose was used, the oral dose value was halved. Use of a gel preparation is indicated by the letter 'G'. This coding allows approximate ranking of the trials by misoprostol dosage, and enables readers to assess the effect of dosage on results. We detected no discrepancies in the sample of data extraction performed in duplicate.

Excluded studies

For details of excluded studies, *see* table of Characteristics of excluded studies.

Risk of bias in included studies

With the exception of 13 double-blind trials (100G Fletcher 1993; 050 El-Azeem 1997; 043 Farah 1997; 050 Surbek 1997; 050 Gotschall 1998; 025G Srisomboon 1998; 043 Diro 1999; 100 Montealegre 1999; 025 Stitely 2000; 048 Khoury 2001; 058 Ferguson 2002; 038 Meydanli 2003; 050 Ramsey 2003 - blinded low versus high dose misoprostol comparison only), allocation was by means of sealed envelopes or unspecified, and treatment was not blinded. There is therefore a real possibility of bias affecting both the clinical management of the women (e.g. decisions to undertake caesarean section) and the assessment of outcomes. Such biases might operate in either direction (for example, a clinician enthusiastic about the potential of misoprostol might be less likely to perform caesarean section in the misoprostol group, while one anxious about the experimental nature of misoprostol might be more likely to perform caesarean section in this group).

We performed limited sensitivity analysis excluding non-blinded studies for primary outcomes with significant heterogeneity and 10 or more trials included. For the comparison misoprostol versus vaginal prostaglandins, all women: the outcome vaginal delivery not achieved in 24 hours was unchanged; the outcome uterine hyperstimulation with FHR changes was no longer statistically significant (small numbers). For the comparison misoprostol versus oxytocin: the outcomes vaginal delivery not achieved in 24 hours and caesarean section were no longer statistically significant (small numbers remaining in the analysis).

The possibility of bias must be kept in mind in the interpretation of the results.

In the study of 050 Le Roux 2002, 93 of 573 enrolled women were excluded for 'protocol violations'. There did not appear to be a selective loss from any group, and the baseline data were similar between groups.

In 050 Pandis 2001, 235/670 were excluded after randomisation, mainly for spontaneous delivery before induction or induction by amniotomy for cervical score seven or more.

In 075 Ghidini 2001, seven of 65 enrolled women were excluded due to emergence of exclusion criteria. The groups were somewhat unbalanced (32 received 50 mcg and 26 received 100 mcg)

In 150 De la Torre 2001, 50 of 410 enrolled were withdrawn for protocol deviation (16), patient withdrawal (7), or missing data (27). The final groups differed in numbers (misoprostol 168, oxytocin 192). This raises the possibility of selective withdrawal from the misoprostol group.

In 088 Garry 2003, 14 women of 200 enrolled were withdrawn for physician request(10), used wrong medication (2), patient request (1) and unknown breech presentation (1). It suggests deviation from the intention to treat analysis.

The 2009 update used the new methodology of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a) regarding the evaluation of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, report of incomplete outcome data, selective outcome reporting bias and other sources. We have presented the quality evaluation of each included study in the corresponding risk of bias table. This update includes 54 comparisons with more than 10 study results in the pooled analyses, 19 of them in primary outcomes. Five out of these 19 comparisons present asymmetrical funnel plots suggesting potential publication bias.

Effects of interventions

We have included 121 studies in this review. We sought all the outcomes listed under 'Types of outcome measures', and sub-groups defined in 'Types of participants'. Only those with data appear in the analysis tables.

Vaginal misoprostol versus placebo

Primary outcomes

The 10 studies (1141 women) included in this part of the review (100G Fletcher 1993; 100G Srisomboon 1996; 025 Stitely 2000; 050 Thomas 2000; 025 Incerpi 2001; 050 Ortiz 2002; 025 McKenna 2004; 050 Gelisen 2005; 025 Krupa 2005; 025 Oboro 2005) showed a trend towards failure to deliver within 24 hours (five trials, 735 women, average relative risk (RR) 0.56, 95% CI 0.31 to 1.03).

Secondary outcomes

We found a clear effect of misoprostol on cervical ripening (two trials, average RR of unchanged cervix at 12 to 24 hours 0.09, 95% confidence interval (CI) 0.03 to 0.24).

Uterine hyperstimulation without FHR changes was increased (six trials, 794 women RR 3.52, 95% CI 1.78 to 6.99). Six trials (100G Fletcher 1993; 025 Stitely 2000; 050 Thomas 2000; 050

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Ortiz 2002; 050 Gelisen 2005; 025 Krupa 2005) with 814 women showed an unexpected reduction of meconium-stained liquor with the use of misoprostol for labour induction.The numbers studied were too small to assess the impact on obstetric management and maternal and neonatal complications.

Vaginal misoprostol versus vaginal prostaglandins

There were 38 included trials with 7022 participants.

Primary outcomes

Failure to achieve vaginal delivery within 24 hours (22 trials, average RR 0.77, 95% CI 0.66 to 0.89) was reduced overall, but not in the two trials using less than 50 mcg misoprostol in the first six hours (038 Wing 1997; 048 Khoury 2001).

Uterine hyperstimulation with FHR changes was variable between trials, but overall tended to be more common with misoprostol (31 trials, average RR 1.43, 95% CI 0.97 to 2.09).

Caesarean sections were variable between trials, with a trend to be reduced with vaginal misoprostol (34 trials RR 0.95, 95%CI 0.87 to 1.03).

Secondary outcomes

Oxytocin augmentation was reduced with misoprostol (36 trials, average RR 0.68, 95% CI 0.60 to 0.76).

Uterine hyperstimulation without FHR changes was more common with misoprostol (26 trials, average RR1.99, 95% CI 1.41 to 2.79).

Epidural analgesia was used less frequently with misoprostol (eight trials, RR 0.92, 95% CI 0.85 to 0.99).

Meconium-stained liquor was more common with misoprostol (18 trials, RR 1.35, 95% CI 1.13 to 1.61). There were no statistically significant differences in perinatal or maternal outcomes.

Results were similar for the sub-groups of women with unfavourable cervices and those with intact membranes and unfavourable cervices.

There were similar trends for women with intact membranes and variable or undefined cervices, but the numbers were too small for clear outcomes.

For subgroups of primiparous or multiparous women, the numbers were small and no differences in any outcomes were shown, except that for all primiparous women, misoprostol shows reduced caesarean section (RR 0.82, 95% CI 0.68 to 0.99), and a trend to reduced vaginal delivery not achieved in 24h (average RR 0.70, 95% CI 0.46 to 1.05).

The results of 048 Khoury 2001 differed somewhat from other studies. This may be because a gel preparation of misoprostol was used, and it is possible that some activity is lost in the preparation or administration (see results of misoprostol gel versus tablets below).

Vaginal misoprostol versus intracervical prostaglandins

There were 27 included trials with 3311 participants.

Primary outcomes

Failure to achieve vaginal delivery within 24 hours was consistently reduced with misoprostol (13 trials, RR 0.63, 95% CI 0.56 to 0.71).

Uterine hyperstimulation with associated FHR changes was variable between trials, but all were consistent with the pooled result showing an increase with misoprostol (20 trials, RR 2.32, 95% CI 1.64 to 3.28). The latter result was similar for the sub-group of trials studying women with intact membranes and unfavourable cervices.

Caesarean sections were variable between trials, with no significant differences overall.

Secondary outcomes

Only one trial reported the outcome 'failure to achieve cervical ripening within 12 hours' (075 Buser 1997); this was reduced with misoprostol (RR 0.68, 95% CI 0.52 to 0.88).

Oxytocin augmentation was used less often with misoprostol (20 trials, average RR 0.55, 95% CI 0.48 to 0.64).

Uterine hyperstimulation without FHR changes was more common with misoprostol (17 trials, RR 1.95, 95% CI 1.57 to 2.42).

The rates of vaginal instrumental delivery were variable between trials. Epidural analgesia was used less frequently with misoprostol (two trials, RR 0.64, 95% CI 0.48 to 0.86). Meconium-stained liquor was increased with misoprostol (14 trials, RR 1.29, 95% CI 1.04 to 1.59). There were no statistically significant differences in perinatal or maternal outcomes.

Most of the trials studied women with unfavourable cervices, for whom the results were similar to the overall results. Results were also similar for women with intact membranes and unfavourable cervices. The two trials with intact membranes and variable or undefined cervix also showed a similar pattern of results.

Vaginal misoprostol versus oxytocin

There were 25 trials with 3074 participants.

Primary outcomes

Misoprostol, in the doses used in these trials, was more effective than oxytocin for labour induction (10 trials, average RR of failure to achieve vaginal delivery within 24 hours 0.65, 95% CI 0.47 to 0.90). Two trials using less than 50 mcg misoprostol showed no reduction (025 Wing 1998b; 025 Haghighi 2006).

Twenty-five studies showed a reduction in caesarean section risk with the use of misoprostol (average RR 0.76, 95% CI 0.60 to 0.96).

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Secondary outcomes

Uterine hyperstimulation without FHR changes was more common with misoprostol (15 trials, RR 2.24 95% CI 1.82 to 2.77 respectively). There was a trend to reduced epidural analgesia with misoprostol (three trials, RR 0.82, 95% CI 0.67 to 1.00). Vaginal instrumental delivery was reduced in the misoprostol group (13 trials, RR 0.74, 95% CI 0.56 to 0.99).

Apgar score less than 7 at five minutes, with 13 studies and 1906 participants in the general group, was substantially reduced with misoprostol use (RR 0.56, 95% CI 0.34 to 0.92). Four studies with 334 participants showed increased risk of maternal side effects (RR 5.04, 95% CI 1.51 to 16.86). There were no differences in other perinatal or maternal outcomes.

One trial in women with previous caesarean section was stopped when uterine rupture occurred in two of the first 17 women who received misoprostol (025 Wing 1998b) and in another study one uterine rupture occurred in 34 women in the misoprostol group (all women with unfavourable cervix, 050 Abdul 2007).

Misoprostol lower dosage regimen versus higher dose

There were 21 trials with 2913 participants. The dosages compared are as follows.

Number of studies	Misoprostol low dosage	Misoprostol high dosage	Interval of use
2	12.5 mcg	25 mcg	4 to 6 hours
11	25 mcg	50 mcg	3 to 6 hours
1	35 mcg	50 mcg	4.5 hours
6	50 mcg	100 mcg	4 to 6 hours

Note: 006 Ewert 2006 was not included because of the mode of misoprostol administration

Primary outcomes

There was no significant difference in the risk of failures to achieve delivery within 24 hours. There was less uterine hyperstimulation with FHR changes in the lower dose groups (16 trials, RR 0.51, 95% CI 0.37 to 0.69).

Serious maternal complications were reported in one study (025 Wing 1996): one maternal death occurred in a primiparous woman, nine hours after a single misoprostol dose and shortly after amnioinfusion and epidural analgesia, from amniotic fluid embolisation. Two caesarean hysterectomies were performed for atonic uterine haemorrhage, 13 and 30 hours after single doses of misoprostol, in one primiparous woman with uncomplicated labour, and in one nulliparous woman who developed chorioamnionitis following prolonged labour induction attempts by oxytocin augmentation. It is not clear whether these three women were allocated to the low (25 mcg) or the higher (50 mcg) dosage regimen misoprostol group.

Secondary outcomes

There was significantly more use of oxytocin (18 trials, average RR 1.30, 95% CI 1.14 to 1.49). This effect was due to the trials with a lower range of doses, and was not seen in the trials in which the lower dosage was 50 mcg. There were no differences in mode of delivery, meconium-stained liquor or maternal side effects. There was less uterine hyperstimulation without FHR changes (14 trials, RR 0.57, 95% CI 0.46 to 0.69). There was a trend to fewer babies being admitted to the neonatal intensive care unit (9 trials, RR 0.82, 95% CI 0.64 to 1.05), particularly in the higher dose ranges. Five perinatal deaths were reported (019 Filho 2007; 050 Majoko 2002a). There was one uterine rupture (038 Has 2002) with the use of low dose of misoprostol and two with the use of higher dose of misoprostol (050 Majoko 2002a; 075 Reyna-Villasmil 2005). However, most studies have not specifically reported these outcomes. We have included only those specified in the reports in the data tables.

Misoprostol gel versus tablets

Primary outcomes

In one trial with 467 participants reviewed (050G Carlan 1997), uterine hyperstimulation with FHR changes was reduced with the gel preparation (RR 0.49, 95% CI 0.29 to 0.83).

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Secondary outcomes

The use of oxytocin (RR 1.26, 95% CI 1.13 to 1.41) and epidural analgesia (RR 1.19, 95% CI 1.03 to 1.38) were increased. It is possible that in the process of gel preparation some potency is lost or that absorption is reduced.

One study showed no benefit from moistening misoprostol prior to insertion with 11 ml 3% acetic acid, versus dry tablets (Sanchez Ramos 2002).

A cost analysis in a high-income country showed that the reduced cost in the misoprostol group (Sterling mean 2134, SD 574 versus 2202, SD 595 per case) was insignificant in relation to the overall cost of labour induction (050 Rozenberg 2001).

DISCUSSION

Overall, this systematic review found that vaginal misoprostol is the more effective option for induction of labour and cervical ripening compared with oxytocin, dinoprostone and placebo. It also found that higher doses of vaginal misoprostol have no comparative advantages to the lower doses. There is, in general, considerable consistency between trials, except with respect to caesarean section rates and to the low misoprostol dosage regimens. The trials show that vaginal misoprostol in dosages ranging from 25 mcg two to three hourly, to 50 mcg four hourly (most studies), to 100 mcg six to 12 hourly, appear to be more effective than oxytocin or dinoprostone in the usual recommended doses for induction of labour, but with increased rates of uterine hyperstimulation both without and with associated FHR changes. The rates of caesarean section were inconsistent, tending to be reduced with misoprostol. The indication for caesarean section was not a prespecified outcome in this review. However, there was a consistent pattern of more operations for fetal distress and fewer for poor labour progress in the misoprostol groups (see 'Characteristics of included studies' table under 'Outcomes').

No differences in perinatal or maternal outcome were shown. However, the trials were not sufficiently large to assess the likelihood of uncommon, serious adverse perinatal and maternal complications. Of particular concern are several reports of uterine rupture following misoprostol use in women with and without previous caesarean section. One maternal death from amniotic fluid embolism following misoprostol induction was reported.

The possibility of inadvertent bias because of the unblinded nature of these studies should be kept in mind.

Lower dosage regimens of misoprostol were not less effective than higher doses in terms of failure to achieve vaginal birth within 24 hours. Adverse effects were reduced, with lower rates of uterine hyperstimulation and a trend to fewer admissions to neonatal intensive care unit.

The finding of a significantly more meconium-stained liquor with misoprostol versus vaginal or intracervical prostaglandins is of interest. Wing et al (088 Wing 1995a) suggested the possibility of meconium passage in response to uterine hyperstimulation or a direct effect of absorbed misoprostol metabolites on the fetal gastrointestinal tract. We have previously observed an increased rate of meconium-stained liquor in women who have ingested castor oil, though causality was not proven, and suggested a possible direct effect of the castor oil metabolites on fetal bowel (Mitri 1987). It is unlikely that the small amount of hydrogenated castor oil found in misoprostol tablets (075 Chuck 1995) would have any pharmacological effect, but the possibility that misoprostol metabolites may directly stimulate fetal bowel is of interest. We have shown an in vitro effect of misoprostol on isolated rat ileum (as well as myometrium) (Matonhodze 2002).

In countries in which misoprostol is being used for non-registered obstetric indications, there is a need for health authorities and professional organisations to clarify the medicolegal implications. Particularly in countries in which conventional prostaglandins are unaffordable, health authorities need to decide whether misoprostol should be used in specific circumstances and, if so, take steps to legalise and regulate such use.

The trials reviewed lacked information on women's views with respect to this method of labour induction.

AUTHORS' CONCLUSIONS

Implications for practice

The comparison between oral and vaginal misoprostol is dealt with in a separate Cochrane review (Alfirevic 2006). That review suggests that the optimal route for administration of misoprostol for labour induction is oral, not vaginal. The reasons for this are as follows.

1. Safety. The oral route is associated with considerably less uterine hyperstimulation with FHR changes (9% versus 24.6%; RR 0.37, 95%CI 0.23 to 0.59).

2. Convenience and comfort for the woman.

3. Because of a short half-life, the oral dose can be titrated against the uterine response, commencing with a low dose such as 25 mcg 2-hourly, and increasing if necessary in nulliparous women to a maximum dose of 50 mcg 2-hourly.

4. Accuracy of dosage. In many countries, misoprostol is available only as 200 mcg or 100 mcg tablets. Breaking these tablets into small fragments for vaginal administration carries the risk of inappropriate dosage. Accurate oral dosage can be achieved by dissolving misoprostol in tap water, shaking well and administering as a solution. Left over solution should be discarded 24 hours after preparation.

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The relative disadvantages of oral versus vaginal misoprostol are greater need for oxytocin augmentation (RR 1.28, 95% CI 1.11 to 1.48), and increased meconium staining of the amniotic fluid (RR 1.27, 95% CI 1.10 to 1.60).

The results of this review are therefore of limited practical importance: in dosages of 25 mcg three hourly or more, vaginal misoprostol is more effective than conventional methods of cervical ripening and labour induction. However, uterine hyperstimulation with FHR changes are increased. Although no differences in perinatal outcome were shown, the studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. The increase in meconium-stained liquor is also of concern. Anecdotal reports of uterine rupture following labour induction with misoprostol are cause for concern (Gherman 1999; Daisley 2000; Hill 2000; Majoko 2002b).

The limited information on lower dosage regimens (25 mcg four hourly or less) suggests that they may be as effective as other prostaglandins, without increased uterine hyperstimulation.

Though misoprostol shows promise as a highly effective, inexpensive and convenient agent for labour induction, the lack of registration for this purpose, and thus of well-established regimens, is problematic.

In most countries misoprostol is not registered for use for labour induction. In countries in which its use is considered advantageous, it is important that health authorities provide guidelines for practitioners to ensure the greatest possible level of safety in its use.

Implications for research

While this review assessed the efficacy and safety of vaginal misoprostol (including its different regimens) based on data from its comparison to oral misoprostol, the vaginal route should not be researched further.

Because of the potential economic and clinical advantages of misoprostol, there is the need for further trials to establish its safety, particularly the relative safety of various dosages of oral administration. On the basis of this review, such trials should have the following features.

(1) Randomised, double blind.

(2) Oral or sublingual route of administration.

(3) Sample size sufficient to detect moderate differences in important uncommon complications such as serious perinatal morbidity/mortality.

(4) Meconium-stained liquor included as an outcome measure.

(5) Women's views included as an outcome.

Randomised trials sufficiently large to assess rare events such as uterine rupture are not feasible. Alternative research methods are necessary such as case-control studies and prospective audits of complications in services in which misoprostol is used routinely for labour induction.

We would be grateful to receive reports of rare serious complications such as uterine rupture in order to compile a register of such incidents.

ACKNOWLEDGEMENTS

Clinical Effectiveness Support Unit, Royal College of Obstetricians and Gynaecologists (Tony Kelly, Josephine Kavanagh, Jane Thomas), for primary data extraction. Zarko Alfirevic, Jim Neilson and Sonja Henderson, Tony Kelly and Josephine Kavanagh for contributions to development of the generic protocol for reviews of labour induction. Edwin S-Y Chan and Ken Gu of the NMRC Clinical Trials and Epidemiology Unit, Ministry of Health, Singapore for translating two Chinese papers. Linan Cheng for retrieving, translating and assessing 28 Chinese papers.

REFERENCES

References to studies included in this review

006 Ewert 2006 ***{published data only}***
Ewert K, Powers B, Robertson S, Alfirevic Z. Controlled-release misoprostol vaginal insert in parous woman for labor induction. *Obstetrics & Gynecology* 2006;**108**:1130–7.

013 Papanikolaou 2004 ***{published data only}***
Papanikolaou EG, Plachouras N, Drougia A, Andronikou S, Vlachou C, Theodoros S, et al.Comparison of misoprostol and dinoprostone for elective induction of labour in nulliparous women at full term: a randomized prospective study. *Reproductive Biology and Endocrinology* 2004;**2**:70–7.

013 Tedesco 2002 ***{published data only}***
Tedesco RP, Cecatti JG, Lourenco N, Filho M. Effectiveness of two different doses of vaginal misoprostol for cervical ripening and labor induction [Efetividade de duas diferentes doses de misoprostol por via vaginal para preparo cervical e inducao do parto]. *Revista Brasileira de Ginecologia e Obstetricia* 2002;**24**(10):614–6.

019 Filho 2007 ***{published data only}***
Filho FAR, Alencar Junior CA, Feitosa FE, Arcanjo FCN. Low-dose vaginal misoprostol (12.5 versus 25mcg) for induction of labor at term [Baixas doses de misoprostol vaginal (12.5 versus 25mcg) para indução de parto a termo].

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Revista Brasileira de Ginecologia e Obstetrícia 2007;**29**(12): 639–46.

025 Elhassan 2005a ***{published data only}***
Elhassan EM, Mirghani OA, Adam I. Cervical ripening and labor induction with 25mcg versus 50mcg of intravaginal misoprostol. *International Journal of Gynecology & Obstetrics* 2005;**90**:234–35.

025 Haghighi 2006 ***{published data only}***
Haghighi L. Intravaginal misoprostol in preterm premature rupture of membranes with low Bishop scores. *International Journal of Gynecology & Obstetrics* 2006;**94**(2):121–2.

025 Incerpi 2001 ***{published data only}***
Incerpi M, Fassett M, Kjos S, Tran S, Wing D. Vaginally administered misoprostol for outpatient labor induction in pregnancies with diabetes mellitus [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**184**(1):S120.
* Incerpi MH, Fassett MJ, Kjos SL, Tran SH, Wing DA. Vaginally administered misoprostol for outpatient cervical ripening in pregnancies complicated by diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2001;**185**: 916–9.

025 Krupa 2005 ***{published data only}***
Da Graca Krupa F, Cecatti JG, De Castro Surita FG, Milanez HM, Parpinelli MA. Misoprostol versus expectant management in premature rupture of membranes at term. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(9):1284–90.

025 Kumar 2001 ***{published data only}***
Kumar S, Awasthi RT, Kapur A, Srinivas S, Parikh H, Sarkar S. Induction of labour with misoprostol - a prostaglandin E1 analogue. *Medical Journal Armed Forces of India* 2001; **57**:107–9.

025 Majoko 2001 ***{published data only}***
Majoko F, Zwizwai M, Lindmark G, Nystrom L. A randomised controlled trial of labour induction with misoprostol and prostaglandin F2α gel. 20th Conference on Priorities in Perinatal Care in Southern Africa; 2001 March 6-9; KwaZulu-Natal, South Africa. 2001.

025 Majoko 2002c ***{published data only}***
Majoko F, Zwizwai M, Nystrom L, Lindmark G. Vaginal misoprostol for induction of labour: a more effective agent than prostaglandin F2α gel and prostaglandin E2 pessary. *Central African Journal of Medicine* 2002;**48**(11-12):123–8.

025 McKenna 2004 ***{published data only}***
McKenna DS, Ester JB, Poffitt M, Waddell KR. Misoprostol outpatient cervical ripening without subsequent induction of labor: a randomized trial. *Obstetrics & Gynecology* 2004; **104**(3):579–84.

025 Meyer 2005 ***{published data only}***
Meyer M, Pflum J. Outpatient administration of misoprostol decreases induction time. *American Journal of Obstetrics and Gynecology* 2002;**187**(6 Pt 2):S167.
Meyer M, Pflum J, Howard D. Outpatient misoprostol compared with dinoprostone gel for preinduction cervical ripening: a randomized controlled trial. *Obstetrics & Gynecology* 2005;**105**:466–72.

025 Oboro 2005 ***{published data only}***
Oboro VO, Tabowei TO. Outpatient misoprostol cervical ripening without subsequent induction of labor to prevent post-term pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 2005;**84**(7):628–31.

025 Sheela 2007 ***{published data only}***
Sheela CN, Mhaskar A, George S. Comparison of vaginal misoprostol and oral misoprostol with intracervical dinoprostone gel for labour induction at term. *Journal of Obstetrics and Gynaecology of India* 2007;**57**(4):327–30.

025 Stitely 2000 ***{published data only}***
Stitely ML, Browning J, Fowler M, Gendron RT, Gherman RB. Outpatient cervical ripening with intravaginal misoprostol. *Obstetrics & Gynecology* 2000;**96**:684–8.

025 Wang 1998 ***{published data only}***
Wang H, Li L, Pu L. The effect of 25mcg misoprostol on induction of labour in late pregnancy. *Chinese Journal of Obstetrics and Gynecology* 1998;**33**:469–71.

025 Wing 1996 ***{published data only}***
Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1996;**175**: 158–64.

025 Wing 1998a ***{published data only}***
* Wing DA, Paul RH. Induction of labor with misoprostol for premature rupture of membranes beyond 36 weeks gestation. *American Journal of Obstetrics and Gynaecology* 1998;**179**(1):94–9.
Wing DA, Paul RH. Induction of labor with misoprostol for premature rupture of membranes beyond 36 weeks gestation. *American Journal of Obstetrics and Gynecology* 1998;**178**:S93.

025 Wing 1998b ***{published and unpublished data}***
Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labour induction in women with previous cesarean delivery. *Obstetrics & Gynecology* 1998;**91**(5 Pt 2):828–30.

025G Srisomboon 1998 ***{published data only}***
Srisomboon J, Singchai S. A comparison between 25 micrograms and 50 micrograms of intravaginal misoprostol for labor induction. *Journal of the Medical Association of Thailand* 1998;**81**(10):779–82.

030 Moodley 2003 ***{published data only}***
Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term - a comparative study. *South African Medical Journal* 2003;**93**:371–4.

038 Aquino 2003 ***{published data only}***
De Aquino MM, Cecatti JG. Misoprostol versus oxytocin for labor induction in term and post-term pregnancy: randomized controlled trial. *Sao Paulo Medical Journal* 2003;**121**(3):102–6.

038 Cecatti 2000 ***{published data only}***
Cecatti JG, Aquino MMA, Garcia GM, Rodrigues TMC. Misoprostol versus oxytocin for labor induction:

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

randomized controlled trial. XVI FIGO World Congress of Obstetrics and Gynecology; 2000 Sept 3-8; Washington DC, USA (Book 4). 2000:28.

038 Clark 1998 *{published data only}*
Clark A, Cook V, Hill P, Spinnato J. Cervical ripening and labor induction: misoprostol vs dinoprostone. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S30.

038 El-Sherbiny 2001 *{published data only}*
El-Sherbiny M. Vaginal misoprostol for labor induction 25ug versus 50ug dose regimens. XVI FIGO World Congress of Obstetrics and Gynecology; 2000 Sept 3-8; Washington DC, USA (Book 4). 2000:30.
* El-Sherbiny MT, El-Gharieb IH, Gewley HA. Vaginal misoprostol for induction of labor: 25 vs. 50 ug dose regimen. *International Journal of Gynecology & Obstetrics* 2001;**72**:25–30.

038 Eroglu 2007 *{published data only}*
Eroglu D, Oktem M, Yanik F, Kuscu E. Labor induction at term: a comparison of the effects of 50 microg and 25 microg vaginal misoprostol. *Clinical and Experimental Obstetrics and Gynecology* 2007;**34**(2):102–5.

038 Gregson 2005 *{published data only}*
Gregson S, Waterstone M, Norman I, Murrells T. A randomised controlled trial comparing low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**:438–44.

038 Has 2002 *{published data only}*
Has R, Batukan C, Ermis H, Cevher E, Araman A, Kilic G, et al.Comparison of 25 and 50 mcg vaginally administered misoprostol for preinduction of cervical ripening and labor induction. *Gynecologic and Obstetric Investigation* 2002;**53**: 16–21.

038 Kidanto 2006 *{published data only}*
Kidanto HL, Kaguta MM, Van Roosmalen J. Induction of labor with misoprostol or oxytocin in Tanzania. *International Journal of Gynecology & Obstetrics* 2006;**96**(1): 30–1.

038 Krithika 2008 *{published data only}*
Krithika KS, Aggarwal N, Suri V. Prospective randomised controlled trial to compare safety and efficacy of intravaginal misoprostol with intracervical cerviprime for induction of labour with unfavourable cervix. *Journal of Obstetrics and Gynaecology* 2008;**28**(3):294–7.

038 Meydanli 2003 *{published data only}*
Meydanli MM, Caliskan E, Burak F, Narin MA, Atmaca R. Labor induction post-term with 25 micrograms vs 50 micrograms of intravaginal misoprostol. *International Journal of Gynecology & Obstetrics* 2003;**81**:249–55.

038 Murthy 2006 *{published data only}*
Murthy BK, Arkalgud MS. Misoprostol alone versus a combination of dinoprostone and oxytocin for induction of labour. *Journal of Obstetrics and Gynaecology of India* 2006; **56**(5):411–6.

038 Van Gemund 2004 *{published data only}*
Van Gemund N, Scherjon S, LeCessie S, Van Leeuwen JH, Van Roosmalen J, Kanhai HH. A randomised trial comparing low dose vaginal misoprostol and dinoprostone for labour induction. *BJOG: an international journal of obstetrics and gynaecology* 2004;**111**:42–9.

038 Wing 1997 *{published data only}*
Wing DA, Ortiz-Omphroy G, Paul RH. A comparison of intermittent vaginal administration of misoprostol with continuous dinoprostone for cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1997;**177**:612–8.
Wing DA, Paul RH. Vaginally administered misoprostol (Cytotec) versus the dinoprostone vaginal insert (Cervidil) for preinduction cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1997;**176**: S113.

043 Diro 1999 *{published data only}*
Diro M, Adra A, Gilles JM, Nassar A, Rodriguez A, Salamat SM, et al.A double-blind randomized trial of two dose regimens of misoprostol for cervical ripening and labor induction. *Journal of Maternal-Fetal Medicine* 1999;**8**(3): 114–8.

043 Farah 1997 *{published data only}*
Farah LA, Sanchez-Ramos L, Rosa C, Del Valle GO, Gaudier FL, Delke I, et al.Randomised trial of two doses of the prostaglandin E1 analog misoprostol for labor induction. *American Journal of Obstetrics and Gynecology* 1997;**177**:364–9.
Sanchez-Ramos L, Farah L, Rosa C, Johnson J, Delke I, Del Valle G. Comparative study of a two dose schedule of the PGE1 analogue misoprostol for labor induction in patients with an unfavorable cervix. *American Journal of Obstetrics and Gynecology* 1996;**171**(1 Pt 2):319.

044 Chen 2005 *{published data only}*
Chen DC, Yuan SS, Su HY, Lo SC, Ren SS, Wu GJ. Urinary cyclic guanosine 3',5'-monophosphate and cyclic adenosine 3',5'-monophosphate changes in spontaneous and induced onset active labor. *Acta Obstetricia et Gynecologica Scandinavica* 2005;**84**:1081–6.

044 Nanda 2007 *{published data only}*
Nanda S, Singhal SR, Papneja A. Induction of labour with intravaginal misoprostol and prostaglandin E2 gel: a comparative study. *Tropical Doctor* 2007;**37**(1):21–4.

044 Wing 1995b *{published data only}*
Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: an effective agent for cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1995;**172**:1811–6.

048 Khoury 2001 *{published data only}*
Khoury A, Zhou Q, Gorenberg D, Nies B, Manley G, Mecklenburg F. A randomized clinical trial comparing misoprostol suppositories with continuous dinoprostone for

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

cervical ripening and labor induction [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**184**(1):S118.
* Khoury AN, Zhou Q-P, Gorenberg DM, Nies BM, Manley GE, Mecklenburg FE. A comparison of intermittent vaginal administration of two different doses of misoprostol suppositories with continuous dinoprostone for cervical ripening and labor induction. *Journal of Maternal Fetal Medicine* 2001;**10**:186–92.

050 Abdul 2007 ***{published data only}***
Abdul MA, Ibrahim UN, Yusuf MD, Musa H. Efficacy and safety of misoprostol in induction of labour in a Nigerian tertiary hospital [L'efficacité et la sûreté de misoprosotl dans l'induction de travail dans un Hôpital Tertiaire Nigerian]. *West African Journal of Medicine* 2007;**26**(3):213–6.

050 Agarwal 2003 ***{published data only}***
Agarwal N, Gupta A, Kriplani A, Bhatla N, Parul N. Six hourly vaginal misoprostol versus intracervical dinoprostone for cervical ripening and labor induction. *Journal of Obstetrics and Gynaecology Research* 2003;**29**(3):147–51.

050 Ayad 2002 ***{published data only}***
Ayad IAA. Vaginal misoprostol in managing premature rupture of membranes. *Eastern Mediterranean Health Journal* 2002;**8**(4 & 5):515–20.

050 Bounyasong 2000 ***{published data only}***
Bounyasong S. A randomized comparison between 25 microgram misoprostol gel and 50 microgram vaginal misoprostol tablet for induction of labour. *Thai Journal of Obstetrics and Gynecology* 2000;**12**(1):21–5.

050 Calder 2008 ***{published data only}***
* Calder AA, Loughney AD, Weir CJ, Barber JW. Induction of labour in nulliparous and multiparous women: a UK, multicentre, open-label study of intravaginal misoprostol in comparison with dinoprostone. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(10):1279–88.
Calder AA, Loughney AJ, Denison F, Polson D, Erskine K, Dally JJ, et al.A randomised, open-label comparison of intravaginal (APL202) and dinoprostone for cervical ripening and labour induction in nulliparae. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115** (s1):58–9.

050 Campos Perez 1994 ***{published data only}***
* Campos GA, Guzman S, Rodriguez JG, Voto LS, Margulies M. Misoprostol--a PGE1 analog for induction of labor at term: comparative and randomized study with oxytocin [Misoprostol—un analogo de la PGE1—para la induccion de parto a termino: estudio comparativo y randomizado con oxitocina]. *Revista Chilena de Obstetricia y Ginecologia* 1994;**59**:190–6.
Campos Perez GA, Margulies M, Ortega I, Voto LS. Induction of labor with misoprostol, a PGE1 analog. Proceedings of 2nd European Congress on Prostaglandins in Reproduction; 1991 April 30-May 3; The Hague, Netherlands. 1991:97.
Margulies M, Campos Perez G, Voto LS. Misoprostol to induce labour [letter]. *Lancet* 1992;**339**:64.

050 Charoenkul 2000 ***{published data only}***
Charoenkul S, Sripramote M. A randomized comparison of one single dose of vaginal 50 mcg misoprostol with 3 mg dinoprostone in pre-induction cervical ripening. *Journal of the Medical Association of Thailand* 2000;**83**:1026–34.

050 Denguezli 2007 ***{published data only}***
Denguezli W, Trimech A, Haddad A, Hajjaji A, Saidani Z, Faleh R, et al.Eficacy and safety of six hourly vaginal misoprostol versus intracervical dinoprostone: a randomised controlled trial. *Archives of Gynecology and Obstetrics* 2007; **276**(2):119–24.

050 El-Azeem 1997 ***{published data only}***
El-Azeem S, Samuels P, Welch G, Staisch K. Term labor induction with PGE1 misoprostol versus PGE2 dinoprostone. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S113.

050 Elhassan 2004 ***{published data only}***
Elhassan M, Mirghani OA, Adam I. Intravaginal misoprostol versus dinoprostone as cervical ripening and labour inducing agents. *International Journal of Gynecology & Obstetrics* 2004;**85**:285–6.

050 Elhassan 2005b ***{published data only}***
Elhassan EM, Mirghani OA, Adam I. Misoprostol versus oxytocin for induction of labor. *International Journal of Gynecology & Obstetrics* 2005;**91**:254–5.

050 Frohn 2002 ***{published data only}***
Frohn WE, Simmons S, Carlan SJ. Prostaglandin E2 gel versus misoprostol for cervical ripening in patients with premature rupture of membranes after 34 weeks. *Obstetrics & Gynecology* 2002;**99**(2):206–10.

050 Gelisen 2005 ***{published data only}***
Gelisen O, Caliskan E, Dilbaz S, Ozdas E, Dilbaz B, Ozdas E, et al.Induction of labor with three different techniques at 41 weeks of gestation or spontaneous follow up until 42 weeks in women with definitely unfavorable cervical scores. *European Journal of Obstetrics & Gynecology and Reprodutive Biology* 2005;**120**(2):164–9.

050 Gotschall 1998 ***{published data only}***
Gottschall D, Borgida AF, Feldman DM, Alberti W, Rodis JF. Preinduction cervical ripening comparing 50 and 100 mcg of misoprostol. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S93.

050 Kovavisarach 1997 ***{published data only}***
Kovavisarach E, Wattanasiri S. Comparison of intravaginal misoprostol and dinoprostone for cervical ripening and labour induction at term with unfavorable cervix: a randomized controlled study. *Thai Journal of Obstetrics and Gynaecology* 1997;**9**(3):175–81.

050 Kovavisarach 1998 ***{published data only}***
Kovavisarach E, Worachet W. Randomized controlled trial of intravaginal 50 mcg misoprostol and 3 mg dinoprostone for cervical ripening and labour induction at term with unfavorable cervix. *Thai Journal of Obstetrics and Gynaecology* 1998;**10**(1):27–32.

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050 Le Roux 2002 ***{published data only}***
Le Roux PA, Olarogun JO, Penny J, Anthony J. Oral and vaginal misoprostol compared with dinoprostone for induction of labor: a randomized controlled trial. *Obstetrics & Gynecology* 2002;**99**(2):201–5.

050 Lokugamage 2003a ***{published data only}***
Lokugamage AU, Forsyth SF, Sullivan KR, El Refaey H, Rodeck CH. Randomized trial in multiparous patients: investigating a singe vs. two-dose regimen of intravaginal misoprostol for induction of labor. *Acta Obstetricia et Gynecologica Scandinavica* 2003;**82**:138–42.

050 Lokugamage 2003b ***{published data only}***
Lokugamage AU, Forsyth SF, Sullivan KR, El Refaey H, Rodeck CH. Dinoprostone versus misoprostol: a randomized study of nulliparous women undergoing induction of labour. *Acta Obstetricia et Gynecologica Scandinavica* 2003;**82**:133–7.

050 Majoko 2002a ***{published data only}***
Majoko F, Nystrom L, Lindmark G. No benefit, but increased harm from high dose (100ug) misoprostol for induction of labour: a randomised trial of high vs. low (50ug) dose misoprostol. *Journal of Obstetrics and Gynaecology* 2002;**22**(6):614–7.

050 Mosquera 1999 ***{published data only}***
Mosquera J, Mesa JC, Navarro H, Cobo E, Neira C, Zuniga J. Study of the efficacy of misoprostol compared with oxytocin for labor induction in women with prolonged amenorrhea [Estudio de la eficacia de misoprostol comparado con oxitocina, en la induccion del parto en la amenorrea prolongada]. *Revista Colombiana de Obstetricia y Ginecologia* 1999;**50**(1):7–12.

050 Neiger 2001 ***{published data only}***
Neiger R, Greaves PC. Comparison between vaginal misoprostol and cervical dinoprostone for cervical ripening and labor induction. *Tennessee Medicine* 2001;**94**(1):25–7.

050 Ortiz 2002 ***{published data only}***
Morgan-Ortiz F, Castro EQ, Martinez CBC, Barraza JB, Ramirez IO. Misoprostol and oxytocin for induction of cervical ripening and labor in patients with term pregnancy and premature membrane rupture [Misoprostol y oxitocina para induccion de madurez cervical y trabajo de parto en pacientes con embarazo a termino y ruptura prematura de membranas]. *Ginecologia y Obstetricia de Mexico* 2002;**70**: 469–76.

050 Pandis 2001 ***{published data only}***
Pandis GK, Papageorghiou AT, Otigbah CM, Howard RJ, Nikolaides KH. Randomized study of vaginal misoprostol (PGE1) and dinoprostone gel (PGE2) for induction of labour at term. *Ultrasound in Obstetrics and Gynaecology* 2001;**18**:629–35.

050 Ramsey 1998 ***{published data only}***
Ramsey PS, Harris DY, Ogburn PL, Heise RH, Magtibay PM, Ramin KD. Comparative cost analysis of prostaglandin analogues dinoprostone and misoprostol as labor preinduction agents [abstract]. *Primary Care Update for Ob/Gyns* 1998;**5**(4):182.

050 Ramsey 2003 ***{published data only}***
Ramsey P, Harris D, Ogburn P, Heise R, Magtibay P, Ramin K. Comparative efficacy of prostaglandin analogues dinoprostone and misoprostol as labor preinduction agents. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S94.
Ramsey P, Meyer L, Harris D, Ogburn P, Ramin K. Characterization of cardiotocographic abnormalities associated with dinoprostone and misoprostol cervical ripening/labor induction. *American Journal of Obstetrics and Gynecology* 2001;**184**(1):S115.
* Ramsey PS, Harris DY, Ogburn PL, Heise RH, Magtibay PM, Ramin KD. Comparative efficacy and cost of the prostaglandin analogs dinoprostone and misoprostol as labor preinduction agents. *American Journal of Obstetrics and Gynecology* 2003;**188**(2):560–5.

050 Ramsey 2005 ***{published data only}***
Ramsey PS, Meyer L, Walkes BA, Harris D, Ogburn Jr PL, Heise RH, et al.Cardiotocographic abnormalities associated with dinoprostone and misoprostol cervical ripening. *Obstetrics & Gynecology* 2005;**105**(1):85–90.

050 Rozenberg 2001 ***{published data only}***
Rozenberg P, Chevret S, Goffinet F, Durand-Zaleski I, Ville Y, Vayssiere C, et al.Induction of labour with a viable infant: a randomised clinical trial comparing intravaginal misoprostol and intravaginal dinoprostone. *BJOG: an international journal of obstetrics and gynaecology* 2001;**108**: 1255–62.

050 Rozenberg 2004 ***{published data only}***
Rozenberg P, Chevret S, Senat MV, Bretelle F, Bonnal AP, Ville Y. A randomized trial that compared intravaginal misoprostol and dinoprostone vaginal insert in pregnancies at high risks of fetal distress. *American Journal of Obsterics and Gynecology* 2004;**191**:247–53.

050 Sahu 2004 ***{published data only}***
Sahu L, Chakravertty B. Comparison of prostaglandin E1 (misoprostol) with prostaglandin E2 (dinoprostone) for labour induction. *Journal of Obsterics and Gynecology of India* 2004;**54**(2):139–42.

050 Sifakis 2007 ***{published data only}***
Sifakis S, Angelakis E, Avgoustinaks E, Fragouli Y, Mantas N, Koukoura O, et al.A randomized comparison between intravaginal misoprostol and prostaglandin E2 for labour induction. *Archives of Gynecology and Obstetrics* 2007;**275**: 263–7.

050 Surbek 1997 ***{published data only}***
* Surbek DV, Boesiger H, Hoesli I, Pavic N, Holzgreve W. A double-blind comparison of the safety and efficacy of intravaginal misoprostol and prostaglandin E2 to induce labor. *American Journal of Obstetrics and Gynecology* 1997; **177**(5):1018–23.
Surbek DV, Bosiger H, Hosli I, Pavic N, Holzgreve W. Cervical priming and labor induction with intravaginal misoprostol versus PGE2: a double-blind randomized trial.

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American Journal of Obstetrics and Gynecology 1997;**176**(1 Pt 2):S112.
Surbek DV, Bosiger H, Pavic N, Hosli I, Stoz F, Holzgreve W. The safety of misoprostol for labor induction. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):36.
Surbek DV, Bosiger H, Pavic N, Stoz F, Holzgreve W. Misoprostol (Cytotec) for labor induction in term pregnancies [Misoprostol (Cytotec) zur geburtseinleitung am termin]. 20th Congress of the Swiss Society of Gynecology and Obstetrics; 1997 June; Lugano, Switzerland. 1997:11.

050 Thomas 2000 ***{published data only}***
Thomas N, Longo SA, Rumney PJ, Nageotte MP, Asrat T. Intravaginal misoprostol in prelabor rupture of membranes at term. *American Journal of Obstetrics and Gynecology* 2000; **182**(1 Pt 2):S136.

050G Carlan 1997 ***{published data only}***
Carlan SJ, Bouldin S, O'Brien WF. Extemporaneous preparation of misoprostol gel for cervical ripening: a randomized trial. *Obstetrics & Gynecology* 1997;**90**(6): 911–5.

058 Ferguson 2002 ***{published data only}***
Ferguson J, Head B, Frank F, Frank M, Singer J, Stefos T, et al.Misoprostol versus low-dose oxytocin for cervical ripening: a prospective, randomized, double-masked trial. *American Journal of Obstetrics and Gynecology* 2002;**187**: 273–80.

063 Varaklis 1995 ***{published data only}***
Varaklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin E2 gel for induction of labor at term. *Obstetrics & Gynecology* 1995;**86**:541–4.

075 Buser 1997 ***{published data only}***
Arias F, Buser D, Mora G. Randomized comparison of misoprostol vs dinoprostone for cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S141.
* Buser D, Mora G, Arias F. A randomized comparison between misoprostol and dinoprostone for cervical ripening and labor induction in patients with unfavorable cervices. *Obstetrics & Gynecology* 1997;**89**(4):581–5.

075 Chang 1997 ***{published data only}***
Chang CH, Chang FM. Randomized comparison of misoprostol and dinoprostone for preinduction cervical ripening and labor induction. *Journal of the Formosan Medical Association* 1997;**96**:366–9.

075 Chuck 1995 ***{published data only}***
Chuck F, Huffaker J. Labor induction with intravaginal prostaglandin E1 (PGE1) (Misoprostol, Cytotec) vs intracervical prostaglandin E2 (PGE2) (Dinoprostone, Prepidil gel): a randomized comparison. *American Journal of Obstetrics and Gynecology* 1995;**172**:424.
* Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E2 gel (Prepidil gel): randomized comparison. *American Journal of Obstetrics and Gynecology* 1995;**173**:1137–42.

075 Danielian 1999 ***{published data only}***
* Danielian P, Porter B, Ferri N, Summers J, Templeton A. Misoprostol for induction of labour at term: a more effective agent than dinoprostone vaginal gel. *British Journal of Obstetrics and Gynaecology* 1999;**106**(8):793–7.
Danielian PJ, Porter B. Induction of labour with misoprostol. *Journal of Obstetrics and Gynaecology* 1998;**18** (Suppl 1):S18–S19.

075 Escudero 1997 ***{published data only}***
Escudero F, Contreras H. A comparative trial of labor induction with misoprostol versus oxytocin. *International Journal of Gynecology & Obstetrics* 1997;**57**:139–43.

075 Fuchs 2006 ***{published data only}***
Fuchs K, Brard L, Hodgman D, Silver H. Prostaglandin E1 gel vs. oxytocin for induction of labor at term. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1): S101.

075 Ghidini 2001 ***{published data only}***
Ghidini A, Spong CY, Korker V, Mariani E. Randomized controlled trial of 50 and 100 mcg of misoprostol for induction of labor at term. *Archives of Gynecology and Obstetrics* 2001;**265**:128–30.

075 Kolderup 1999 ***{published data only}***
Kolderup L, McLean L, Grullon K, Safford K, Kilpatrick SJ. Misoprostol is more efficacious for labor induction than prostaglandin E2, but is it associated with more risk?. *American Journal of Obstetrics and Gynecology* 1999;**180**(6 Pt 1):1543–50.

075 Lemancewicz 1999 ***{published data only}***
Lemancewicz A, Urban R, Scotnicki MZ, Karpiuk A, Urban J. Uterine and fetal Doppler flow changes after misoprostol and oxytocin therapy for induction of labor in post-term pregnancies. *International Journal of Gynecology & Obstetrics* 1999;**67**:139–45.

075 Magtibay 1998 ***{published data only}***
Magtibay P, Ogburn P, Harris D, Suman V, Ramin K. Misoprostol as a labor induction agent: a pilot study comparing efficacy, safety and cost. *American Journal of Obstetrics and Gynecology* 1996;**174**(1 Pt 2):327.
* Magtibay PM, Ramin KD, Harris DY, Ramsey PS, Ogburn PL. Misoprostol as a labor induction agent. *Journal of Maternal Fetal Medicine* 1998;7(1):15–8.

075 Megalo 2004 ***{published data only}***
Megalo A, Petignat P, Hohlfeld P. Influence of misoprostol or prostaglandin E2 for induction of labor on the incidence of pathological CTG tracing: a randomized trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2004;**116**:34–8.

075 Mundle 1996 ***{published data only}***
Mundle WR, Young DC. Vaginal misoprostol for induction of labor: a randomized controlled trial. *Obstetrics & Gynecology* 1996;**88**(4 Pt 1):521–5.

075 Reyna-Villasmil 2005 ***{published data only}***
Reyna-Villasmil E, Guerra-Velasquez M, Torres-Montilla M, Reyna-Villasmil N, Mejia-Montilla J, Labarca-Vincero N. Comparative study of intravaginal misoprostol effect at

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

50 and 100 mcg in cervical ripening and labour induction [Estudio comparativo del efecto del misoprostol intravaginal a dosis de 50 y 100 mcg en la maturación cervical y la inducción del parto]. *Investigacion Clinica* 2005;**46**(2): 179–86.

075 S-Ramos 1997 ***{published data only}***
Sanchez-Ramos L, Chen A, Briones D, Del Valle GO, Gaudier FL, Delke I. Premature rupture of membranes at term: induction of labor with intravaginal misoprostol tablets (PGE1) or intravenous oxytocin. *American Journal of Obstetrics and Gynecology* 1994;**170**:377.
* Sanchez-Ramos L, Chen AH, Kaunitz AM, Gaudier FL, Delke I. Labor induction with intravaginal misoprostol in term premature rupture of membranes: a randomized study. *Obstetrics & Gynecology* 1997;**89**:909–12.

075 Sahin 2002 ***{published data only}***
Sahin HG, Sahin HA, Kocer M. Induction of labor in toxemia with misoprostol. *Acta Obstetricia et Gynecologica Scandinavica* 2002;**81**:252–7.

075 Saleen 2006 ***{published data only}***
Saleem S. Efficacy of dinoprostone, intracervical foleys and misoprostol in labour induction. *Journal of the College of Physicians and Surgeons Pakistan* 2006;**16**(4):276–9.

075 Tabor 1995 ***{published data only}***
Tabor B, Anderson J, Stettler B, Wetwiska N, Howard T. Misoprostol vs prostaglandin E2 gel for cervical ripening. *American Journal of Obstetrics and Gynecology* 1995;**172**: 425.

075 Urban 2003 ***{published data only}***
Urban R, Lemancewicz A, Urban J, Skotnicki MZ, Kretowska M. Misoprostol and dinoprostone therapy for labor induction: a Doppler comparison of uterine and fetal hemodynamic effects. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2003;**106**:20–4.

075 Webb 1997 ***{published data only}***
Webb GW, Raynor BD, Huddleston JF, Fandall HW. Induction of labor with an unfavorable cervix: a randomized prospective trial. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S22.

075 Zeteroglu 2004 ***{published data only}***
Zeteroglu S, Sahin HG, Sahin HA. Induction of labour with misoprostol in grand multiparous patients. *International Journal of Gynecology & Obstetrics* 2004;**87**:155–6.

075 Zeteroglu 2006a ***{published data only}***
Zeteroglu S, Engin-Üstün Y, Üstün Y, Güvercinçi M, Sahin G, Kamaci M. A prospective randomized study comparing misoprostol and oxytocin for premature rupture of membranes at term. *Journal of Maternal-Fetal and Neonatal Medicine* 2006;**19**(5):283–7.

075 Zeteroglu 2006b ***{published data only}***
Zeteroglu S, Sahin HG, Sahin HA. Induction of labour in great multipara with misoprostol. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2006;**126** (1):27–32.

075 Zeteroglu 2006c ***{published data only}***
Zeteroglu S, Sahin GH, Sahin HA. Induction of labor with misoprostol in pregnancies with advanced maternal age.. *European Journal of Obstetrics & Gynecology and Reproductive Health* 2006;**129**(2):140–4.

088 Garry 2003 ***{published data only}***
Garry D, Figueroa R, Kalish RB, Catalano CJ, Maulik D. Randomized controlled trial of vaginal misoprostol versus dinoprostone vaginal insert for labor induction. *Journal of Maternal-Fetal and Neonatal Medicine* 2003;**13**:254–9.

088 Pi 1999 ***{published data only}***
Pi P, Zhu F. Clinical observation of misoprostol on induction in late pregnancy. *Bulletin of Humam Medical University* 1999;**24**:195–7.

088 Saggaf 2001 ***{published data only}***
Saggaf A, Rouzi AA, Radhan B, Alshehry S, Yamani T, Abduljabbar H. Misoprostol for preinduction cervical ripening and induction of labor: a randomized controlled trial. *Saudi Journal of Obstetrics and Gynecology* 2001;**1**(2): 89–93.

088 Sanchez Ramos 1998 ***{published data only}***
Sanchez-Ramos L, Peterson DE, Delke I, Gaudier FL, Kaunitz AM. Labor induction with prostaglandin E1 misoprostol compared with dinoprostone vaginal insert: a randomized trial. *Obstetrics & Gynecology* 1998;**91**(3): 401–5.

088 Wing 1995a ***{published data only}***
Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E2 gel for preinduction cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 1995;**172**: 1804–10.

100 Fletcher 1994 ***{published data only}***
Fletcher H, Mitchell S, Frederick J, Simeon D, Brown D. Intravaginal misoprostol versus dinoprostone as cervical ripening and labor-inducing agents. *Obstetrics & Gynecology* 1994;**83**:244–7.

100 Herabutya 1997 ***{published data only}***
Herabutya Y, O-Prasertsawat P, Pokirom J. A comparison of intravaginal misoprostol and intracervical prostaglandin E2 gel for ripening of unfavourable cervix and labor induction. *Journal of Obstetrics and Gynaecology Researc* 1997;**23**: 369–74.

100 Howarth 1996 ***{published data only}***
* Howarth GR, Funk M, Steytler P, Pistorius L, Makin J, Pattinson RC. A randomised controlled trial comparing vaginally administered misoprostol to vaginal dinoprostone gel in labour induction. *Journal of Obstetrics and Gynaecology* 1996;**16**:474–8.
Steytler P, Howarth G, Makin J. Cervical ripening and labour induction. Randomised controlled trial comparing misoprostol and dinoprostone vaginal gel. Proceedings of the 14th Conference on Priorities in Perinatal Care in South Africa; 1995 March 7-10; South Africa. 1995:167–70.
Steytler P, Howarth GR, Funk M, Pistorius L, Makin J, Pattinson RC. A randomised control trial comparing

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

severe preeclampsia remote from term. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(176):37.

eeverria 1995 ***{published data only}***
Echeverria E, Rocha M. Randomised comparative study of induced labor with oxytocin and misoprostol in prolonged pregnancies. *Revista Chilena de Obstetricia y Ginecologia* 1995;**60**:108–11.

ekhavi 2002 ***{published data only}***
Eftekhavi N. A comparison of vaginal misoprostol with intravenous oxytocin for cervical ripening and labor induction [abstract]. *Journal of Obstetrics and Gynaecology Research* 2002;**28**(1):47–8.

Din 2000 ***{published data only}***
El-Din NMN, El Moghazt DAM. Cervical ripening and induction of labour with misoprostol, prostaglandin E2 or prostaglandin E2 gel: a randomized comparative clinical trial [abstract]. XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA (Book 4). 2000:29.

alante 1993 ***{published data only}***
Escalante G, Ribas D, Esquivel A, Moya R, Sanchez LO, Pena YC. Misoprostol intracervical or vaginal. Clinical characteristics in delivery induction [Misoprostol intracervical vs. vaginal: caracteristicas clinicas en la induccion del parto]. *Revista Costarricense de Ciencias Medicas* 1993;**14**(3):43–50.

nseca 2007 ***{published data only}***
Fonseca L, Lucas M, Wood H, Phat'Ak D, Susan R, Gilstrap L, et al.RCT of misoprostol pre-induction ripening vs oxytocin induction. *American Journal of Obstetrics and Gynecology* 2007;**197**(6 Suppl 1):S106, Abstract no: 348.
* Fonseca L, Wood HC, Lucas MJ, Ramin SM, Patak D, Gilstrap III LC, et al.Randomized trial of preinduction cervical ripening: misoprostol vs oxytocin. *American Journal of Obstetrics and Gynecology* 2008;**199**:305–e1-305-e5.

ija 2006 ***{published data only}***
Girija S, Manjunath AP. Randomized controlled trial of vaginal misoprostol: single 50 mcg dose versus multiple 25 mcg dose for labour induction. 49th All India Congress of Obstetrics and Gynaecology; 2006 January 6-9; Cochin, Kerala State, India. 2006:40.

rzelac 1999 ***{published data only}***
Leszczynska-Gorzelak B, Laskowska M, Oleszczuk J. Using of misoprostol for preinduction and induction in term pregnancy. *Ginekologia Polska* 1999;**70**(12):881–9.

rzelac 2001 ***{published data only}***
Leszczynska-Gorzelak B, Laskowska M, Oleszczuk J. Comparative analysis of the effectiveness of misoprostol and prostaglandin E2 in the pre-induction and induction of labor. *Medical Science Monitor* 2001;7(5):1023–8.

rms 2001 ***{published data only}***
Harms K, Nguyen C, Toy EC, Baker B. Intravaginal misoprostol versus cervidil for cervical ripening in term pregnancies [abstract]. Obstetrics & Gynecology 2001; Vol. 97, issue 4 Suppl:36S.

Hoesli 2003 ***{published data only}***
Hoesli I, Gairing A, Lapaire O, Tercanli S, Holzgreve W. Induction of labour: cervical length measurement beside misoprostol or dinoproston - is it a reliable factor both for patients and their obstetrical team?. *Ultrasound in Obstetrics & Gynecology* 2003;**22**(Suppl 1):149.

How 2001 ***{published data only}***
How H, Leaseburge L, Khoury J, Siddiqi T, Sibai B. Is there an ideal route of misoprostol administration for cervical ripening and labor indoction?. *American Journal of Obstetrics and Gynecology* 2001;**184**(1):S118.

Hu 2005 ***{published data only}***
Hu JL, Liu ML, Zhang MX. Study on the medication of misoprostol to induce premature rupture of membranes at term. *Practical Clinical Medicine* 2005;**6**(8):71–4.

Jackson 1999 ***{published data only}***
Jackson N, Irvine R, Edmonds D, Paterson-Brown S. Random allocation controlled trial of intravaginal misoprostol versus intravaginal dinoprostone for the induction of labour. *Journal of Obstetrics and Gynaecology* 2000;**20**(Suppl 1):S52.
Jackson NV, Irvine R, Paterson-Brown S. Randomised, controlled trial of intravaginal misoprostol versus intravaginal dinoprostone gel in the induction of labour at term. Womens Health - into the new millennium. Proceedings of the 4th International Scientific Meeting of the Royal College of Obstetricians and Gynaecologists; 1999 Oct 3-6; Cape Town, South Africa. 1999:32.
Jackson NV, Terzidou V, Irvine RV, Edmonds DK, Paterson-Brown S. Randomised controlled trial of intravaginal misoprostol versus intravaginal dinoprostone for the induction of labour. XVI FIGO World Congress of Obstetrics & Gynecology; 2000 Sept 3-8; Washington DC, USA (Book 4). 2000:29–30.

Jazayeri 2003 ***{published data only}***
Jazayeri A, Jazayeri M, Jamal A, Eslamian L, Maoorsi V, Borna S. Prospective randomized clinical trial of cervical ripening with misoprostol for either 8 or 24 hours. *American Journal of Obstetrics and Gynecology* 2003;**6 Suppl 1**:S70.

Jouatte 2000 ***{published data only}***
Jouatte F, Subtil D, Marquis P, Plennevaux JL, Puech F. Medical indications of labor induction: a comparison between intravaginal misoprostol and intravenous dinoprostone [Declenchement du travail d'indication medicale: comparaison du misoprostol intravaginal avec une prostaglandine E2 administree par voie intraveineuse]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction (Paris)* 2000;**29**:763–71.

Kwon 1999 ***{published data only}***
Kwon JS, MacKenzie VP, Davies GAL. A comparison of oral and vaginal misoprostol for induction of labour at term: a randomized trial. *American Journal of Obstetrics and Gynecology* 1999;**180**(1 Pt 2):S128.

pyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

American Journal of Obstetrics and Gynecology 1999;**180**(1 Pt 2):S127.

Yang 2000 ***{published data only}***
Yang R. Clinical study of labour induced by low dose misoprostol in late gestation. *Continuing Medical Education* 2000;**14**(2):43–4.

Young 2001 ***{published data only}***
Young D, Delaney T, Armson T, Fanning C. Lower dose vaginal and oral misoprostol in labor induction - rct [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**185**(6 Suppl):S203.

Zang 1997 ***{published data only}***
Zhang LJ, Qu LP, Guo WX, Liu ZH. Clinical study of labour induced by low dose misoprostol. *Journal of Ningxia Medicine* 1997;**19**(6):362.

Zang 2003 ***{published data only}***
Zang CY. Clinical study of different doses of misoprostol for the induction of labour. *Chinese Clinical Medicine Journal* 2003;**59**:9839–40.

Zhao 2003 ***{published data only}***
Zhao YL. Clinical study of labour induced by low dose misoprostol in late gestation. *China Clinical Medicine Research Journal* 2003;**81**:134–42.

Zhu 1998 ***{published data only}***
Zhu HX, Hu LY, Luo Y, Li XQ. Clinical study on labour induction by low dose misoprostol. *Jiang Shu Clinical Medical Journal* 1998;**2**(3):255–6.

Zhuang 2000 ***{published data only}***
Zhuang G, Su Q, Zhang J, Xie J, Zhu J, Cheng L. Study on misoprostol suspension per os for inducing term labor. *Chinese Journal of Obstetric and Gynaecological Practice* 2000; **16**(8):481–3.

References to studies awaiting assessment

Abedi-Asl 2007 ***{published data only}***
Abedi-Asl Z, Farrokhi M, Rajaee M. Comparative efficacy of misoprostol and oxytocin as labor preinduction agents: a prospective randomized trial. *Acta Medica Iranica* 2007;**45** (6):443–8.

Bebbington 2003a ***{published data only}***
Bebbington M, Pevzner L, Schmuel E, Bernstein P, Dayal A, Barnhard J, et al.Uterine tachysystole and hyperstimulation during induction of labor [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):S211.

Bebbington 2003b ***{published data only}***
Bebbington M, Schmuel E, Pevzner L, Bernstein P, Dayal A, Barnhard J, et al.Misoprostol versus dinoprostone for labor induction at term: a randomized controlled trial [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):S211.

Bolnick 2002b ***{published data only}***
Bolnick JM, Velazquez MD, Gonzalez JL, Rappaport VJ, McIlwain-Dunivan G, Rayburn WF. Randomized trial between two active labor management protocols in the presence of an unfavorable cervix. *American Journal of Obstetrics and Gynecology* 2004;**190**(1):124–8.

Bricker 2007 ***{published data only}***
Bricker L, Peden H, Alfirevic Z. The prommis trial: a multicentre randomised trial to evaluate a low dose misoprostol regimen for induction of labour in the presence of prelabour rupture of the amniotic membranes. *Journal of Obstetrics and Gynaecology* 2007;**27**(Suppl 1):S22–S23.

Bricker 2008 ***{published data only}***
Bricker L, Peden H, Tomlinson AJ, Al-Hussaini TK, Idama T, Candelier C, et al.Titrated low-dose vaginal and/or oral misoprostol to induce labour for prelabour membrane rupture: a randomised trial. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(12):1503–11.

Deng 1999 ***{published data only}***
Deng LL, Huang ZJ. Observation on the efficacy of intravaginal misoprostol for cervical ripening in the third trimester of pregnancy. *Journal of Nursing Science* 1999;**14** (2):67–8.

ElSedeek 2009 ***{published data only}***
ElSedeek M, Awad EE, ElSebaey SM. Evaluation of postpartum blood loss after misoprostol-induced labour. *BJOG: an international journal of obstetrics and gynaecology* 2009;**116**(3):431–5.

Gupta 2006 ***{published data only}***
Gupta N, Mishra SL, Shradha J. A randomized clinical trial comparing misoprostol and dinoprostone for cervical ripening and labor induction. *Journal of Obstetrics and Gynecology of India* 2006;**56**(2):149–51.

Li 2000 ***{published data only}***
Li FM. A study of misoprostol on induction of labor in term pregnancy. *Journal of Practical Obstetrics and Gynecology* 2000;**16**(3):139–41.

Lughmani 2009 ***{published data only}***
Lughmani S. Vaginal misoprostol versus oxytocin infusion for labour induction in great grand multipara. A randomized controlled trial. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S250.

Milchev 2003 ***{published data only}***
Milchev N, Kuzmanov B, Terzhumanov R. Cytotec: an effective drug for the induction of labor [Cytotec: efektivno sredstvo za induktsiia na razhdaneto]. *Akusherstvo i Ginekologiia* 2003;**42**(3):9–11.

Moodley 2003 ***{published data only}***
Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term - a comparative study. *South African Journal of Obstetrics and Gynaecology* 2003;**9** (2):34–7.

Nigam 2010 ***{published data only}***
Nigam A, Madan M, Puri M, Agarwal S, Trivedi SS. Labour induction with 25 micrograms versus 50 micrograms intravaginal misoprostol in full term pregnancies. *Tropical Doctor* 2010;**40**(1):53–5.

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Ozkan 2009 *{published data only}*

Ozkan S, Caliskan E, Doger E, Yucesoy I, Ozeren S, Vural B. Comparative efficacy and safety of vaginal misoprostol versus dinoprostone vaginal insert in labor induction at term: a randomized trial. *Archives of Gynecology and Obstetrics* 2009;**280**(1):19–24.

Pevzner 2008 *{published data only}*

Pevzner L, Rumney P, Petersen R, Wing D. Predicting a successful induction of labor: a secondary analysis of misoprostol vaginal insert trial. *American Journal of Obstetrics and Gynecology* 2008;**199**(6 Suppl 1):S72.

Pevzner 2009a *{published data only}*

Pevzner L, Alfirevic Z, Powers B, Wing D. Cardiotocographic abnormalities associated with misoprostol and dinoprostone cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 2009;**201**(6 Suppl 1):S124.

Pevzner 2009b *{published data only}*

Pevzner L, Rayburn WF, Rumney P, Wing DA. Factors predicting successful labor induction with dinoprostone and misoprostol vaginal inserts. *Obstetrics & Gynecology* 2009; **114**(2 Pt 1):261–7.

Prager 2008 *{published data only}*

Prager M, Eneroth-Grimfors E, Edlund M, Marions L. A randomised controlled trial of intravaginal dinoprostone, intravaginal misoprostol and transcervical balloon catheter for labour induction. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(11):1443–50.

Tabasi 2007 *{published data only}*

Tabasi Z, Behrashi M, Mahdian M. Vaginal misoprostol versus high dose of oxytocin for labor induction: a comparative study. *Pakistan Journal of Biological Sciences* 2007;**10**(6):920–3.

Wang 2000 *{published data only}*

Wang YZ, Zhu BL, Li M, Bu YG. Clinical observation of the effects of accelerating the maturation of the cervix and induction by various doses of misoprostol. *Anhui Medical Journal* 2000;**21**(2):23–4.

Wing 2008 *{published data only}*

Wing DA, for the Misoprostol Vaginal Insert Consortium. Misoprostol vaginal insert compared with dinoprostone vaginal insert: a randomized controlled trial. *Obstetrics & Gynecology* 2008;**112**(4):801–12.

Yin 2006 *{published data only}*

Yin CY, Zhou JZ, Wang BP, Lu XY. Effect and risk analysis of misoprostol in stimulating cervical maturity for post-term pregnancy. *Nan Fang Yi Ke Da Xue Xue Bao//Journal of Southern Medical University* 2006;**26**(2):182-4; 188.

References to ongoing studies

Botero 1998 *{unpublished data only}*

Botero L. Labor induction with unfavourable cervix. Randomized controlled trial. Double blind method. Oxytocin versus misoprostol. Personal communication 1998.

Gregson 2003 *{published data only}*

Gregson S. To compare the safety and efficacy of 'low dose' vaginal misoprostol and dinoprostone vaginal gel for induction of labour at term. Current Controlled Trials (www.controlled-trials.com/mrct) (accessed 15 September 2004).

Jackson 2000 *{published data only}*

Jackson N, Paterson-Brown S. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of the membranes [letter]. *BJOG: an international journal of obstetrics and gynaecology* 2000;**107**(9):1181–2.

Additional references

Alfirevic 2006

Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD001338.pub2]

Bennett 1997

Bennett BB. Uterine rupture during induction of labor at term with intravaginal misoprostol. *Obstetrics & Gynecology* 1997;**89**(5 Pt 2):832–3.

Bishop 1964

Bishop EH. Pelvic scoring for elective induction. *Obstetrics & Gynecology* 1964;**24**:266–8.

Blanchette 1999

Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labor in a community hospital. *American Journal of Obstetrics and Gynecology* 1999;**180**:1551–9.

Boulvain 2001

Boulvain M, Kelly AJ, Lohse C, Stan CM, Irion O. Mechanical methods for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD001233]

Boulvain 2005

Boulvain M, Stan CM, Irion O. Membrane sweeping for induction of labour. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD000451.pub2]

Boulvain 2008

Boulvain M, Kelly AJ, Irion O. Intracervical prostaglandins for induction of labour. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD006971]

Bricker 2000

Bricker L, Luckas M. Amniotomy alone for induction of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002862]

Choy-Hee 2001

Choy-Hee L, Raynor BD. Misoprostol induction of labor among women with a history of cesarean delivery. *American Journal of Obstetrics and Gynecology* 2001;**184**:1115–7.

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Clarke 2000
Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1 [updated June 2000]. In: Review Manager (RevMan) [Computer program]. Version 4.1 Oxford, England: The Cochrane Collaboration, 2000.

Costa 1993
Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. *Lancet* 1993;**341**:1258–61.

Curtis 1987
Curtis P, Evans S, Resnick J. Uterine hyperstimulation. The need for standard terminology. *Journal of Reproductive Medicine* 1987;**32**:91–5.

Daisley 2000
Daisley H. Maternal mortality following the use of misoprostol. *Medicine, Science and the Law* 2000;**40**(1): 78–82.

Deeks 2001
Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.

Egarter 1990
Egarter CH, Husslein PW, Rayburn WF. Uterine hyperstimulation after low-dose prostaglandin E2 therapy: tocolytic treatment in 181 cases. *American Journal of Obstetrics and Gynecology* 1990;**163**:794–6.

Fonseca 1991
Fonseca W, Alencar AJC, Mota FSB, Coelho HLL. Misoprostol and congenital malformations. *Lancet* 1991; **338**:56.

French 2001
French L. Oral prostaglandin E2 for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003098]

Gherman 1999
Gherman RB, McBrayer S, Browning J. Uterine rupture associated with vaginal birth after cesarean section: a complication of intravaginal misoprostol?. *Gynecologic and Obstetric Investigation* 2000;**50**:212–3.

Hapangama 2009
Hapangama D, Neilson JP. Mifepristone for induction of labour. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002865.pub2]

Higgins 2008a
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Higgins 2008b
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008.. Available from www.cochrane-handbook.org.

Hill 2000
Hill DA, Chez RA, Quinlan J, Fuentes A, LaCombe J. Uterine rupture and dehiscence associated with intravaginal misoprostol cervical ripening. *Journal of Reproductive Medicine* 2000;**45**:823–6.

Hofmeyr 2009
Hofmeyr GJ, Alfirevic Z, Kelly AJ, Kavanagh J, Thomas J, Neilson JP, et al.Methods for cervical ripening and labour induction in late pregnancy: generic protocol. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002074.pub2]

Howarth 2001
Howarth G, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD003250]

Hutton 2001
Hutton EK, Mozurkewich EL. Extra-amniotic prostaglandin for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003092]

Kavanagh 2001
Kavanagh J, Kelly AJ, Thomas J. Sexual intercourse for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003093]

Kavanagh 2005
Kavanagh J, Kelly AJ, Thomas J. Breast stimulation for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD003392.pub2]

Kavanagh 2006a
Kavanagh J, Kelly AJ, Thomas J. Corticosteroids for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003100.pub2]

Kavanagh 2006b
Kavanagh J, Kelly AJ, Thomas J. Hyaluronidase for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003097.pub2]

Keirse 1993
Keirse MJNC. Prostaglandins in preinduction cervical ripening: meta-analysis of worldwide clinical experience. *Journal of Reproductive Medicine* 1993;**38 Suppl**:89–98.

Kelly 2001a
Kelly AJ, Tan BP. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD003246]

Kelly 2001b
Kelly AJ, Kavanagh J, Thomas J. Relaxin for cervical ripening and induction of labour. *Cochrane Database*

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of Systematic Reviews 2001, Issue 2. [DOI: 10.1002/14651858.CD003103]

Kelly 2001c
Kelly AJ, Kavanagh J, Thomas J. Castor oil, bath and/or enema for cervical priming and induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003099]

Kelly 2003
Kelly AJ, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003101]

Kelly 2008
Kelly AJ, Kavanagh J. Nitric oxide donors for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD006901]

Khosla 2002
Khosla AH, Sirohiwal D, Sangwan K. A still birth and uterine rupture during induction of labour with oral misoprostol. *Australia and New Zealand Journal of Obstetrics and Gynaecology* 2002;**42**(4):412.

Luckas 2000
Luckas M, Bricker L. Intravenous prostaglandin for induction of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002864]

MacKenzie 1997
MacKenzie IZ, Burns E. Randomised trial of one versus two doses of prostaglandin E2 for induction of labour: 1. Clinical outcome. *British Journal of Obstetrics and Gynaecology* 1997;**104**:1062–7.

Mariani Neto 1987
Mariani Neto C, Leao EJ, Baretto EM, Kenj G, De Aquino MM. Use of misoprostol for labour induction in stillbirths. *Revista Paulista de Medicina* 1987;**105**:325–8.

Mariani Neto 1988
Mariani Neto C, Delbin AL, Val RD. Tocographic pattern caused by misoprostol [Padrao tocografico desencadeado pelo misoprostol]. *Revista Paulista de Medicina* 1988;**106**:205–8.

Matonhodze 2002
Matonhodze BB, Katsoulis LC, Hofmeyr GJ. Labor induction and meconium: in vitro effects of oxytocin, dinoprostone and misoprostol on rat ileum relative to myometrium. *Journal of Perinatal Medicine* 2002;**30**(5):405–10.

Matthews 1999
Mathews JE, Mathai M, George A. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *American Journal of Obstetrics and Gynecology* 1999;**181**(3):626–9.

Merrell 1995
Merell DA, Koch MAT. Induction of labour with misoprostol in the second and third trimesters of pregnancy. *South African Medical Journal* 1995;**85**:1088–90.

Merrell 1996
Merrell DA, Koch MAT, Thomas PC. Experience with vaginal and rectal misoprostol as an oxytocic agent in pregnancy.. PAFMACH Conference; 1996; Johannesburg, South Africa. 1996.

Mitri 1987
Mitri F, Hofmeyr GJ, Van Gelderen CJ. Meconium during labour: self-medication and other associations. *South African Medical Journal* 1987;**71**:431–3.

Muzonzini 2004
Muzonzini G, Hofmeyr GJ. Buccal or sublingual misoprostol for cervical ripening and labour induction. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004221.pub2]

Norman 1991
Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991;**338**:1233–6.

Plaut 1999
Plaut MM, Schwartz ML, Lubarsky SL. Uterine rupture associated with the use of misoprostol in the gravid patient with a previous cesarean section. *American Journal of Obstetrics and Gynecology* 1999;**180**(6 pt 1):1532–42.

Ravasia 2000
Ravasia DJ, Wood SL, Pollard JK. Uterine rupture during induced trial of labor among women with previous cesarean delivery. *American Journal of Obstetrics and Gynecology* 2000;**183**:1176–9.

RevMan 2008
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Sanchez-Ramos 1997
Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstetrics & Gynecology* 1997;**89**:633–42.

Sciscione 1998
Sciscione AC, Nguyen L, Manley JS, Shlossman PA, Colmorgen GH. Uterine rupture during preinduction cervical ripening with misoprostol in a patient with a previous caesarean delivery. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1998;**38**(1):96–7.

Senior 1993
Senior J, Marshall K, Sangha R, Clayton JK. In vitro characterisation of prostanoid receptors on human myometrium at term pregnancy. *British Journal of Pharmacology* 1993;**108**:501–6.

Smith 2003
Smith CA. Homoeopathy for induction of labour. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003399]

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Smith 2004

Smith CA, Crowther CA. Acupuncture for induction of labour. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD002962.pub2]

Thomas 2001

Thomas J, Kelly AJ, Kavanagh J. Oestrogens alone or with amniotomy for cervical ripening or induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD003393]

Wing 1999b

Wing DA. Labor induction with misoprostol. *American Journal of Obstetrics and Gynecology* 1999;**181**(2):339–45.

Zieman 1997

Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstetrics & Gynecology* 1997;**90**:88–92.

References to other published versions of this review

CDSR 1999

Hofmeyr GJ. Misoprostol administered vaginally for cervical ripening and labour induction in the third trimester (Cochrane Review). *Cochrane Database of Systematic Reviews* 1998, Issue 3.

CDSR 2000

Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). *Cochrane Database of Systematic Reviews* 2000, Issue 4.

CDSR 2004

Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour (Cochrane Review). *Cochrane Database of Systematic Reviews* 2004, Issue 1.[Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.pub2]

* *Indicates the major publication for the study*

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DATA AND ANALYSES

Comparison 1. Misoprostol versus placebo/no treatment: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved in 24 hours	5	769	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 1.03]
2 Uterine hyperstimulation with FHR changes	5	777	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.95, 5.99]
3 Caesarean section	10	1141	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.05]
4 Neonatal encephalopathy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cervix unfavourable/unchanged after 12-24 hours	2	107	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.64]
6 Oxytocin augmentation	5	429	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.38, 1.02]
7 Uterine hyperstimulation without FHR changes	6	794	Risk Ratio (M-H, Fixed, 95% CI)	3.52 [1.78, 6.99]
8 Uterine rupture	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Instrumental vaginal delivery	3	184	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.65, 1.77]
10 Meconium-stained liquor	6	814	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.87]
11 Apgar score < 7 at 5 minutes	4	717	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.34, 11.80]
12 Neonatal intensive care unit admission	6	852	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.48]
13 Perinatal death	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.14]
14 Maternal side effects	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.12, 66.62]
15 Postpartum haemorrhage	3	184	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.19, 4.62]
16 Serious maternal complication	3	272	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.87]
17 Maternal death	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Misoprostol versus placebo/no treatment: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved in 24 hours	4	619	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.23, 2.15]
2 Uterine hyperstimulation with FHR changes	4	627	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.73, 5.71]
3 Caesarean section	7	862	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.69, 1.30]
4 Cervix unfavourable/unchanged after 12-24 hours	2	107	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.64]
5 Oxytocin augmentation	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.26, 0.58]
6 Uterine hyperstimulation without FHR changes	5	714	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [1.63, 7.38]
7 Uterine rupture	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Instrumental vaginal delivery	2	107	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.50, 2.12]

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9 Meconium-stained liquor	4	612	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.31, 0.89]
10 Apgar score < 7 at 5 minutes	3	567	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.34, 11.80]
11 Neonatal intensive care unit admission	3	505	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.35, 2.05]
12 Perinatal death	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Maternal side effects	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.12, 66.62]
14 Postpartum haemorrhage	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.13, 6.37]
15 Serious maternal complication	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Maternal death	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Misoprostol versus placebo/no treatment: all women, intact membranes, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved in 24 hours	2	112	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.22, 0.70]
2 Uterine hyperstimulation with FHR changes	3	227	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.52, 10.16]
3 Caesarean section	5	355	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.75, 1.79]
4 Epidural analgesia	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.26]
5 Cervix unfavourable/unchanged after 12-24 hours	2	107	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.64]
6 Oxytocin augmentation	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.26, 0.58]
7 Uterine hyperstimulation without FHR changes	3	167	Risk Ratio (M-H, Fixed, 95% CI)	10.11 [1.91, 53.60]
8 Uterine rupture	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Instrumental vaginal delivery	2	107	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.50, 2.12]
10 Meconium-stained liquor	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.28, 1.77]
11 Apgar score < 7 at 5 minutes	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Neonatal intensive care unit admission	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.04, 3.70]
13 Perinatal death	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Maternal side effects	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.12, 66.62]
15 Postpartum haemorrhage	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.13, 6.37]
16 Serious maternal complication	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Maternal death	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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Comparison 4. Misoprostol versus placebo/no treatment: all women, ruptured membranes, variable or undefined cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine hyperstimulation with FHR changes	1	150	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.46, 34.96]
2 Vaginal delivery not achieved in 24 hours	2	257	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.31, 0.73]
3 Caesarean section	4	386	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.36, 0.91]
4 Apgar score < 7 at 5 minutes	2	257	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Neonatal intensive care unit admission	2	227	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.82]
6 Neonatal encephalopathy	1	150	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Oxytocin augmentation	2	202	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.29, 1.32]
8 Serious maternal complications	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.87]
9 Perinatal death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.14]
10 Instrumental delivery	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.56, 2.22]
11 Postpartum haemorrhage	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.82]
12 Meconium-stained liquor	3	309	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.38, 1.81]
13 Uterine hyperstimulation without FHR changes	1	107	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.38]

Comparison 5. Misoprostol versus placebo/no treatment: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.49, 2.41]

Comparison 6. Misoprostol versus placebo/no treatment: all primiparae and unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.49, 2.41]

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Characteristics of studies pp 30 to 130, and Graphs pp 134 to 444 not printed - available in electronic version.

British Journal of Obstetrics and Gynaecology
August 1999, Vol 106, pp. 798–803

8.

Misoprostol for induction of labour: a systematic review

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Objective To determine, from the best available evidence, the effectiveness and safety of misoprostol administered vaginally or orally for third trimester cervical ripening or induction of labour.

Methods Clinical trials of misoprostol used for cervical ripening or labour induction in the third trimester were identified from the register of randomised trials maintained by the Cochrane Pregnancy and Childbirth Group. All identified trials were considered for inclusion in the review according to a prespecified protocol. Primary outcomes were chosen to address clinical effectiveness (delivery within 24 hours) and safety (uterine hyperstimulation, caesarean section, serious maternal and neonatal morbidity) and were determined *a priori*. All meta-analyses were based on the intention-to-treat principle. In the absence of heterogeneity the summary statistics have been expressed as typical relative risk (RR) and 95% confidence interval (CI).

Results *Vaginal misoprostol:* one small study showed that the use of misoprostol results in more effective cervical ripening and reduced need for oxytocin when compared with placebo. When compared with oxytocin, vaginal misoprostol was more effective for labour induction. The relative risk of failure to achieve vaginal delivery within 24 hours was 0·48 (95% CI 0·35 to 0·66). However, the relative risks for uterine hyperstimulation with and without fetal heart rate abnormalities were 2·54 (95% CI 1·12 to 5·77) and 2·96 (95% CI 2·11 to 4·14), respectively. In three out of four trials which studied women with intact membranes and unfavourable cervices, failure to achieve vaginal delivery within 24 hours was reduced with misoprostol when compared with other prostaglandins (RR 0·71, 95% CI 0·62 to 0·81). Vaginal misoprostol was associated with increased uterine hyperstimulation both without fetal heart rate changes (RR 1·67, 95% CI 1·30 to 2·14) and with associated fetal heart rate changes (RR 1·45, 95% CI 1·04 to 2·04). There was also an increase in meconium stained amniotic fluid following vaginal misoprostol (RR 1·38, 95% CI 1·06 to 1·79). *Oral misoprostol:* one small trial suggests that, when compared with placebo, oral misoprostol reduces the need for oxytocin and shortens the time between induction and delivery. Compared with other prostaglandins one small trial showed a reduced need for oxytocin with oral misoprostol. Two trials compared oral with vaginal misoprostol using different doses. No significant differences were evident.

Conclusions Overall, misoprostol appears to be more effective than conventional methods of cervical ripening and labour induction. Although no differences in perinatal outcome were shown, the studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. In particular the increase in uterine hyperstimulation with fetal heart rate changes following misoprostol is a matter for concern. It is possible that, if sufficient numbers are studied, an unacceptably high number of serious adverse events including uterine rupture and asphyxial fetal deaths may occur. The data at present are not robust enough to address the issue of safety. Thus, though misoprostol shows promise as a highly effective, inexpensive and convenient agent for labour induction, it cannot be recommended for routine use at this stage. Lower dose misoprostol regimens should be investigated further.

INTRODUCTION

Induction of labour in the third trimester of pregnancy may be considered beneficial in many clinical circumstances. The main problems associated with induction of labour are ineffective labour and excessive uterine activity, which may cause fetal distress. Both problems may lead to an increased risk of caesarean section. Failed induction of labour is most likely when the cervix is unfavourable and, in this circumstance, vaginal prostaglandin preparations have proved to be beneficial[1]. However, prostaglandin preparations that have been registered for cervical ripening and labour induction are expensive and unstable, requiring refrigerated storage. Uterine hyperstimulation has been identified as

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An electronic version of this review has been published in the Cochrane Library as two separate reviews.

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a particular problem during labour induction with prostaglandins, and has been treated with tocolysis[2].

Misoprostol (Cytotec, Searle, Illinois, USA) is a methyl ester of prostaglandin E_1 additionally methylated at C-16. It is marketed for use in the prevention and treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. In addition, misoprostol acts as an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors[3]. The drug is inexpensive, easily stored at room temperature and has few systemic side effects. It is rapidly absorbed orally and vaginally. A randomised comparison between oral and vaginal administration of 400 μg misoprostol showed that peak levels after oral administration were higher (227 pg/mL *versus* 165 pg/mL) and occurred sooner (34 *versus* 80 minutes) but appear to be more prolonged[4].

The ability of misoprostol to stimulate uterine contractions has been used for clinical purposes. Misoprostol is shown to be an effective abortifacient, both alone and following pre-treatment with mifepristone[5,6].

Mariani-Neto *et al.*[7] first reported using oral misoprostol (400 μg four hourly) for induction of labour following intrauterine death. Along with its effectiveness, the authors, described cases of excessive uterine activity with misoprostol use at term. A recent meta-analysis suggested that vaginal misoprostol use at term for cervical ripening/induction of labour is safe because no increase in adverse fetal outcome could be shown despite a statistically significant increase in uterine hyperstimulation[8]. However, uncertainty about the safety persists and lower vaginal doses[9] and oral administration have been investigated[10–15].

In this review we have focused on the effectiveness and safety of misoprostol administered vaginally or orally for cervical ripening and labour induction in the third trimester of pregnancy. The primary aim of the review was to ascertain whether the data from randomised controlled trials are robust enough to justify the use of misoprostol in routine clinical practice.

METHODS

This review has drawn on the search strategy developed for the Cochrane Pregnancy and Childbirth Group. Relevant trials were identified from the Group's Specialised Register of Controlled Trials[16]. In addition, the Cochrane Controlled Trials Register who currently includes over 200,000 records of controlled clinical trials was searched using the word *misoprostol*[17].

Eligibility criteria for inclusion included clinical trials comparing misoprostol administered vaginally or orally for third trimester cervical ripening or labour induction with no treatment, placebo or other methods for induction; viable fetus; random allocation to treatment and comparison groups; reasonable measures to ensure allocation concealment; violations of allocated management not sufficient to materially affect outcomes. Trials with inadequate allocation concealment were excluded (e.g. alternation). Formal quality assessment other than assessment of allocation concealment was not planned as there were no planned exclusions or subgroup analysis based on quality. Pre-specified primary comparisons for vaginal and oral misoprostol were as follows:

1. Misoprostol *vs* placebo/no treatment.
2. Misoprostol *vs* oxytocin.
3. Misoprostol *vs* prostaglandins.
4. Misoprostol *vs* mechanical methods.
5. Low dose misoprostol regimen *vs* higher dose regimens. Low dose was defined as doses of ≤ 25 μg at 4 hourly or less frequent intervals.

Subgroup analyses were planned based on the status of membranes (intact or ruptured), cervical status (favourable, unfavourable or undefined) and were limited to the primary outcomes. Five primary outcomes were chosen:

1. Vaginal delivery not achieved within 24 hours.
2. Uterine hyperstimulation with fetal heart rate changes.
3. Caesarean section.
4. Serious neonatal morbidity or perinatal death.
5. Serious maternal morbidity or death.

Secondary outcomes relate to measures of effectiveness, complications and satisfaction. The full list of secondary outcomes can be found in the electronic version of the review[18].

The terminology of uterine hyperstimulation is problematic[19]. We used the phrase *uterine hyperstimulation without fetal heart rate changes* to include uterine tachysystole (> 5 contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and *uterine hyperstimulation with fetal heart rate changes* to denote uterine hyperstimulation syndrome (tachysystole or hypersystole with fetal heart rate changes such as persistent decelerations, tachycardia or decreased short term variability) in this review.

Data were extracted from the sources and entered onto the Review Manager (RevMan) computer software (Update Software, Oxford, UK; Nordic Cochrane Centre, Copenhagen, Denmark) and double checked for accuracy. For dichotomous data, relative risks and 95% confidence intervals were calculated, and in the absence of heterogeneity, results were pooled using a fixed effects model.

Description of included studies

In the vaginal misoprostol review thirty-nine trials were

assessed for eligibility, eight were excluded. One was excluded because allocation was not random[20], two because vaginal misoprostol was compared with cervical misoprostol, which was not a predefined comparison of the review[21,22]. One trial was available only in abstract form, with inadequate data for inclusion[12]. Four trials were excluded for possible inclusion in the review of oral misoprostol for labour induction. Two trial reports were not available to us for assessment[23,24].

In all the studies of misoprostol *versus* prostaglandins, the prostaglandin used was dinoprostone intravaginally as a gel, tablet or slow-release pessary, or intracervically as a gel. In most of the studies oxytocin was used with similar protocols for both the misoprostol and the prostaglandin group. The exception was the study by Kadanali[25] in which oxytocin was started if indicated after six hours in the dinoprostone group and only after 24 hours in the misoprostol group. The effective comparison in this trial is therefore misoprostol *versus* dinoprostone plus early oxytocin. The results are in keeping with those of other studies.

Five trials evaluated oral misoprostol[26]. One study compared oral misoprostol to placebo[10], two studies to vaginal prostaglandins[13,14] and two studies to vaginal misoprostol[11,15].

With the exception of four double-blind placebo controlled trials, the treatment was not blinded. There is therefore a real possibility of bias affecting both the clinical management of the women (e.g. decisions to undertake caesarean section) and the assessment of outcomes. Such biases might operate in either direction. For example, a clinician enthusiastic about the potential of misoprostol might be less likely to perform caesarean section in the misoprostol group, while one anxious about the experimental nature of misoprostol might be more likely to perform caesarean section in this group.

The possibility of such bias must be kept in mind in the interpretation of the results.

RESULTS

The primary outcomes and summary data are shown in the tables. Readers are referred to *The Cochrane Library*[18] for individual trial data and secondary outcomes.

The one small study included in this part of the review[27] showed a beneficial effect of misoprostol on cervical ripening and need for oxytocin. The randomisation to delivery interval was reduced with misoprostol, but the numbers studied were too small to assess the impact on obstetric management and maternal and neonatal complications.

Misoprostol, in the doses used in these trials, was more effective than oxytocin for labour induction (Table 1). However, uterine hyperstimulation was more common both without and with associated fetal heart rate changes. The trial results with respect to caesarean section were inconsistent, ranging from a large reduction[28] following misoprostol administration to no significant difference[29]. Subgroup analysis showed a reduced rate of caesarean section with misoprostol for the group with intact membranes, but not with ruptured membranes, though the numbers studied in the latter comparison were small. A possible explanation for differences between trials is that they could be related to differences in management of misoprostol-related uterine hyperstimulation in different centres. There were no differences in perinatal or maternal outcomes.

In one trial[30] reporting the outcome of vaginal misoprostol compared with dinoprostone, failure to achieve cervical ripening within 12 hours was reduced with misoprostol (RR 0·68, 95% CI 0·52 to 0·88). Failure to achieve vaginal delivery within 24 hours was reduced with misoprostol in all six trials (RR 0·70, 95% CI 0·62 to 0·79). The effectiveness of misoprostol was less pronounced in one trial[31] with a low misoprostol regimen. Oxytocin augmentation was used less often with misoprostol (RR 0·64, 95% CI 0·58 to 0·71). The only trial not consistent with this result was the low dose misoprostol trial[31]. Uterine hyperstimulation without fetal heart rate changes was more common with misoprostol (RR 1·67, 95% CI 1·30 to 2·14), though the findings of the low dose misoprostol trial showed no such increase. Uterine hyperstimulation with associated fetal heart rate abnormalities was variable between trials, but the data from individual trials were consistent with the pooled result showing an increase of this adverse outcome in the vaginal misoprostol group. Caesarean section rates were variable between trials, with no significant differences overall. Meconium stained liquor was increased with misoprostol (RR 1·38, 95% CI 1·06 to 1·79). There were no statistically significant differences in perinatal or maternal outcomes.

In one trial the lower dosage regimen (misoprostol 25 μg six hourly *versus* three hourly) was associated with more failures to achieve delivery within 24 hours, significantly more use of oxytocin (RR 1·23, 95% CI 1·02–1·48) and a trend towards less uterine hyperstimulation with fetal heart rate changes[31]. There were no differences in mode of delivery, meconium stained amniotic fluid, perinatal outcome or maternal side effects. The participants had intact membranes and unfavourable cervices.

Serious maternal complications were reported in only one study[31]. One maternal death occurred from amniotic fluid embolism in a primiparous woman nine hours after a single 25 μg vaginal misoprostol dose, shortly after amnioinfusion and epidural analgesia. Two caesarean hysterectomies were performed for atonic uterine haemorrhage, 13 and 30 hours after single 25 μg doses of

vaginal misoprostol. One of these two women was primiparous with uncomplicated labour; the other was a nulliparous woman who developed chorioamnionitis following prolonged labour induction attempts by oxytocin augmentation. It is not clear whether these three women were allocated to the low or the higher dosage regimen misoprostol group. No other maternal deaths and any uterine ruptures or perinatal deaths were reported in any of the other studies. However, most studies were not designed to evaluate these outcomes.

One small trial suggests that, when compared with placebo, oral misoprostol reduces the need for oxytocin and shortens the time between induction and delivery (Table 1).

When compared with vaginal prostaglandin preparations, oral administration reduces the need for oxytocin (one trial[13], RR 0·62, 95% CI 0·47 to 0·82). The higher rate of caesarean section after oral misoprostol does not reach statistical significance (two trials[13,14], RR 1·29, 95% CI 0·90 to 1·86). The results of two trials[13,14] comparing oral *versus* vaginal misoprostol were not consistent.

Oral regimens were different in the two trials that compared oral with vaginal misoprostol. Toppozada *et al.*[11] used 100 μg three hourly and Adair *et al.*[15] used 200 μg six hourly. The caesarean section rate was 21·8% in the oral misoprostol group, compared with 13·5% in the vaginal misoprostol group (RR 1·62, 95% CI 0·85, 3·09). The pooled uterine hyperstimulation rate with oral misoprostol was 37·5% (36/96), compared with 28% (25/89) for vaginal misoprostol (RR 1·32, 95% CI 0·86, 2·04). The data on uterine hyperstimulation need to be interpreted with caution because there was significant heterogeneity between two trials for this outcome.

DISCUSSION

The trials show that vaginal misoprostol in doses ranging from 25 μg three hourly, to 50 μg four hourly (most studies) and 100 μg six to 12 hourly, appear to be more effective than oxytocin or dinoprostone used in the usual recommended doses. The rate of caesarean section varied following vaginal misoprostol. However, increased rates of uterine hyperstimulation both with and without associated fetal heart rate changes is worrying. The trials were not sufficiently large to assess the likelihood of uncommon, serious adverse perinatal and maternal complications. The possibility of bias because of the unblinded nature of these studies should be kept in mind.

A lower dosage regimen of vaginal misoprostol (25 μg six hourly) was less effective than a higher dose

Table 1. Summary data of primary outcomes for women randomly allocated to induction of labour with misoprostol or alternative methods. FHR = fetal heart rate.

	Trials (*n*)	Experiment (*n*/*n* (%))*	Control (*n*/*n* (%))	Relative risk	95% confidence interval
Vaginal misoprostol *vs* placebo					
Caesarean section	1	2/24 (8·3)	3/21 (14·3)	0·58	0·11–3·16
Vaginal misoprostol *vs* oxytocin (all women)					
No vaginal delivery within 24 h	4	43/258 (16·7)	94/269 (34·9)	0·48	0·35–0·66
Uterine hyperstimulation with FHR changes	3	18/191 (9·4)	7/199 (3·5)	2·54	1·12–5·77
Caesarean section	6	62/426 (14·5)	82/439 (18·6)	0·78	0·58–1·06
Vaginal misoprostol *vs* dinoprostone (all women)					
No vaginal delivery within 24 h	6	220/539 (40·8)	317/546 (58·0)	0·70	0·62–0·79
Uterine hyperstimulation with FHR changes	14	73/974 (7·4)	49/961 (5·0)	1·45	1·04–2·04
Caesarean section	16	211/1111 (18·9)	218/1095 (19·9)	0·95	0·80–1·12
Serious neonatal morbidity or death	7	75/588 (12·7)	77/596 (12·9)	0·98	0·73–1·30
Low dose *vs* higher dose vaginal misoprostol					
No vaginal delivery within 24 h	2	193/451 (42·7)	184/468 (39·3)	1·08	0·93–1·25
Uterine hyperstimulation with FHR changes	2	17/451 (3·7)	27/468 (5·7)	0·66	0·36–1·19
Caesarean section	2	78/451 (17·2)	86/468 (18·3)	0·94	0·71–1·23
Serious neonatal morbidity or death	2	65/451 (14·4)	84/468 (17·9)	0·79	0·59–1·06
Oral misoprostol *vs* placebo					
Uterine hyperstimulation with FHR changes	1	1/39 (2·6)	0/41 (0·0)	3·15	0·13–75·09
Caesarean section	1	3/39 (7·7)	3/41 (7·3)	1·05	0·23–4·90
Oral misoprostol *vs* vaginal prostaglandins					
Caesarean section	2	55/272 (20·2)	42/270 (15·5)	1·29	0·90–1·86
Oral *vs* vaginal misoprostol					
No vaginal delivery within 24 h	1	7/76 (9·2)	8/69 (11·5)	0·79	0·30–2·08
Caesarean section	2	21/96 (21·8)	12/89 (13·4)	1·62	0·85–3·09

*Experiment group refers to the first control to the second intervention listed in the left hand column.

(25 μg three hourly), with possibly reduced rates of uterine hyperstimulation.

The finding of a significant increase in meconium stained amniotic fluid with vaginal misoprostol is of concern. Wing *et al.*[32] suggested the possibility of meconium passage in response to uterine hyperstimulation, or a direct effect of absorbed misoprostol metabolites on the fetal gastrointestinal tract. We have previously observed an increased rate of meconium stained amniotic fluid in women who have ingested castor oil, though causality was not proven[33]. It is unlikely that the small amount of hydrogenated castor oil found in misoprostol tablets[34] would have any pharmacological effect, but the possibility that misoprostol metabolites may stimulate fetal bowel activity merits further investigation.

Data on the effectiveness of misoprostol are promising. However, the data at present are not robust enough to address the issue of safety.

CONCLUSIONS

Current evidence suggests that in vaginal doses of 25 μg three hourly or more, misoprostol is more effective than conventional methods of cervical ripening and labour induction. There is limited information on the effectiveness of lower doses but these may be safer. The increase in uterine hyperstimulation with fetal heart rate changes associated with the use of misoprostol is a matter for concern. Although no differences in perinatal outcome were shown, the studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. The increase in meconium stained amniotic fluid also requires further investigation.

Misoprostol may be the only affordable prostaglandin preparation for cervical ripening and labour induction in many poorly resourced countries. Considering its clinical effectiveness it seems likely that its use will continue. However, the limited information on the safety of misoprostol reviewed here is sufficiently worrying to limit further widespread use. We recommend that vaginal doses of 25 μg three to six hourly should be used only if these women can be kept under constant supervision, preferably as part of controlled trials. In centres where misoprostol is used for labour induction, maternal and perinatal outcome should be audited regularly to ascertain whether there is an association with rare adverse events, such as uterine rupture and perinatal and maternal death. Methodologically sound controlled trials testing the efficacy of lower dose oral and vaginal regimens should be a priority both in developing and industrialised countries.

Acknowledgements

We acknowledge the support of the University of the Witwatersrand Harold Katz fund, and the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Geneva, Switzerland.

References

1 Keirse MJNC. Vaginal prostaglandins for cervical ripening [revised 03 April 1992]. In: Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C, editors. Pregnancy and Childbirth Module of *The Cochrane Pregnancy and Childbirth Database* [database on disk and CDROM]. *The Cochrane Collaboration*; Issue 2, Oxford: Update Software, 1995.

2 Egarter CH, Husslein PW, Rayburne WF. Uterine hyperstimulation after low-dose prostaglandin E_2 therapy: tocolytic treatment in 181 cases. *Am J Obstet Gynecol* 1990; **163**: 794–796.

3 Senior J, Marshall K, Sangha R, Clayton JK. In vitro characterisation of prostanoid receptors on human myometrium at term pregnancy. *Br J Pharm* 1993; **108**: 501–506.

4 Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90**: 88–92.

5 Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991; **338**: 1233–1236.

6 El-Refaey H, Templeton A. Early induction of abortion by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception* 1994; **49**: 111–114.

7 Neto CM, Delbin AL, Junior RDV. Padrão tocográfico desencadeado pelo misoprostol [Tocographic pattern induced by misoprostol]. *Rev Paul Med* 1988; **106**, 205–208 (in Portuguese).

8 Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstet Gynecol* 1997; **89**: 633–642.

9 Wing DA, Ortiz-Omphroy G, Paul RH. A comparison of intermittent vaginal administration of misoprostol with continuous dinoprostone for cervical ripening and labor induction. *Am J Obstet Gynecol* 1997; **177**: 612–618.

10 Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. *Obstet Gynecol* 1996; **87**: 923–926.

11 Toppozada MK, Anwar MY, Hassan HA, el-Gazaerly WS. Oral or vaginal misoprostol for induction of labor. *Int J Gynecol Obstet* 1997; **56**: 135–139.

12 Wicker R, Albert J, Laurent S, Bellitt P. Evaluation of misoprostol and dinoprostone in cervical ripening. *Am J Obstet Gynecol* 1995; **172**: 424.

13 Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. *Obstet Gynecol* 1997; **89**: 392–397.

14 Tessier F, Dansereau J. A double-blind randomised controlled trial comparing oral misoprostol to vaginal prostaglandin E_2 gel for the induction of labour at or near term. *Am J Obstet Gynecol* 1997; **176**: S111.

15 Adair CD, Weeks JW, Barrilleaux PS, Philibert L, Edwards MS, Lewis DF. Labor induction with oral versus vaginal misoprostol: a randomised, double-blind trial. *Am J Obstet Gynecol* 1998; **178**: 93.

16 Collaborative Review Group Search Strategy. Pregnancy and Childbirth Module of *The Cochrane Database of Systematic Reviews*, [updated 02 December 1997]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 1998.

17 The Cochrane Controlled Trials Register. Available in *The Cochrane Library* [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 1998.

18 Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 2. Oxford: Update Software, 1999.

19 Curtis P, Evans S, Resnick J. Uterine hyperstimulation. The need for standard terminology. *J Reprod Med* 1987; **32**: 91–95.

20 Bugalho A, Bique C, Machungo F, Bergstrom S. Vaginal misoprostol as an alternative to oxytocin for induction of labor in women with late fetal death. *Acta Obstet Gynecol Scand* 1995; **74**: 194–198.

21 Escalante G, Ribas D, Moya R, Sanchez LO, Pena C. Misoprostol intracervical vs. vaginal: caracteristicas clinicas en la induccion del parto [Misoprostol intracervical or vaginal. Clinics characteristics in delivery induction]. *Rev Costarric Cienc Med* 1993; **14**: 43–50 (in Spanish).
22 Srisomboon J, Piyamongkol W, Aiewsakul P. Comparison of intracervical and intravaginal misoprostol for cervical ripening and labour induction in patients with an unfavourable cervix. *J Med Assoc Thai* 1997; **80**: 189–194.
23 Echeverria E, Rocha M. Randomised comparative study of induced labor with oxytocin and misoprostol in prolonged pregnancies. *Rev Clin Obstet Gynecol* 1995; **60**: 108–111.
24 Lee HY. A randomised double-blind study of vaginal misoprostol vs dinoprostone for cervical ripening and labour induction in prolonged pregnancy. *Singapore Med J* 1997; **38**: 292–294.
25 Kadanali S, Kucukozkan T, Zor N, Kumtepe Y. Comparison of labor induction with misoprostol vs. oxytocin/prostaglandin E_2 in term pregnancy. *Int J Gynecol Obstet* 1996; **55**: 99–104.
26 Alfirevic Z, Howarth G, Gausmann A. Oral misoprostol for induction of labour with a viable fetus (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 1999.
27 Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. *Br J Obstet Gynaecol* 1993; **100**: 641–644.
28 Campos GA, Guzman S, Rodriguez JG, Voto LS, Margulies M. Misoprostol—un analogo de la PGE1—para la induccion de parto a termino: estudio comparativo y randomizado con oxitocina. [Misoprostol-a PGE1 analog for induction of labor at term: comparative and randomized study with oxytocin]. *Rev Chil Obstet Ginecol* 1994; **59**: 190–196 (in Spanish).
29 Escudero F, Contreras H. A comparative trial of labor induction with misoprostol versus oxytocin. *Int J Gynecol Obstet* 1997; **57**: 139–143.
30 Buser D, Mora G, Arias F. A randomized comparison between misoprostol and dinoprostone for cervical ripening and labor induction in patients with unfavorable cervices. *Obstet Gynecol* 1997; **89**: 581–585.
31 Wing DA, Ortiz-Omphroy G, Paul RH. A comparison of intermittent vaginal administration of misoprostol with continuous dinoprostone for cervical ripening and labor induction. *Am J Obstet Gynecol* 1997; **177**: 612–618.
32 Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E_2 gel for preinduction cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; **172**: 1804–1810.
33 Mitri F, Hofmeyr GJ, Van Gelderen CJ. Meconium during labour: self-medication and other associations. *S Afr Med J* 1987; **71**: 431–433.
34 Chuck F, Huffaker J. Labor induction with intravaginal prostaglandin E_1 (PGE_1) (Misoprostol, Cytotec) vs intracervical prostaglandin E_2 (PGE_2) (Dinoprostone, Prepidil gel): a randomized comparison. *Am J Obstet Gynecol* 1995; **172**: 424.

Accepted 9 March 1999

9.

Induction of labour with misoprostol

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Misoprostol, an orally active prostaglandin E1 analogue, has been used widely by the vaginal and oral routes for labour induction at or near term. Several recent trials have confirmed that it is highly effective. Overall caesarean section rates appear to be reduced, despite a relative increase in caesarean sections for fetal heart rate abnormalities. Concern remains regarding increased rates of uterine hyperstimulation and meconium-stained amniotic fluid, although data on perinatal outcomes have been reassuring. Recent reports reviewed here have raised the possibility that postpartum haemorrhage may be increased after the induction of labour with misoprostol, and isolated reports of uterine rupture with or without previous caesarean section, continue to appear. Using small dosages appears to reduce adverse outcomes. Very large trials are needed to evaluate rare adverse outcomes. Curr Opin Obstet Gynecol 13:577–581. © 2001 Lippincott Williams & Wilkins.

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Current Opinion in Obstetrics and Gynecology 2001, 13:577–581

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1040-872X

Introduction

Misoprostol, an orally active, stable prostaglandin E1 analogue, has entered clinical use in obstetrics and gynaecology on a wide scale without having been registered for such use [1••]. This has given rise to considerable controversy. The manufacturers have distanced themselves from its off-licence use [2]. Misoprostol is highly effective for first and second trimester pregnancy termination. Its wide availability has resulted in self-medication by women who lack access to pregnancy termination services. Its use for the prevention or treatment of postpartum haemorrhage is as yet unsupported by evidence of effectiveness from randomized trials [3].

This literature update deals with the use of misoprostol for labour induction at or near term, which has also raised considerable controversy, and has been the subject of several reviews [4–6,7••,8]. The writer and co-workers have maintained a conservative approach because of safety concerns, recommending that it should not be recommended for general use until more is known about the risks and optimal dosage [4–6]. This approach has attracted criticism [9]. Other reviewers have concluded that misoprostol for the induction of labour safely reduces the rate of caesarean section [7••]. The American College of Obstetricians and Gynecologists' guidelines for the induction of labour recommend that misoprostol at a dose of 25 μg 3–6 hourly is effective for the induction of labour (level A evidence), and 50 μg 6 hourly may be appropriate in some situations, although an increased risk of complications has been reported (level B evidence) [10•]. This opinion has recently been endorsed [11•] after a drug warning issued by the manufacturer.

In this update we will consider the contribution of recently published papers to the two key questions that should be asked for any new intervention: does it work? and is it safe?

Does it work?

Previous and current placebo-controlled trials have clearly shown that misoprostol is an effective drug for labour induction when administered vaginally [5] or orally [6,12•].

Several studies [13•,14••,15•,16••,17–21,22•], most with small numbers of subjects, have recently been published comparing vaginal or oral misoprostol with other methods of cervical ripening or labour induction.

The trials reviewed were generally consistent with the results of previous meta-analyses [4–6,7••], finding misoprostol to be equally or more effective than other methods of cervical ripening and labour induction. Brief examples follow.

Misoprostol 50 μg vaginally, up to two doses 6 h apart, was more effective than intracervical dinoprostone 0.5 mg for cervical ripening, but uterine hyperstimulation (4/32 versus 0/29) and maternal fever (10/32 versus 2/29) were increased [13•].

Misoprostol 25–50 μg 4 hourly vaginally was randomly compared with dinoprostone 10 mg insert in 120 women. Labours were shorter with misoprostol, intrapartum complications were similar and the postpartum course was longer, with a trend to more postpartum complications (12/60 versus 5/60) [14••].

In 123 women, misoprostol 50 μg 4 hourly had similar effectiveness and complications to extra-amniotic saline infusion with intravenous oxytocin [15•].

For preinduction cervical ripening, misoprostol 50 μg 4 hourly was randomly compared with a transcervical Foley catheter bulb. There were no differences in cervical ripening or labour induction success. Misoprostol was associated with more uterine contraction abnormalities (20 versus 0%) and meconium (22 versus 5%). There was one rupture of a scarred uterus with misoprostol [16••].

In a retrospective analysis of 84 cases, misoprostol 50 μg was more effective than intravenous dinoprostone for labour induction, but hyperstimulation was more frequent [22•].

Recent evidence is therefore in keeping with previous studies that have shown that misoprostol in most of the dosage regimens used is at least as effective as conventional methods of labour induction.

Does it work better when administered vaginally, or orally?

The majority of trials to date have used the vaginal route of administration. Systematic review of randomized trials comparing oral with vaginal routes of administration has found the oral route to be associated with slower labours but fewer caesarean sections [6]. Similar results have been shown in two recent trials with oral misoprostol [23••,24•], and one using buccal misoprostol 200 μg 6 hourly twice then 300 μg four times, compared with a vaginal regimen using 50 then 100 μg [25•].

Oral compared with vaginal administration of misoprostol 400 μg has a shorter time to peak serum level (34 versus 80 min) and a higher peak (165 versus 227 pg/ml), but far briefer activity [26]. This is reflected in a more rapid and pronounced initial increase but less persistence in uterine tonus with the oral route [27]. The short duration of action with the oral route may be advantageous in the event of uterine hyperstimulation. It may also be a reason to use frequent dosing schedules. In most studies, oral misoprostol has been administered 4 or 6 hourly. In view of the short duration of action, we have used oral misoprostol 2 hourly for labour induction. To accommodate variability in the response of individuals, we have commenced with a dose of 20 μg, increased if necessary to 40 μg after two to three doses. To administer such small doses, we dissolve 200 μg misoprostol in 200 ml water, and shake well before each administration. The solution is discarded after 12 h. In a multicentre randomized trial in 695 women, this method was found to be similar to vaginal dinoprostone 2 mg, repeated after 6 h, with respect to effectiveness, uterine hyperstimulation, caesarean section rates and perinatal outcome [28••].

Another advantage with oral administration is that in some services, vaginal administration may only be carried out by doctors [7••], whereas oral dosages may be administered by nurses. This highlights the role and responsibilities of nursing staff in labour induction with misoprostol [29,30]. There is as yet no certainty as to which route of administration is the better.

What dosage should be used?

Systematic review of trials comparing lower with higher dosages of vaginal misoprostol showed that the lower dosage regimens (misoprostol 25 μg 6 hourly versus 3 hourly, or 25 versus 50 μg 3 hourly) required more oxytocin use and were associated with less uterine hyperstimulation. The effectiveness, mode of delivery and maternal side-effects were similar. A recent trial has shown similar results [31••].

Is it safe?

Areas of concern regarding safety relate mainly to uterine hyperstimulation, and the possible effects of this on the mother and baby.

Uterine hyperstimulation

An important issue regarding the use of misoprostol for labour induction has been uterine hyperstimulation [32–34]. Previous reviews have found misoprostol to be associated with more uterine hyperstimulation than other methods of labour induction. Similar findings occurred in two recent randomized trials [13•,16••] and one retrospective study [22•].

Meconium-stained liquor

Previous reviews have shown a trend towards more meconium passage with misoprostol than with other

agents [4–6]. We have previously postulated that certain myometrial stimulants may cross the placenta to stimulate fetal bowel smooth muscle and cause meconium passage [35]. Among the recent trials under review, one reported increased meconium passage [16••] (22 versus 5%) and one did not [31••].

Precipitate delivery

Precipitate delivery (labour <2h) has been described as a possible complication of misoprostol [5,36], and occurred more frequently with misoprostol in one recent trial (6/47 versus 1/49) [12•]. Another recent report described an extensive cervical laceration after rapid misoprostol-induced labour [37•]. Most previous reviews and trials have not documented the occurrence of precipitate delivery. In fact, the mean time to delivery is frequently given as a primary end-point. Precipitate deliveries may contribute to apparently favourable delivery times, without being identified as an unfavourable outcome. The importance of precipitate delivery is that it may be a marker for excessive uterine response to misoprostol and a risk of uterine rupture.

Uterine rupture

There have been occasional reports of rupture of an unscarred uterus after misoprostol labour induction [5,38,39]. A recent report [40•] described labour induction with one dose of misoprostol 50 μg administered vaginally in a healthy woman with uneffaced cervix. After 4 h the cervix was effaced, and 2 h later a healthy child was born. Half an hour later her condition deteriorated and she died despite resuscitation attempts. Post-mortem examination revealed a ruptured uterus as the cause of death.

Women with previous caesarean section

Misoprostol has been used to induce labour in women with previous caesarean section [41]. Several cases of rupture of uterine scars have been reported [42•]. No data are available from randomized trials, except for one trial that was terminated after uterine scar rupture in two of the first 17 cases induced with low dosage misoprostol [43]. A recent retrospective study [44•] found significantly more cases of uterine rupture or dehiscence after cervical ripening with misoprostol than when oxytocin or prostaglandin E2 were used. In a pilot study of misoprostol 50 μg administered orally 4 hourly for cervical ripening in women with previous caesarean section [45•], uterine rupture occurred in one out of 10 women. Most authors recommended that misoprostol should not be used in women with uterine scars.

Caesarean section

The relationship between misoprostol use and caesarean section is a complex one. The trend in previous randomized trials has been an increase in caesarean sections for fetal heart rate abnormality and a reduction for poor progress of labour, giving an overall reduction. In line with these findings, two recent trials showed an increase in caesarean sections for suspected fetal distress with misoprostol [23••,24•].

Perinatal outcome

Despite increases in uterine hyperstimulation, most reviews and trials have shown no significant difference in perinatal outcome after misoprostol versus other methods.

Postpartum haemorrhage

A recent observation, which has not been included in previous reviews, is a possible increase in postpartum haemorrhage after misoprostol labour induction [36]. Increased postpartum haemorrhage was noted in a retrospective study compared with the general obstetric population [46•], and in a randomized trial after labour induction with vaginal misoprostol 50 versus 25 μg 4 hourly (9.8 versus 2.2%) [31••].

Conclusion

Recent reports have confirmed that misoprostol is a highly effective agent for labour induction. Complications remain a matter of concern, particularly uterine hyperstimulation, precipitate labour, meconium-stained liquor and uterine rupture. Recently, postpartum haemorrhage has been added to the list of possible complications. Results suggest that risks can be minimized with the use of small dosages, and that the starting dose should not exceed 25 μg. It is not yet clear whether the oral or the vaginal route is preferable. There is a need for very large-scale randomized trials comparing low-dose misoprostol regimens with conventional methods, to determine with more certainty the relative rates of rare adverse outcomes.

Acknowledgements

The author would like to thank Zarko Alfirevic and Metin Gülmezoglu for collaboration with systematic reviews of this topic, and the University of the Witwatersrand for support.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 •• Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med 2001; 344:38–47.
An excellent overview of the use of misoprostol in pregnancy, concluding that research results support its continued use.

2 Friedman MA. Manufacturer's warning regarding unapproved uses of misoprostol. N Engl J Med 2001; 344:61.

3 Gülmezoglu AM. Prostaglandins for prevention of postpartum haemorrhage (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update Software; 2001.

4 Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labor: a systematic review. Br J Obstet Gynaecol 1999; 106:798–803.

5 Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update Software; 2001.

6 Alfirevic Z. Oral misoprostol for induction of labour (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update Software; 2001.

7 •• Sanchez-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labor induction: a systematic review of the literature. Clin Obstet Gynecol 2000; 43:475–488.
A review of 44 prospective randomized clinical trials including 5735 women gave this meta-analysis a 90% chance of detecting an increase in neonatal intensive care admission from 14 to 18%, or the rate of low 5 min Apgar scores from 1.4 to 1.8%. No differences were shown in these outcomes. Uterine tachysystole and hyperstimulation were increased with misoprostol. Misoprostol was more effective than other methods, and the cesarean section rate was reduced. There were fewer caesarean sections with oral than with vaginal misoprostol. They conclude that misoprostol for labour induction safely reduces caesarean section rates, although more information is needed on the oral route. Outpatient use, and use in patients with previous caesarean section are not recommended.

8 Song J. Use of misoprostol in obstetrics and gynecology. Obstet Gynecol Surv 2000; 55:503–510.

9 Day L, Tailor A, Howard R, Burrell S. Misoprostol for induction of labour at term. Br J Obstet Gynaecol 2000; 107:576–577.

10 • Morey SS. ACOG develops guidelines for induction of labor. Am Fam Phys 2000; 62:445.
The American College of Obstetricians and Gynecologists' guidelines recommend that misoprostol 25 μg 3–6 hourly is effective for the induction of labour.

11 • American College of Obstetricians and Gynecologists. Response to Searle's drug warning on misoprostol. ACOG Committee Opinion 248. Washington, DC: December 2000.
Reaffirms that misoprostol is a safe and effective agent for cervical ripening and labour induction when used appropriately. To minimize risks, they recommend an initial vaginal dose of 25 μg, at intervals of 3–6 h or more, no use of oxytocin less than 4 h after the last dose, and avoidance in women with previous caesarean delivery.

12 • Hoffmann RA, Anthony J, Fawcus S. Oral misoprostol vs. placebo in the management of prelabor rupture of membranes at term. Int J Gynaecol Obstet 2001; 72:215–221.
Delivery within 24 h was more frequent with misoprostol 100 μg orally, repeated if necessary after 6 h, (44/47) than placebo (29/49), as was precipitate delivery within 2 h (six versus one).

13 • Neiger R, Greaves PC. Comparison between vaginal misoprostol and cervical dinoprostone for cervical ripening and labor induction. Tenn Med 2001; 94:25–27.
Misoprostol 50 μg administered vaginally, up to two doses 6 h apart, was more effective than intracervical dinoprostone 0.5 mg for cervical ripening, but uterine hyperstimulation (4/32 versus 0/29) and maternal fever (10/32 versus 2/29) were increased.

14 •• Harms K, Nguyen C, Toy EC, Baker B. Intravaginal misoprostol versus cervidil for cervical ripening in term pregnancies. Obstet Gynecol 2001; 97 (4 Suppl. 1):S36.
Misoprostol 25–50 μg 4 hourly was randomly compared with dinoprostone 10 mg insert in 120 women. Labours were shorter with misoprostol, intrapartum complications were similar and the postpartum course was longer, with a trend to more postpartum complications (12/60 versus 5/60).

15 • Buccellato CA, Stika CS, Frederiksen MC. A randomized trial of misoprostol versus extra-amniotic sodium chloride infusion with oxytocin for induction of labor. Am J Obstet Gynecol 2000; 182:1039–1044.
In 123 women, vaginal misoprostol 50 μg 4 hourly had similar effectiveness and complications to extra-amniotic saline infusion with intravenous oxytocin.

16 •• Sciscione AC, Nguyen L, Manley J, *et al.* A randomized comparison of transcervical Foley catheter to intravaginal misoprostol for preinduction cervical ripening. Obstet Gynecol 2001; 97:603–607.
For preinduction cervical ripening, misoprostol 50 μg 4 hourly was randomly compared with a transcervical Foley catheter bulb. There were no differences in cervical ripening or the success of labour induction. Misoprostol was associated with more uterine contraction abnormalities (20 versus 0%) and meconium (22 versus 5%). There was one rupture of a scarred uterus with misoprostol.

17 Birlain M. Comparison of low doses of misoprostol with the traditional use of oxytocin for effective cervical ripening and labor induction. Obstet Gynecol 2001; 97 (Suppl):S67.

18 Charoenkul S, Sripramote M. A randomized comparison of one single dose of vaginal 50 microg misoprostol with 3 mg dinoprostone in pre-induction cervical ripening. J Med Assoc Thailand 2000; 83:1026–1034.

19 Belfrage P, Smedvig E, Gjessing L, *et al.* A randomized prospective study of misoprostol and dinoproston for induction of labor. Acta Obstet Gynecol Scand 2000; 79:1065–1068.

20 de la Torre S, Gilson GJ, Flores S, *et al.* Is high-dose misoprostol able to lower the incidence of cesarean section? A randomized controlled trial. J Matern Fetal Med 2001; 10:85–90.

21 Bartha JL, Comino-Delgado R, Garcia-Benasach F, *et al.* Oral misoprostol and intracervical dinoprostone for cervical ripening and labor induction: a randomized comparison. Obstet Gynecol 2000; 96:465–469.

22 • Jouatte F, Subtil D, Marquis P, *et al.* Medical indications of labor induction: a comparison between intravaginal misoprostol and intravenous prostaglandin E2 [in French]. J Gynecol Obstet Biol Reprod (Paris) 2000; 29:763–771.
In a retrospective analysis of 84 cases, misoprostol 50 μg was more effective than intravenous dinoprostone for labour induction, but hyperstimulation was more frequent.

23 •• Kwon JS, Davies GA, Mackenzie VP. A comparison of oral and vaginal misoprostol for induction of labour at term: a randomised trial. Br J Obstet Gynaecol 2001; 108:23–26.
Oral versus vaginal administration of misoprostol 50 μg 6 hourly was associated with fewer deliveries within 24 h (44/78 versus 76/95), more oxytocin augmentation, and fewer caesarean sections for suspected fetal distress (0/78 versus 5/82). Overall caesarean section rates (13/78 versus 19/82) and neonatal outcomes were similar.

24 • Shetty A, Danielian P, Templeton A. A comparison of oral and vaginal misoprostol tablets in induction of labour at term. Br J Obstet Gynaecol 2001; 108:238–243.
Oral versus vaginal administration of misoprostol 50 μg 4 hourly was associated with fewer vaginal deliveries within 24 h (44/92 versus 76/95), more oxytocin augmentation, less uterine hyperstimulation and fewer caesarean sections for fetal distress. Overall caesarean section rates (30/122 versus 28/123) and neonatal outcomes were similar.

25 • Blust D, Carlan SJ. Buccal versus vaginal misoprostol for cervical ripening and labor induction. Obstet Gynecol 2001; 97 (Suppl):S5.
Buccal misoprostol 6 hourly in dosages three to four times greater had similar outcomes to a vaginal regimen.

26 Zieman M, Fong SK, Benowitz NL, *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997; 90:88–92.

27 Danielsson KG, Marions L, Rodriguez A, *et al.* Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999; 93:275–280.

28 •• Hofmeyr GJ, Alfirevic Z, Matonhodze B, *et al.* Titrated oral misoprostol solution for induction of labour: a multicentre, randomised trial. Br J Obstet Gynaecol 2001; 108: (in press)
In this randomized trial of labour induction, 695 women were studied. No significant differences were found in substantive outcomes between labour induction with titrated oral misoprostol solution (commencing with 20 μg 2 hourly), or up to two doses of vaginal dinoprostone 2 mg administered 6 h apart.

29 Wilson C. The nurse's role in misoprostol induction: a proposed protocol. J Obstet Gynecol Neonatal Nurs 2000; 29:574–583.

30 Cullen M. Use of cytotec (misoprostol) for labor induction. J Obstet Gynecol Neonatal Nurs 2001; 30:11.

31 •• El-Sherbiny MT, El-Gharieb IH, Gewely HA. Vaginal misoprostol for induction of labor: 25 vs 50 microg dose regimen. Int J Gynaecol Obstet 2001; 72:25–30.
Vaginal misoprostol 25 μg compared with 50 μg 4 hourly was associated with fewer deliveries within 24 h (81/93 versus 87/92) and a greater use of oxytocin (35/93 versus 24/92), but less uterine hyperstimulation (0/93 versus 6/92) and postpartum haemorrhage (9.8 versus 2.2%). No significant differences were found in the incidence of caesarean section, abnormal cardiotocograph, meconium-stained liquor, meconium aspiration syndrome or other perinatal outcomes.

32 Akhan SE, Yidirim A, Iyibozkurt AC, Turfanda A. The evaluation of misoprostol-related tachysystole in normal and high risk pregnancies. Clin Exp Obstet Gynecol 2000; 27:207–211.

33 Crane JM, Young DC, Butt KD, *et al.* Excessive uterine activity accompanying induced labor. Obstet Gynecol 2001; 97:926–931.

34 Ngai SW, Chan YM, Lam SW, Lao TT. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of the membranes. Br J Obstet Gynaecol 2000; 107:222–227.

35 Mitri F, Hofmeyr GJ, Van Gelderen CJ. Meconium during labour: self-medication and other associations. S Afr Med J 1987; 71:431–433.

36 Hsieh YY, Tsai HD, Chang CC, *et al.* Precipitate delivery and postpartum hemorrhage after term induction with 200 micrograms misoprostol. Zhonghua Yi Xue Za Zhi (Taipei) 2000; 63:58–61.

37 Oyelese Y, Landy HJ, Collea JV. Cervical laceration associated with misoprostol induction. Int J Gynaecol Obstet 2001; 73:161–162.
Labour induction with four 3 hourly doses of misoprostol 25 μg was followed by rapid labour and an extensive posterior cervical laceration.

38 Khabbaz AY, Usta IM, El-Hajj MI, *et al.* Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. J Matern Fetal Med 2001; 10:141–145.

39 Mathews JE, Mathai M, George A. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. Int J Gynaecol Obstet 2000; 68:43–44.

40 Daisley Jr H. Maternal mortality following the use of misoprostol. Med Sci Law 2000; 40:78–82.
Three maternal deaths are reported, two after the self-administration of misoprostol for first trimester abortion (one was an ectopic pregnancy), and one after labour induction with a single dose of misoprostol 50 μg administered vaginally and a rapid labour with ruptured uterus.

41 Choy-Hee L, Raynor BD. Misoprostol induction of labor among women with a history of cesarean delivery. Am J Obstet Gynecol 2001; 184:1115–1117.

42 Gherman RB, McBrayer S, Browning J. Uterine rupture associated with vaginal birth after cesarean section: a complication of intravaginal misoprostol? Gynecol Obstet Invest 2000; 50:212–213.
The rupture of a uterine scar was found during minilaparotomy for tubal ligation 28 h after vacuum delivery. The labour had been induced with one 25 μg vaginal dose of misoprostol, and oxytocin.

43 Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with prior cesarean delivery. Obstet Gynecol 1998; 91:828–830.

44 Hill DA, Chez RA, Quinlan J, *et al.* Uterine rupture and dehiscence associated with intravaginal misoprostol cervical ripening. J Reprod Med 2000; 45:823–826.
In 24 women with previous caesarean section who underwent cervical ripening with misoprostol 50 μg vaginally, three ruptures occurred after a single dose, and one dehiscence occurred after two doses. Scar rupture occurred in one of 89 labours induced with oxytocin and none of 24 induced with prostaglanin E2.

45 Gherman RB, Heath T. Trial of labor after cesarean delivery: a pilot study of oral misoprostol for preinduction cervical ripening. Obstet Gynecol 2001; 97 (4 Suppl. 1):S68.
Uterine rupture occurred in one of 10 women receiving misoprostol 50 μg orally 4 hourly.

46 Fletcher H, Hutchinson S. A retrospective review of pregnancy outcome after misoprostol (prostaglandin E1) induction of labour. West Indian Med J 2001; 50:47–49.
Retrospectively, labours induced with misoprostol 50–100 μg daily compared with the general obstetric population had fewer caesarean sections and more postpartum haemorrhage (58/1037 versus 394/11255).

10.

SYSTEMATIC REVIEW CORNER

25 μg vaginal misoprostol is less effective than 50 μg for induction of labour, but has lower risks – meta-analysis

Sanchez-Ramos L, Kaunitz AM, Delke I. Labour induction with 25 μg versus 50 μg intravaginal misoprostol: a systematic review. Obstet Gynecol 2002; 99: 145–151.

OBJECTIVE To compare the efficacy and safety of two doses of vaginal misoprostol for cervical ripening and induction of labour.

DESIGN Meta-analysis of randomized, controlled trials.

DATA SOURCES Computerized searches of MEDLINE, EMBASE, Current Contents, Silver Platter, and the Cochrane Controlled Trials Register, and hand searches of abstract books from scientific meetings and reference lists of relevant articles. The searches covered the period 1987–2001.

STUDY SELECTION Studies in any language that compared repeated doses of 25 and 50 μg vaginal misoprostol for cervical ripening and induction of labour. Studies were assessed for methodological quality.

DATA EXTRACTION Data were extracted into 2 × 2 tables independently by two reviewers.

MAIN OUTCOME MEASURES Odds ratio (OR, 95% CI) for tachysystole, hyperstimulation, need for oxytocin augmentation, vaginal delivery within 24 hours, cesarean delivery, and adverse neonatal outcomes, in women receiving 25 μg, compared to 50 μg, misoprostol.

MAIN RESULTS Five studies, published between 1997 and 2001, and involving 933 women, were included in the meta-analysis. Three of the studies were of moderate size (100–200 subjects per group) and two were small (~25 subjects per group). The dosing intervals varied from 3 to 6 hours. Delivery after a single dose of misoprostol occurred in 27% of cases with the 25 μg dose, compared to 39% with the 50 μg dose (OR 0.6, CI 0.3–1.0) and delivery occurred within 24 hours in 56 and 63% of cases, respectively (OR 0.7, CI 0.5–1.0). Oxytocin was required more often with the 25 μg dose (OR 1.9, CI 1.4–2.6) and the time-to-delivery was almost 5 hours longer, on average. The incidence of hyperstimulation was 4.4% with 25 μg misoprostol and 9.3% with 50 μg (OR 0.4, CI 0.3–0.8). The incidences of tachysystole were 8.9 and 21%, respectively (OR 0.4, CI 0.2–0.5). There was no significant difference between doses in the rates of operative vaginal delivery or cesarean delivery. However, cesarean delivery for fetal heart rate abnormalities was non-significantly lower with the 25 μg dose (OR 0.7, CI 0.4–1.1), as were Apgar score <7 at 5 min (OR 0.5, CI 0.2–1.3) and neonatal intensive care admissions (OR 0.6, CI 0.3–1.1).

CONCLUSION Vaginal misoprostol, used for cervical ripening and induction of labour, is less efficacious when repeated doses of 25 μg are used, compared to doses of 50 μg. However, the risks of hyperstimulation and tachysystole are greater with 50 μg misoprostol and perinatal safety may be compromised.

1361-259X/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1054/ebog.2002.0080

Commentary

Labour induction is an essential part of obstetrical practice, particularly in situations in which continued pregnancy is hazardous for mother or baby. A great variety of medical and mechanical methods have been used for labor induction. Various prostaglandin preparations have been found effective when the uterine cervix is 'unfavorable'. Prostaglandin preparations registered for labour induction are expensive and, in many countries, simply unaffordable. Misoprostol has the advantages of affordability and simplicity of use. Because it has not been registered for labour induction, appropriate dosage regimens have not been established by the manufacturers. Studies which provide evidence of safety and efficacy of various regimens are, therefore, of importance worldwide.

A previous systematic review comparing lower vs higher vaginal misoprostol dosage regimens (not specifically 25 vs 50 μg) also found the lower dosages to be associated with significantly more oxytocin use (relative risk [RR] 1.26, 95% CI 1.12–1.42), significantly less uterine hyperstimulation (RR 0.50, 95% CI 0.33–0.78), and non-significantly fewer neonatal intensive care admissions (RR 0.75, 95% CI 0.53–1.07), but no significant difference in the rate of failed vaginal delivery within 24 hours (RR 1.09, 95% CI 0.94–1.26).[1]

The present meta-analysis used a defined approach to the collection, selection, and analysis of data from randomized trials comparing vaginal misoprostol dosages of 25 μg with 50 μg. A confounding factor, pointed out by the authors, is that the dosage intervals varied between studies from 3 to 6 hourly. This difference in protocol may have accounted for some of the variation in results. For example, uterine hyperstimulation syndrome occurred in 5.2–7.2 percent of women to whom misoprostol 25 μg was administered 3 hourly, but in none of 117 women treated every 4–6 hours. The authors cast doubt on their finding of increased uterine hyperstimulation syndrome with the 50 μg dose, because the effect occurred mainly in one trial with a short dosage interval of 3 hours. However, a more recent trial using 4-hourly doses supports the finding of increased hyperstimulation syndrome with the 50 μg dose (16/56 vs 7/58, RR 2.91, 95% CI 1.09–7.8).[2]

The authors also pointed out that the meta-analysis was underpowered to detect clinically relevant differences in less common adverse neonatal outcomes. Thus, although the frequencies of low Apgar scores and neonatal intensive care admissions were 40–50% lower in the 25 μg group, these differences were not statistically significant.

Several important clinical issues are outside the scope of this meta-analysis: the relative efficacy and safety of vaginal misoprostol vs other agents and vs the oral and buccal routes of misoprostol administration; whether dosages should be adjusted for parity and cervical favorability; and whether titration of the misoprostol dosage against individual uterine response might improve the safety profile.[3] The numbers available for this meta-analysis were insufficient to provide reassurance that the 50 μg dose is as safe as 25 μg. If vaginal misoprostol is chosen as the method of labor induction, the data favor the use of the 25 μg dose, at least as the initial dose, until such time as sufficient data become available to compare the relative safety of 25 and 50 μg with greater certainty.

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Literature cited

1. Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour (Cochrane Review). In: The Cochrane Library, Issue 3. Oxford: Update Software, 2002.
2. Has R, Batukan C, Ermis H et al. Comparison of 25 and 50 μg vaginally administered misoprostol for preinduction of cervical ripening and labor induction. Gynecol Obstet Invest 2002; 53: 16–21.
3. Hofmeyr GJ, Alfirevic Z, Matonhodze B et al. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. Br J Obstet Gynaecol 2001; 108: 952–959.

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Best Practice & Research Clinical Obstetrics & Gynaecology
Vol. 17, No. 5, pp. 777–794, 2003
doi:10.1016/S1521-6934(03)00037-3, www.elsevier.com/locate/jnlabr/ybeog

BEST PRACTICE & RESEARCH

7

Induction of labour with an unfavourable cervix

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Labour induction is undertaken when the advantages for the mother and/or the baby are considered to outweigh the disadvantages. When the uterine cervix is unfavourable, oxytocin, with or without amniotomy, is frequently ineffective. Vaginal prostaglandin E_2 is most commonly used if it is affordable. Evidence regarding many alternative methods is discussed in this chapter. Of particular interest are misoprostol and extra-amniotic saline infusion.

Misoprostol, an orally active prostaglandin E_1 analogue, has been used widely by the vaginal and oral routes for labour induction at or near term. Several recent trials have confirmed that it is highly effective. Overall Caesarean section rates appear to be reduced, despite a relative increase in Caesarean sections for fetal heart rate abnormalities. Concern remains regarding increased rates of uterine hyperstimulation and meconium-stained amniotic fluid, although data on perinatal outcome have been reassuring. Postpartum haemorrhage may be increased following labour induction with misoprostol, and isolated reports of uterine rupture, with or without previous Caesarean section, have appeared. Using small dosages appears to reduce adverse outcomes. Very large trials are needed to evaluate rare adverse outcomes.

Extra-amniotic saline infusion is an effective method which appears to reduce the risk of uterine hyperstimulation that occurs with the use of exogenous uterotonics.

Key words: labour induction; unfavourable cervix; prostaglandins; misoprostol; extra-amniotic saline.

Induction of labour refers to the use of artificial methods to bring about labour after the age of fetal viability (24 weeks in the UK) and before the spontaneous onset of labour. Similar methods used before fetal viability are called induction of abortion or termination of pregnancy, and after the onset of labour are called augmentation of labour. The distinction between induction and augmentation of labour is sometimes blurred by uncertainty concerning the diagnosis of early labour.

Labour induction is one of the most frequent procedures in pregnant women. In the United States of America, the rate increased during the 1990s from about 10 to 20%.[1]

A distinction is sometimes drawn between methods used with the intention of 'ripening' the uterine cervix, and similar methods used with the intention of inducing labour. The former may progress unavoidably to the latter.

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The decision to induce labour is usually a matter of rather complex clinical judgement which takes into account a number of factors:

- Anticipated benefits to the mother—for example, improving a medical condition which is caused or aggravated by pregnancy, such as pre-eclampsia, placental abruption, certain respiratory, hepatic and cardiac disorders; relieving discomfort, such as from multiple pregnancy, polyhydramnios or spontaneous symphysiotomy; relieving emotional distress after intrauterine death; or alleviating anxiety about the baby's wellbeing.
- Estimated risks to the mother—for example, increased pain and need for analgesia, increased chance of requiring Caesarean section, infection, other complications of the procedures, postpartum haemorrhage, (rarely) uterine rupture, anxiety if the induction is protracted or unsuccessful, and loss of self-esteem because of perceived failure to give birth normally.
- Anticipated benefits to the fetus—for example, improved growth and development when intrauterine growth is suboptimal, reduced risk of intrauterine death from complications such as diabetes, prolonged pregnancy (beyond 41 weeks)[2], amnionitis, ruptured membranes, rhesus immunization, fetal distress and cholestasis of pregnancy.
- Estimated risks to the fetus—for example, prematurity and uterine hyperstimulation.

Several factors influence the decision:

- The condition of the mother.
- The condition of the baby.
- The gestational age of the baby, and level of certainty about the baby's age. When fetal lung maturity is uncertain, amniocentesis may be performed to assess markers for lung maturity such as the alcohol 'shake' test, lecithin/sphingomyelin ratio and phosphatidyl glycerol level.
- Previous Caesarean section.
- The preference of the mother (and sometimes the care provider).
- The likelihood that induction of labour will be easy and vaginal delivery successful.

The last factor is dependent mainly on the state of the uterine cervix. Where other factors are equivocal, the state of the cervix may influence the decision whether or not to proceed with labour induction.

THE UNFAVOURABLE UTERINE CERVIX

The process of softening, shortening and partial dilation of the cervix usually takes place in the days or weeks prior to the onset of labour, but the timing of this process is extremely variable. An unfavourable or 'unripe' cervix is one which has undergone minimal change and is more resistant to attempts at induction of labour. In the first trimester, 50% of the dry weight of the cervix is tightly aligned collagen, 20% smooth muscle and the rest is ground substance composed of elastin and glycosaminoglycans (chondroitin, dermatan sulphate and hyaluronidase).[3] During pregnancy, hyaluronidase increases from 6 to 33%, whereas dermatin and chodroitin, which bind collagen more

Table 1. Modified 'Bishop' cervical score.

Score	0	1	2	3
Cervical dilation (cm)	0	1–2	3–4	5+
Cervical length (cm)	3	2	1	<1
Station of the presenting part	−3	−2	−1, 0	+1 or more
Consistency	Firm	Moderate	Soft	
Position	Posterior	Midposition	Anterior	

tightly, decrease. Collagenase and elastase enzymes increase, as do the vascularity and water content.

A standardized method of semi-quantitative clinical scoring of the cervix was described by Bishop in 1964[4], and has since been modified (see Table 1). A score of six or more predicts the likelihood of successful induction of labour. A score of five or less is regarded as being unfavourable for induction of labour, and use of artificial rupture of the amniotic sac and/or oxytocin infusion is unlikely to be successful.

More recently, measurement of fibronectin in cervicovaginal secretions has been used to predict the imminence of labour[5], with variable success.[6] The mainstay of induction of labour with an unfavourable cervix is the use of exogenous prostaglandins[7,8], or methods to stimulate the release of endogenous prostaglandins, in order to 'ripen' the cervix.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS' GUIDELINES

Guidelines developed by the Royal College of Obstetricians and Gynaecologists (RCOG)[9] recommend offering an ultrasound scan before 20 weeks to confirm the gestational age; membrane 'sweeping' after 40 weeks; labour induction after 41 weeks; if declined, fetal monitoring from 42 weeks with induction of labour recommended if the monitoring is abnormal. In the case of pregnancy complications, membrane sweeping or labour induction are offered at the appropriate gestation.

METHODS OF INDUCTION OF LABOUR WITH AN UNFAVOURABLE CERVIX

Prostaglandin E_2 (PGE_2) and oxytocin

Vaginal prostaglandins

Labour induction with prostaglandin $F_{2\alpha}$ was introduced in the 1960s. Subsequently, formulations of prostaglandin E_2 were developed which largely replaced the use of $F_{2\alpha}$ in countries such as the UK. The most common route of administration is vaginal, and tablets, suppositories, gels and pessaries have been developed. A recent randomized comparison found similar effectiveness for a 10 mg PGE_2 sustained-release vaginal insert compared with 3 mg PGE_2 vaginal tablets twice at a 6-hour interval. In seven out of eight women with uterine hyperstimulation, removal of the vaginal insert

was sufficient to normalize uterine activity. In the PGE_2 tablet group eight of nine with uterine hyperstimulation required medical treatment.[10]

A wide variety of dosages and dosing intervals are in use. A limiting factor for the use of prostaglandin E_2 preparations in many countries has been the cost.

Systematic review of vaginal prostaglandin E_2 compared with placebo or no treatment showed that prostaglandins were clearly effective in bringing about delivery (relative risk of failure to deliver within 24 hours 0.03, 95% confidence interval 0.02–0.05).[11]

The RCOG recommends the use of intravaginal PGE_2 irrespective of the woman's parity or cervical status. PGE_2 tablets (3 mg 6–8 hourly to a maximum dose of 6 mg) are recommended in preference to PGE_2 gel (2 mg for nulliparous women with modified Bishop cervical score <4, 1 mg to all others, repeated 6 hourly to a maximum dose of 4 mg).

In the case of ruptured membranes, intravenous oxytocin is recommended as an alternative initiating agent. If oxytocin is used after PGE_2, 6 hours should elapse after the last dose of PGE_2 to reduce the risk of hyperstimulation. Oxytocin is recommended as an intravenous infusion of 30 iu in 500 ml normal saline, in titrated dosages from 1 to 32 mIU per minute, for up to 5 hours. The effectiveness of oxytocin is optimized with ruptured membranes.

Comparison of methods of induction of labour with an unfavourable cervix

As vaginal PGE_2 with or without oxytocin infusion is widely recognized and accepted as a standard method of labour induction, this chapter focuses on alternative methods which are less well established, comparing them with PGE_2 as the conventional method. Particular attention is paid to misoprostol because of the controversy surrounding its use and the volume of recent research.

Comparisons of alternative methods are most reliably based on the results of well-conducted randomized clinical trials. To manage the complexity of several hundred reported randomized trials comparing various combinations of 25 methods of labour induction, the Pregnancy and Childbirth Group of the Cochrane Collaboration, in collaboration with the Clinical Effectiveness Support Unit, RCOG, developed a strategy to review well-defined clusters of comparisons in a series of 'primary' systematic reviews using standardized outcomes and clinical sub-groups.[12] This enables comparisons across reviews for specific clinical categories to be made. For the purposes of this chapter, data have been extracted from these reviews from available trials in all women (Table 2), and in all women with unfavourable cervices (Table 3), comparing PGE_2 administered vaginally (as the 'gold standard') with any other method.

Intracervical prostaglandins

PGE_2 may be administered into the cervical canal, in smaller dosages than those used vaginally, with the objective of optimizing the local effect on the cervix. Administration is somewhat more cumbersome, and no clear advantages over vaginal administration have emerged.

Table 2. Various methods of labour induction in all women compared with PGE_2 administered vaginally as the 'gold standard' control method, extracted from the respective systematic reviews in the Cochrane Library.

Method compared with PGE_2	Outcomes				
	Vaginal delivery not achieved within 24 hours	Uterine hyperstimulation with fetal heart rate changes	Caesarean section	Serious neonatal morbidity or perinatal death	Serious maternal morbidity or death
Intravenous oxytocin	1.9 (1.4–2.4) [360]	0.35 (0.04–3.3) [767]	1.1 (0.95–1.3) [4649]	3.0 (0.3–29) [3084]	1.1 (0.15–7.6) [275]
Amniotomy		No events [260]	1.2 (0.38–3.8) [260]		
Intravenous oxytocin with amniotomy	0.9 (0.46–1.8) [42]	0.81 (0.45–1.5) [739]	1.06 (0.79–1.4) [1140]	1.00 (0.07–15) [612]	No events [378]
Vaginal misoprostol	0.70 (0.61–0.81) [1079]	1.2 (0.78–2.0) [1396]	0.93 (0.74–1.2) [238]		
Vaginal $PGF_{2\alpha}$	0.51 (0.05–5.4) [75]	1.0 (0.07–14) [106]	1.0 (0.47–2.2) [107]		
Oral misoprostol	1.2 (0.94–1.5) [691]	0.87 (0.49–1.6) [929]	0.90 (0.70–1.2) [959]	No events [267]	No events [962]
Mechanical methods	1.7 (1.2–2.5) [109]	No events [75]	1.2 (0.94–1.6) [786]		No events [88]
Membrane sweeping			0.70 (0.44–1.1) [339]		
Extra-amniotic prostaglandins	1.26 (1.0–1.6) [261]	No events [261]	0.89 (0.42–1.9) [142]		
Oral prostaglandins			0.69 (0.33–1.5) [63]		
Oestrogens (with amniotomy)		5.0 (0.25–100) [60]			

Comparisons are expressed as relative risks (95% confidence intervals), [*n*], using a fixed-effects model. A relative risk below 1 indicates that the outcome was less frequent in the method being compared with PGE_2. No data were available for intracervical or intravenous prostaglandins, buccal or sublingual misoprostol, mifepristone, corticosteroids, relaxin, hyaluronidase, castor oil, bath and enema, acupuncture, breast stimulation, homoeopathic methods or nitrous oxide.

Table 3. Various methods of labour induction in women with unfavourable cervices compared with PGE_2 administered vaginally as the 'gold standard' control method, extracted from the respective systematic reviews in the Cochrane Library.

Method compared with dinoprostone	Outcomes				
	Vaginal delivery not achieved within 24 hours	Uterine hyperstimulation with fetal heart rate changes	Caesarean section	Serious neonatal morbidity or perinatal death	Serious maternal morbidity or death
Intravenous oxytocin	1.9 (1.4–2.4) [360]	0.36 (0.01–8.7) [209]	1.3 (0.95–1.7) [1144]	No events [342]	No events [40]
Intravenous oxytocin with amniotomy	0.90 (0.46–1.8) [42]		0.98 (0.48–2.0) [106]		No events [60]
Vaginal misoprostol	0.70 (0.61–0.81) [436]	1.2 (0.66–2.2) [1035]	0.86 (0.66–1.1) [1038]		
Vaginal $PGF_{2\alpha}$	0.51 (0.05–5.4) [75]	1.0 (0.07–14) [106]	1.0 (0.47–2.2)		
Mechanical methods	1.7 (1.2–2.5) [109]	0.18 (0.04–0.79) [456]	1.2 (0.92–1.6) [738]		No events [60]
Membrane sweeping			0.67 (0.41–1.1) [252]		
Extra-amniotic prostaglandins	1.1 (0.81–1.4) [126]	No events [126]	0.89 (0.42–1.9) [142]		
Oral prostaglandins			0.69 (0.33–1.5) [63]		
Oestrogens		5.0 (0.25–100) [60]	0.88 (0.36–2.1) [60]		

Comparisons are expressed as relative risks (95% confidence intervals), [*n*], using a fixed-effects model. A relative risk below 1 indicates that the outcome was less frequent in the method being compared with dinoprostone. No data were available for intracervical or intravenous prostaglandins, amniotomy alone, oral, buccal or sublingual misoprostol, mifepristone, corticosteroids, relaxin, hyaluronidase, castor oil, bath and enema, acupuncture, breast stimulation, homoeopathic methods or nitrous oxide.

Extra-amniotic $PGF_{2\alpha}$ gel

This method is not widely used. A recent randomized comparison found 5 mg extra-amniotic $PGF_{2\alpha}$ gel to be less effective than misoprostol 50 μg vaginally.[13]

Intravenous oxytocin alone

Traditionally, the use of oxytocin has been accompanied by amniotomy. In countries with a high prevalence of HIV amniotomy may increase the risk of mother-to-child transmission of HIV. In a systematic review[14], the only trial comparing intravenous oxytocin alone versus placebo or expectant management for women with unfavourable cervix was in women with spontaneous rupture of the membranes.[15] Vaginal delivery was greatly enhanced with oxytocin. However, oxytocin without amniotomy is significantly less effective than vaginal PGE_2 for labour induction in women with unfavourable cervices (see Table 3).

Amniotomy

Rupturing of the amniotic membranes through the cervix has been documented as a method of labour induction for over 200 years.[16] A purpose-designed plastic hook or artery forceps may be used. The presumed mechanism of action is the release of endogenous prostaglandins, which in turn, may result in cervical changes and labour. A rise in prostaglandin metabolites with a relationship to the induction-delivery interval following artificial rupture of membranes has been demonstrated.[17] This method has the advantage that the use of exogenous uterine stimulants, with the problems of uterine hyperstimulation, is avoided, and the amniotic fluid may be observed. However, the procedure may be uncomfortable and it gives rise to the possibility of ascending infection. Prolonged rupture of the membranes may increase the risk of fetal infections such as HIV, and the procedure itself might place the fetus at increased risk of HIV if the skin of the presenting part is scratched. With unfavourable cervix, amniotomy is often not technically possible.

Intravenous oxytocin with amniotomy

The combination of intravenous oxytocin and amniotomy in women with unfavourable cervix has been studied in too few and small randomized trials to draw meaningful conclusions as to benefits or risks.[18] As for amniotomy alone, the unfavourable cervix may preclude the possibility of amniotomy as an initiating action for labour induction. Amniotomy is more suited to labour induction with a favourable cervix, or the augmentation of inefficient labour.

Misoprostol

Misoprostol, an orally active, stable prostaglandin E_1 analogue, has entered clinical use in obstetrics and gynaecology on a wide scale without having been registered for such use.[19] Misoprostol is highly effective for first- and second-trimester pregnancy termination. Its use for prevention of postpartum haemorrhage is as yet unsupported by evidence of effectiveness from randomized trials.[20]

The use of misoprostol for labour induction at or near term has been the subject of several reviews.[21–25] The writer and co-workers have maintained a conservative approach, because of safety concerns, which has attracted criticism.[26] Other reviewers have concluded that misoprostol for labour induction safely reduces the Caesarean section rate[24]; the American College of Obstetricians and Gynecologists' Guidelines for induction of labour recommend that misoprostol 25 μg 3- to 6-hourly is effective for induction of labour (level A evidence), and 50 μg 6-hourly may be appropriate in some situations, although increased risk of complications has been reported (level B evidence).[27] This opinion was endorsed[28] following a drug warning issued by the manufacturer.[29]

Effectiveness of misoprostol

Reviews of placebo-controlled trials have clearly shown that misoprostol is an effective drug for labour induction when administered vaginally[22] or orally.[23] In most of the dosage regimens used it is at least as effective as conventional methods of labour induction. In doses above 25 μg 4–6-hourly vaginally, misoprostol is associated with fewer failures than dinoprostone to deliver vaginally within 24 hours.[22] The greater efficiency of misoprostol has been related to more rapid cervical ripening.[30]

Oral versus vaginal route of administration of misoprostol

The majority of trials to date have studied the vaginal route of administration.

Oral compared with vaginal administration of misprostol 400 μg has a shorter time to peak serum level (34 versus 80 minutes) and a higher peak (227 pg/ml versus 165 pg/ml), but far briefer activity.[31] This is reflected in more rapid and pronounced initial increase but less persistence in uterine tonus with the oral route.[32] The short duration of action with the oral route may be advantageous in the event of uterine hyperstimulation. It may also be a reason to use frequent dosing schedules. In most studies oral misoprostol has been administered 4- or 6-hourly. We have used oral misoprostol 2-hourly for labour induction. To accommodate variability in the response of individuals, we commenced with a dose of 20 μg, increased if necessary to 40 μg after two or three doses. To administer such small doses, we dissolved 200 μg misoprostol in 200 ml water, and shook well before each administration. The solution was discarded after 12 hours. In a multicentre randomized trial in 695 women, this method was found to be similar to vaginal dinoprostone 2 mg, repeated after 6 hours, with respect to effectiveness, uterine hyperstimulation, Caesarean section rates and perinatal outcome.[33]

Another advantage referred to for oral administration is that, in some services, vaginal administration may be carried out only by doctors[24], whereas oral dosages may be administered by nurses.

Systematic review of randomized trials comparing oral with vaginal routes of administration has found the oral route to be associated with slower labours but fewer Caesarean sections.[23]

There is as yet no certainty as to which route of administration is the preferable one.

Buccal or sublingual misoprostol

The pharmacokinetic parameters of sublingual, oral, vaginal and vaginal with addition of water, have been compared in 40 pregnant women undergoing termination of pregnancy by suction evacuation.[34] The highest serum peak concentration after

administration of 400 μg was found in the sublingual group (574.8 ± 250.7 pg/ml) followed by the oral group (287.6 ± 144.3 pg/ml), the vaginal with addition of water group (162.8 ± 57.1 pg/ml) and the vaginal group (125 ± 53.8 pg/ml). The time to peak concentration was shortest in the sublingual and oral routes (26.0 ± 11.5 and 27.5 ± 14.8 minutes, respectively). The sublingual route appears to combine the shorter onset of the oral route and the longer duration and greater bioavailability of the vaginal route.

In one trial, buccal misoprostol 200 μg 6-hourly × 2 then 300 μg × 4, had similar outcomes to a vaginal regimen using 50 then 100 μg.[35]

Rectal misoprostol

The rectal route for third-stage management was first used in a randomized trial in 1998[36], based on clinical experience of the effectiveness of this route for the induction of labour (D.A. Merrell, unpublished data).

In one small study, similar efficacy for labour induction was found when misoprostol was administered vaginally or rectally.[37]

Dosage of vaginal misoprostol

Systematic review of trials comparing lower dosages (ranging from 25 μg 6-hourly to 50 μg 4-hourly) with higher dosages of vaginal misoprostol showed that the lower dosage regimens required more oxytocin use, had similar rates of delivery within 24 hours and Caesarean section and were associated with significantly less uterine hyperstimulation.[22] There is a strong case to be made for using a small dose (e.g. 25 μg)[38], at least initially.

Complications of misoprostol

Areas of concern regarding safety relate mainly to uterine hyperstimulation, and possible effects of this on the mother and baby.

Uterine hyperstimulation

Systematic review has found vaginal misoprostol in the dosages used to be associated with more uterine hyperstimulation with non-reassuring fetal heart rate changes than is PGE_2.[22] As misoprostol was also more potent as a uterine stimulant in these trials, it is difficult to be sure whether the difference is pharmacological or purely dose-related.

Meconium-stained liquor

Meconium-stained liquor was significantly more common with labour induction with misoprostol than with either vaginal or intracervical PGE_2.[22] We have previously postulated that certain myometrial stimulants may cross the placenta to stimulate fetal bowel smooth muscle and cause meconium passage.[39] We measured the response of rat myometrium and ileum to both misoprostol and dinoprostone in vivo.[40] Both stimulated both tissues, and we did not demonstrate a greater effect on ileum relative to myometrium for misoprostol than for PGE_2. An alternative explanation for the increased meconium passed during misoprostol induction of labour is that the resistance of misoprostol to placental 15-hydroxyprostaglandin dehydrogenase enables more misoprostol to enter the fetal circulation than does PGE_2.

Precipitate delivery

Precipitate delivery (labour < 2 hours) has been described as a possible complication of misoprostol[41], and occurred in 6/47 labours induced with misoprostol in a recent trial.[42] Another recent report describes an extensive cervical laceration following rapid misoprostol-induced labour.[43] Most previous reviews and trials have not documented the occurrence of precipitate delivery. In fact 'mean time to delivery' is frequently given as a primary end-point. Precipitate deliveries may contribute to apparently favourable mean induction to delivery times, without being identified as an unfavourable outcome. The importance of precipitate delivery is that it may be a marker for excessive uterine response to misoprostol and risk of uterine rupture.

Rupture of the unscarred uterus

There have been isolated reports of rupture of an unscarred uterus following misoprostol labour induction[22,44–46], including a maternal death within 7 hours of labour induction with one dose of misoprostol 50 μg vaginally in a healthy woman with uneffaced cervix.[47] Without a reliable basis of comparison, it is unclear whether the risk of uterine rupture following misoprostol induction is greater or less than with other methods of labour induction.

Women with previous Caesarean section

Misoprostol has been used to induce labour in women with previous Caesarean section.[48] Several cases of rupture of uterine scars have been reported.[49] No data are available from randomized trials, except for one trial which was terminated following uterine scar rupture in two of the first 17 cases induced with low-dosage misoprostol.[50] A recent retrospective study found significantly more cases of uterine rupture or dehiscence following cervical ripening with misoprostol than when oxytocin or prostaglandin E_2 was used.[51] In a pilot study of misoprostol 50 μg orally 4-hourly for cervical ripening in women with previous Caesarean section, uterine rupture occurred in one of 10 women.[52] Most authors recommend that misoprostol should not be used in women with uterine scars.

Caesarean section

The relationship between misoprostol use and Caesarean section is a complex one. The trend in previous randomized trials has been an increase in Caesarean sections for fetal heart rate abnormality and a reduction for poor progress of labour, giving a reduction overall. Two recent trials also showed an increase in Caesarean sections for suspected fetal distress with misoprostol.

Perinatal outcome

Despite increases in uterine hyperstimulation, most reviews and trials have shown no significant difference in perinatal outcome following misoprostol versus other methods.

Postpartum haemorrhage

A possible increase in postpartum haemorrhage has been observed following misoprostol labour induction.[53] Increased postpartum haemorrhage was noted in a retrospective study compared with the general obstetric population (58/1037 versus 394/11255)[54], and in a randomized trial following labour induction with vaginal misoprostol 50 μg versus 25 μg 4-hourly (9.8 versus 2.2%).[55]

Conclusion

Recent reports have confirmed that misoprostol is a highly effective agent for labour induction. Complications remain a matter of concern, particularly uterine hyperstimulation, precipitate labour, meconium stained liquor, uterine rupture and postpartum haemorrhage. Results suggest that risks can be minimized with the use of small dosages, and that the starting dose should not exceed 25 μg. It is not yet clear whether the oral or the vaginal route is preferable. There is a need for large-scale randomized trials, comparing low-dose misoprostol regimens with conventional methods, to determine with more certainty the relative rates of rare adverse outcomes.

Mechanical methods, including extra-amniotic Foley catheter

Mechanical methods of dilating the cervix are among the oldest known methods of labour induction. The presumed method of action, apart from physical stretching of the cervix, is release of endogenous prostaglandins as a result of stimulation of the cervix and lower uterine segment. Placement of an extra-amniotic balloon catheter such as a Foley catheter or the 'Atad' double balloon catheter have been associated with a somewhat slower effect than PGE_2, but less uterine hyperstimulation with fetal heart rate changes.[56] In a more recent randomized trial, extra-amniotic Foley catheter placement was associated with similar effectiveness and fewer Caesarean sections compared with vaginal PGE_2.[57]

For pre-induction cervical ripening, misoprostol 50 μg 4-hourly was randomly compared with a transcervical Foley catheter bulb. There were no differences in cervical ripening or labour induction success. Misoprostol was associated with more uterine contraction abnormalities (20 versus 0%) and meconium-stained liquor (22 versus 5%). There was one rupture of a scarred uterus with misoprostol.[58]

Extra-amniotic saline infusion

The stimulatory effect of the extra-amniotic balloon catheter may be enhanced by infusion of normal saline into the extra-amniotic space at 50 ml per hour. In a study of 123 women, extra-amniotic saline infusion with intravenous oxytocin had similar effectiveness and complications to misoprostol 50 μg 4-hourly.[59]

In a more recent study, 200 women with unfavourable cervices were randomly allocated to labour induction with extra-amniotic saline infused through a Foley catheter, or vaginal misoprostol, 25 μg 4-hourly.[60] Oxytocin was used in both groups. With extra-amniotic saline the time to delivery was shorter (970 ± 503 minutes versus 1323 ± 700; $P = 0.006$); abnormal fetal heart rate tracings less frequent (19 versus 30%; $P = 0.05$); and tachysystole less frequent (1 versus 8%; $P = 0.02$). There were no differences in the routes of delivery or neonatal outcomes.

The limited data from randomized trials suggest that extra-amniotic saline infusion is a safe and effective method of labour induction.[60]

Membrane sweeping

Separating the membranes from the lower uterine segment by a circular motion of a finger inserted through the cervix is a common procedure used to curtail pregnancy. It is associated with an increase in circulating prostaglandins and reduced formal labour

inductions, but is uncomfortable and not possible when the cervix is closed or very posterior.[61]

Extra-amniotic prostaglandins

Both PGE_2 and $PGF_{2\alpha}$ may be injected via a Foley catheter into the extra-amniotic space as a gel or saline solution. Studies of this method are limited, and it has largely been replaced by vaginal placement of prostaglandins.[62]

Intravenous prostaglandins

Limited trials have found that intravenous prostaglandin has no benefits over oxytocin, and has more maternal and fetal side-effects.[63]

Oral prostaglandins

Oral prostaglandins have not been shown to have advantages over conventional methods of labour induction, and are associated with more vomiting.[64]

Mifepristone

There is insufficient information from trials to guide clinical practice regarding the use of mifepristone for labour induction.[65]

Oestrogens and corticosteroids

There is evidence of the role of oestrogens and corticosteroids in the onset of labour in sheep, but none to support their clinical use to induce labour in women.[66,67]

Relaxin

Relaxin is of interest as a cervical ripening agent as it may be free of concomitant uterine stimulation activity. Further research is required to determine whether it is of clinical use for cervical ripening.[68]

Hyaluronidase

Hyaluronidase may enhance cervical ripening when injected into the cervix, but no randomized trials are available to evaluate whether it is clinically useful.[69]

Castor oil, bath, and/or enema

Castor oil, bath and enema were a time-honoured method of inducing labour. Only one randomized trial has evaluated castor oil, with inconclusive results.[70] It has been suggested that castor oil, a cathartic, may cause meconium passage by a direct effect on the fetal bowel.[39]

Acupuncture

Observational studies have suggested that acupuncture for labour induction is safe and may be effective.[71] In a recent small randomized trial, acupuncture at points LI 4 and SP 6 on alternate days from the date of conception was associated with a shorter interval to delivery.[72]

Breast stimulation

Breast stimulation has been used to stimulate uterine contractions for contraction stress testing, and for labour induction. Review of six randomized trials showed a reduction in the number of women undelivered after 72 hours, and of postpartum haemorrhage. The trials were not adequate to address safety concerns, and, therefore, the reviewers do not advocate its use in routine practice.[73]

Sexual intercourse

Sexual intercourse might induce labour by several mechanisms: physical stimulation of the cervix and lower uterine segment, prostaglandins in the semen, or oxytocin release as a result of breast stimulation or orgasm. One small randomized trial has been inadequate to evaluate this method.[74]

Homoeopathic methods

Homoeopathic remedies are increasing in popularity in Western countries. Caulophyllum thalictroides is used for labour induction or augmentation. One small randomized trial has inadequate data to evaluate its use.[75]

INDUCTION OF LABOUR WITH PREVIOUS CAESAREAN SECTION

Reports of uterine rupture when labour is induced with misoprostol are referred to above. A recent trial found PGE_2 tablets to be more effective than extra-amniotic Foley catheter alone, but was far too small to address issues of safety.[76] In a retrospective study, uterine scar rupture was found in 6/58 (10%) of labours induced with PGE_2 inserts, compared with 8/732 (1.1%) without.[77] In another retrospective study the rates of rupture of a scarred uterus were: 2.5% for labours induced with prostaglandins; 0.77% for other methods of labour induction and 0.52% for spontaneous labour.[78] The Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists has concluded that the risk of uterine rupture during attempts at vaginal birth after Caesarean section is substantially increased with the use of various prostaglandin cervical ripening agents for the induction of labour, and their use for this purpose is discouraged.[79]

PRETERM LABOUR INDUCTION

When labour is induced before term, the cervix is often unfavourable. Interestingly, a recent case–control study found shorter labours and fewer cases of severe postpartum haemorrhage in preterm than in term or post-term pregnancies induced with PGE_2 gel.[80]

Practice points

- weigh up benefits and risks carefully before embarking on labour induction with an unfavourable cervix
- oxytocin and/or amniotomy are less effective for labour induction when the cervix is unfavourable
- PGE_2 is commonly used for labour induction when the cervix is unfavourable, in various vaginal formulations
- the sustained-release vaginal insert has the advantage of easy removal in the event of uterine hyperstimulation
- misoprostol is more effective than PGE_2 in certain regimens, but with increased risk of uterine hyperstimulation and fetal heart rate changes. The differential effectiveness and risks may be dose-related
- extra-amniotic Foley catheter with saline infusion is an effective method for labour induction when the cervix is unfavourable, with a low risk of uterine hyperstimulation

Research agenda

Adequate trials are needed to answer many outstanding questions, including:

- the relative benefits and risks of labour induction in certain clinical circumstances (e.g. fetal growth impairment and twin pregnancy at specific gestational ages)
- the optimal route and dosage schedule for misoprostol
- the risk of rare events such as uterine rupture and precipitate labour with the various induction methods discussed
- the effectiveness of several alternative methods of labour induction discussed above

SUMMARY

The most important consideration with respect to labour induction is not how, but whether, labour induction should be undertaken. Careful consideration must be given to potential benefits and risks to mother and baby, both physical and emotional, as well as to the state of the uterine cervix. When the cervix is unfavourable, oxytocin infusion and/or artificial rupture of the membranes are less likely to be effective in inducing labour. PGE_2 administered vaginally in various formulations is the usual method of labour induction. Misoprostol is a less expensive method which is more effective than PGE_2 when 50 μg is used vaginally 4-hourly. However, at this dosage more uterine hyperstimulation occurs. At dosages of about 25 μg 4-hourly vaginally, both the effectiveness and side-effects appear similar to those for PGE_2.

Mechanical methods of labour induction stimulate the cervix and lower uterine segment to release endogenous prostaglandins. Infusion of saline through an extra-amniotic Foley catheter appears to be an effective method of labour induction with a low rate of uterine hyperstimulation.

Several other methods of labour induction have not been adequately assessed by randomized trials so they cannot be advocated for general use.

ACKNOWLEDGEMENTS

The following are acknowledged for their collaboration in developing a strategy to review data from randomized trials of methods of labour induction for publication in the Cochrane Library: Alfirevic Z, Henderson S, Kelly T, Kavanagh J, Thomas J, Brocklehurst P and Neilson JP. I also acknowledge the University of the Witwatersrand for support.

REFERENCES

1. Zhang J, Yancey MK & Henderson CE. U.S. national trends in labor induction, 1989–1998. *Journal of Reproductive Medicine* 2002; **47:** 120.
2. Crowley P. Interventions for Preventing or improving the outcome of delivery at or beyond term (Cochrane Review). *The Cochrane Library,* Issue 4, Oxford: Update Software, 2002.
* 3. Rayburn WF. Preinduction cervical ripening: basis and methods of current practice. *Obstetric and Gynecological Survey* 2002; **57:** 683–691.
4. Bishop EH. Pelvic scoring for elective induction. *Obstetrics and Gynecology* 1964; **24:** 266–268.
5. Kiss H, Ahner R & Hohlagschandtner M. Fetal fibrinectin as a predictor of term labor: a literature review. *Acta Obstetrica et Gynaecologica Scandinavica* 2000; **79:** 3–7.
6. Ojutiku D, Jones G & Bewley S. Quantitative foetal fibronectin as a predictor of successful induction of labour in post-date pregnancies. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2002; **101:** 143–146.
7. Keirse MJNC. Prostaglandins in preinduction cervical ripening: meta-analysis of worldwide clinical experience. *Journal of Reproductive Medicine* 1993; **38**(supplement)**:** 89–98.
8. MacKenzie IZ & Burns E. Randomised trial of one versus two doses of prostaglandin E2 for induction of labour: 1. Clinical outcome. *British Journal of Obstetrics and Gynaecology* 1997; **104:** 1062–1067.
9. Royal College of Obstetricians and Gynaecologists (RCOG), *Evidence-Based Clinical Guideline No 9. Induction of Labour,* London: RCOG Press, 2002.
10. Rabl M, Joura EA, Yucel Y & Egarter C. A randomized trial of vaginal prostaglandin E2 for induction of labor. Insert vs. tablet. *Journal of Reproductive Medicine* 2002; **47:** 115–119.
* 11. Kelly AJ, Kavanagh J & Thomas J. Vaginal prostaglandin (PGE_2 and $PGF_{2\alpha}$) for induction of labour at term (Cochrane Review), *The Cochrane Library,* Issue 4, Oxford: Update Software, 2002.
12. Hofmeyr GJ, Alfirevic Z, Kelly T, et al. Methods for cervical ripening and labour induction in late pregnancy: generic protocol (Protocol for a Cochrane Review), *The Cochrane Library,* Issue 4, Oxford: Update Software, 2002.
13. Majoko F, Zwizwai M, Lindmark G & Nystrom L. Labor induction with vaginal misoprostol and extra-amniotic prostaglandin F2alpha gel. *International Journal of Gynaecology and Obstetrics* 2002; **76:** 127–133.
14 Intravenous oxytocin alone for cervical ripening and induction of labour (Cochrane Review). *The Cochrane Library,* (Issue 4), Oxford: Update Software 2002.
15. Wagner MV, Chin VP, Peters CJ et al. A comparison of early and delayed induction of labor with spontaneous rupture of membranes at term. *Obstetrics and Gynecology* 1989; **74:** 93–97.
16. Bricker L & Luckas M. Amniotomy alone for induction of labour (Cochrane Review), *The Cochrane Library,* Issue 4, Oxford: Update Software, 2002.
17. Husslein P, Kofler E, Rasmussen A et al. Oxytocin and initiation of human parturition: IV. Plasma concentrations of oxytocin and 13, 14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ during induction of labor by artificial rupture of membranes. *American Journal of Obstetrics and Gynecology* 1983; **147:** 503–507.
18. Howarth GR & Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour (Cochrane Review), *The Cochrane Library,* Issue 4, Oxford: Update Software, 2002.

* 19. Goldberg AB, Greenberg MB & Darney PD. Misoprostol and pregnancy. *New England Journal of Medicine* 2001; **344:** 38–47.
20. Gülmezoglu AM. Prostaglandins for prevention of postpartum haemorrhage (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2001.
21. Hofmeyr GJ, Gulmezoglu AM & Alfirevic Z. Misoprostol for induction of labor: a systematic review. *British Journal of Obstetrics and Gynaecology* 1999; **106:** 798–803.
* 22. Hofmeyr GJ & Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 1, Oxford: Update Software, 2003.
* 23. Alfirevic Z. Oral misoprostol for induction of labour (Cochrane Review). *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
24. Sanchez-Ramos L & Kaunitz AM. Misoprostol for cervical ripening and labor induction: a systematic review of the literature. *Clinical Obstetrics and Gynecology* 2000; **43:** 475–488.
25. Song J. Use of misoprostol in obstetrics and gynecology. *Obstetrical and Gynecological Survey* 2000; **55:** 503–510.
26. Day L, Tailor A, Howard R & Burrell S. Misoprostol for induction of labour at term. *British Journal of Obstetrics and Gynaecology* 2000; **107:** 576–577.
27. Morey SS. ACOG develops guidelines for induction of labor. *American Family Physician* 2000; **62:** 445.
28. American College of Obstetricians and Gynecologists, *Response to Searle's Drug Warning on Misoprostol. ACOG Committee Opinion 248*. Washington, DC: ACOG, 2000. December.
29. Friedman MA. Manufacturer's warning regarding unapproved uses of misoprostol. *New England Journal of Medicine* 2001; **344:** 61.
30. Raio L, Ghezzi F, Di Naro E et al. Shorter delivery time after induction with misoprostol. *Zentralblatt füe Geburtshilfe und Neonatologie* 2001; : 147–151. In German.
* 31. Zieman M, Fong SK, Benowitz NL et al. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstetrics and Gynecology* 1997; **90:** 88–92.
* 32. Danielsson KG, Marions L, Rodriguez A et al. Comparison between oral and vaginal administration of misoprostol on uterine contractility. *Obstetrics and Gynecology* 1999; **93:** 275–280.
* 33. Hofmeyr GJ, Alfirevic Z, Matonhodze B et al. Titrated oral misoprostol solution for induction of labour: a multicentre, randomised trial. *British Journal of Obstetrics and Gynaecology* 2001; **108:** 952–959.
* 34. Tang OS, Schweer H, Seyberth HW et al. Pharmacokinetics of different routes of administration of misoprostol. *Human Reproduction* 2002; **17:** 332–336.
35. Blust D & Carlan SJ. Buccal versus vaginal misoprostol for cervical ripening and labor induction. *Obstetrics and Gynecology* 2001; **97**(supplement 1): S5.
36. Bamigboye AA, Hofmeyr GJ & Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1998; **179:** 1043–1046.
37. Pi P & Zhu F. Clinical observation of misoprostol on induction in late pregnancy. *Bulletin of Hunan Medical University* 1999; : 195–197. In Chinese.
38. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Safety* 2002; **25:** 665–676.
39. Mitri F, Hofmeyr GJ & van Gelderen CJ. Meconium during labour: self-medication and other associations. *South African Medical Journal* 1987; **71:** 431–433.
40. Matonhodze BB, Katsoulis LC & Hofmeyr GJ. Labor induction and meconium: in vitro effects of oxytocin, dinoprostone and misoprostol on rat ileum relative to myometrium. *Journal of Perinatal Medicine* 2002; **30:** 405–410.
41. Hsieh YY, Tsai HD, Chang CC et al. Precipitate delivery and postpartum hemorrhage after term induction with 200 micrograms misoprostol. *Zhonghua Yi Xue Za Zhi (Taipei)* 2000; **63:** 58–61.
42. Hoffmann RA, Anthony J & Fawcus S. Oral misoprostol vs. placebo in the management of prelabor rupture of membranes at term. *International Journal of Gynaecology and Obstetrics* 2001; **72:** 215–221.
43. Oyelese Y, Landy HJ & Collea JV. Cervical laceration associated with misoprostol induction. *International Journal of Gynaecology and Obstetrics* 2001; **73:** 161–162.
44. Khabbaz AY, Usta IM, El-Hajj MI et al. Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *Journal of Maternal Fetal Medicine* 2001; **10:** 141–145.
45. Mathews JE, Mathai M & George A. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *International Journal of Gynaecology and Obstetrics* 2000; **68:** 43–44.
46. Akhan SE, Iyibozkurt AC & Turfanda A. Unscarred uterine rupture after induction of labor with misoprostol: a case report. *Clinical and Experimental Obstetrics and Gynecology* 2001; **28:** 118–120.
47. Daisley Jr. H. Maternal mortality following the use of misoprostol. *Medical Science Law* 2000; **40:** 78–82.

48. Choy-Hee L & Raynor BD. Misoprostol induction of labor among women with a history of cesarean delivery. *American Journal of Obstetrics and Gynecology* 2001; **184:** 1115–1117.
49. Gherman RB, McBrayer S & Browning J. Uterine rupture associated with vaginal birth after cesarean section: a complication of intravaginal misoprostol? *Gynecological and Obstetric Investigation* 2000; **50:** 212–213.
50. Wing DA, Lovett K & Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with prior cesarean delivery. *Obstetrics and Gynecology* 1998; **91:** 828–830.
51. Hill DA, Chez RA, Quinlan J et al. Uterine rupture and dehiscence associated with intravaginal misoprostol cervical ripening. *Journal of Reproductive Medicine* 2000; **45:** 823–826.
52. Gherman RB & Heath T. Trial of labor after cesarean delivery: a pilot study of oral misoprostol for preinduction cervical ripening. *Obstetrics and Gynecology* 2001; **97**(supplement 1)**:** S68.
53. Hsieh YY, Tsai HD, Chang CC et al. Precipitate delivery and postpartum hemorrhage after term induction with 200 micrograms misoprostol. *Zhonghua Yi Xue Za Zhi (Taipei)* 2000; **63:** 58–61.
54. Fletcher H & Hutchinson S. A retrospective review of pregnancy outcome after misoprostol (prostaglandin E1) induction of labour. *West Indian Medical Journal* 2001; **50:** 47–49.
55. El-Sherbiny MT, El-Gharieb IH & Gewely HA. Vaginal misoprostol for induction of labor: 25 vs. 50 microg dose regimen. *International Journal of Gynaecology and Obstetrics* 2001; **72:** 25–30.
* 56. Boulvain M, Kelly A, Lohse C, et al. Mechanical methods for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
57. Ghezzi F, Massimo F, Raio L et al. Extra-amniotic Foley catheter and prostaglandin E(2) gel for cervical ripening at term gestation. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2001; **97:** 183–187.
58. Sciscione AC, Nguyen L, Manley J et al. A randomized comparison of transcervical Foley catheter to intravaginal misoprostol for preinduction cervical ripening. *Obstetrics and Gynecology* 2001; **97:** 603–607.
59. Buccellato CA, Stika CS & Frederiksen MC. A randomized trial of misoprostol versus extra-amniotic sodium chloride infusion with oxytocin for induction of labor. *American Journal of Obstetrics and Gynecology* 2000; **182:** 1039–1044.
60. Mullin PM, House M, Paul RH & Wing DA. A comparison of vaginally administered misoprostol with extra-amniotic saline solution infusion for cervical ripening and labor induction. *American Journal of Obstetrics and Gynecology* 2002; **187:** 847–852.
61. Boulvain M, Stan C & Irion O. Membrane sweeping for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
62. Hutton E & Mozurkewich E. Extra-amniotic prostaglandin for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
63. Luckas M & Bricker L. Intravenous prostaglandin for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
64. French L. Oral prostaglandin E2 for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
65. Neilson JP. Mifepristone for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
66. Thomas J, Kelly AJ & Kavanagh J. Oestrogens alone or with amniotomy for cervical ripening or induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
67. Kavanagh J, Kelly AJ & Thomas J. Corticosteroids for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
68. Kelly AJ, Kavanagh J & Thomas J. Relaxin for cervical ripening and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
69. Kavanagh J, Kelly AJ & Thomas J. Hyaluronidase for cervical priming and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
70. Kelly AJ, Kavanagh J & Thomas J. Castor oil, bath and/or enema for cervical priming and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
71. Smith CA & Crowther CA. Acupuncture for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
72. Rabl M, Ahner R, Bitschnau M et al. Acupuncture for cervical ripening and induction of labor at term—a randomized controlled trial. *Wiener Klinische Wochenschrift* 2001; **113:** 942–946.
73. Kavanagh J, Kelly AJ & Thomas J. Breast stimulation for cervical ripening and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
74. Kavanagh J, Kelly AJ & Thomas J. Sexual intercourse for cervical ripening and induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.
75. Smith CA. Homoeopathy for induction of labour (Cochrane Review), *The Cochrane Library*, Issue 4, Oxford: Update Software, 2002.

76. Ben-Aroya Z, Hallak M, Segal D et al. Ripening of the uterine cervix in a post-cesarean parturient: prostaglandin E2 versus Foley catheter. *Journal of Maternal, Fetal and Neonatal Medicine* 2002; **12:** 42–45.
77. Taylor DR, Doughty AS, Kaufman H et al. Uterine rupture with the use of PGE_2 vaginal inserts for labor induction in women with previous cesarean sections. *Journal of Reproductive Medicine* 2002; **47:** 549–554.
* 78. Lydon-Rochelle M, Holt VL, Easterling TR & Martin DP. Risk of uterine rupture during labor among women with a prior cesarean delivery. *New England Journal of Medicine* 2001; **345:** 3–8.
79. Committee opinion, Induction of labor for vaginal birth after cesarean delivery. *Obstetrics and Gynecology* 2002; **99:** 679–680.
80. Abelin Tornblom S, Ostlund E, Granstrom L & Ekman G. Pre-term cervical ripening and labor induction. *European Journal of Obstetrics, Gynecology and Reproductive Biolology* 2002; **104:** 120–123.

Labour induction at term — a randomised trial comparing Foley catheter plus titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone

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Objectives. To compare three methods of labour induction.

Design. Randomised controlled trial.

Setting. Academic hospitals in Johannesburg, South Africa.

Subjects. Women with intact membranes due for induction of labour.

Method. Randomised, sealed opaque envelopes were used to allocate women to labour induction with extra-amniotic Foley catheter/titrated oral misoprostol solution (N = 174), titrated oral misoprostol solution alone (N = 176), or vaginal dinoprostone (N = 176). Misoprostol was dissolved in water and 20 - 40 g was given 2-hourly.

Outcome measures. These were failure to deliver vaginally within 24 hours, additional measures for induction or augmentation of labour, analgesia, and maternal and fetal complications.

Results. In the Foley catheter group, misoprostol was required in all but 1 case. Failure to deliver vaginally within 24 hours was similar for the three groups (79/174 v. 70/176 v. 70/176 respectively). Labour augmentation, caesarean section and instrumental delivery were used somewhat more frequently in the Foley/misoprostol group than in the misoprostol alone group, but these differences were not statistically significant. More analgesia was used in the Foley catheter/misoprostol group than in the misoprostol group (64/172 v. 46/175). Side-effects and neonatal complications were similar for the three groups.

Conclusions. Use of extra-amniotic Foley catheter placement showed no measurable benefits over the use of oral misoprostol alone, or vaginal dinoprostone.

S Afr Med J 2003; **93**: 375-379.

Mechanical methods (catheters or hygroscopic dilators introduced into the extra-amniotic space via the cervical canal) were among the first methods of cervical ripening and labour induction developed.[1] Potential advantages include simplicity of use, low cost and few side-effects. Despite the availability of pharmacological methods over recent decades, the Foley catheter[2] and the 'Atad' double balloon catheter[3] are still in use, with or without the injection of saline solution or prostaglandins into the extra-amniotic space.[4] In a systematic review of 45 randomised trials, mechanical methods of labour induction were found to be less effective than prostaglandins and reduced the risk of uterine hyperstimulation; compared with oxytocin, there were fewer caesarean sections with mechanical methods.[5] A recent small study[6] found that the combination of an extra-amniotic Foley catheter with vaginal misoprostol was not significantly more effective than misoprostol alone, although there was a trend to fewer cases of tachysystole.

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Prostaglandin E_2 (PGE2) is regarded as the 'gold standard' for labour induction, but is unaffordable in many resource-poor settings.

Misoprostol is a unique prostaglandin E_1 analogue that has found wide application in clinical medicine including cervical ripening and labour induction.[7-11] One of the major problems has been finding the ideal dose to minimise its side-effects, particularly uterine hyperstimulation. Several cases of uterine rupture have also been reported.[12] Following completion of a small dose-finding pilot study,[13] we developed a novel approach to the use of misoprostol for labour induction, administering 20 - 40 g of misoprostol solution orally every 2 hours, titrated against the uterine response. This new method was compared with conventional labour induction using vaginal dinoprostone in a multicentre trial in Johannesburg and Liverpool.[14] Because it may be difficult to eliminate uterine hyperstimulation completely with this method, we also investigated the effectiveness of a mechanical method (Foley's catheter) followed when necessary by oral misoprostol titration. A randomised study design was used, nested within the larger trial. Those women with intact membranes enrolled at the South African sites were randomly allocated to Foley catheter/oral misoprostol, oral misoprostol alone or vaginal dinoprostone. This report presents the results of that three-way comparison.

Methods

Eligible women with clinical indications for labour induction at or after 34 weeks' gestation and intact membranes were recruited into the study at Coronation Women's and Children's Hospital and at Chris Hani Baragwanath Hospital in Johannesburg. The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Signed and informed consent was obtained from each participant and baseline demographic details were completed. Exclusion criteria were: uterine scar, uncontrolled medical complications such as diabetes mellitus and severe hypertension, non-vertex presentations, multiple pregnancy, fetal distress and antepartum haemorrhage. Baseline cardiotocography was performed to rule out fetal compromise, followed by a cervical score assessment. A modified Bishop's score of < 7 was classified as unfavourable.[15] Membrane status was noted. The next in a series of opaque, sealed and numbered treatment envelopes in computer-generated random sequence was taken out of one of four dispensers for: intact membranes/unfavourable cervix, intact membranes/favourable cervix, ruptured membranes/unfavourable cervix and ruptured membranes/favourable cervix. The first two categories reflected the three-way randomisation reported here. Management followed the protocol indicated in the envelope unless clinical imperatives dictated otherwise. Analysis was by 'intention to treat', The protocols were as follows:

Foley catheter/titrated oral misoprostol solution

The cervix was visualised using a sterile bivalved vaginal speculum. An 18 - 20-gauge Foley catheter with a 30 ml bulb was passed through the cervix, and the bulb inflated with 50 ml sterile saline or water. The speculum was removed and the catheter taped to the woman's slightly flexed leg with light traction. If the bulb did not fall out within 24 hours it was deflated and removed. If, after removal or spontaneous expulsion of the catheter, labour contractions had not commenced, titrated oral misoprostol solution was started. A 200 µg misoprostol tablet was dissolved in 200 ml tap water in a medicine bottle and shaken before use. Twenty ml (= 20 µg), increasing to 40 ml after three doses, was taken orally every 2 hours until active labour (three contractions per 10 minutes, with each contraction lasting 30 seconds or more). If after established labour the contractions became inadequate, augmentation with misoprostol solution (5 µg hourly, increasing if necessary to 10 and 20 µg) was used. If the clinician judged that misoprostol augmentation was ineffective, standard oxytocin augmentation was used.

Titrated oral misoprostol

Titrated oral misoprostol solution was used as described above.

Conventional method (dinoprostone)

Dinoprostone gel 2 mg was inserted into the posterior vaginal fornix, and repeated after 6 hours if the patient was not in established labour. If not in active labour after 12 hours, oxytocin infusion was commenced, starting at 2 mIU (6 drops) per minute and increased every 20 minutes until adequate contractions occurred. Labour was augmented with oxytocin if contractions became inadequate.

If hypersystole (more than five contractions per 10 minutes for at least 20 minutes) or hypertonus (a contraction lasting at least 2 minutes) occurred, the woman was placed in the left lateral position with continuous fetal heart rate monitoring. If there were accompanying fetal heart rate abnormalities, oxygen was administered using a face mask, and 5 - 10 µg hexoprenaline was administered intravenously over 5 - 10 minutes.

Routine artificial rupture of membranes to augment labour was discouraged in all three groups because of a high prevalence of hepatitis, HIV and other perinatal infections. Artificial rupture of membranes, therefore, was generally used only if additional augmentation was considered necessary or delivery was imminent. Continuous fetal heart rate monitoring was not possible in all low-risk women, because of the shortage of cardiotocograph machines and personnel. In most cases intermittent electronic monitoring was used. The cardiotocograph tracings were analysed by one of the authors (BBM), blinded to the treatment, for uterine contraction and fetal heart rate abnormalities, and entered separately onto the database.

The sample size calculation was based on the incidence of the primary outcome, failed vaginal delivery within 24 hours, of 58% in randomised trials of vaginal misoprostol versus dinoprostone.[11] To detect a reduction to 40% with 95% certainty and 90% power required 171 women in each group.

Data were entered into the Epi-info 6 statistical package and analysed independently by one of the authors (JL). Differences between groups were expressed as relative risks with 95% confidence intervals (CIs). Prespecified subgroups for analysis were by cervical status.

Results

The baseline data are shown in Table I. There were slightly more primiparous women in the Foley catheter/misoprostol group (44%), compared with the misoprostol group (37%) and the dinoprostone group (36%). In all other respects the groups were well matched.

In the Foley catheter group, misoprostol was used in addition to the Foley catheter in all but 1 woman.

The primary outcome, failure to deliver vaginally within 24 hours, was similar for the three groups (79/174 v. 70/176 v.

Table I. Baseline data expressed as mean values (standard deviation), or proportions (%)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)	
Maternal age (yrs) (mean (SD))	26.7	(6.0)	27.8	(6.5)	27.3	(6.2)
Gestation (wks) (mean (SD))	40	(1.9)	39.9	(2.1)	39.7	(2.4)
Primiparous	76/173	(44%)	65	(37%)	63/174	(36%)
Cervical score < 7	129	(74%)	132	(75%)	128	(73%)
Primary indication for IOL:						
Impaired growth	21	(12%)	17	(10%)	22	(13%)
Post-term	97	(56%)	90	(51%)	96	(55%)
Hypertension	37	(21%)	48	(27%)	38	(22%)
Poor obstetric history	10	(6%)	12	(7%)	10	(6%)
Maternal request	1	(0.69%)	2	(1%)	1	(0.6%)
Maternal health concerns	2	(1%)	2	(1%)	1	(0.6%)
Fetal concerns	6	(3%)	4	(2%)	7	(4%)
Other	0	-	1	(0.6%)	1	(0.6%)

IOL= induction of labour.

Table II. Primary* and secondary outcomes expressed as proportions (%). Differences are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
	N	%	*N*	%	*N*	%	Combined v. misoprostol	Combined v. dinoprostone
No vaginal delivery < 24 hours*	79	45	70	40	70	40	1.14 (0.89 - 1.46)	1.14 (0.89 - 1.46)
Amniotomy	50/168	30	47/174	27	44/165	26	1.10 (0.79 - 1.57)	1.12 (0.79 - 1.57)
Oxytocin augmentation	23	13	11	6	43	24	2.11 (1.06 - 4.21)	0.54 (0.34 - 0.86)
Misoprostol augmentation	20	11	21	12	0	-	0.96 (0.54 - 1.71)	-
Any augmentation	38	22	29	16	43	24	1.33 (0.86 - 2.05)	0.89 (0.61 - 1.31)
Vaginal bleeding	9/168	5	4	2	6/174	3	2.36 (0.74 - 7.51)	1.55 (0.57 - 4.27)
Uterine tachysystole	6/163	4	13/161	8	12/164	7	0.46 (0.18) - 1.17)	0.50 (0.19 - 1.31)
Uterine hypersystole	1/163	1	1/161	1	1/164	1	0.99 (0.06 - 15.66)	1.01 (0.06 - 15.95)
Hyperstimulation syndrome	6/163	4	7/161	4	8/164	5	0.85 (0.29 - 2.46)	0.75 (0.27 - 2.13)
Fetal heart rate (FHR changes)	8/163	5	7/161	4	8/164	5	1.13 (0.42 - 3.04)	1.01 (0.39 - 2.62)
Tocolysis	9/164	5.5	7/170	4	7/170	4	1.18 (0.44 - 3.19)	1.38 (0.49 - 3.90)
Analgesia (epidural or opioid)	64/172	37	46/175	26	56/175	32	1.42 (1.03 - 1.94)	1.16 (0.87 - 1.55)
Meconium	17/168	10	13/174	7.5	15/171	8.8	1.35 (0.68 - 2.70)	1.15 (0.6 - 2.23)
Caesarean section*	36	21	24	14	43	24	1.52 (0.95 - 2.43)	0.85 (0.57 - 1.25)
Instrumental delivery (vacuum or outlet forceps)	4	2	5	3	4	2	0.81 (0.22 - 2.96)	1.01 (0.26 - 3.98)
Indication for caesarean or instrument delivery								
Delay	25/173	14	14/175	8	23/172	13	1.81 (0.97 - 3.36)	1.08 (0.64 - 1.83)
Fetal distress	13/173	8	13/175	7	17/172	10	1.01 (0.48 - 2.12)	0.76 (0.38 - 1.52)
Other	2/173	1	2/175	1	3/172	2	1.01 (0.14 - 7.10)	0.66 (0.11 - 3.92)

70/176 respectively) (Table II). Overall augmentation, caesarean section and instrumental delivery were somewhat more frequent in the Foley/misoprostol group than in the misoprostol alone group, but the differences were not statistically significant.

Analgesia was used more frequently in the Foley catheter/misoprostol than the misoprostol group (64/172 v. 46/175, relative risk 1.42, 95% CI 1.03 - 1.94).

Side-effects were very similar between the three groups, except that diarrhoea was more common in the

Table III. Maternal side-effects and complications, expressed as proportions (%). Differences are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
	N	%	*N*	%	*N*	%	Combined v misoprostol	Combined v. dinoprostone
Blood loss > 500 ml	42/174	24	43/175	25	43/174	25	0.98 (0.58 - 1.64)	0.98 (0.67 - 1.41)
Pyrexia > 38°C	3/172	2	1/174	1	2/175	1	3.03 (0.32 - 28.99)	1.53 (0.26 - 9.02)
Retained placenta	1/172	1	1/174	1	0	-	1.01 (0.06 - 16.04)	
Other	6/172	3	5/174	3	7/175	4	1.20 (0.37 - 3.86)	0.86 (0.30 - 2.51)
Nausea	31/149	21	23/151	15	19/151	12	1.37 (0.84 - 2.23)	1.65 (0.98 - 2.79)
Diarrhoea	20/148	14	6/150	4	6/165	4	3.38 (1.4 - 8.17)	3.72 (1.53 - 9.0)
Shivering	57/149	38	69/150	46	66/164	41	0.83 (0.64 - 1.09)	0.95 (0.72 - 1.25)
Any side-effect	86/149	58	82/151	54	82/165	50	1.06 (0.87 - 1.30)	1.02 (0.84 - 1.24)

Table IV. Neonatal outcomes and complications expressed as proportions (%) or mean values (standard deviation, SD). Differences between proportions are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
							Combined v. misoprostol	Combined v. dinoprostone
Birth weight (g) (mean (SD))	3 066	(518)	3 129	(505)	3 103	(542)		
Missing data	1	-	0	-	1	-		
5 min Apgar < 7	6/171	(3%)	6/173	(3%)	9/175	(5%)	1.01 (0.33 - 3.08)	0.67 (0.24 - 1.84)
Neonatal ICU admission	2/171	(1%)	3/174	(2%)	3/175	(2%)	0.68 (0.11 - 4.01)	0.68 (0.12 - 4.03)
Perinatal death	1/171	(0.6%)	0	-	1/174	(0.6%)	-	1.02 (0.06 - 16.1)
Neonatal seizures	1/170	(0.6%)	1/173	(0.6%)	0	-	1.02 (0.06 - 16.0)	-
Neonatal sepsis	1/171	(0.6%	0	-	0	-	-	-
Other	6/171	(4%)	6/173	(3%)	4/174	(2%)	1.01 (0.33 - 3.08)	1.53 (0.44 - 5.31)

Foley/misoprostol group (Table III). There were no cases of uterine rupture or sepsis.

Neonatal complications were also very similar (Table IV), although the event rates were too low for meaningful statistical comparison.

Discussion

In terms of inducing labour contractions, Foley catheter insertion was less successful than has been reported previously. In all but 1 case, misoprostol was required to induce labour contractions. Neither did preliminary 'ripening' of the cervix with the Foley catheter produce measurable benefits in terms of shorter labour or fewer complications, although the numbers studied were too small to exclude the possibility of a reduction in infrequent events such as uterine tachysystole.

This study provides no evidence of an advantage to using the Foley catheter method followed when necessary by misoprostol induction in women with intact membranes, particularly as this adds expense to the procedure, and is uncomfortable for the woman. However, the fact that failure to deliver within 24 hours of randomisation was similar across groups does suggest that the Foley catheter had an influence on the process of labour induction. Misoprostol was used only after expulsion or removal (at 24 hours) of the Foley catheter, and greatly increased randomisation to delivery times would be expected had the Foley catheter been ineffective.

The cardiotocographic data may underestimate complications as electronic monitoring was intermittent in some cases. As this limitation applied to all three groups, the data are presented for comparative purposes.

Further research should focus on the use of the Foley catheter technique in situations in which prostaglandin preparations are not available, or contraindicated. A particular problem is induction of labour in women with previous caesarean section,[16,17] in whom use of prostaglandin preparations, particularly misoprostol, may be hazardous. Although this problem was not addressed directly in this

study, the results suggest that Foley catheter placement alone is unlikely to be adequate. Additional procedures such as extra-amniotic saline infusion, or artificial rupture of membranes after expulsion of the catheter, are worth investigating in these circumstances.

Conclusions

Use of extra-amniotic Foley catheter placement followed when necessary by titrated oral misoprostol solution for induction of labour showed no measurable benefits over the use of oral misoprostol alone, or vaginal dinoprostone.

We thank the women who participated; Professor Cyril van Gelderen for granting permission to include women delivering at Chris Hani Baragwanath Hospital; nursing and medical staff at the trial hospitals for their support; the South African Medical Research Council for funding; Peter Brocklehurst and Sarah Ayers, National Perinatal Epidemiology Unit, Oxford, UK for preparing the randomisation envelopes; and Zarko Alfirevic, University of Liverpool, for advice.

References

1. Thiery M, Baines CJ, Keirse MJNC. The development of methods for inducing labour. In: Chalmers I, Enkin MW, Keirse MJNC, eds. *Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press, 1989: 971.
2. Sciscione AC, Nguyen L, Manley J, Pollock M, Maas B, Colmorgen G. A randomised comparison of transcervical Foley catheter to intravaginal misoprostol for preinduction cervical ripening. *Obstet Gynecol* 2001; **97**: 603-607.
3. Atad J, Hallak M, Auslender R, Porat-Packer T, Zarfati D, Abramovici H. A randomised comparison of prostaglandin E2, oxytocin, and the double-balloon device in inducing labor. *Obstet Gynecol* 1996; **87**; 223-227.
4. Buccellato CA, Stika CS, Frederiksen MC. A randomised trial of misoprostol versus extra-amniotic sodium chloride infusion with oxytocin for induction of labor. *Am J Obstet Gynecol* 2000; **182**: 1039-1044.
5. Boulvain M, Kelly A, Lohse C, Stan C, Irion O. Mechanical methods for induction of labour (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
6. Rust O, Greybush M, Atlas R, Balducci J. Does combination pharmacologic and mechanical pre-induction cervical ripening improve ripening to delivery interval? *Am J Obstet Gynecol* 2000; **182**: S136.
7. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. *N Engl J Med* 2001; **344**: 38-47.
8. Hofmeyr GJ. Induction of labour with misoprostol. *Curr Opin Obstet Gynecol* 2001; **13**: 577-581.
9. Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review. *Br J Obstet Gynecol* 1999; **106**: 798-803.
10. Alfirevic Z, Howarth G, Gausmann A. Oral misoprostol for induction of labour with a viable fetus (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
11. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy (Cochrane review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
12. Mathews JE, Mathai M, George A. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *Int J Gynaecol Obstet* 2000; **68**: 43-44.
13. Hofmeyr GJ, Matonhodze BB, Alfirevic Z, Campbell E, de Jager M, Nikodem C. Titrated oral misoprostol solution: a new method of labour induction. *S Afr Med J* 2001; **91**: 775-776.
14. Hofmeyr GJ, Alfirevic Z, Matonhodze BB, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for labour induction: A multi-centre, randomised trial. *Br J Obstet Gynaecol* 2001; **108**: 952-959.
15. Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol* 1964; **24**: 266-268.
16. Gherman RB, Heath T. Trial of labor after cesarean delivery: a pilot study of oral misoprostol for preinduction cervical ripening. *Obstet Gynecol* 2001; **97**: Suppl 1, S68.
17. Hill DA, Chez RA, Quinlan J, Fuentes A, LaCombe J. Uterine rupture and dehiscence associated with intravaginal misoprostol cervical ripening. *J Reprod Med* 2000; **45**: 823-826.

fetal monitoring ensured a favourable outcome in the majority of pregnancies, notwithstanding the poor obstetrical histories of many patients and the rather overloaded obstetric services at this hospital.

REFERENCES

1. Drury MI. Diabetes in pregnancy — Mathews Duncan revisited. *Br J Obstet Gynaecol* 1984; **153**: 144–151.
2. Editorial. Diabetes in pregnancy. *Lancet* 1985; **i**: 961–962.
3. Fredrikse N, Dooley SL, Metzger BE. Care of the pregnant woman with insulin-dependent diabetes mellitus. *N Engl J Med* 1985; **313**: 96–101.
4. Seeds AE, Knowles HC. Metabolic control of diabetic pregnancy. *Obstet Gynecol* 1981; **24**: 51–64.
5. World Health Organisation Expert Committee on Diabetes Mellitus. Second Report. *WHO Tech Rep Ser* 1980; No. 646.
6. Skeie JS. Self-monitoring of blood glucose. *Med Clin North Am* 1982; **66**: 1227–1249.
7. Peacock I, Hunter JC, Walford S *et al*. Self-monitoring of blood glucose in diabetic pregnancy. *Br Med J* 1979; **2**: 1333–1336.
8. Varner MW. Efficacy of home blood glucose monitoring in diabetic pregnancy. *Am J Med* 1983; **75**: 592–596.
9. Wheeler EC, Golimar CW, Deeb LC. Diabetes and pregnancy in South Carolina: prevalence, perinatal mortality and neonatal morbidity in 1978. *Diabetes Care* 1982; **5**: 561–565.

Meconium during labour — self-medication and other associations

F. MITRI, G. J. HOFMEYR, C. J. VAN GELDEREN

Summary

Prior to artificial rupture of membranes, 498 women were questioned about obstetric and social factors including self-medication during pregnancy. Caesarean section ($P < 0,01$) and low Apgar scores ($P < 0,001$) were significantly more common in pregnancies complicated by fetal meconium passage. Meconium passage was more common in women who had recently taken castor oil ($P < 0,01$) and possibly herbal substances called '*sihlambezo*' (trend $P < 0,2$). Use of laxatives or enemas and other obstetric risk factors were not associated with meconium passage.

S Afr Med J 1987; **71**: 431–433.

The risk to the neonate of inhaled meconium has been clearly established.[1] However, the importance of the passage of meconium as an indicator of fetal distress remains controversial[2] and its mechanism obscure. An increased incidence of meconium passage in fetuses of drug-dependent women has been ascribed to the intestinal hyperperistaltic effect of drug withdrawal.[3] Other mechanisms suggested include arginine vasopressin release during hypoxia,[4] cord compression,[5] vasoconstriction in the fetal gastro-intestinal tract precipitated by hypoxia,[6] and occurrence as a normal physiological event.[7]

An association of fetal meconium passage with maternal ingestion of certain drugs, particularly purgatives, has been suggested but not to our knowledge formally investigated. We have therefore undertaken a prospective study of the association of meconium passage with various obstetric factors, including maternal self-medication.

Patients and methods

The study was conducted at Baragwanath Hospital, which serves a high-risk, predominantly urban, black population. Women in labour for whom the decision to rupture the membranes artificially had been taken were enrolled in the study. They were interviewed by a member of the nursing staff who completed a questionnaire on 13 items relating to their medical and social history, including a careful enquiry into self-medication during the pregnancy. Baseline obstetric variables were also recorded. Artificial rupture of the membranes was then performed, and the appearance of the amniotic fluid recorded as being clear, lightly or heavily meconium-stained, or not visualised. Details of the outcome of the labours were obtained subsequently from the hospital records. Statistical comparisons between the groups were made by means of the *t*-test for continuous variables and the chi-square test for proportions.

Results

The amniotic fluid was examined at the time of rupture of membranes in 478 of the 498 subjects and was meconium-stained in 174 (36%) of these and clear in the remaining 304. Caesarean section, low Apgar score, and the recent ingestion of castor oil were significantly more common in those with meconium-stained amniotic fluid (Table I). There was also a trend towards increased ingestion of *sihlambezo*. No significant association of meconium passage was found with age, parity, gestational age, previous

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TABLE I. COMPARISON OF OBSTETRIC VARIABLES BETWEEN PATIENTS WITH AND WITHOUT MECONIUM STAINING OF THE AMNIOTIC FLUID

	Amniotic fluid		
	Clear	Meconium-stained	Significance
Age (yrs)	25,9 ± 0.37	26.5 ± 0,65	NS
Parity	1,48 ± 0,09	1.57 ± 0,16	NS
Gestation (wks)	38.4 ± 0.22	38,8 ± 0.52	NS
Previous caesarean section	32/304 (10.5%)	19/174 (10,9%)	NS
Decreased fetal movements	15/260 (5.8%)	7/143 (5.0%)	NS
Mother anxious	83/275 (30%)	53/154 (34,4%)	NS
Self-medication	20/304 (6,6%)	8/174 (4.6%)	NS
Laxatives	14/304 (4.6%)	9/174 (5,2%)	NS
Enemas	6/304 (2,0%)	8/174 (4,6%)	NS
Castor oil	19/304 (6,25%)	13/174 (7.5%)	NS
Sihlambezo	15/304 (4,9%)	16/174 (9,2%)	$P < 0,1$
Self-medication during the 2 days before admission			
Laxatives	4/304 (1.3%)	2/174 (1,1%)	NS
Enemas	2/304 (0,7%)	1/174 (0,6%)	NS
Castor oil	0/304 (0%)	4/174 (2,3%)	$P < 0,01$
Sihlambezo	5/304 (1,6%)	7/174 (4,0%)	$P < 0,2$
Duration of labour (h)	11,2 ± 0.59	11,81 ± 1,19	NS
Duration of ruptured membranes (h)	4,4 ± 0.28	4,3 ± 0,43	NS
Caesarean section	36/294 (12,2%)	44/170 (26,0%)	$P < 0,01$
Birth weight (g)	3141 ± 34	3191 ± 56	NS
Male child	152/295 (51.5%)	87/172 (50,5%)	NS
Apgar < 7 at 1 min	12/304 (3,9%)	24/174 (14,0%)	$P < 0,001$

NS = not significant

caesarean section, reported decreased fetal movements, maternal anxiety, hypertension, use of laxatives or enemas, duration of labour or of ruptured membranes, birth weight or sex of the baby.

In Table II, obstetric variables for women who took castor oil and those who took *sihlambezo* are compared. The gestational ages of those who took castor oil or *sihlambezo* were not significantly different from those of the controls, although the birth weight for those who took castor oil was higher.

Discussion

The widespread awareness of the need for caution when prescribing drugs for pregnant women has not been matched by attention to proprietary medicines and herbal remedies taken without prescription during pregnancy.

Castor oil is a bland oil which is hydrolysed in the intestine to glycerol and ricinoleic acid. This fatty acid is absorbed into the circulation and is highly irritant, causing rapid evacuation of bowel contents as well as uterine contractions. It is excreted in breast milk[5] and is contraindicated during pregnancy and lactation. It is still, however, recommended by some for the induction of labour.[6] *Sihlambezo* is a general term for various herbal remedies taken to promote a favourable pregnancy outcome or to induce labour. One substance used for the latter purpose has been shown to cause tetanic contractions of sensitised rat myometrium.[10] The use of *sihlambezo* is widespread in southern Africa, and most sources indicate that the substances are derived from plants which grow on river banks.

An incidence of meconium passage in excess of 30% has been a consistent finding in the population being studied. As this study is concerned with factors related to the passage of fetal meconium, rather than the risk of meconium aspiration syndrome, and as the concentration of meconium is as much dependent upon the volume of amniotic fluid as upon the amount of meconium passed, our analysis is based on the presence or absence of meconium in the amniotic fluid rather than its thickness. Indeed, the poorer outcome found with thick than with thin meconium staining in various studies[11-13] may well be an indication of the poorer outcome known to occur with diminished amniotic fluid volume[14] rather than being related to the amount of meconium passed.

We have failed to show an association between the use of enemas or a variety of laxatives and the passage of fetal meconium. However, recent ingestion of castor oil was significantly associated with meconium passage, and ingestion of *sihlambezo* showed a trend which became significant when only 'heavy' meconium staining was considered. The strength of these associations may have been partially obscured by under-reporting of self-medication because of the mothers' perception that such practices are frowned upon by hospital personnel. The numbers of cases were small in relation to the study population. The findings suggest either that ingestion of these substances results in the passage of fetal meconium, possibly by causing excessive uterine activity or by a direct irritant effect on the fetal bowel, or that women at risk for meconium passage are more likely to take these substances. Although gestational ages were not significantly different between those who took these substances and those who did not, the greater birth weight for infants born to those taking castor oil suggests more advanced fetal maturity in this group, which is a known risk factor for meconium passage. We failed to show any association between meconium passage and pregnancy complications such as hypertension, previous caesarean section and decreased fetal movements, but the outcome of pregnancy in terms of caesarean section rate and low Apgar scores was significantly associated with meconium passage.

TABLE II. OBSTETRIC VARIABLES COMPARED FOR SELF-MEDICATION GROUPS WHICH SHOWED SOME ASSOCIATION WITH MECONIUM PASSAGE

	Sihlambezo									
	Castor oil in the 2 days before admission			Any time			2 days before admission			
	Not used	Used	Significance	Not used	Used	Significance	Not used	Used	Significance
Age (yrs)	26,1 ± 0,3	28,3 ± 0,3	NS	26,2 ± 0,2	25,00 ± 1,0	NS	26,2 ± 0,3	24,1 ± 1,6	NS
Parity	1,5 ± 0,07	1,8 ± 0,9	NS	1,5 ± 0,07	1,3 ± 0,26	NS	1,5 ± 0,07	1,15 ± 0,4	NS
Gestational age (wks)	38,6 ± 0,2	39,2 ± 0,5	NS	38,7 ± 0,11	39 ± 0,5	NS	38,6 ± 0,2	39,5 ± 0,9	NS
Birth weight (g)	3 152 ± 26,0	3 767 ± 268,0	$p < 0,05$	3151	3238	NS	3 156 ± 26,0	3 209 ± 93,0	NS

NS not significant.

Conclusions

In this study the passage of fetal meconium was predictive of poor labour outcome in terms of Apgar scores and the need for caesarean section. Women who take castor oil or *sihlambezo* in late pregnancy should be identified as a high-risk group for the passage of fetal meconium. Whether or not the association is causal cannot be answered on the basis of the small number of cases identified in the study. As castor oil still has its proponents for use in clinical practice, larger studies to assess possible harmful effects are necessary. The various substances known as *sihlambezo* need to be identified and assessed for beneficial or harmful effects so that their use can be encouraged or discouraged, keeping in mind the cultural importance of such medication to the user.

The aetiology and pathogenesis of fetal meconium passage remain enigmatic. Perhaps what is most remarkable is the fact that the fetus, which will usually begin to pass meconium with ease shortly after birth, seldom does so before birth. The key to the uncertainty surrounding the passage of fetal meconium may well lie in fetal mechanisms which inhibit the passage of meconium *in utero*.

We acknowledge the excellent assistance of the nursing staff at Baragwanath Hospital, and statistical analysis by Dr G. Reinach, Southern Transvaal Branch, South African Medical Research Council.

REFERENCES

1. Hobbs JE, Eidelmen AI. *The Meconium Aspiration Syndrome: Clinical Management of Mother and Newborn*. New York: Springer-Verlag, 1979.
2. Mitchell J, Schulman H, Fleischer A, Farmavides G, Nadeau D. Meconium aspiration and fetal acidosis. *Obstet Gynecol* 1985; **65:** 352-355.
3. Ostrea EM, Naqvi M. The influence of gestational age on the ability of the fetus to pass meconium *in utero*. *Acta Obstet Gynecol Scand* 1982; **61:** 275-277.
4. De Vane GW, Naden RP, Porter JC, Rosenfeld CR. Mechanism of arginine vasopressin release in the sheep fetus. *Pediatr Res* 1982; **16:** 504-507.
5. Hon EH. The foetal heart rate. In: Corey HM. ed. *Modern Trends in Human Reproductive Physiology*. London: Butterworths, 1963: 24-25.
6. Saling E, Schneider D. Biochemical supervision of the foetus during labour. *J Obstet Gynaecol Br Cwlth* 1967; **74:** 799-811.
7. Fenton A, Steer CM. Fetal distress. *Am J Obstet Gynecol* 1962; **83:** 354-362.
8. Bergerson BS. *Pharmacology in Nursing*, 14th ed. St Louis: CV Mosby, 1979: 705.
9. Davis L. The use of castor oil to stimulate labour in patients with premature rupture of membranes. *J Nurse-Midwife* 1984; **29:** 366-370.
10. Larsen JV. Msane CL, Monkhe MC. The Zulu traditional birth attendant. *S Afr Med J* 1983; **63:** 540-542.
11. Miller FC, Sacks DA, Yeh SY *et al*. Significance of meconium during labor. *Am J Obstet Gynecol* 1975; **122:** 573-580.
12. Miller FC. Meconium staining of the amniotic fluid. *Clin Obstet Gynecol* 1979; **6:** 359.
13. Meis PJ, Hull M, Marshall JR, Hobel CJ. Meconium passage: a new classification for risk assessment during labor. *Am J Obstet Gynecol* 1978; **131:** 509-513.
14. Chamberlain PF, Manning FA, Morrison I, Harman CR, Lange IR. Ultrasound evaluation of amniotic fluid volume: I. The relationship of marginal and decreased amniotic fluid volume to perinatal outcome. *Am J Obstet Gynecol* 1984; **150:** 245-249.

J. Perinat. Med.
30 (2002) 405–410

Labor induction and meconium: *in vitro* effects of oxytocin, dinoprostone and misoprostol on rat ileum relative to myometrium

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1 Introduction

Misoprostol (Cytotec®, Searle) is a methyl ester of prostaglandin E1 additionally methylated at C-16 and is marketed for use in the prevention and treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. The structural changes to prostaglandin E_1 provided orally activity with increased duration of action. It is a potent inhibitor of gastric secretion, while producing much less diarrhea, rhinitis and emesis than the naturally occurring 15-hydroxy prostaglandins [3]. Numerous preclinical studies have shown that misoprostol may have a role in treating diverse disease states such as allergic disorders, peripheral vascular disease, hyperlipidemia, peridontal disease, osteoporosis, cystic fibrosis, pain, burn injury and ophthalmic conditions [4]. Other recent uses of misoprostol are for various pregnancy-related indications, including induction of labor [7, 8]. For induction of labor, the oral, vaginal and rectal routes have been used.

Induction of labor is a common obstetric intervention, which is used in a variety of clinical situations in which the benefits of early delivery are considered to outweigh the risks of the induction procedure. Many methods of labor induction have been studied, including mechanical methods such as artificial rupture of membranes, oxytocin and various prostaglandin preparations. The latter are most effective when the uterine cervix is 'unfavorable'.

The conventional prostaglandin most commonly used is dinoprostone (prostaglandin E2, Prostin E_2), usually as an intracervical or vaginal gel or vaginal pessary. Misoprostol is a cheap alternative to dinoprostone. It is easily stored at room temperature and has few systemic side effects. It is rapidly absorbed orally and vaginally allowing for convenient administration.

Dinoprostone, a C-15 hydroxy prostaglandin is a substrate for the rapidly acting 15-hydroxyprostaglandin dehydrogenase (PGDH), an enzyme that provides a barrier preventing transfer of primary prostaglandins to the fetal circulation. The chemical modifications to misoprostol have made it resistant to PGDH.

In most pregnancies, the fetus does not pass meconium (fetal bowel contents) until after birth. Passage of fetal meconium before birth occurs in 8–16% of pregnancies [25]. It occurs mainly in term and post-term pregnancies. It may be associated with fetal compromise, but is also common in uncompromised labors [9], and in many cases no reason for meconium passage is found. Thick but not thin meconium staining of the amniotic fluid is associated with poor perinatal outcome [15]. Meconium aspiration may occur before birth, or during and after the birth process, causing meconium aspiration syndrome, which is associated with significant mortality. Airways suctioning of the neonate may reduce, but does not eliminate the occurrence of meconium aspiration [5].

We have previously found a trend to increased

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meconium passage in women taking castor oil or herbal remedies (isihlambezo) [16], and shown *in vitro* that individual constituents of isihlambezo stimulate both rat myometrium and ileum [12, 13, 23, 24]. We postulated that there may be direct effect on fetal bowel action of substances ingested by the mother which cross the placenta to the fetus [16].

Systematic reviews of labor induction trials have shown increased meconium passage with vaginal misoprostol use versus intracervical dinoprostone use [18, 25], with oral versus vaginal misoprostol [1] and a trend to more meconium passage with prostaglandin use than with oxytocin for prelabor rupture of membranes at term [21]. In the latter review, maternal nausea and vomiting were also more common with prostaglandins than with oxytocin.

Overall objective. To determine whether the *in vitro* ileal contractile activities of dinoprostone, misoprostol and oxytocin are in keeping with the variation in rates of meconium staining observed during labor induction with these substances.

Experimental hypotheses

1. Misoprostol and dinoprostone stimulate both bowel smooth muscle and myometrium.
2. The relative stimulatory effect of misoprostol on bowel smooth muscle compared with myometrium is greater than that of dinoprostone, and both are greater than that of oxytocin.

2 Methods

Rat tissue preparations. Virgin Spraque-Dawley rats weighing approximately 250 g were estrogenised by injection with stilbestrol (10 µg/100 g) (Maybaker (SA)) i.p. 24 hours before being euthanased with CO_2. Uterine and ileal tissue was dissected out and mounted in Tyrode's solution (136 mM NaCl, 2.68 mM KCl, 1.80 mM $CaCl_2$, 1.05 mM $MgCl_2$, 11.9 mM $NaHCO_3$, 0.42 mM NaH_2PO_4, 5.55 mM glucose). The ileum was maintained at 37 °C and the uterus at 26 °C to decrease spontaneous contractions [14]. The organ baths were oxygenated with carbogen (5 % CO_2 in O_2). Organs were allowed to equilibrate in the organ baths for at least 30 min during which time the baths were rinsed frequently. Isotonic contractions of the organs were measured against 1 g resistance and recorded electronically using potentiometer recorders. The organs were challenged with cumulative doses of either reference agonists or study medications according to Van Rossum [22]. Standard curves using the relevant reference agonist alone were run at the start of each experiment and between each test challenge. The range of drug concentrations used was chosen to obtain a dose response curve. Repeat experiments were carried out using tissues from different rats.

The response to each concentration of drug was expressed as a percentage of the maximal response to acetylcholine measured prior to the test challenge.

Materials. Oxytocin (Syntocinon®, Sandoz), dinoprostone (Sigma) and misoprostol tablets (Cytotec®, Searle) were compared against the reference standard acetylcholine chloride (Sigma).

Ideally pure misoprostol should have been used but Searle have dissociated themselves from the use of misoprostol in obstetrics and gynecology [6], making the pure compound unobtainable at the time of this study. Even though the use of tablets raises the question of the accuracy of the dosages used, the main results of interest are the relative effects of the compounds on ileum versus myometrium, which are independent of absolute drug concentration.

Since misoprostol was obtained from tablets and dinoprostone was obtained as a pure compound, the calculated dosages of the two preparations used should not be directly compared.

Analysis. Student-t tests were used to test the differences between the contractile response from the ileum and the uterus to each concentration of drug.

3 Results

Oxytocin. The maximal uterine response to oxytocin and acetylcholine are equivalent (figure 1a), whereas oxytocin has no measurable effect on the ileum for the concentrations used (figure 1b). The uterine tissue returned to baseline lengths more quickly after being challenged with acetylcholine than when challenged with oxytocin (data not shown). For the above three reasons, acetylcholine was used as the reference drug for the comparison between dinoprostone and misoprostol.

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Dinoprostone. The uterine response to dinoprostone was significantly larger than the ileal response ($P < 0.05$) for the concentrations 1.6 μM to 0.4 mM (figure 2). The mean maximal response of the uterus to dinoprostone relative to the uterine response to acetylcholine was 91.3 % whereas the maximal response of the ileum relative to the maximum response of the ileum to acetylcholine was 70.3 % (table I). The EC50 was an order of magnitude lower in the uterus than in the ileum.

Misoprostol. The contractile response to misoprostol was significantly larger in the uterus then in the ileum ($P < 0.05$) for the misoprostol concentrations 0.1 nM to 32 nM (figure 3). The maximal response of the uterus to misoprostol relative to the uterine response to acetylcholine was 79.8 % whereas the maximal response of the ileum to misoprostol relative to the maximum response of the ileum to acetylcholine was 61.8 % (table I). As for dinoprostone, misoprostol is more potent on the uterus than the ileum (table I).

Misoprostol and dinoprostone. For each drug, the response (expressed as a fraction of the acetylcholine Emax) to the maximal concentrations for the ileal tissue was calculated as a proportion of that for the uterine tissue from the same animal. The mean results were 70.2 % for misoprostol and 70.5 % for dinoprostone. These values are equivalent ($DF = 8$; $P = 0.980$).

4 Discussion

The concentrations at which the isolated rat uterine tissue responded to oxytocin and misoprostol corresponded to physiological concentrations of oxytocin [20] and plasma concentrations of misoprostol [26]. However, for dinoprostone, the rat uterus only reached maximal contractions at concentrations far exceeding plasma levels attained during labor induction using endocervical gel ap-

Table I. Maximal responses to dinoprostone and misoprostol relative to their maximal responses to acetylcholine.

		Uterus	Ileum
		% Maximal response	% Maximal response
Dinoprostone		91.3	70.3
	95 % CI	81.3–101.1	46.1–94.4
Misoprostol		79.8	61.6
	95 % CI	66.1–93.4	35.0–88.7

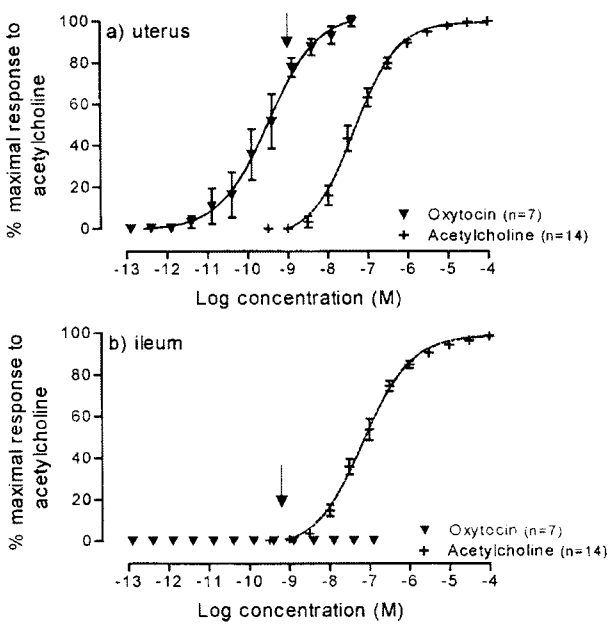

Figure 1. Comparison of contractile response to oxytocin of rat uterus a) compared with rat ileum b) muscle. There was no measurable ileal response to oxytocin within the concentration range studied. The downward arrows indicate the mean plasma concentrations of oxytocin during spontaneous labor.

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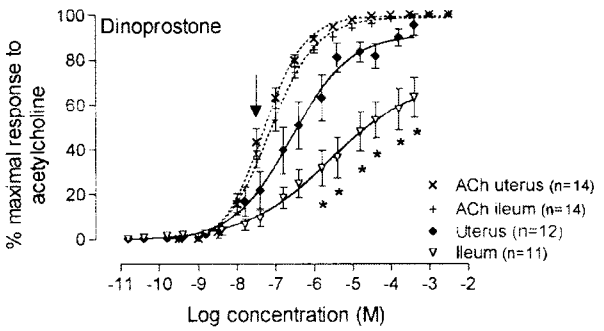

Figure 2. Comparison of contractile response to dinoprostone of rat uterus compared with rat ileum muscle. The plots represent the mean with the SEM and the asterisks indicate the concentrations at which the uterine and ileal responses to dinoprostone are significantly different ($p < 0.05$). The downward arrow indicates the mean plasma concentrations of prostaglandin E_2 in women undergoing labor induction with the application of endocervical gel.

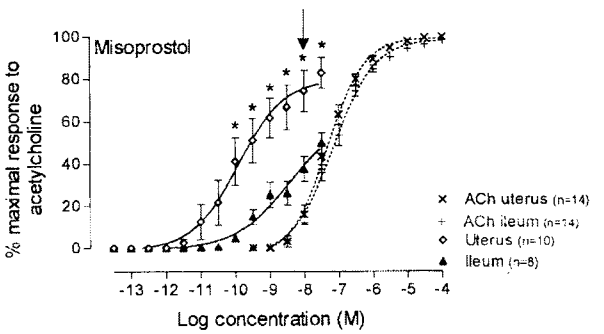

Figure 3. Comparison of contractile response to misoprostol of rat uterus compared with rat ileum muscle. The asterisks indicate the concentrations of misoprostol at which the differences between the uterine and ileal responses to misoprostol are statistically significant ($p < 0.05$). The downward arrow indicates the mean peak serum concentration of misoprostolic acid following oral administration.

plication of dinoprostone. (Expected plasma concentrations are indicated by the downward pointing arrows in figures 1–3).

The lack of intestinal contractile activity of oxytocin at doses which cause maximal contractions of uterine muscle, compared to the relatively high ileal contractile activity of both prostaglandins, is in keeping with the trend to less meconium passage with oxytocin use than with prostaglandin use [21].

On the contrary, the increase in meconium passage with vaginal misoprostol use versus intracervical dinoprostone is not confirmed by a variation in ileal contractile activity. Both drugs elicited contractions from ileal and uterine tissue. There were no differences in ratios between ileal and uterine contractile activity between misoprostol and dinoprostone. These results infer that pharmacodynamic differences in the contractile activity between these drugs do not contribute towards the higher incidence of meconium passage with vaginal misoprostol use versus intracervical dinoprostone use [10, 11].

It is more likely that the resistance of misoprostolic acid to placental PGDH enables the misoprostolic acid to enter the fetal circulation more readily than does dinoprostone. That is why we hypothesize that the different pharmacokinetic properties of dinoprostone and misoprostol are responsible for the differences in rates of meconium passage associated with these two drugs.

The higher peak in plasma concentrations of misoprostol acid with oral administration than with vaginal administration [7, 26] is also in keeping with the higher incidence of meconium passage with oral versus vaginal misoprostol [1].

Further elucidation of the above would be to investigate whether meconium passage is more prevalent in at-term babies when elevated levels of cortisol compete with and displace progesterone from the glucocorticoid receptor, resulting in inhibition of PGDH transcription and activity [2, 17].

5 Conclusions

Unlike oxytocin, misoprostol and dinoprostone stimulate bowel smooth muscle as well as myometrium. Misoprostol and dinoprostone stimu-

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late the bowel smooth muscle equally (relative to their uterotonic activity) and therefore we postulate that the pharmacokinetic properties rather than the pharmacodynamic properties of the two drugs are responsible for the variations in meconium passage associated with their use.

Abstract

Background. Oxytocin and various prostaglandin preparations are commonly used for pharmacological induction of labor at term. Some prostaglandin preparations appear to be associated with more fetal meconium passage and maternal gastrointestinal side effects than is oxytocin. These adverse effects may be caused by stimulation of bowel smooth muscle in the mother and in the fetus.

Aim. To determine whether the *in vitro* ileal contractile activities of dinoprostone, misoprostol and oxytocin are in keeping with the variation in rates of meconium staining observed during labor induction with these substances.

Methods. The contractile activity of the drugs was tested on isolated rat uterus and ileum mounted in Tyrode's solution.

Results. Uterine contractions were stimulated by all three drugs, whereas ileal contractions were only stimulated by dinoprostone and misoprostol. Oxytocin had no contractile activity on the ileum. Dinoprostone and misoprostol stimulated significantly ($p < 0.05$) larger uterine contractions than ileal contractions.

Conclusion. These results provide a pharmacological basis for the increased rate of maternal gastrointestinal complaints and meconium passage with labor induction using dinoprostone and misoprostol compared to oxytocin. Based on the above findings, we postulate that the difference in the rates of meconium passage following misoprostol and dinoprostone administration is caused by pharmacokinetic rather than pharmacodynamic differences between the two drugs.

Keywords: Dinoprostone, labor induction, meconium, misoprostol, oxytocin, prostaglandin dehydrogenase.

Abbreviations

PGDH = 15-hydroxyprostaglandin dehydrogenase

References

[1] Alfirevic Z: Oral misoprostol for induction of labor (Cochrane Review). In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software

[2] Challis JR, FA Patel, F Pomini: Prostaglandin dehydrogenase and the initiation of labor. J Perinatal Med 27 (1999) 26

[3] Collins PW, R Pappo, EZ Dajani: Chemistry and synthetic development of misoprostol. Dig Dis Sci 30 (1985) 114S

[4] Davies NM, J Longstreth, F Jamali: Misoprostol therapeutics revisited. Pharmacotherapy 21 (2001) 60

[5] Davis RO, JB Phillips, BA Harris, JF Huddleston: Fatal meconium aspiration syndrome occurring despite airway management considered appropriate. Am J Obstet Gynecol 151 (1985) 731

[6] Friedman MA: Manufacturer's warning regarding unapproved uses of misoprostol. N Engl J Med 344 (2001) 61

[7] Goldberg AB, MB Greenberg, PD Darney: Misoprostol and pregnancy. N Engl J Med 344 (2001) 38

[8] Hale RW, S Zinberg: Misoprostol and pregnancy. N Engl J Med 344 (2001) 59

[9] Hofmeyr GJ, J Esser, VC Nikodem, M Lawson, T Kramer, AM Gulmezoglu: Do high fetal catecholamine levels affect heart rate variability and meconium passage during labor? S Afr Med J 83 (1993) 739

[10] Hofmeyr GJ, AM Gulmezoglu, Z Alfirevic: Misoprostol for induction of labor: a systematic review. Br J Obstet Gynaecol 106 (1999) 798

[11] Hofmeyr GJ, AM Gulmezoglu. Vaginal misoprostol for cervical ripening and labor induction in late pregnancy (Cochrane review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software

[12] Kaido TL, DJH Veale, I Havlik, DBK Rama: Preliminary screening of plants used in South Africa as traditional herbal remedies during pregnancy and labor. J Ethnopharmacol 55 (1997) 185

[13] Katsoulis LC, DJH Veale, I Havlik: The pharmacological action of *Rhoicissus tridentata* on isolated rat uterus and ileum. Phytother Res 14 (2000) 460

[14] Kumagai H, S Ebashi, F Takeda: A newer method of biological standardization of the oxytocic principle of the posterior pituitary. Jap J Pharmacol 2 (1952) 65

[15] Mahomed K, R Nyoni, D Masona: Meconium-staining of the liquor in a low-risk population. Paediatric Perinat Epidem 8 (1994) 292

[16] Mitri F, GJ Hofmeyr, CJ Van Gelderen: Meconium during labor: self-medication and other associations. S. Afr Med J 71: (1987) 431

[17] Patel FA, VL Clifton, K Chwalisz, JR Challis: Steroid regulation of dehydrogenase activity and

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expression in human term placenta and chorio-decidua in relation to labor. J Clin Endocrinol Metab 84 (1999) 291

[18] Senior J, K Marshall, R Sangha, JK Clayton: In vitro characterisation of prostaniod receptors on human myometrium at term pregnancy. Br J Pharm 108 (1993) 501

[19] Siqueira M, J Neves, M Arteaga, M Bicho, A Silva Cruz: Plasma prostaglandin E2 in pregnant women undergoing labor induction with endocervical gel application. Rev Esp Med Nucl 18 (1999) 268

[20] Stocche RM, JG Klamt, J Antunes Rodrigues, LV Garcia, AC Moreira: Effects of intrathecal sufentanil on plasma oxytocin and cortisol concentrations in women during the first stage of labor. Reg Anesth Pain Med 26 (2001) 545

[21] Tan BP, ME Hannah: Prostaglandins versus oxytocin for prelabor rupture of membranes at term (Cochrane Review). In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software

[22] Van Rossum JM: Cumulative growth-response curves: II. Arch Int Pharmacodynamie Therapie 143 (1963) 299

[23] Veale DJH, I Havlik, DW Oliver, TG Dekker: Pharmacological effects of *Agapanthus africanus* on the isolated rat uterus. J Ethnopharmacol 66 (1999) 257

[24] Veale DJH, DW Oliver, NS Arangies, KI Furman: Preliminary isolated organ studies using an aqueous extract of *Clivia miniata* leaves. J. Ethnopharmacol 27 (1989) 341

[25] Woods JR, JC Glantz: Significance of amniotic fluid meconium. In: Creasy RK, Resnick R, eds. Maternal Fetal Medicine: Principles and practice. 3rd ed. WB Saunders, Philadelphia 1994, pp 413

[26] Zieman M, SK Fong, NL Benowitz, D Banskter, PD Darney: Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 90 (1997) 88

Received December 3, 2001. Revised April 23, 2002. Accepted May 7, 2002.

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British Journal of Obstetrics and Gynaecology
September 1998, Vol. 105, pp. 971–975

16.

A randomised placebo controlled trial of oral misoprostol in the third stage of labour

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Objective To compare oral misoprostol 400 μg with placebo in the routine management of the third stage of labour.

Design A double-blind placebo controlled trial.

Setting The labour ward of an academic hospital in Johannesburg, South Africa with 7000 deliveries per annum.

Participants Low-risk women expected to deliver vaginally.

Methods Women in labour were randomly allocated to receive either misoprostol 400 μg orally or placebo after the birth. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Postpartum blood loss in the first hour was measured by collection in a special flat plastic bedpan. Side effects were recorded.

Main outcome measures Measured blood loss ≥ 1000 ml within the first hour after birth. Use of additional oxytocics.

Results The groups were well matched. Measured blood loss ≥ 1000 ml occurred in 15/250 (6%) after misoprostol and 23/250 (9%) after placebo (relative risk 0·65; 95% confidence interval 0·35–1·22). The difference may have been reduced by the greater use of conventional oxytocics in the placebo group, which was statistically significant for intravenous oxytocin infusion (2·8% *vs* 8·4%, relative risk 0·33, 95% confidence interval 0·14–0·77). Shivering was more common in the misoprostol group (19% *vs* 5%, relative risk 3·69; 95% confidence interval 2·05–6·64).

Conclusions Shivering has been shown in this study to be a specific side effect of misoprostol administered orally in the puerperium. No serious side effects were noted. Misoprostol shows promise as a method of preventing postpartum haemorrhage. Because of the potential benefits for childbearing women, particularly those in developing countries, further research to determine its effects with greater certainty should be expedited.

INTRODUCTION

Postpartum haemorrhage is an important cause of maternal mortality and morbidity. In sub-Saharan Africa the maternal mortality rate is estimated to be 655 per 100,000 live births[1]. As many as 25% of maternal deaths in rural areas are due to postpartum haemorrhage[2]. In Britain, where most women have access to medical care including the use of oxytocic drugs, the risk of maternal death from haemorrhage is about 1 in 100,000 births[3].

The routine use of oxytocics, such as syntometrine (oxytocin 5IU and ergometrine 0·5 mg) or oxytocin alone is associated with a significant reduction in the occurrence of postpartum haemorrhage[4,5]. In a recent placebo controlled, randomised trial published in this *Journal*, blood loss > 800 ml occurred in 8·8% of women who received oxytocin 10IU, compared with 15·2% who received saline[6]. Sulprostone, a prostaglandin E analogue, is effective in preventing the recurrence of atonic postpartum haemorrhage[7]. Prostaglandin F_2 α has been used for the management of postpartum haemorrhage[8]. Oral ergometrine, on the other hand, is insufficiently effective for routine use[9].

Misoprostol (Cytotec, Searle) is a methyl ester of prostaglandin E_1 additionally methylated at C-16 and is marketed for use in the prevention and/or

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treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. It is inexpensive, easily stored at room temperature, rapidly absorbed orally, and it has few side effects. It has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus[10,11], selectively binding to EP-2/EP-3 prostanoid receptors[12]. Its use in the third stage of labour has recently been suggested[13]. An uncontrolled study published in this *Journal* confirmed the feasibility of its use, and pointed out the need for randomised trials to determine whether it is effective[14]. A dose–response study[15] of the effect of oral misoprostol after delivery on intrauterine pressures showed that 400 μg produced good uterotonic effects with fewer side effects than 600 or 800 μg. The objective of the present study is to compare the effectiveness of misoprostol 400 μg, administered orally, with placebo in the routine management of the third stage of labour.

METHODS

The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand in November 1995. A randomised pilot study in 70 women was undertaken to determine whether the buccal route of administration of misoprostol would be effective. After delivery, misoprostol 400 μg or placebo tablets were chewed and kept in the mouth until dissolved. There was no difference in the measured blood loss between the two groups. We postulated that buccal absorption might be poor because of the lack of an acid environment, such as is found in the stomach and vagina, which may promote the conversion of misoprostol to misoprostol acid for absorption. We therefore chose to use the oral route (swallowed) for the main trial. The pilot study confirmed previous reports that with careful measurement, the average blood loss postpartum is around 500 ml (in the recent Swedish trial[6] mean blood loss with oxytocin was 407 ml and with placebo 527 ml). We therefore chose measured blood loss ≥ 1000 ml as a clinically meaningful primary endpoint.

Women in labour at Coronation Hospital, Johannesburg, were asked to participate in the study and participating women gave informed consent. Those with oxytocin infusion in progress at the time of delivery, hypertension, diabetes or previous caesarean section were excluded. Baseline data were recorded. Immediately after delivery the women were asked to swallow two tablets directly from the next in a series of numbered, opaque test tubes, with a sip of water. The tablets were either misoprostol 2×200 μg or two placebo tablets similar in size and colour but not shape. Efforts to obtain identical placebo tablets were unsuccessful. This method of blinding proved to be effective. In only one case did the attending midwife inadvertently catch sight of the tablets. The containers were ordered according to a computer-generated random sequence, in balanced blocks of eight. The placenta was removed by cord traction once firm uterine contraction was diagnosed by palpation.

Within a minute of delivery, linen soiled with amniotic fluid was removed, a fresh, disposable absorbent linen-saver sheet with plastic backing placed under the woman, and a low profile wedge-shaped plastic 'fracture' bedpan was slid under the woman's buttocks. This was found to be a comfortable and efficient way of collecting the great majority of blood lost after delivery, and could be left in place without discomfort even during perineal suturing. When active bleeding had stopped, any blood clots were expressed from the uterus, the bedpan was removed and a sanitary towel was applied. The blood in the bedpan was measured in a measuring jug. One hour after delivery, any bloodstained linen-savers and sanitary towels were placed in a plastic bag and weighed in grammes. The known dry weight of the linen savers and sanitary towels was subtracted to give the approximate volume of blood in millilitres. This was added to the measured blood volume from the bedpan to give the total measured blood loss in the first hour after delivery.

Because conventional oxytocics were not given routinely, the protocol required that very close observation be maintained, and conventional therapy be given immediately if the bleeding was considered to be more than usual. The caregiver could choose to use intramuscular synometrine (1 ampoule) or oxytocin (10 IU) or in more severe cases an intravenous infusion of oxytocin (20 IU in 100 ml saline). Because this intervention might obscure differences in blood loss between groups, the need for conventional oxytocics was chosen as a second primary endpoint.

A sample size of 496 was calculated to detect a reduction in the incidence of measured blood loss ≥ 1000 ml from 12·5% to 5% with 80% power at the 5% level of certainty. All data were entered onto a database (Epi-info 6) for analysis. The randomisation code was broken only after entry and checking of data. Comparisons were by the χ^2 test or Fisher's exact probability test and relative risks with 95% confidence intervals (95% CI) for categorical data.

RESULTS

There were no withdrawals after randomisation, and all outcomes were analysed in the allocated group.

Table 1. Comparison of baseline variables between women randomly allocated to receive oral misoprostol 400 μg or placebo for third stage of labour management. Values are shown as mean [SD] or *n* (%).

	Misoprostol *n* = 250	Placebo *n* = 250
Age (years)	26·3 [5·9]	26·0 [5·5]
Primiparous	68 (27)	70 (28)
Parity 4+	15 (6)	16 (6.4)
Episiotomy/tear	99 (40)	97 (39)
Birthweight (g)	3064 [502]	3033 [487]

DISCUSSION

This is, to our knowledge, the first reported placebo-controlled evaluation of the clinical effectiveness of oral misoprostol for routine management of the third stage of labour. The use of placebo treatment was considered acceptable by the university Ethics Committee, specifically within the context of a research environment in which blood loss was closely and accurately monitored, and conventional oxytocics administered as soon as blood loss was thought to be more brisk than usual. Placebo use has similarly been considered acceptable in a recent Swedish trial[6].

Table 2. Comparison of outcome variables between women randomly allocated to receive oral misoprostol 400 μg or placebo for third stage of labour management. Values are given as *n* (%).

	Misoprostol *n* = 250	Placebo *n* = 250	RR (95% CI)	*P*
Primary outcomes				
Blood loss > 1000 ml	15 (6)	23 (9·2)	0·65 (0·35–1·22)	0·18*
Additional oxytocic used	21 (8·4)	33 (13)	0·64 (0·38–1·07)	0·08*
Syntocinon 10 u IMI	12 (4·8)	13 (5·2)	0·92 (0·43 -1.98)	0·84*
Syntometrine IMI	4 (1·6)	11 (4·4)	0·36 (0·12–1·13)	0·07*
Syntocinon infusion	7 (2·8)	21 (8·4)	0·33 (0·14–0·77)	0·006*
Blood loss ≥ 1000 ml or additional oxytocic	25 (10)	38 (15·2)	0·66 (0·41–1·06)	0·07*
Secondary outcomes				
3rd stage ≥ 30 min†	8 (3·2)	5 (2)	1·59 (0·53–4·80)	0·40*
Manual removal of placenta	1 (0·4)	2 (0·8)	0·50 (0·05–5·48)	1·00**
Blood transfusion	1 (0·4)	1 (0·4)	1·0 (0·06–15·9)	1·00**
Side effects	54 (22)	26 (10)	2·08 (1·35–3·20)	0·001*
Shivering	48 (19)	13 (5·2)	3·69 (2·05–6·64)	<0·0001*
Abdominal pain	2 (0·8)	7 (2·8)	0·29 (0·06–1·36)	0·18*
Dizziness	0 (0)	6 (2·4)	0·00 (0·00–0·92)	0·03**
Other	5 (2)	3 (1·2)	1·67 (0·40–6·90)	0·72**

*Chi-square test.
**Fisher exact probability test (two-tailed).
†Incomplete data: *n* = 249 (misoprostol), 248 (placebo).

The randomisation process was successful in producing well-matched groups (Table 1). The outcome variables are shown in table 2. The reduction in the rate of measured blood loss ≥ 1000 ml in the misoprostol group was not statistically significant at the 95% level and was consistent with anything between a large reduction and a small increase. The less frequent use of conventional oxytocics in the misoprostol group was statistically significant only for the intravenous infusion of oxytocin, which would have been used in more severe cases of haemorrhage. All cases responded well to standard therapy. One woman in the misoprostol and two in the placebo group required manual removal of the placenta and one in each group required blood transfusion. Shivering was more common in the misoprostol group.

Two previous reports have suggested that postpartum misoprostol causes shivering[13,14], but lacked the control groups necessary to quantify this effect, as shivering is a common symptom after childbirth (5% in our control group). With 400 μg misoprostol shivering was significantly increased to 19%. A rate of 60% has been reported using 600 μg[14]. This finding is of relevance to the choice of the ideal dosage for postpartum use. The confirmation of the occurrence of misoprostol-induced shivering, which to our knowledge has not been observed in the non-puerperal situation, is of interest in terms of possible prostaglandin-related mechanisms and their relevance to thermoregulatory physiology.

The definition of 'postpartum haemorrhage' is dependent upon the method of assessment of blood

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loss. Visual estimation of blood loss has been shown to under-estimate true blood loss by about one-half[16], the error increasing as the volume lost increases[17]. Thus blood loss of 500 ml is regarded as postpartum haemorrhage when the blood loss is estimated, but is the average blood loss when it is measured[6,16]. The rates of measured blood loss > 1000 ml in our study were, as expected, similar to reported rates of estimated blood loss ≥ 500 ml. We recommend that postpartum haemorrhage be defined as blood loss ≥ 1000 ml when the blood loss is measured. In two large trials the incidence of blood loss ≥ 1000 ml in the groups receiving syntocinon 10 IU routinely after delivery was only 1% in the study in which estimation was used[18] and 4·7% in the trial in which blood loss was measured[19].

The incidence of blood loss ≥ 1000 ml in our study (6% for misoprostol and 9.2% for placebo) was very similar to the rates in the recent Swedish trial (6·2% for oxytocin and 8·8% for placebo). In the Swedish trial blood loss > 800 ml was the primary endpoint (8·8% for oxytocin and 15·2% for placebo). The corresponding figures in our study were 28 (11·2%) for misoprostol and 43 (17·2%) for placebo (relative risk (RR) 0·65, 95% CI 0·42–1·01; $P = 0·055$). These data were not included in the Results section above as this was not a predefined endpoint in our study.

The estimates for our power calculation were based on the incidence of measured blood loss ≥ 1000 ml in our pilot study of 14%, and data from two previous randomised trials which showed a reduction in estimated postpartum haemorrhage from 13·5% with physiological to 4·1% with active management of the third stage[20,21].

The actual difference between the groups in the current study may have been limited by the policy of early conventional oxytocic management the moment bleeding appeared to be more than usual. The need for intravenous oxytocin infusion was significantly greater in the control group. The potential benefit of misoprostol may be greater in an environment in which conventional oxytocics are not available.

The trend towards increased need for manual removal of the placenta in the Swedish study[6] (3·5% for oxytocin *vs* 2·3% for placebo) was not seen in this study, though the numbers were very small (0·4% for misoprostol *vs* 0·8% for placebo). Our use of blood transfusion (0·4% for misoprostol and 0·4% for placebo) was also somewhat less than in the Swedish study (1·4% for syntocinon and 1% for placebo).

CONCLUSIONS

We have shown that misoprostol 400 μg administered orally after delivery commonly causes shivering. The absence of serious side effects makes its use in the third stage of labour feasible. The results of this study suggest, but not conclusively, that misoprostol may reduce the risk of postpartum haemorrhage. The study was not designed to determine whether misoprostol is more or less effective than conventional oxytocics. The foundation has been laid for a large randomised comparison of misoprostol with conventional oxytocics.

Acknowledgements

We acknowledge support from the South African Medical Research Council, and the excellent assistance of the nursing staff, Coronation Hospital.

References

1 Kwast BE. Postpartum haemorrhage: its contribution to maternal mortality. *Midwifery* 1991; 7: 64–70.
2 Fawcus S, Mbizvo MT, Lindmark G, Nystrom L. Maternal mortality study group. Community based investigation of causes of maternal mortality in rural and urban Zimbabwe. *Cent Afr J Med* 1995; 41: 105–113.
3 Department of Health. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993*. London: HMSO, 1996: 32–47.
4 Elbourne D, Prendiville W, Chalmers I. Choice of oxytocic preparation for routine use in the management of third stage of labour. An overview of evidence from controlled trials. *Br J Obstet Gynaecol* 1988; **95**: 17–30.
5 Prendiville WJ. The prevention of post partum haemorrhage: optimising routine management of the third stage of labour. *Eur J Obstet Gynecol Reprod Biol* 1996; **69**: 19–24.
6 Nordstrom L, Fogelstam G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled trial. *Br J Obstet Gynaecol* 1997; **104**: 781–786.
7 Van Selm M, Kanhai HHH, Keirse MJNC. Preventing the recurrence of atonic postpartum haemorrhage, a double-blind trial. *Acta Obstet Gynecol Scand* 1995; **74**: 270–274.
8 Jacobs M, Arias F. Intramyometrial prostaglandin F2 in the treatment of severe postpartum hemorrhage. *Obstet Gynecol* 1980; **55**: 665–666.
9 de Groot ANJA, van Roosmalen J, van Dongen PWJ, Borm GF. A placebo-controled trial of oral ergometrine to reduce postpartum hemorrhage. *Acta Obstet Gynecol Scand* 1996; **75**: 464–468.
10 Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet*, **338**: 1233–1236.
11 Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized control trial. *Obstet Gynecol* 1997; **89**: 392–397.
12 Senior J, Marshall K, Sangha R, Clayton JK. In vitro characterisation of prostanoid receptors on human myometrium at term pregnancy. *Br J Pharm* 1993; **108**: 501–506.
13 El-Rafacy H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. *Lancet* 1996; **347**: 1257.
14 El-Refacy H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997; **104**: 336–339.
15 Chong YS, Chua S, Arulkumaran S. Can Oral Misoprostol be used as an alternative to parenteral oxytocics in the active management of the third stage of labour? A preliminary study of its effect on the postpartum uterus [abstract]. The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists Combined Scientific Meeting, Brisbane 28 April–2 May, 1997; p. 61.
16 Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM. Blood vol-

Best Practice & Research Clinical Obstetrics and Gynaecology
Vol. 22, No. 6, pp. 1025–1041, 2008
doi:10.1016/j.bpobgyn.2008.08.005
available online at http://www.sciencedirect.com

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3

Misoprostol for the prevention and treatment of postpartum haemorrhage

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Postpartum haemorrhage (PPH) causes preventable maternal deaths, mainly in low-income countries. Misoprostol has powerful uterotonic effects and, because it is well absorbed orally and sublingually, has the potential to be used more widely than would be possible with injectable uterotonics alone. Misoprostol is clearly less effective than oxytocin. Placebo-controlled studies have had variable results, although two recent trials in low-income communities have shown promising results. The main recognized side effects have been dose-related pyrexia and shivering, including occasional hyperpyrexia. In the randomized trials reported to date, there has been a trend to more deaths with misoprostol than with the control groups. The dose that has been most commonly used in clinical trials for preventing PPH is 600 μg orally. Meta-analysis of direct and adjusted indirect comparisons between 600 and 400 μg showed very similar effectiveness. To date, there is very limited evidence for the effectiveness of misoprostol, the lowest effective dose and the magnitude of adverse effects, both direct and indirect. The need for further research is a matter of great urgency.

Key words: maternal death; misoprostol; postpartum haemorrhage; prostaglandin; uterotonic.

INTRODUCTION

Misoprostol for postpartum haemorrhage: a global issue

The use of misoprostol for preventing or treating postpartum haemorrhage (PPH) has become a high-profile issue globally. Apart form the usual clinical and public health

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considerations, the subject has been complicated by sensitivities surrounding the off-label use of misoprostol during pregnancy, dissociation of the original patent-holding company from the drug evaluation process and the global imperative to reduce maternal mortality as a matter of urgency.[1] This chapter presents an overview of the topic, addressing all these issues.

Postpartum haemorrhage: pathopysiology

Placental bed haemostasis following childbirth is a remarkable physiological process. During pregnancy, trophoblast invasion of the maternal spiral arterioles creates wide-diameter, non-contractile vessels, ensuring a high volume blood flow to the placenta. After the birth of the baby, the placenta separates from the uterine wall and the severed placental blood vessel lumina are compressed by extrinsic pressure from the surrounding mesh of myometrial fibres. Central to this process is the efficient and sustained contraction of the myometrium, under the influence of endogenous uterotonic hormones.

This physiological process is imperfect. Under the relatively ideal circumstances of low-risk women enrolled in randomized clinical trials of active versus expectant management of the third stage of labour, in the 'physiological' (natural third stage) group estimated blood loss in excess of 1000 mL occurred in 83 of 3158 women (2.6%).[2] With routine clinical intervention, including administration of a uterotonic drug and controlled traction on the clamped umbilical cord, this number was reduced to 27 of 3126 women (0.9%) [relative risk (RR) 0.33, 95% confidence interval (CI) 0.21 to 0.51]. Clinical estimation has been found to underestimate blood loss by at least 50%.

Uterotonic drugs

Effective uterotonic drugs have existed for many years. Systematic review of randomized trials found that prophylactic administration of oxytocin reduced severe PPH from 83/1136 (7%) to 48/1107 (4.3%) (RR 0.61, 95% CI 0.44 to 0.87).[3] Prophylactic use of intravenous ergot alkaloids reduced severe PPH from 11/724 (1.5%) to 1/705 (0.14%) (RR 0.09, 95% CI 0.01 to 0.72).[4] In randomized trials comparing oxytocin–ergometrine with oxytocin alone, oxytocin–ergometrine was marginally more effective than oxytocin alone but with more side-effects.[5]

Postpartum haemorrhage: disease burden

The disease burden associated with imperfect postpartum haemostasis is immense.[6] PPH is a major cause of maternal mortality in low-income countries. Rates as high as 40 maternal deaths per 100,000 births in parts of sub-Saharan Africa[7] are in stark contrast to the approximately 1 in 100,000 births in the United Kingdom. The potential to save mothers' lives with medical interventions for haemorrhage is thus considerable.[8] No significant reduction in rates of PPH has been reported by industrialized countries in recent times.[9]

In contrast to the considerable body of randomized trials of preventive measures, there is remarkably little information from randomized trials concerning the treatment of PPH. Uterotonics are generally used empirically for treatment, extrapolating from their demonstrated effectiveness in reducing blood loss when used prophylactically.

Although PPH can be caused by factors such as genital tract injury, infection, retained products of conception and coagulopathy, the most important cause is uterine

atony. Thus, a crucial aspect of both prevention and treatment of PPH is uterotonic therapy. The most commonly used agents are injectable oxytocin and/or ergometrine. Why should we be considering the use of misoprostol for the prevention or treatment of PPH when well-established, effective uterotonics already exist?

Attempts to reduce deaths from PPH worldwide are complicated by the fact that: (1) many deaths occur in out-of-hospital settings; (2) death can occur within a short space of time, before transfer to a health facility is possible; and (3) the primary methods of prevention and treatment have depended on injectable uterotonics, which are often not available at a community level.

Misoprostol

Misoprostol is a methyl ester (a synthetic analogue) of natural prostaglandin E1 additionally methylated at C16. It is well absorbed from the stomach, appearing in the circulation within 90 seconds, and undergoes rapid de-esterification to its biologically active metabolite, misoprostolic acid (MPA). It is thermostable and is relatively inexpensive. Misoprostol has been shown to stimulate uterine contractility in early pregnancy[10] and at term.[11] Administered orally or vaginally, it is an effective agent for the induction of abortion[12] and of labour[13], although it is not without problems and risks.[14–16]

The development of misoprostol as a drug for use during pregnancy is unusual in that from the outset the patent-holding company distanced itself from the process. Most developments have occurred through the opportunistic efforts of clinicians, researchers, consumers and other advocates.

RATIONALE FOR CONSIDERING THE USE OF MISOPROSTOL FOR PREVENTION OR TREATMENT OF POSTPARTUM HAEMORRHAGE

Research into the possible use of misoprostol in the third stage of labour commenced in the mid-1990s. There were several compelling reasons to consider the use of misoprostol for the prevention and/or treatment of PPH:

- Misoprostol had well-established uterotonic effects.
- Misoprostol might be more effective than currently available uterotonics.
- Misoprostol might have synergistic effects when used in addition to conventional uterotonics.
- Even if less effective than conventional uterotonics, misoprostol might have some benefit in situations in which conventional uterotonics were not available. In particular, the fact that it is a thermostable compound that is effective when given orally, sublingually, vaginally or rectally, raised the exciting possibility that it might be used by traditional birth attendants, or self-administered, for births taking place remote from health services and health personnel, where women are at most risk from the rapidly fatal effects of severe PPH.

IF MISOPROSTOL WERE TO BE USED IN THE THIRD STAGE OF LABOUR, WHAT WOULD BE THE OPTIMAL ROUTE AND DOSAGE?

We sought evidence from the following[17]: pharmacokinetic studies in pregnant and non-pregnant subjects; physiological studies in pregnant women; and randomized

clinical trials comparing different routes but the same dosage of misoprostol, which included an outcome reflecting the effect of misoprostol on pregnant uterine contractility. The data from pharmacokinetic and physiological studies were tabulated and analysed semi-quantitatively and qualitatively.

Pharmacokinetic studies

Zieman et al randomized ten pregnant women undergoing first-trimester abortions and ten non-pregnant women to oral or vaginal administration of misoprostol 400 μg.[18] Danielsson et al studied plasma misoprostol levels after administration of 200 μg (six women, data not included in Table 1) or 400 μg misoprostol (12 women) orally or vaginally in the first trimester of pregnancy.[19] Tang et al compared the pharmacokinetic parameters of four different routes: sublingual, oral, vaginal and vaginal with addition of water (data not included) in 40 pregnant women undergoing suction termination of pregnancy.[20] Abdel-Aleem et al measured serum and colostrum misoprostol acid levels after misoprostol 600 μg orally in the postpartum period.[21] Misoprostol acid appeared in the serum at 2 minutes (92 pg/mL) and reached peak levels after 20 minutes (345 + 269 pg/mL), falling to low levels by 2 hours (28 + 15 pg/mL). Misoprostol appeared in the colostrum in small amounts (21 + 13 pg/mL). Khan et al

Table 1. Serum misoprostol values and time course expressed as mean (standard deviation) following misoprostol administration by various routes.

Author [ref. no.]	Dose (*n*)	Route of administration		Rectal	Vaginal
		Oral	Sublingual		
Time to peak concentration (minutes)					
Zieman[18]	400 μg (20)	34 (17)			80 (27)
Danielsson[19]	400 μg (12)	30			60–120
Tang[20]	400 μg (40)	28 (15)	26 (12)		'Longer'
A-Aleem[21]	600 μg (20)	20			
Khan[22]	600 μg (20)	18 (8.8)		40.5 (16)	
Peak concentration (pg/mL)					
Zieman[18]	400 μg (20)	227 (124)			165 (86)
Danielsson[19]	400 μg (12)	+280*			+65*
Tang[20]	400 μg (40)	±288 (144)	575 (251)		±125 (54)
A-Aleem[21]	600 μg (20)	345 (269)			
Khan[22]	600 μg (20)	328 (103)		184 (64.5)	
Andolina[23]	400 μg (10)	381			
Area under curve to 4 hours (pg/hours/mL)					
Zieman[18]	400 μg (20)	273 (110)			503 (297)
Khan[22]	600 μg (20)	190 (125)		311 (141)	
Area under curve to 6 hpirs (pg/hours/mL)					
Zieman[18]	400 μg (20)	300 (103)**			957 (542)**
Tang[20]	400 μg (40)	403 (152)	744 (291)		434 (183)

* Estimated from published graph.
** 10 non-pregnant women only.

randomized 20 postpartum women to rectal or oral administration of misoprostol 600 μg.[22] Andolina et al studied 20 postpartum women given 400 μg postpartum as tablet or crushed in methylcellulose capsules (capsule data not included).[23]

The data in Table I suggest a more rapid time to peak concentration with oral and sublingual than with vaginal or rectal administration, highest peak concentrations with sublingual, and greatest area under the time curve with sublingual and vaginal administration.

Physiological studies

Chong et al measured intrauterine pressures in 57 healthy women after delivery.[24] After 30 minutes of baseline recording, the women sequentially received syntometrine 1 mL or misoprostol 200, 400, 500, 600 or 800 μg (10 per group except the last group, which contained 7 women). The seventh woman receiving 800 μg developed life-threatening hyperthermia. The onset of increased uterine activity was significantly slower with misoprostol than with syntometrine. There were no significant differences between groups for the increase in uterine activity or the duration of action. Danielsson et al studied intrauterine pressure in 30 women after administration of 200 or 400 μg misoprostol orally or vaginally in the first trimester of pregnancy.[19] Time to onset and to maximum tonus, respectively, were as follows: 400 μg orally: 7.8 + 3.0 minutes and 25.5 + 5.0 minutes; 400 μg vaginally: 20.9 + 5.3 minutes and 46.3 + 20.7 minutes. The initial increase in tonus was more pronounced after oral than after vaginal administration. Aronsson et al studied intrauterine pressure in 32 women at 8 to 11 weeks' gestation, for 4 hours following misoprostol 400 μg orally, vaginally or sublingually.[25] The time to increased tonus was shorter with oral (7.8) and sublingual (10.7–11.5) than with the vaginal route (19.4 minutes). The time to maximum tonus was also shorter (39.5, 47.1–51.7 and 62.2 minutes, respectively). Increase in uterine activity after 2 hours was greater for the sublingual and vaginal than the oral route.

Labour induction studies

To evaluate the relative clinical efficacy of misoprostol by various routes, we systematically reviewed randomized clinical trials in which similar dosages of misoprostol were administered by different routes for labour induction at term. Outcomes related to the uterine activity response to misoprostol were compared. Data were combined using the Review Manager (RevMan) computer program, version 4.2 for Windows (The Nordic Cochrane Centre, Copenhagen) and a fixed effects model (there was no significant heterogeneity).

In three studies, involving a total of 587 women, failed vaginal delivery in 24 hours was less with the vaginal than the oral route (RR 0.60, 95% CI 0.49 to 0.73). In four studies (548 women), induction or randomization to delivery time was also less (weighted mean difference −4.8, 95% CI −6.4 to −3.2 hours). In one study of 100 women, failed vaginal delivery in 24 hours was less with the sublingual than the oral route (RR 0.56, 95% CI 0.37 to 0.84), as was the induction to delivery time (mean difference −8.3, 95% CI −15.4 to −1.2 hours).[26] Overall, there was consistently greater clinical efficacy, at equivalent doses, with the vaginal and buccal/sublingual routes than with the oral route. In one small study, similar efficacy for labour induction was found when misoprostol was administered vaginally and rectally.[27]

Cervical ripening study

In a prospective, randomized clinical trial, 150 women received 400 μg misoprostol 3 hours prior to suction evacuation of the uterus by the sublingual, oral or vaginal route (50 women per group).[28] The basal cervical dilatation prior to evacuation was higher with the sublingual (9.9 ± 2.1 mm; $P < 0.001$) than the oral (8.2 ± 2.6 mm, 4.9 ± 1.7 minutes) or vaginal routes (7.6 ± 2.6 mm, 5.2 ± 1.8 minutes).

Discussion

There is no doubt that misoprostol has strong uterotonic effects. In the context of PPH, the important question is whether a route and dose can be found with rapid absorption, a clinically significant effect and acceptable side effects. To date, the pharmacokinetic data indicate that oral and sublingual routes have the advantage of rapid onset of action, whereas the sublingual, vaginal and rectal routes have the advantage of prolonged activity and greater bioavailability. The increased bioavailability of non-oral routes is thought to be contributed to by the avoidance of the first pass intestinal–hepatic circulation. As clearance of the drug is likely to be rapid irrespective of the route of administration, the prolonged activity of the vaginal and sublingual routes is presumably due to continued absorption over an extended period of time. Duration of absorption is therefore likely to correlate with the retention of the tablet in the respective site over time. This could be a limitation of the sublingual route in an unstable or unconscious patient. The vaginal route is unlikely to be suitable for management of PPH because of the difficulty of ensuring retention in the vagina and absorption in the presence of vaginal bleeding.

The physiological studies reviewed showed more rapid onset of uterine activity with oral and sublingual than with vaginal administration of misoprostol, and more sustained effects with the sublingual and vaginal routes. In the oral groups, no statistically significant difference in uterine contractility was demonstrated for dosages ranging from 200 to 800 μg.

Clinical trials during pregnancy have shown that, at equivalent dosage, the vaginal and sublingual routes produce greater clinical efficacy than the oral route, and the rectal route is possibly similar to the vaginal route. Theoretical considerations therefore favour the sublingual route for further clinical evaluation.

CLINICAL TRIALS OF MISOPROSTOL FOR PREVENTING POSTPARTUM HAEMORRHAGE

The first randomized trials of misoprostol for preventing PPH were initiated in 1995.[29,30] Initial results were variable and somewhat disappointing. A very large randomized trial co-ordinated by World Health Organization (WHO) found that misoprostol 600 μg orally was unequivocally less effective than oxytocin 10 units intramuscularly or intravenously and had more side effects (mainly shivering and pyrexia).[31] Blood loss >1000 mL occurred in 366/9214 women with misoprostol, versus 263/9228 women with oxytocin (RR 1.39, 955 CI 1.19 to 1.63).

Systematic review of trials of misoprostol given orally, sublingually or rectally versus injectable uterotonics showed results similar to the WHO trial for blood loss >1000 mL (G.J. Hofmeyr, unpublished data). For misoprostol 600–800 μg: 9 trials, 404/11,397 versus 298/11,430, RR 1.36, 95% CI 1.17 to 1.68; for misoprostol 400–500 μg: 15 trials, 117/4178 versus 122/5592; RR 1.23, 95% CI 0.96 to 1.58.

The crucial remaining question was whether misoprostol was more effective than placebo, either in addition to conventional uterotonics, or for use when conventional uterotonics were not available.

Following variable results from several small placebo-controlled studies (Figure 1), two studies in low-income countries showed a significant reduction in severe PPH with misoprostol 600 μg.

In the first study, Hoj and colleagues[32] compared misoprostol 600 μg sublingually with placebo as part of the active management of the third stage of labour in a primary care clinic in Guinea-Bissau. Measured blood loss >1000 mL was surprisingly common, occurring in 37/330 versus 56/331 women (RR 0.66, 95% CI 0.45 to 0.98). One unexplained maternal death occurred in a woman in the misoprostol group with blood loss of 1400 mL. Subsequent correspondence in the *British Medical Journal* included the suggestion that the maternal death be regarded as an adverse event potentially related to misoprostol use[33], and a call for a trial of misoprostol for treatment of PPH with maternal death as the primary endpoint.[34]

In the second study, Derman and colleagues[35] compared misoprostol 600 μg orally with placebo in 1620 women delivering at home or primary care centres in four primary health centre areas of Belgaum District, Karnataka State, India. Women were delivered by auxillary nurse midwives and active management of the third stage of labour was not used. Measured blood loss >1000 mL occurred in 2/812 versus 10/808 (RR 0.20, 95% CI 0.04 to 0.910).

In our initial systematic review analysis for misoprostol versus placebo, excluding the rectal route, there was significant heterogeneity ($I^2 > 50\%$) in the results for

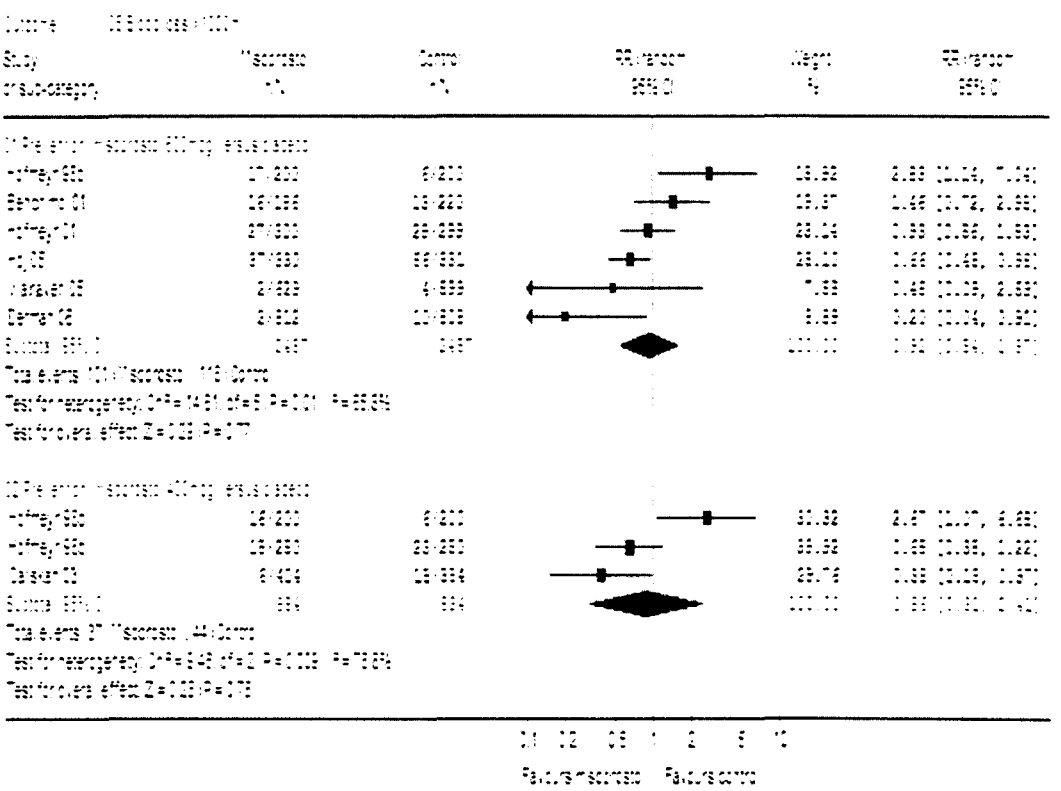

Figure 1. Randomized trials of misoprostol orally (eight trials) or sublingually compared with placebo for the prevention of postpartum haemorrhage (from ref. 33).

600 μg (4914 women, RR 0.92, 95% CI 0.54 to 1.57, heterogeneity $I^2 = 66\%$) and for 400 μg (1688 women, RR 0.86, 95% CI 0.31 to 2.41, random effects model; heterogeneity $I^2 = 79\%$). The heterogeneity could not be accounted for by route of administration nor trial quality. It appeared to be related to a single outlier study[36], which contributed data to both subgroups. Removal of this study from the meta-analysis eliminated the significant heterogeneity ($I^2 < 50\%$). After exclusion of the outlier, compared with placebo: blood loss ≥1000 mL was reduced with misoprostol 600 μg (4514 women, RR 0.77, 95% CI 0.59 to 1.00; trend, fixed effects model) and with misoprostol 400 μg (1288 women, RR 0.54, 95% CI 0.32 to 0.91).

One small trial comparing misoprostol 200 μg versus placebo (over and above an oxytocin infusion) at caesarean section found no statistically significant difference in blood loss >1000 mL (352 women, RR 1.13, 95% CI 0.66 to 1.94).

MISOPROSTOL FOR TREATING POSTPARTUM HAEMORRHAGE

Seven case reports or small series of the use of misoprostol (various doses and routes, mostly 1000 μg rectally) for treating PPH found dramatic results (subjectively assessed prompt cessation of bleeding in 65/82 cases).[13] One unblinded, randomized trial also found misoprostol to be much more effective than oxytocin/ergometrine plus oxytocin infusion in terms of subjective cessation of bleeding.[37] However, review of two small, blinded, placebo-controlled trials of misoprostol for the treatment of PPH over and above routine methods of treatment, found more modest results.[13] Blood loss ≥500 mL after enrolment was reduced by misoprostol 600–1000 μg in split dosages orally, sublingually and rectally compared with placebo (397 women, RR 0.57, 95% CI 0.34 to 0.96).

MISOPROSTOL AND MATERNAL MORTALITY

The main objective of using misoprostol for preventing or treating PPH is to reduce maternal mortality. Because mortality is a rare outcome, no randomized trials have been powered to investigate the effect on mortality. Reduced risk of PPH is taken intuitively as a proxy outcome for mortality.

In response to the correspondence following the report by Hoj et al (see above)[32], we conducted a systematic review to investigate the possible relationship between misoprostol use and maternal death or severe morbidity (G.J. Hofmeyr, unpublished data). Because any adverse effects might be dose related, we also evaluated the effectiveness and side effects of misoprostol in relation to the dosage used.

We reviewed randomized controlled trials of misoprostol used for preventing or treating PPH, compared with placebo or other uterotonics.

To assess the effect of dose on effectiveness and side effects, we used as primary outcomes blood loss ≥1000 mL or ≥500 mL after the diagnosis of PPH, and pyrexia (≥38 °C or as defined by trial authors).

We followed the search strategy used by the Cochrane Collaboration's Pregnancy and Childbirth Group.

Forty-seven trials were included with more than 40,000 participants. Maternal deaths were reported in five trials.[31,35,38–40] Three other trials specified that there were no maternal deaths.[41–43] No additional maternal deaths were identified through communication with the authors of the included trials.

Of 11 deaths reported in the five trials, 8 occurred in women receiving misoprostol [RR 2.0, 95% CI 0.68 to 5.83; Peto odds ratio (OR) 2.49, 95% CI 0.76 to 8.13] (Table 2).

Table 2. Maternal deaths reported in randomized trials of misoprostol compared with placebo or other uterotonics for the prevention (four trials) or treatment (Hofmeyr 2004) of postpartum haemorrhage.

Trial and year	Misoprostol		Control	Maternal deaths		Clinical features
	Dose (μg)	Route		Misoprostol	Control	
Hoj 2005[33]	600	SL	Placebo	1/330	0/331	PPH
Derman 2006[36]	600	PO	Placebo	0/812	1/808	No PPH
Walraven 2005[40]	600	PO	Oral ergometrine	2/630	0/599	PPH
WHO 2001[32]	600	PO	Oxytocin	2/9264	2/9266	Not reported
Hofmeyr 2004[41]	1000	PO/SL/R	Placebo	3/117	0/121	PPH
Total				8/11153	3/11125	

PO, by mouth; PPH, postpartum haemorrhage; R, rectal; SL, sublingual.
Dose in micrograms. Overall relative risk = 2.00, 95% confidence interval = 0.68 to 5.83.

The occurrence of maternal deaths in several women receiving misoprostrol in reported randomized trials raised the possibility that misoprostol might have side effects that increase the risk of death despite beneficial effects on blood loss.[44] It is plausible that a drug with ubiquitous pharmacologic effects might have unanticipated adverse effects when used in the third stage of labour. The most prominent side effects observed in the third stage of labour are shivering and pyrexia. Life-threatening hyperpyrexia has been reported with misoprostol 800 μg orally in the third stage of labour[45], and pyrexia >40 °C was recorded following the use of 600 μg orally in the WHO trial,[31] and in 50/967 women following the use of 800 μg sublingually.[46]

The concept that a drug might have proven beneficial effects on a life-threatening condition yet increase mortality is counterintuitive but plausible. For example, class I antiarrhythmics are used routinely for postmyocardial care because of their proven suppression of ventricular premature depolarizations, a common cause of postmyocardial infarction death. However, in a double-blind, placebo-controlled trial in 3549 patients with myocardial infarction and left ventricular dysfunction, at 1 year from the time of randomization to blinded therapy, mortality in the active drug-treated patients was 10% compared with 5% in the placebo-treated group ($P = 0.0006$).[47] Monitoring for unexpected adverse effects is a basic principle for the introduction of any new medical intervention.

The limitations of this review must be emphasized. First, the number of deaths is small, with wide confidence limits and is consistent, at the 95% confidence level, with anything between a modest reduction and a large increase in maternal mortality with misoprostol. Second, this was a post-hoc analysis in response to an observed clustering of maternal deaths, and the statistical calculations need to be interpreted with circumspection. We recommend prospective surveillance of all randomized trials and implementation programs for further evidence for or against an association of misoprostol with maternal death.

DOSE-RELATED EFFECTS

Effectiveness

To determine the relative effectiveness of 600 μg misoprostol versus smaller dosages (e.g. 400 μg), we reviewed trials comparing different dosages. In view of the lack of

adequate data on blood loss >1000 mL from direct randomized comparisons, we supplemented the direct data with adjusted indirect comparisons. In this method, comparisons of each of the two dosages with a similar control group (placebo or other uterotonic) from different trials are combined to provide an estimate of the relative effectiveness of the two dosages.[48] The method has been shown to usually but not always agree with direct comparisons in 44 meta-analyses.[49] Three-way comparisons of 600 μg versus 400 μg versus placebo or another uterotonic were included only in the direct comparisons.

Studies of the rectal route were excluded from the dosage studies because of uncertain absorption via this route.

For the direct and indirect comparisons the primary outcome measure was blood loss ≥1000 mL. As the effectiveness outcome was blood loss measured within 1 hour, additional doses of misoprostol given after 1 hour were ignored. There was adequate data on pyrexia ≥38 °C from the direct data. Adjusted indirect comparisons were made for this outcome to validate the method in this study population.

All but one of the trials were conducted in settings using routine active management of the third stage of labour. To determine whether the results were affected by the use of active management, a sensitivity analysis was performed excluding the trial in which active management was not practised.[35]

Meta-analysis of direct and adjusted indirect data from randomized trials showed no evidence of benefit of 600 μg over 400 μg in terms of the outcome blood loss ≥1000 mL (RR 1.02, 95% CI 0.71 to 1.48; Table 3). A sensitivity analysis excluding the trial in which active management was not practised[35] produced similar results (data not shown).

PYREXIA (≥38 °C OR AS DEFINED BY AUTHORS)

Pyrexia was increased with misoprostol in all subgroups. There was quantitative but not qualitative heterogeneity in the subgroup misoprostol 400–500 μg versus other uterotonics ($I^2 = 65\%$), which could not be explained by route of administration or trial quality.

The relative effect on pyrexia, both versus placebo and versus other uterotonics with 600 μg, was more than twice that with 400–500 μg: misoprostol 600 μg versus placebo, 3685 women, RR 6.71, 95% CI 4.83 to 9.32; 400 μg versus placebo, 1996 women, RR 3.90, 95% CI 2.27 to 6,69; 600 μg versus other uterotonics, 22,337 women, RR 6.76, 95% CI 5.54 to 8.25; 400–500 μg versus other uterotonics, 8135 women, RR 3.05, 95% CI 2.45 to 3.81. In the two treatment trials, pyrexia was increased with misoprostol (392 women, RR 2.78, 95% CI 1.39 to 5.53).

Table 3. Meta-analysis of direct and adjusted indirect comparisons of misoprostol 600 μg versus 400 μg for risk of blood loss ≥ 1000 mL.

Postpartum haemorrhage	Estimate RR	Lower	Upper
Direct 600 vs. 400	0.841	0.501	1.411
Indirect 600 vs. 400 (placebo comparisons)	1.420	0.790	2.555
Indirect 600 vs. 400 (uterotonic comparisons)	0.931	0.599	1.446
All	1.023	0.707	1.481

RR, relative risk, with lower and upper 95% confidence intervals.

Meta-analysis of direct and adjusted indirect data from randomized trials showed an overall increase in pyrexia with 600 μg over 400 μg (RR 2.53, 95% CI 1.78 to 3.60; Table 4). There was consistency between the estimates from the direct and the adjusted indirect comparisons.

All the studies reviewed that reported maternal deaths in the misoprostol group used misoprostol 600 μg or more. Physiological studies have shown uterotonic effects with doses as low as 200 μg.[24] Our direct and indirect comparison of data from randomized trials showed no difference in effect size between 600 and 400 μg doses. In view of the fact that side effects of misoprostol, such as pyrexia and shivering, are dose-related, we suggest that further research be undertaken to establish the smallest effective dosage of misoprostol.

SHOULD THE USE OF MISOPROSTOL FOR MANAGEMENT OF THE THIRD STAGE OF LABOUR IN ROUTINE CLINICAL PRACTICE BE ENCOURAGED NOW?

Programmes to implement the use of misoprostol for routine prevention of PPH have been initiated in several countries.[50,51] The use of misoprostol in routine practice presents a dilemma, as there are several factors in favour of – and others against – such use, and levels of certainty regarding effectiveness and risks fall far short of that which would ordinarily be required for registration of a drug for this purpose.

Favourable factors

- There is a global imperative to address the appalling rates of maternal mortality from preventable cause such as PPH in low-income countries.[52]
- There is some evidence that misoprostol might be effective, and therefore the possibility that at individual level benefits outweigh risks.
- Because of stability and ease of administration, it might be possible to implement the use of misoprostol in settings in which use of an injectable uterotonic would be difficult or impossible.

Unfavourable factors

- At the individual level, it is not yet certain that the benefits of misoprostol outweigh the risks.
- The lowest effective dose has not yet been determined.

Table 4. Meta-analysis of direct and adjusted indirect comparisons of misoprostol 600 μg versus 400 μg for risk of pyrexia (≥38 °C).

Pyrexia	Estimate RR	Lower	Upper
Direct 600 vs. 400	2.059	1.399	3.031
Indirect 600 vs. 400 (placebo comparisons)	1.944	0.676	5.596
Indirect 600 vs. 400 (uterotonic comparisons)	2.656	1.878	3.758
All	2.532	1.779	3.604

RR, relative risk, with lower and upper 95% confidence intervals.

- The popularity of misoprostol – because it is innovative and easy to administer – can result in its use instead of oxytocin, which is known to be more effective and safer, even where oxytocin should be available.
- At a public health level, programmes to introduce misoprostol might detract from efforts to make more effective injectable uterotonics as widely available as possible.
- Widespread use of misoprostol at delivery can result in occasional inadvertent or ill-advised use of misoprostol before birth to induce or augment labour, or in error. A single dose as low as 100 μg (half a tablet) has been associated with uterine rupture in a nulliparous woman. The risk of uterine rupture appears increased when both misoprostol and oxytocin are used.[53] For women with previous caesarean section, the use even of doses as small as 25 μg vaginally has been associated with high rates of uterine rupture.[54]
- Inadvertent use of misoprostol before the birth of an undiagnosed second twin might also result in uterine rupture.

Conclusions

The theoretical evidence reviewed suggests that the sublingual route is likely to be the most suitable for further research on the use of misoprostol in the third stage of labour. This review found a trend towards increased maternal deaths in randomized trials of misoprostol 600 μg or more versus placebo or other uterotonics. Misoprostol was less effective than conventional uterotonics in the prevention of PPH. Compared with placebo, severe blood loss $\geq$1000 mL appeared to be reduced with both 600 μg and 400 μg misoprostol. Compared with both placebo and other uterotonics, pyrexia ($\geq$38 °C or as defined by trial authors) was increased about three-fold with 400–500 μg and about six-fold with 600 μg.

In settings in which uterotonics are not currently available or in use, the first consideration should be to implement oxytocin use (possibly in single-use plastic delivery systems) as this is the gold-standard uterotonic for the prevention of PPH. If oxytocin use is not possible, misoprostol should be considered.

Given the fact that prophylactic use of misoprostol in the third stage of labour involves administration to large numbers of low-risk women in varied settings in which side effects are a major concern, the results presented support the use of a dosage not exceeding 400 μg for the prevention of PPH if misoprostol is to be used. This policy would not exclude the possibility of administering an additional 200 μg to women who develop PPH, should future research show a clear benefit for the higher dose.

Because of the enormous potential benefits of an effective, orally active third stage uterotonic, and the likelihood that misoprostol will be used on a large scale worldwide, further research is essential to measure the possible beneficial and harmful effects of misoprostol more accurately.

INTRAUMBILICAL MISOPROSTOL FOR TREATMENT OF RETAINED PLACENTA

One small trial compared misoprostol 800 μg dissolved in 30 mL saline ($n = 21$) with oxytocin 50 units in 30 mL saline ($n = 20$) and 30 mL saline ($n = 13$).[55] Manual removal of the placenta was less frequent with misoprostol than with the other two groups. Although the evidence is very limited, the likelihood of harm from an intraumbilical injection is very low, and the benefit from a conservative method of treatment of

retained placenta in settings with limited facilities is high. These data suggest that in settings in which no injectible uterotonics are available, misoprostol 800 μg in 30 mL saline injected into the umbilical vein can be used for the treatment of retained placenta. Use of misoprostol for this indication needs further evaluation from both a safety and effectiveness point of view.

PUBLISHED GUIDELINES FOR THE USE OF MISOPROSTOL TO PREVENT OR TREAT POSTPARTUM HAEMORRHAGE

Several guidelines on the use of misoprostol for preventing or treating PPH have been published.[56,57]

World Health Organization recommendations

The WHO held a technical consultation on the prevention of PPH in Geneva between 18 and 20 October 2006, to discuss the various issues related to prevention of PPH and develop guidelines. This is available online at: http://whqlibdoc.who.int/hq/2007/WHO_MPS_07.06_eng.pdf.

The recommendations relating to the use of misoprostol were:

- In the context of active management of the third stage of labour, skilled attendants should offer oxytocin for the prevention of PPH in preference to oral misoprostol (600 μg). (Strong recommendation, high-quality evidence.)
- In the context of the active management of third stage of labour, skilled attendants should not offer sublingual(strong recommendation, very-low-quality evidence) or rectal misoprostol (strong recommendation, low-quality evidence) for the prevention of PPH in preference to oxytocin
- In the absence of active management of third stage of labour, a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for the prevention of PPH (strong recommendation, moderate quality). For misoprostol, this recommendation places a high value on the potential benefits of avoiding PPH and ease of administration of an oral drug in settings in which other care is not available, but notes there is only one study. The only trial relevant to this recommendation used 600 μg of misoprostol. The efficacy of lower doses has not been evaluated. There is still uncertainity about the lowest effective dose and optimal route of administration.
- Key discussion points: misoprostol has unpleasant side effects, which are dose related. A dose of 400 μg has been shown to be effective in preventing PPH but has not been compared directly with 600 μg. Most trials have used 600 μg because the largest trial by WHO has used that dosage. It may be prudent to use the lowest effective dose to avoid undesirable side effects but this has to be determined based on further trials.

Practice points

Preventing PPH

- Routine active management of the third stage of labour is recommended.

- Oxytocin 10 units is more effective than misoprostol for routine use in the third stage of labour, and has fewer side effects.
- Data on the effectiveness of misoprostol versus placebo are conflicting.
- The use of misoprostol has been recommended by WHO in situations in which active management of third stage of labour is not practised.
- Most trials have empirically chosen 600 μg orally for preventing PPH. Limited data, and direct and adjusted indirect comparisons, suggest that 400 μg has similar efficacy with fewer side effects.

Treating postpartum haemorrhage

- Ergometrine is somewhat more effective than oxytocin but with more risks and side-effects. This profile supports its use in the treatment of PPH rather than for routine prophylaxis.
- Limited evidence suggests that misoprostol can reduce blood loss when used in addition to the conventional treatment of PPH.
- There is to date no evidence that the use of misoprostol for the prevention or treatment of PPH reduces mortality. In randomized trials conducted to date, there is a trend to increased mortality.

Research agenda

Because of the global imperative to reduce maternal mortality, further research on the role of misoprostol is urgently needed. Key questions are:

- Is misoprostol more effective than placebo for preventing or treating PPH?
- What is the lowest effective dose?
- What is the magnitude of risks with various doses?
- If effective, does reduced blood loss translate to reduced mortality?
- What are the operational implications of using misoprostol for routine third-stage management, particularly with respect to ill-advised or erroneous use prior to birth?

CONFLICT OF INTEREST

There is no known conflict of interest.

FUNDING SOURCES

GJH is supported by the Effective Care Research Unit, University of the Witwatersrand and University of Fort Hare, and Eastern Cape Department of Health.

REFERENCES

*1. Potts M & Hemmerling A. The worldwide burden of postpartum haemorrhage: policy development where inaction is lethal. *Int J Gynaecol Obstet* 2006 Nov; **94**(Suppl. 2): S116–S121.
2. Prendiville WJ, Elbourne D & McDonald S. Active versus expectant management in the third stage of labour. *Cochrane Database Syst Rev* 2000; (Issue 3). Art. NoCD000007.
3. Cotter A & NessTolosa J. Prophylactic oxytocin for the third stage of labour. *Cochrane Database Syst Rev* 2001; (Issue 4). Art. NoCD001808.
4. Liabsuetrakul T, Choobun T, Peeyananjarassri K et al. Prophylactic use of ergot alkaloids in the third stage of labour. *Cochrane Database Syst Rev* 2007; (Issue 2). Art. NoCD005456.
5. McDonald S, Abbott JM & Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. *Cochrane Database Syst Rev* 2004; (Issue 1). Art. NoCD000201.
*6. Ronsmans C & Graham WJ. Maternal mortality: who, when, where, and why. *Lancet* 2006; **368:** 1189–1200.
7. Fawcus S, Mbizvo MT, Lindmark G et al. Maternal mortality study group. Community based investigation of causes of maternal mortality in rural and urban Zimbabwe. *Cent Afr J Med* 1995; **41:** 105–113.
8. Ramanathan G & Arulkumaran S. Postpartum hemorrhage. *J Obstet Gynaecol Can* 2006 Nov; **28**(11): 967–973.
9. McDonald S. Management of the third stage of labor. *J Midwifery Womens Health* 2007; **52**(3): 254–261.
10. Norman JE, Thong KJ & Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991; **338:** 1233–1236.
11. Mariani Neto C, Delbin AL & do Val Junior R. Tocographic pattern induced by misoprostol. *Rev Paul Med* 1988; **106:** 205–208.
12. el-Refaey H & Templeton A. Early induction of abortion by a combination of oral mifepristone and misoprostol administered by the vaginal route. *Contraception* 1994; **49:** 111–114.
13. Hofmeyr GJ, Gulmezoglu AM & Alfirevic Z. Misoprostol for induction of labour: a systematic review. *BJOG* 1999; **106:** 798–803.
14. Hofmeyr GJ. Misoprostol in obstetrics and gynaecology–unregistered, dangerous and essential. *S Afr Med J* 1998; **88:** 535–536.
15. Tang OS, Gemzell-Danielsson K & Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *Int J Gynaecol Obstet* 2007 Dec; **99**(Suppl. 2): S160–S167.
16. Moore ML. Misoprostol-is more research needed? *J Perinat Educ* 2002 Summer; **11**(3): 43–47.
*17. Hofmeyr GJ, Walraven G, Gulmezoglu AM et al. Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005 May; **112**(5): 547–553.
18. Zieman M, Fong SK, Benowitz NL et al. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90:** 88–91.
19. Danielsson KG, Marions L, Rodriguez A et al. Comparison between oral and vaginal administration of misoprostol on uterine contractility. *Obstet Gynecol* 1999; **93:** 275–280.
20. Tang OS, Schweer H, Seyberth HW et al. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002; **17:** 332–336.
21. Abdel-Aleem H, Villar J, Gülmezoglu AM et al. The pharmacokinetics of the prostaglandin E1 analogue misoprostol in plasma and colostrum after postpartum oral administration. *Eur J Obstet Gynecol Reprod Biol* 2003; **108**(1): 25–28.
22. Khan R-U & El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol* 2003; **101:** 968–974.
23. Andolina KL, Tolosa JE, Monzo JM et al. Oral misoprostol is rapidly absorbed in postpartum women at term. *J Matern Fetal Neonatal Med* 2003; **14:** 229–232.
*24. Chong YS, Chua S, El-Refaey H et al. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. *Br J Obstet Gynaecol* 2001; **108:** 41–47.
25. Aronsson A, Bygdeman M & Gemzell-Danielsson K. Effects of misoprostol on uterine contractility following different routes of administration. *Human Reproduction* 2004; **19:** 81–84.
26. Shetty A, Danielian P & Templeton A. Sublingual misoprostol for the induction of labour at term. *Am J Obstet Gynecol* 2002; **186:** 72–76.

27. Pi P & Zhu F. Clinical observation of misoprostol on induction in late pregnancy (Chinese). *Bull of Hunan Med Univ* 1999; **24:** 195–197.
28. Saxena P, Sarda N, Salhan S et al. A randomised comparison between sublingual, oral and vaginal route of misoprostol for pre-abortion cervical ripening in first-trimester pregnancy termination under local anaesthesia. *Aust N Z J Obstet Gynaecol* 2008 Feb; **48**(1): 101–106.
29. Bamigboye A, Merrell DA, Mitchel R et al. Randomised comparison of misoprostol with syntometrine for management of third stage of labor. *Acta Obstet Gynecol Scand* 1998; **77:** 178–182.
30. Hofmeyr GJ, Nikodem VC, de Jager M et al. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynaecol* 1998; **105:** 971–975.
*31. Gülmezoglu AM, Villar J, Ngoc NN, et al, for the WHO Collaborative Group To Evaluate Misoprostol in the Management of the Third Stage of Labour. The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the management of the third stage of labour. *Lancet* 2001; **358:** 689–695.
*32. Hoj L, Cardosa P, Nielsen BB et al. Effect of sublingual misoprostol on severe postpartum haemorrhage in aprimary health centre in Guinea-Bissau: randomized double blind clinical trial. *BMJ* 2005; **331:** 723.
33. Morgan SC. Inadequate reporting of safety issues from clinical trials in academic journals. *BMJ* October 2005; **14**.
34. Sloan NL, Winikoff B & Blum J. Questions for authors regarding the effect of sublingual misoprostol on postpartum haemorrhage. Rapid Response to Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Peter Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind control trial. *BMJ* 2005; **331:** 723.
*35. Derman RJ, Kodkany BS, Goudar SS et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. *Lancet* 2006; **368:** 1248–1253.
36. Hofmeyr GJ, Nikodem VC, de Jager M et al. Side-effects of oral misoprostol in the third stage of labour - a randomised placebo-controlled trial. *S Afr Med J* 1998; **91:** 432–435.
37. Lokugamage AU, Sullivan KR, Niculescu I et al. A randomized study comparing rectally administered misoprostol versus syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; **80:** 835–839.
38. Cook CM, Spurrett B & Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. *Aust N Z J Obstet Gynaecol* 1999; **39:** 414–419.
39. Walraven G, Blum J, Dampha Y et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. *BJOG* 2005; **112:** 1277–1283.
40. Hofmeyr GJ, Ferreira S, Nikodem VC et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]. *BMC Pregnancy Childbirth* 2004; **4:** 16.
41. Baskett TF, Persad VL, Clough HJ et al. Misoprostol versus oxytocin for the reduction of postpartum blood loss. *Int J Gynaecol Obstet* 2007; **97:** 2–5.
42. Walley RL, Wilson JB, Crane JM et al. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. *BJOG* 2000; **107:** 1111–1115.
43. Kundodyiwa TW, Majoko F & Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. *Int J Gynaecol Obstet* 2001; **75:** 235–241.
44. Hofmeyr GJ & Gulmezoglu AM. Misoprostol in the third stage of labour and maternal mortality: a review. Rapid Response to Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Peter Aaby P. Effect of sublingual misoprostol on severe postpartum heamorrhage in aprimary health centre in Guinea-Bissau: randomised double blind control trial. *BMJ* 2005; **331:** 723.. BMJ, 2006.
*45. Chong YS, Chua S & Arulkumaran S. Severe hyperthermia following oral misoprostol in the immediate postpartum period. *Obstet Gynecol* 1997 Oct; **90**(4): 703–704.
46. Winikoff B, Barrera G, Leon W, et al. A case review of high fevers occurring after treatment administration for primary postpartum hemorrhage. Oral Communication, XVIII FIGO World Congress of Gynecology & Obstetrics, November 2006, Kuala Lumpur, Malaysia.
47. Epstein AE, Hallstrom AP, Rogers WJ et al. Mortality following ventricular arrhythmia suppression by encainide, flecainide, and moricizine after myocardial infarction. The original design concept of the cardiac arrhythmia suppression trial (CAST). *JAMA* 1993; **270:** 2451–2455.
48. Bucher HC, Guyatt GH, Griffith LE et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; **50:** 683–691.

*49. Song F, Altman DG, Glenny AM et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003; **326:** 472.
50. Htay TT. Making pregnancy safer in Myanmar: introducing misoprostol to prevent post-partum haemorrhage as part of active management of the third stage of labour. *Reprod Health Matters* 2007 Nov; **15**(30): 214–215.
51. Jadesimi A & Okonofua FE. Tackling the unacceptable: Nigeria approves misoprostol for postpartum haemorrhage. *J Fam Plann Reprod Health Care* 2006 Oct; **32**(4): 213–214.
52. Geller SE, Adams MG, Kelly PJ et al. Postpartum hemorrhage in resource-poor settings. *Int J Gynaecol Obstet* 2006 Mar; **92**(3): 202–211.
53. Matsuo K, Scanlon JT, Atlas RO et al. Staircase sign: a newly described uterine contraction pattern seen in rupture of unscarred gravid uterus. *J Obstet Gynaecol Res* 2008 Feb; **34**(1): 100–104.
54. Wing DA, Lovett K & Paul RH. Disruption of prior uterine incision following misoprostol for labour induction in women with previous cesarean delivery. *Am J Obstet Gynecol* 1998; **91**(5): 828–830.
55. Rogers MS, Yuen PM & Wong S. Avoiding manual removal of placenta: evaluation of intra-umbilical injection of uterotonics using the Pipingas technique for management of adherent placenta. *Acta Obstet Gynecol Scand* 2007; **86**(1): 48–54.
56. Alfirevic Z, Blum J, Walraven G et al. Prevention of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet* 2007 Dec; **99**(Suppl. 2): S198–S201.
57. Blum J, Alfirevic Z, Walraven G et al. Treatment of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet* 2007 Dec; **99**(Suppl. 2): S202–S205.

South Africa. This is important for all women, but perhaps more so for women of low socio-economic status who may have little else by way of affirmation should their family life break down.

References

1. Canetto SS, Sakinofsky I. The gender paradox in suicide. *Suicide Life Threat Behav* 1998; **28**: 1-23.
2. World Health Organisation. *Statistics Annual*. Geneva: WHO, 1991.
3. Williams M. *Cry of Pain: Understanding Suicide and Self-harm*. London: Penguin, 1997.
4. Wassenaar DR, Naidoo P. Suicide rates amongst Indians and Whites in Pietermaritzburg: a comparison with South African suicide data. In: Schlebusch L, ed. *Suicidal Behaviour 3*. Durban: University of Natal, 1995; 172-186.
5. Pillay AL, Van der Veen MBW. Factors precipitating suicidal behaviour in women. In: Schlebusch L, ed. *Suicidal Behaviour 3*. Durban: University of Natal, 1995; 120-129.
6. Canetto SS, Lester D. Gender and primary prevention of suicide mortality. *Suicide Life Threat Behav* 1995; **25**: 58-69.
7. Jack R. *Women and Attempted Suicide*. Hove, UK: Lawrence Erlbaum, 1992.
8. Pillay AL, Vawda NBM. Alcohol-related parasuicide among married people. *S Afr Med J* 1989; **75**: 120-121.
9. Wassenaar DR, Van der Veen MBW, Pillay AL. Women in cultural transition: suicidal behaviour in South African Indian women. *Suicide Life Threat Behav* 1998; **28**: 82-93.
10. Pillay AL, Wassenaar DR. Psychological intervention, spontaneous remission, hopelessness and psychiatric disturbance in adolescent parasuicides. *Suicide Life Threat Behav* 1995; **25**: 386-392.
11. Platt S, Kreitman, N. Trends in parasuicide and unemployment among men in Edinburgh, 1968 - 1982. *BMJ* 1984; **289**: 1029-1032.
12. Pillay AL. Methods of self-destructive behaviour in adolescents and young adults. *Psychol Rep* 1988; **63**: 552-554.
13. Wassenaar DR. Brief strategic family therapy in the management of adolescent Indian parasuicide patients in the general hospital setting. *S Afr J Psychol* 1987; **17**: 93-99.
14. Bergman B, Brismer B. Suicide attempts by battered wives. *Acta Psychiatr Scand* 1991; **83**: 380-384.
15. Shneidman E. *Suicide Thoughts and Reflections*. New York: Human Sciences, 1981.
16. Gath DH. The alcoholic patient. In: Weatherall DJ, Ledingham JGG, Warrel A, eds. *Oxford Textbook of Medicine*. Oxford: Oxford University Press, 1983; **2**: 38-40.
17. Pillay AL, Van der Veen MBW. Prevalence of parental substance abuse among child psychiatric inpatients. *Percept Mot Skills* 1997; **84**: 947-955.

SHORT REPORT

SIDE-EFFECTS OF ORAL MISOPROSTOL IN THE THIRD STAGE OF LABOUR — A RANDOMISED PLACEBO-CONTROLLED TRIAL

G Justus Hofmeyr, V Cheryl Nikodem, Marinda de Jager, Andrew Drakely

Background. Misoprostol, an inexpensive, stable, orally active prostaglandin analogue, has been suggested for use in the prevention of postpartum haemorrhage. Potential side-effects, however, need to be quantified.

Objective. To compare the rate of postpartum shivering and pyrexia following oral misoprostol 600 µg and placebo.

Design. A double-blind placebo-controlled trial. Women in labour were randomly allocated to receive either misoprostol 600 µg orally or placebo after delivery. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Side-effects were recorded. Postpartum blood loss in the first hour was measured by collection in a special flat plastic bedpan.

Setting. The labour ward of an academic hospital in Johannesburg, with 7 000 deliveries per annum.

Main outcome measures. Shivering and pyrexia.

Results. The groups were well matched. Misoprostol use was associated with more shivering (44% versus 11%, relative risk (RR) 4.03, 95% confidence interval (CI) 2.85 - 5.70), pyrexia ≥ 37.8°C (38% v. 6%, RR 6.23, CI 3.89 - 9.97), 1-hour systolic blood pressure ≥ 140 mmHg (33% v. 25%, RR 1.32, CI 1.03 - 1.70), and diastolic blood pressure ≥ 90 mmHg (10.5% v. 3.0%, RR 3.44, CI 1.67 - 7.11). There were no other significant differences. The study was not designed to be large enough to assess a difference in blood loss ≥ 1 000 ml (9% v. 9.7%, RR 0.93, CI 0.56 - 1.53). Possible effects on blood loss may have been obscured by the lesser use of additional oxytocics in the misoprostol group (14% v. 18%, RR 0.78, CI 0.54 - 1.13).

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Conclusions. This study has shown the association of postpartum oral misoprostol 600 µg with shivering, pyrexia and hypertension. The increased blood pressure, as for the trend towards increased abdominal pain, may be secondary to the uterotonic effect of misoprostol. Large randomised trials are needed to assess the effectiveness of misoprostol in the prevention of postpartum haemorrhage, against which the disadvantages demonstrated here can be weighed.

S Afr Med J 2001; 91: 432-435.

The use of misoprostol, an inexpensive, stable, orally active prostaglandin analogue, for the prevention of postpartum haemorrhage, was first reported in 1996.[1] If effective, this therapy would have profound implications for the health of childbearing women worldwide. A limiting factor may be side-effects of misoprostol.[2] In a preliminary randomised trial, we observed shivering in 19% of puerperal women who received oral misoprostol 400 µg, compared with 5% of those who received placebo treatment.[3] As shivering was not a primary outcome of the latter study, underreporting may have occurred. We have therefore conducted a prospective, randomised, placebo-controlled trial specifically to assess the side-effects of misoprostol use after delivery.

Patients and methods

The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Women in labour at Coronation Hospital, Johannesburg, were asked to participate in the study, and to sign informed consent. Baseline data were recorded. Immediately after delivery the women were asked to swallow three tablets directly from the next in a series of numbered, opaque test tubes, with a sip a water. The tablets were either misoprostol 200 µg or placebo tablets similar in size and colour but not shape. Efforts to obtain identical placebo tablets were unsuccessful. This method of blinding proved to be effective. The containers were ordered according to a computer-generated random sequence, in balanced blocks of 18. The placenta was removed by cord traction once the uterus was palpated to have contracted firmly.

Within a minute after delivery, linen soiled with amniotic fluid was removed, a fresh, disposable absorbent linen saver sheet with plastic backing was placed under the woman, and a low-profile wedge-shaped plastic 'fracture' bedpan was slid under her buttocks. When active bleeding had stopped, any blood clots were expressed from the uterus, the bedpan was removed and a sanitary towel was applied. The blood in the bedpan was measured in a measuring jug. One hour after delivery, any bloodstained linen savers and sanitary towels were placed in a plastic bag and weighed in grams. The known dry weight of the linen savers and sanitary towels was subtracted to give the approximate volume of blood in millilitres. This was added to the measured blood volume from the bedpan to give the total measured blood loss in the first hour after delivery.

Because conventional oxytocics were not given routinely, the protocol required that close observation be maintained, and conventional therapy be given immediately if the bleeding was considered to be more than usual. The caregiver could choose to use intramuscular Syntometrine 1 ampoule or oxytocin 10 IU, or in more severe cases an intravenous infusion of oxytocin 20 IU in 1 000 ml saline.

All data were entered onto a database (EpiInfo 6) for analysis. The randomisation code was broken only after entry and checking of data. Comparisons were by the chi-square test with Yates' correction or Fisher's exact probability test if any cell was < 5, and relative risks with Taylor Series 95% confidence intervals.

Results

There were no withdrawals after randomisation and all outcomes were analysed in the allocated group.

The randomisation process was successful in producing well-matched groups (Table I). The outcome variables are shown in Table II. Shivering, pyrexia ≥ 37.8°C and hypertension were significantly more common in the misoprostol group. There was somewhat less frequent use of conventional oxytocics in the misoprostol group.

Table I. Comparison of baseline variables between women randomly allocated to receive misoprostol 600 µg or placebo for third stage of labour management

	Misoprostol	Placebo
Number	300	300
Age (years)	26.6 (5.6)	27.4 (5.8)
Primiparous	94 (31%)	85 (28%)
Parity 4+	10 (3.3%)	7 (2.3%)
Episiotomy/tear	146 (49%)	141 (47%)
Birth weight (grams)	3 047 (528)	3 076 (528)

Results are expressed as mean values (standard deviation) or numbers (%). There were no statistically significant differences.

Discussion

The use of placebo treatment was considered acceptable by the University Ethics Committee, specifically within the context of a research environment in which blood loss was closely and accurately monitored, and conventional oxytocics were administered as soon as blood loss was thought to be more

Table II. Comparison of outcome variables between women randomly allocated to receive misoprostol 600 µg or placebo for third stage of labour management

	Misoprostol		Placebo				
	No. of women observed	No. of women with negative outcomes (%)	No. of women observed	No. of women with negative outcomes (%)	RR	95% CI	*P*-value
Primary outcomes							
Shivering	300	133 (44)	300	33 (11)	4.03	2.85 - 5.70	0.0000
Temperature ≥ 37.8°C	299	114 (38)	294	18 (6.1)	6.23	3.89 - 9.97	0.0000
Temperature ≥ 40°C	299	1 (0.3)	294	0 (0)	—	—	1.00
Secondary outcomes							
Nausea	300	5 (1.7)	300	1 (0.3)	5.00	0.59 - 42.5	0.22
Vomiting	300	4 (1.3)	300	2 (0.7)	2.00	0.37 - 10.8	0.68
Diarrhoea	300	1 (0.3)	300	1 (0.3)	1.00	0.06 - 15.9	1.00
Abdominal pain	300	47 (15.7)	300	31 (10.3)	1.52	0.99 - 2.32	0.07
Blood pressure at 1 hour	300	2 (0.7)	300	2 (0.7)	1.00	0.14 - 7.05	1.00
Systolic ≥ 140 mmHg	299	100 (33)	296	75 (25)	1.32	1.03 - 1.70	0.04
Diastolic ≥ 90 mmHg	296	31 (10.5)	296	9 (3.0)	3.44	1.67 - 7.11	0.0006
Blood loss ≥ 1 000 ml	300	27 (9)	299	29 (9.7)	0.93	0.56 - 1.53	0.88
Additional oxytocic needed	300	42 (14)	300	54 (18)	0.78	0.54 - 1.13	0.22
Third stage ≥ 30 min	299	6 (2)	300	3 (1)	1.99	0.50 - 7.87	0.50
Manual removal of placenta	300	2 (0.7)	300	2 (0.7)	1.00	0.14 - 7.05	1.00
Blood transfusion	299	1 (0.3)	300	2 (0.7)	0.50	0.05 - 5.50	1.00

Results are expressed as numbers (%).
RR = relative risk; CI = confidence interval.

brisk than usual. Placebo use has also been considered acceptable in a recent Swedish trial.[7]

Two previous reports[8] have suggested that postpartum misoprostol causes shivering in as many as 60% of women, but these studies lacked the control groups necessary to quantify this effect. After completing the current study, we participated in a World Health Organisation multicentre pilot trial comparing misoprostol 600 µg and 400 µg and Syntocinon 10 units intramuscularly.[9] Although different cut-off points were chosen, both trials documented a clear thermogenic effect of puerperal misoprostol. In only one case in the current trial did the temperature exceed 40°C, and in no case was the temperature problematic. However, it is most important that clinicians be aware of this side-effect to avoid unnecessary investigation or treatment of 'unexplained' postpartum pyrexia.

This is the first randomised trial to show an increase in postpartum hypertension with misoprostol. As misoprostol in non-pregnant hypertensive patients is associated with slight lowering of blood pressure,[10] the most likely explanation for this finding is that blood pressure was increased as a result of increased uterine contractility. Physiological studies have demonstrated a clear uterotonic effect of misoprostol in the puerperium.[11] Similarly, the near-significant increase in abdominal pain is likely to reflect increased uterine contraction.

One possible method of reducing side-effects of misoprostol in the third stage of labour is use of the rectal route.[12]

No conclusions should be drawn from the lack of a significant reduction in postpartum haemorrhage in this study, firstly because the numbers studied were not adequate to detect a modest reduction, and secondly because the ready use of conventional oxytocics, which were required more frequently in the control group, is likely to have obscured any benefit from misoprostol. The potential benefit of misoprostol may be greater in an environment in which conventional oxytocics are not available.

CONCLUSIONS

This study has quantified certain side-effects of postpartum misoprostol. It is essential for clinicians who use misoprostol in the postpartum period to be aware of these side-effects. Very large randomised trials, such as the trial currently being undertaken by the World Health Organisation, are needed to determine the effectiveness of oral misoprostol in the prevention of postpartum haemorrhage, against which the disadvantages of the side-effects documented in this study can be weighed.

We acknowledge support from the South African Medical Research Council and the University of the Witwatersrand, and the excellent assistance of the nursing staff at Coronation Hospital.

References

1. El-Refaey H, O'Brien P, Morata A, Walder J, Rodeck C. Misoprostol for third stage of labour. *Lancet* 1996; **347**: 1257.
2. El-Refaey H, O'Brien P, Morata A, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997; **104**: 339–339.
3. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynaecol* 1998; **105**: 971–975.
4. Nordstrom L, Fogelstam K, Fridman G, Carlsson A, Rychstroem H. Routine oxytocin in the third stage of labour: a placebo controlled trial. *Br J Obstet Gynaecol* 1997; **104**: 781–786.
5. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Piaggio A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. *Br J Obstet Gynaecol* 1999; **106**: 304–308.
6. Kailasam MT, Lin MC, Cervenka JH, *et al*. Effects of an oral pGE1 agonist on blood pressure and its determinants in essential hypertension. *J Hum Hypertens* 1994; **8**: 515–520.
7. Chong YS, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of the third stage of labour? A preliminary study of its effect on the postpartum uterus (Abstract). The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists 1997 Combined Scientific Meeting, Brisbane 28 April - 2 May 1997.
8. Barrugboye A, Merrell DA, Mitchel R, Hofmeyr GJ. Randomised comparison of misoprostol with Syntometrine for management of third stage labor. *Acta Obstet Gynecol Scand* 1998; **77**: 178–181.
9. Barrugboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. *Am J Obstet Gynecol* 1998; **179**: 1043–1046.

Accepted 6 August 2000.

VIDEO

Kangaroo Mother Care

Restoring the Original Paradigm for Infant Care and Breastfeeding



Kangaroo Mother Care is a method of care for all newborn babies, but especially prematures. This is the eagerly awaited original video of Dr Nils Bergman's highly popular talks on the subject. The video provides the latest up-to-date research and evidence to prove that the newborn thrives best in its original "rightful" place - on its mother's chest. **Kangaroo Mother Care** has the following vital components:

Skin to skin contact

The naked baby is placed against the mother's skin, where the temperature is perfectly controlled all the time. A mother's temperature will naturally rise 2° C to warm a cold baby. The baby's breathing is markedly improved.

Breastfeeding

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Acta Obstetricia et Gynecologica Scandinavica
ISSN 0001-6349

ORIGINAL ARTICLE

Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor

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Acta Obstet Gynecol Scand 1998; 77: 178–181. © Acta Obstet Gynecol Scand 1998

Background. The search for an effective, easily stored, affordable uterotonic agent in preventing postpartum hemorrhage is of importance, especially in the developing world. The objective of this study was to randomly compare the effectiveness of rectal misoprostol with Syntometrine in the management of the third stage of labor.
Methods. Four hundred and ninety-one low risk women in labor were randomly allocated to receive either misoprostol 400 microgram rectally or Syntometrine 1 ampuole intramuscularly, and postpartum blood loss was estimated as the principal end point. Comparisons were by the chi-square test or Fisher's test and relative risks with 95% confidence intervals for categorical data, and the Mann-Whitney test for ranked continuous variables.
Results. The baseline characteristics in terms of hemoglobin estimation in antenatal clinic, mean age, parity, and duration of labor in the 250 patients who received Syntometrine and 241 patients who received misoprostol were similar. However, there was a significant difference in the pre-delivery blood pressure of the two groups because of the non-protocol exclusion of women with elevated blood pressure allocated to receive Syntometrine. Duration of third stage of labor, blood loss postpartum and hemoglobin estimation post partum were all similar. Postpartum diastolic hypertension was more common in the Syntometrine group (p= 0.002). No other apparent side effect was noted in either group.
Conclusion. Misoprostol rectally for management of the third stage of labor merits further investigation.

Key words: misoprostol; postpartum hemorrhage; randomized comparison; syntometrine

Submitted 3 January, 1997
Accepted 8 June, 1997

Postpartum hemorrhage is an important cause of maternal mortality and morbidity worldwide, and particularly in developing countries (1–3).

It has been demonstrated that the routine use of oxytocics such as Syntometrine or syntocinon is associated with a significant reduction in the occurrence of postpartum hemorrhage (4, 5). Sulprostone, a prostaglandin E analogue, has been shown to be effective in preventing the recurrence of atonic postpartum hemorrhage (6). Prostaglandin F2 alpha has been used for the management of postpartum hemorrhage (7). Oral ergometrine has been found to be insufficiently effective for routine use (8).

Misoprostol (Cytotec, Searle), a methyl ester of prostaglandin E1 additionally methylated at C–16, marketed for use in the prevention and/or treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors, has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus (9, 10) selectively binding to EP-2/EP-3 prostanoid receptors (11). Its use

Abbreviations:
PPH: postpartum hemorrhage; BP: blood pressure; Hb: hemoglobin.

in the third stage of labor has been suggested in a recently published letter and report (12, 13).

Misoprostol is inexpensive, easily stored at room temperature, rapidly absorbed orally and has few side effects. Syntometrine (syntocinon 5 units with ergometrine 0.5 mg), on the other hand, needs parenteral administration, and refrigeration to ensure its efficacy, which is not always feasible in the developing world (14). It is not without side-effects, notably hypertension.

The vaginal route has been used for misoprostol administration for termination of pregnancy, to achieve a prolonged action. The rectal route has also been found to be clinically effective for the induction of labor (DA Merrell, personal communication). As the vaginal route is not feasible after delivery, the rectal route was chosen for this study. Practical advantages of the rectal route are ease of administration in patients who are vomiting, unable to take orally or under anesthesia.

The objective of this study is to randomly compare the effectiveness of misoprostol 400 micrograms administered rectally, with Syntometrine 1 ampoule intramuscularly in the routine management of the third stage of labor.

Patients and methods

The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand in November 1995 (Certificate R14/49). Low risk women in labor at Natalspruit Hospital, Johannesburg, were asked to participate in the study. Baseline data such as age, parity, antenatal hemoglobin level and blood pressure during labor, were recorded. Allocation was by means of sealed opaque envelopes, in computer-generated random sequence. During the second stage of labor, the next in the series of envelopes was opened to allocate the patient to receive either misoprostol 400 micrograms rectally or Syntometrine 1 ampoule intramuscularly, after delivery. Blood loss within an hour of delivery was estimated, perineal trauma noted (episiotomy or tear), and third stage of labor duration was recorded.

Blood pressure was checked an hour after delivery, and patients were thereafter transferred to the postnatal ward for a further 24 hours' observation. Possible side effects were noted during this period. At about 24 hours after delivery, a blood specimen was taken for hemoglobin estimation.

The trial procedures were carried out by midwifery staff in a busy labor ward. About halfway through enrolment it was discovered that a small number of women had been excluded from the Syntometrine group because of hypertension detected after enrolment (thus contraindicating the use of Syntometrine). The Syntometrine envelopes had been reallocated to subsequent participants, and it was not possible to trace the women originally allocated. Baseline hypertension was therefore less frequent in the Syntometrine group (Table I). If anything, these violations of the randomization protocol would have biased the results in favor of the Syntometrine group, by the exclusion of higher risk women from this group. In other respects the groups were well matched. No other sources of potential bias were identified.

All data were entered onto a database (Epiinfo 6) for analysis. Comparisons were by the chi-square test or Fisher's exact probability test and relative risks with 95% confidence intervals for categorical data, and the Mann-Whitney test for ranked continuous variables.

Results

The outcome variables are shown in Table II. Recording of trial data was incomplete in several

Table I. Comparison of baseline variables between women randomly allocated to receive misoprostol versus syntometrine for third stage management, expressed as mean values (standard deviation) or numbers (%). Missing data indicated by N values, the number of patients included in each analysis

	Misoprostol			Syntometrine			
	N			N			*p*
Total	241			250			
Age (years)	238	25	(5.8)	248	25	(6.4)	0.9
Primiparous (No.)	234	84	(36%)	240	92	(38%)	0.6
Parity 4+ (No.)	234	44	(19%)	240	44	(18%)	0.9
Antenatal hb (g%)	200	12.0	(1.3)	189	12.0	(1.4)	0.5
BP during labor							
systolic (mmHg)	179	129	(12)	188	126	(11)	0.01
diastolic (mmHg)	179	76.4	(9.3)	188	75.6	(9)	0.6
Labor (hours)	230	7.7	(3.0)	242	8.0	(3.4)	0.5
2nd stage (minutes)	220	15.7	(12.6)	229	14.8	(11.4)	0.6
Episiotomy/tear (No.)	240	175	(73%)	247	174	(70%)	0.6

Table II. Comparison of outcome variables between women randomly allocated to receive misoprostol versus syntometrine for third stage management, expressed as mean values (standard deviation) or numbers (%). Missing data indicated by N values, the number of patients included in each analysis

	Misoprostol			Syntometrine			Relative risk 95% CI		
	N			N					*p*
Enrolled	241			250					
3rd stage (min)	232	7.7	(6.7)	244	7.9	(6.8)			0.7
Estimated blood loss (ml)	231	187	(92)	233	183	(68)			0.7
Blood loss >500ml (No.)	231	2	(0.9%)	233	1	(0.4%)	2.02	(0.18–22)	0.6
Postpartum hb (g%)	161	11.7	(1.6)	163	11.7	(1.8)			0.9
Postpartum hb<10g% (No.)	161	22	(14%)	163	27	(17%)	0.82	(0.49–1.39)	0.6
BP postpartum:									
systolic (mmHg)	236	123	(14)	246	127	(16)			0.003
systolic >140 mmHg (No.)	236	35	(15%)	246	46	(19%)	0.79	(0.53–1.2)	0.3
diastolic (mmHg)	235	70.0	(12)	246	73.8	(13)			0.002
diastolic >90 mmHg (No.)	235	11	(4.6%)	246	31	(13%)	0.37	(0.19–0.72)	0.004
Difference between postpartum and antepartum results:									
hb	83	−0.23	(1.6)	83	−0.28	(1.9)			0.9
systolic BP (mmHg)	93	−8.7	(16.7)	115	2.8	(18.1)			0.00004
diastolic BP (mmHg)	93	−9.7	(13.6)	115	−0.87	(14.1)			0.00007

cases, as indicated by the 'N' values for each case.

In order to evaluate the possible bias introduced by the exclusion of hypertensive women from the Sytometrine group, the data were reanalysed after excluding all women with systolic blood pressure ≥140 mmHg, or diastolic ≥90 mmHg during labor (45 in the misoprostol and 39 in the Syntometrine group). The results were essentially the same as for the whole data set.

The duration of the third stage of labor was similar between groups. No difference was found in the mean estimated blood loss between the groups. This finding was corroborated by the more objective finding of no difference in hemoglobin levels on the first day after delivery. The sample size was insufficient to compare the incidence of postpartum hemorrhage (estimated blood loss >500 ml). Blood transfusion was not required in any case. Additional oxytocic management was given because the uterine contraction was considered inadequate in four cases in the misoprostol group and one in the Syntometrine group. In only one of the former cases was blood loss estimated to be above 500ml. Manual removal of the placenta was required in only one case, in the Syntometrine group.

Diastolic hypertension after delivery was more common in the Syntometrine group.

There were no positive responses to a general enquiry about side-effects. Specific potential side-effects such as shivering were not asked about directly.

The cost ratio of misoprostol 400 μg to Syntometrine, syringe, needle and alcohol swab was 1 to 3.4 (cost of refrigeration of Syntometrine not included).

Discussion

Visual estimation of blood loss has been shown to underestimate true blood loss (15). However, as a method of comparing the results of different methods of managing third stage of labor, it has been found to be an acceptable method in several previous randomized trials (6).

The results of this exploratory trial must be interpreted in the light of the methodological shortcomings described above. Such bias as might have been introduced by exclusions after enrolment is likely to have favored the Syntometrine group. It is therefore reassuring that no evidence of greater blood loss in the misoprostol group was found, and there is clearly justification for further randomized trials of sufficient size to compare the incidence of postpartum hemorrhage between women managed with misoprostol and with conventional oxytocics. Further research is required to determine the optimal dose and route of misoprostol administration.

The comparison of the use of additional oxytocic management (in four women in the misoprostol and one in the Syntometrine group) is subject to bias, as the clinical threshold for additional parenteral oxytocic management would be expected to be lower in a group who had not received the conventional parenteral management.

A striking finding was the greater incidence of diastolic hypertension after delivery in the Synto-

metrine group. This is unlikely to be due to the antihypertensive effect of misoprostol, as this effect is modest (16). It is more likely to be due to the known hypertensive effect of Syntometrine administration after delivery (6).

Acknowledgments

We acknowledge the contribution of the nursing staff, Natalspruit Hospital, and the support of the South African Medical Research Council.

References

1. Kwast BE. Postpartum haemorrhage: its contribution to maternal mortality. Midwifery 1991; 7: 64–70.
2. Faweus S, Mbizvo MT, Lindmark G, Nystrom L. Maternal mortality study group. Community based investigation of causes of maternal mortality in rural and urban Zimbabwe. Cent Afr J Med 1995; 41: 105–13.
3. Spies CA, Bam RH, Cronje HS, Schoon MG, Wiid M, Niemand I. Maternal deaths in Boemfontein, South Africa, 1986–1992. S Afr Med J 1995; 85: 753–5.
4. Elbourne D, Prendiville W, Chalmers I. Choice of oxytocic preparation for routine use in the management of third stage of labour: An overview of evidence from controlled trials. Br J Obstet Gynaecol 1988; 95: 17–30.
5. Prendiville WJ. The prevention of post partum haemorrhage – optimising routine management of the third stage of labour. Eur J Obstet Gynecol Reprod Biol 1996; 69: 19–24.
6. Van Selm M, Kanhai HHH, Keirse MJNC. Preventing the recurrence of atonic postpartum haemorrhage, a double-blind trial. Acta Obstet Gynecol Scand 1995; 74: 270–4.
7. Jacobs M, Arias F. Intramyometrial prostaglandin F2 in the treatment of severe postpartum hemorrhage. Obstet Gynecol 1980; 55: 665–6.
8. de Groot ANJA, van Roosmalen J, van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstet Gynecol Scand 1996; 75: 464–8.
9. El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med 1995; 332: 983–7.
10. Merrell DA, Koch MAT. Induction of labour with intravaginal misoprostol in 2nd and 3rd trimester of pregnancy. S Afr Med J 1995; 85: 1088–90.
11. Senior J, Marshall K, Sangha R, Clayton JK. *In vitro* characterisation of prostanoid receptors on human myometrium at term pregnancy. Br J Pharmacol 1993; 108: 501–6.
12. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. Lancet 1996; 347: 1257.
13. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997; 104: 336–9.
14. Walker GJA, Hogerzeil HV, Lindgren U. Potency of ergometrine in tropical countries. Lancet 1988; 2: 393.
15. Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM. Blood volume changes in pregnancy and the puerperium. Am J Obstet Gynecol 1962; 84: 172.
16. Kailasam MT, Lin MC, Cervenka JH, Parmer RJ, Kennedy BP, Ziegler MG et al. Effects of an oral PGE1 agonist on blood pressure and its determinants in essential hypertension. J Hum Hypertens 1994; 8: 515–20.

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Rectal misoprostol in the prevention of postpartum hemorrhage: A placebo-controlled trial

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OBJECTIVE: This study investigated the effectiveness of rectal misoprostol in preventing postpartum hemorrhage.

STUDY DESIGN: In a randomized, placebo-controlled study, 550 women were randomly allocated to rectally receive 400 μg misoprostol or nonidentical placebo after normal vaginal delivery. Any excessive bleeding was actively managed with conventional oxytocic agents. Blood loss was measured directly.

RESULTS: The baseline variables were similar. Blood loss of ≥1000 mL occurred in 4.8% (13/270) of the misoprostol group and 7% (19/272) of the placebo group. Additional oxytocic therapy was required by 3.3% and 4.7%, respectively. No predominance of side effects, particularly shivering, was noted in the misoprostol group.

CONCLUSIONS: Postpartum use of 400 μg rectal misoprostol was well tolerated and associated with a statistically nonsignificant trend toward less postpartum hemorrhage. The early active management of excessive bleeding with conventional oxytocic agents may have reduced the potential of the study to detect differences between the groups (Am J Obstet Gynecol 1998;179:1043-6.)

Key words: Misoprostol, placebo, postpartum hemorrhage, randomized trial

Excessive maternal blood loss after childbirth is a major cause of morbidity and mortality, not only in developing countries[1] but also in developed countries.[2] A community-based investigation of causes of maternal mortality in rural Zimbabwe described the leading cause of death as postpartum hemorrhage at 40 per 100,000 births.[3] In rural communities the lack of access to skilled birth attendants who are able to administer parenteral oxytocic agents, the high incidence of anemia in pregnancy, the lack of availability of safe blood transfusion services, and the lack of refrigeration to store oxytocic agents worsens the outcome of postpartum hemorrhage. Most of the world's population lives in rural communities.

Active management of the third stage of labor, which includes use of oxytocic therapy, early cord clamping, and placental delivery by cord traction, has been demonstrated to be an effective prophylactic measure against postpartum hemorrhage.[4] Side effects of conventional oxytocic agents range from nausea, vomiting, and hypertension to postpartum eclampsia, intracerebral hemorrhage, myocardial infarction, cardiac arrest, pulmonary edema, and inadvertent administration of the parenteral oxytocic agent to the neonate, causing neonatal convulsion.[4,5]

Other measures aimed at reducing postpartum hemorrhage have been subjected to evaluation but not shown to be effective. These include early sucking and nipple stimulation[6] and oral ergometrine.[7] Sulproston (Schering AG, Germany), a prostaglandin E_1 analog, has been shown to be effective in preventing the recurrence of atonic postpartum hemorrhage.[8] Prostaglandin $F_{2\alpha}$ has been used to treat postpartum hemorrhage.[9]

In a prospective observational study, oral misoprostol has been suggested as effective in the prevention of postpartum hemorrhage[10]; its uterotonic effect on the postpartum uterus has also been documented.[11] However, no placebo-controlled clinical trial of misoprostol for third-stage management has to our knowledge been published. The objective of this study was therefore to investigate the use of rectal misoprostol compared with placebo in preventing postpartum hemorrhage.

Patients and methods

The study was approved by the Committee for Research on Human subjects of the University of Witwatersrand. The use of placebo treatment was approved specifically within the context of a research environment in which blood loss was closely and accurately monitored, and conventional oxytocic agents were administered as soon as blood loss was thought to be more brisk than usual. Placebo use was also considered accept-

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Received for publication September 3, 1997; revised Decmeber 13, 1996; accepted April 14, 1998.

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0002-9378/98 $5.00 + 0 6/1/91069

Table I. Comparison of baseline variables between women randomly allocated to rectally receive 400 μg misoprostol or placebo in prevention of postpartum hemorrhage

	Misoprostol (N = 271)		*Placebo (N = 275)*	
	n	*Value**	*n*	*Value**
Age (y)	269	26.3 ± 5.8	271	27.3 ± 6.0
Parity	251	2.4 ± 1.3	259	2.6 ± 1.4
Episiotomy (No.)	263	158 (60%)	266	159 (60%)

*Expressed as mean values ± SD or numbers with percentage in parentheses. Missing data are indicated by shortfall in n values (the number of women included in each analysis).

able in a recent Swedish trial of oxytocin versus placebo for third-stage management.[12]

Women at low risk in labor at Natalspruit Hospital, Johannesburg, South Africa, were asked to participate in the trial and gave informed consent. Baseline data were recorded for the 550 women enrolled. Allocation was by means of sealed, opaque containers containing 400 μg misoprostol or placebo tablets in a computer-generated random sequence. The point of randomization, by opening the next in the series of containers, was immediately after delivery of the baby. A limitation of the study was that identical placebo tablets were not available from the manufacturers. The placebo tablets were similar in size and color but were not identical in shape to the misoprostol tablets. Blinding of the midwife administering the tablets was therefore not possible.

The allocated tablets were inserted rectally within 1 minute of the birth of the baby, immediately after clamping of the cord. Linen soiled with blood and liquor was changed and a new absorbent, plastic-backed linen saver and a low-profile plastic "fracture" bedpan were placed beneath the patient's buttocks to facilitate subsequent blood collection. The placenta was either delivered by cord traction or spontaneously expelled. Blood collection in the plastic bedpan continued until 1 hour after delivery of the baby. Perineal trauma (episiotomy, first- or second-degree tear) was noted and sutured if present, taking care to save the swabs used during this procedure for later weighing. The women were carefully observed for features of excessive blood loss; if signs were present, active intervention commenced with intramuscular administration of 1 ampule syntometrine (ergometrine 0.5 mg/oxytocin 5 IU), and if bleeding persisted, 20 U oxytocin (Syntocinon) was infused in 1 L lactated Ringer's solution. Further therapeutic measures were taken as necessary. The duration of the third stage of labor was recorded.

One hour after delivery all blood on the linen saver was scooped into the bedpan with the blood already collected in the bedpan, and the total blood was carefully measured. All linen savers and vaginal pads used were weighed. The known dry weights of the materials used were subsequently subtracted from the measured weight to estimate the amount of blood soiling.

Any apparent side effects were noted. Toward the end of the trial a report of shivering in ±60% of women who received oral misoprostol was published,[10] so shivering was directly asked about or observed for in the final 70 women in the series.

The sample size of 550 was calculated to give an 80% chance of detecting a reduction in blood loss >1000 mL from 12.5% to 5%, determined from data from 2 previous randomized trials showing estimated postpartum hemorrhage of 13.5% with physiologic management of the third stage compared with 4.1% with active management.[13,14] All data were entered onto a database (EpiInfo 6; Centers for Disease Control and Prevention, Atlanta, Ga) before breaking of the randomization code for analysis. Comparisons were by the χ^2 test or Fisher exact test with relative risks and 95% confidence intervals for categoric data and by the Mann-Whitney test for ranked continuous variables.

Results

Records of 4 of the 550 allocations (all from the placebo group) could not be traced. Data for the remaining 546 women were analyzed. The baseline and labor variables are shown in Table I. Age and parity were well matched, as was the occurrence of perineal trauma.

The methods of delivery of the placentas were similar (Table II). Manual removal of the placenta was required in 1 case in the misoprostol group. The mean durations of the third stage of labor were similar, 6.6 minutes (SD 14.8) in the misoprostol group and 6.4 minutes (SD 8.4) in the placebo group.

In the misoprostol group 13 women (4.8%) had blood loss of ≥1000 mL, compared with 19 women (7%) in the placebo group. Oxytocin infusion was required by 5 women (1.8%) in the misoprostol group, versus 13 (4.4%) in the placebo group. One woman in each group vomited (both had postpartum hemorrhage). There were no episodes of diarrhea among the women. Among the last 70 women, for whom shivering was specifically sought as a possible side effect, 1 woman in the misoprostol group and 4 women in the placebo group had shivering.

Comment

Misoprostol, a prostaglandin E_1 analog marketed for use in the prevention and treatment of peptic ulcer disease caused by nonsteroidal anti-inflammatory agents, has been shown to be safe in human beings.[15] It acts as a myometrial stimulant of the pregnant uterus[16] by selectively binding to prostaglandin E_2–sensitive receptor subtypes EP-2 and EP-3[17] and has been clinically proved to be

Table II. Comparison of outcome variables between women randomly allocated to rectally receive 400 μg misoprostol or placebo for prevention of postpartum hemorrhage

	Misoprostol (N = 271)			*Placebo (N = 275)*			*Relative risk*	*95% Confidence interval*	*P*
	n	*No.*	*%*	*n*	*No.*	*%*			
Primary outcomes									
Blood loss ≥1000 mL	270	13	4.8	272	19	7	0.69	0.35-1.37	.37
Need for additional oxytocic agent	271	9	3.3	275	13	4.7	0.70	0.31-1.62	.54
Need for oxytocin infusion	271	5	1.8	275	12	4.4	0.42	0.15-1.18	.15
Secondary outcomes									
Placenta delivered spontaneously	271	76	28	275	71	26	1.09	0.82-1.43	.62
Third stage >30 min*	268	1	0.37	272	2	0.73			
Side effects*									
Shivering	34	1	2.9	36	4	11			
Abdominal pain	271	1	0.37	275	0	0			
Vomiting	271	1	0.37	275	1	0.36			

Missing data are indicated by shortfall in n values (the number of patients included in each analysis).
*Numbers too small for meaningful statistical analysis.

a uterotonic agent when administered orally or vaginally for induction of labor.[18, 19] Side effects of oral misoprostol are essentially gastrointestinal and are dose dependent.[20]

Clinically insignificant hypotensive effects of a high oral dose of misoprostol have been documented,[21] a property that may provide an advantage with respect to the ergot-containing oxytocic agents, which are hypertensive. Misoprostol is affordable, is easily stored at room temperature, and possesses a shelf life of several years. The rectal route used in this trial, if confirmed as effective, would have several advantages. Gastrointestinal side effects might be reduced, and administration to patients who are vomiting, unable to take orally, or under anesthesia would be possible. A previous study from our unit compared rectal misoprostol with syntometrine for management of the third stage of labor.[22] Rectal misoprostol was shown to be well tolerated.

Visual estimation of blood loss after delivery has been shown to underestimate true blood loss.[23] When blood loss is measured, the conventional definition of postpartum hemorrhage as estimated blood loss >500 mL is therefore inappropriate, because about 50% of women have measured blood loss >500 mL. Significant blood loss was therefore taken in this study to be ≥1000 mL measured blood loss.

A limitation of this study was that double-blinding could not be achieved because of our inability to obtain identical-looking placebo tablets from the manufacturer. This is, to our knowledge, a problem common to most trials of misoprostol tablets in obstetrics and gynecology published to date. Of 26 trials of misoprostol for induction of labor recently reviewed,[19] none used misoprostol placebo tablets. Blinding was achieved in only 1 of the 26 trials, by crushing the tablets into a gel for vaginal administration.[24] The problem of observer bias was minimized by using objective measurement of blood loss as the primary outcome. No estimates of blood loss were included. The weighing of bloodstained disposables was carried out by ward assistants unaware of the allocation, and the calculations of total blood loss from the measured and weighed blood were made after completion of the study by persons unaware of the group allocation.

The potential for this trial to demonstrate a difference in the rate of excessive blood loss between the misoprostol and the placebo group was clearly limited by the need to administer conventional oxytocic agents as soon as blood loss appeared to be more than usual. The potential benefit of misoprostol may be greater in an environment in which conventional oxytocic agents are not available. The incidence of postpartum hemorrhage in the control group (7%) was lower than that on which our power calculations were based (12.5%). The reduction to 4.8% in the misoprostol group did not reach statistical significance in the numbers studied. This 31% reduction is similar to that from a recent Swedish trial, in which the incidence of measured blood loss >1000 mL was 6.2% after 10 U oxoytocin and 8.8% after placebo (29% reduction).[12]

Of particular interest was the fact that shivering was noted in only 7.1% of the last 70 women in the series, with no obvious increase in the misoprostol group. In an uncontrolled series of women receiving 600 μg oral misoprostol post partum, shivering was noted in 62%.[10]

Conclusion. In this study there was a trend toward reduced postpartum hemorrhage with 400 μg rectal misoprostol, but with the numbers studied this trend was consistent at the 95% certainty level with anything between a large reduction and a small increase in occurrence. Of importance is the apparent lack of side effects compared with reports of the oral route of administration. The rec-

tal route may thus have advantages if rectal administration of this dose or a larger dose of misoprostol is confirmed as effective in larger clinical trials.

We acknowledge the excellent help of the labor ward staff and matrons, Natalspruit Hospital.

REFERENCES

1. Kwast BE. Postpartum haemorrhage: its contribution to maternal mortality. Midwifery 1991;7:64-70.
2. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987-1990. Obstet Gynaecol 1996;88:161-7.
3. Fawcus S, Mbizvo MT, Lindmark G, Nyström L. A community based investigation of causes of maternal mortality in rural and urban Zimbabwe. Maternal Mortality Study Group. Cent Afr J Med 1995;41:105-13.
4. Prendiville WJ, Elbourne DR, McDonald S. Active versus expectant management of the third stage of labour. In: Neilson JP, Crowther CA, Hodnett E, Hofmeyr GJ, Keirse MJ, editors. Pregnancy and child birth module of the Cochrane database of systematic reviews. The Cochrane collaboration: issue 1. Oxford: Update Software: 1997.
5. McDonald SJ, Prendiville WJ, Blair E. Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of third stage of labour. BMJ 1993;307:1167-71.
6. Bullough CH, Msuku RS, Karonde L. Early suckling and postpartum haemorrhage: controlled trial in deliveries by traditional birth attendants. Lancet 1989;2:522-5.
7. de Groot AN, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstet Gynecol Scand 1996;75:464-8.
8. Van Selm M, Kanhai HH, Keirse MJ. Preventing the recurrence of atonic postpartum haemorrhage, a double-blind trial. Acta Obstet Gynecol Scand 1995;74:270-4.
9. Jacobs M, Arias F. Intramyometrial prostaglandin F2 alpha in the treatment of severe postpartum hemorrhage. Obstet Gynecol 1980;55:665-6.
10. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104:336-9.
11. Chong YS, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of the third stage of labour? A preliminary study of its effect on the postpartum uterus [abstract]. Proceedings of The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists 1997 Combined Scientific Meeting; 1997 April 28-May 2; Brisbane, Australia. p. 61.
12. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997;104:781-6.
13. Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ 1988;297:1295-300.
14. Begley CM. A comparison of "active" and "physiological" management of the third stage of labour. Midwifery 1990;6:13-7.
15. Collins PW. Misoprostol: discovery, development and clinical applications. Med Res Rev 1990;10:149-72.
16. Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991;338:1233-6.
17. Senior J, Marshall K, Sangha R, Clayton JK. In vitro characterization of prostanoid receptors on human myometrium at term pregnancy. Br J Pharmacol 1993;108:501-6.
18. Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. Obstet Gynecol 1997;89:392-7.
19. Hofmeyr GJ. Misoprostol vaginally for cervical ripening and labour induction. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ, Keirse MJ, editors. Pregnancy and childbirth module of the Cochrane database of systematic reviews. The Cochrane collaboration: issue 3. Oxford: Update Software; 1997.
20. Inman WH. Report on current PEM studies: drugs for peptic ulcer or reflux. Prescription Event Monitoring News 1991;7:32-4.
21. Brecht T. Effects of misoprostol on human circulation. Prostaglandins 1987;33(suppl):51-9.
22. Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomised comparison of rectal misoprostol with syntometrine for management of third stage of labor. Acta Obstet Gynecol Scand 1998;77:178-81.
23. Pritchard JA, Baldwin RM, Dickey JC, Wiggins KM. Blood volume changes in pregnancy and the puerperium. II. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, cesarean section, and cesarean section and total hysterectomy. Am J Obstet Gynecol 1962;84:1271-82.
24. Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. Br J Obstet Gynaecol 1993;100:641-4.

ORAL MISOPROSTOL FOR LABOUR THIRD STAGE MANAGEMENT: RANDOMISED ASSESSMENT OF SIDE EFFECTS

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Background

Postpartum haemorrhage is an important cause of maternal mortality and morbidity. In sub-Saharan Africa the maternal mortality rate is established to be 655 per 100 000 live births. As many as 25% of maternal deaths in rural areas are due to postpartum haemorrhage. In Britain, where most women have access to medical care including the use of ocytocic drugs, the risk of maternal death from haemorrhage is about 1 in 100 000 births. The routine use of oxytocics such as Syntometrine (oxytocin 5IU and ergometrine 0.5mg) or oxytocin alone is associated with a significant reduction in the occurrence of postpartum haemorrhage.

Misoprostol (Cytotec, Searle) is a methyl ester of prostaglandin E1 additionally methylated at C-16 and is marked for use in the prevention and/or treatment of peptic ulcer disease caused by prostaglandin synthetase inhibitors. It has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus. Its use in the third stage of labour has recently been suggested. It is inexpensive, easily stored at room termperature, rapidly absorbed orally and has few side-effects. However, preliminary studies have suggested that misoprostol in the puerperium causes shivering in some women. The purpose of this study was to detemine the magnitude of this side-effect and whether it is dose-related.

Setting

An academic hospital in Johannesburg, South Africa with 7000 deliveries per annum.

Method

Women in labour were randomly allocated to receive misoprostol 600μg or placebo orally (part 1), or misoprostol 400μg or 600μg or placebo orally (part 2) after the birth of the baby. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Postpartum blood loss in the first hour was measured by collection in a special flat plastic bedpan. Side-effects up to one hour after delivery were recorded.

Results

	a. 600μg	b. 400μg	c. Placebo	p values	p values	p values
Shivering				a vs c	b vs c	a vs b
Part 1 Part 2 Combined	133/300 (44%) 81/199 (41%) 214/499 (43%)	65/199 (37%)	33/300 (11%) 30/199 (15%) 63/499 (13%)	.0000 .0000 .0000	.0001	.12
Pyrexia > 38						
Part 1 Part 2 Combined	86/2999 (29%) 53/200 (27%) 139/499 (28%)	28/200 (14%)	13/299 (4%) 5/200 (2.5%) 18/499 (3.6%)	.0000 .0000 .0000	.003	.003

Conclusions

Misoprostol 400-600μg orally in the puerperium causes shivering and pyrexia which is dose-related for pyrexia and possibly for shivering, but no serious side effects. These studies were not designed to have sufficient power to assess its effectiveness in preventing postpartum haemorrhage (no significant reduction was found). Because of the potential benefits for childbearing women, particulary those in developing countries, further research to determine its effects with greater certainty should be expedited.

British Journal of Obstetrics and Gynaecology
April 1999, Vol 106, pp. 304–308

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Misoprostol dose-related shivering and pyrexia in the third stage of labour

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For the WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour

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Objective To select the misoprostol dose to be used in a large multicentre randomised trial comparing misoprostol with oxytocin in the routine management of the third stage of labour.

Design Randomised pilot trial, double-blinded with the use of double placebos.

Setting Two of the nine hospitals that will participate in the main multicentre trial. The hospitals were located in Johannesburg, South Africa and Khon Kaen, Thailand.

Population Women during second stage of labour about to be delivered vaginally.

Methods The trial had three arms: misoprostol 400 μg *versus* misoprostol 600 μg *versus* intramuscular oxytocin 10 IU. Each group received an injection and three tablets immediately after the birth of the baby.

Main outcome measures Shivering and pyrexia rates were the main outcome measures. Data on other side effects and characteristics of the third stage of labour were also collected. Side effects were noted as none, mild, moderate or severe.

Results Both shivering and pyrexia (temperature > 38°C) were most common in the 600 μg misoprostol group (28% and 7·5% for shivering and pyrexia, respectively) compared with 400 μg misoprostol (19% and 2%), and the oxytocin group (12·5% and 3%). The increase in shivering in the misoprostol 600 μg group was due primarily to a higher rate of moderate shivering. None of the women had a temperature > 40°C. There were no increases in severe side effects and other adverse events in the misoprostol 600 μg group.

Conclusions When used in the management of the third stage of labour oral misoprostol is associated with an increase in the rate of moderate shivering and pyrexia which seems to be dose-related. Based on the results of this pilot trial, the Steering Committee has decided to use 600 μg misoprostol in the main trial, comparing it with oxytocin, in order to achieve higher effectiveness.

INTRODUCTION

Misoprostol is a prostaglandin E_1 analogue administered orally. Its effects on uterine contractility have been studied in early pregnancy[1] and at term when used for induction of labour[2]. In studies on the termination of early pregnancy misoprostol was shown to be a potent uterotonic agent when administered orally or vaginally to women pre-treated with mifepristone[3,4]. The uterotonic features of misoprostol given alone are also apparent when the compound is used for induction of labour[5].

Recently, El-Refaey *et al.*[6] reported the prophylactic use of misoprostol for the management of the third stage of labour in a prospective uncontrolled study. Six hundred micrograms of misoprostol were given orally to 237 women after vaginal delivery. Postpartum haemorrhage occurred in 6% (estimated blood loss > 500 mL) and 5% needed therapeutic uterotonics. The drug had few side effects, although shivering was noted in 62% of women and there was a mean increase of 0·5°C in body temperature after misoprostol administration when compared with the measurements before delivery. Chong *et al.*[7] observed a case of pyrexia of 41·9°C which continued for three hours after administration of 800 μg misoprostol. Two randomised controlled trials comparing misoprostol with placebo have been conducted in South Africa. In the first trial shivering was reported in 19% of women receiving 400 μg misoprostol, compared with 5·2% of women receiving placebo[8]. In the second trial, conducted in the same centre, shivering was reported in

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41% of women receiving 600 μg misoprostol, 37% after 400 μg and 15% after placebo[9]. Thus, it seems likely that shivering is a misoprostol-related effect specific to its use in the third stage of labour.

During the preparatory phase of a large, World Health Organization multicentre, randomised controlled trial aimed at evaluating the effectiveness of oral misoprostol compared with 10 IU intramuscular oxytocin for the prevention of postpartum haemorrhage[10], there was concern regarding the side-effects of misoprostol, especially shivering and pyrexia at the two doses considered (400 μg and 600 μg). We therefore decided to evaluate the effects of these two doses in a pilot trial before implementing the main trial. The primary objective of this pilot trial was to determine the rates of shivering and pyrexia (temperature > 38°C) within one hour after delivery with two different single doses of oral misoprostol (600 μg and 400 μg) compared with 10 IU of oxytocin during the active management of the third stage of labour.

METHODS

This was a hospital-based, multicentre, double-blind, randomised controlled trial. The two participating centres were Coronation Hospital in Johannesburg, South Africa and Srinagarind Hospital in Khon Kaen, Thailand. Women were not eligible for enrolment if they had asthma or other severe chronic allergic conditions representing a contraindication to use of misoprostol, if the delivery was considered an abortion, if caesarean section was already planned, or if they were not willing or able to give informed consent. Women were approached on admission to the labour ward for consent and to check if they were eligible for participation in the trial.

Specially designed dispensers holding 25 treatment packs were placed in a central place close to delivery beds in the labour wards. The treatment packs were sealed and numbered and could only be taken from the dispenser consecutively. Each treatment pack contained three tablets, one ampoule, one syringe and swabs for injection. The packs were identical in shape, colour, weight and feel. Each woman received an injection and three tablets. Thus, the trial was double-blinded using double placebos.

During the second stage of labour, when there was reasonable certainty that vaginal delivery would occur, the researcher took the next treatment pack and immediately wrote the woman's name on the pack and in the participants' list. Randomisation took place when the number was assigned and the woman's name was entered in the participants' list. If for any reason the contents of the pack were not used, the pack was returned to the WHO co-ordinating centre in Geneva.

Each woman received misoprostol 600 μg, misoprostol 400 μg or 10 IU of oxytocin plus the appropriate placebo. The 600 μg group received three tablets each of 200 μg misoprostol and a placebo injection, the 400 μg group received two active and one placebo tablet and placebo injection, and the oxytocin group received three placebo tablets and oxytocin injection. The third stage of labour was managed actively, as currently practised in the two collaborating hospitals. The active management consisted of the use of an uterotonic, clamping and cutting of the umbilical cord immediately after delivery of the infant, and either fundal or suprapubic pressure with cord traction after signs of placental separation.

Assessment of shivering was made by either observation or indirect questioning (i.e. 'Do you have any complaints?'). If shivering was detected, the woman was asked whether she would consider her experience as mild, moderate or severe. Any side-effect necessitating treatment was marked as severe. A special adverse report form had to be completed for women with side-effects which needed any form of treatment, or any other unexpected side-effects.

Blood loss was measured from the time of delivery of the baby until the mother was transferred to postnatal care. The collected blood was poured into a standard measuring jar provided by WHO and blood loss was measured. The linen was not weighed but small gauze swabs soaked with blood were put into the measuring jar and included in the measurement together with the blood and clots.

The sample size was calculated using the incidence of 'any' shivering as the primary outcome. The calculation was based on an interim result from an on-going randomised controlled trial in South Africa showing a shivering rate of 20% with 400 μg misoprostol. It was considered that, to detect a dose-related increase from 20% to 35% with 90% power at $\alpha = 0{\cdot}05$ (two-sided), 200 women in each group would be required. The results are reported on an intention-to-treat basis with comparisons between 600 μg misoprostol, 400 μg misoprostol and oxytocin (10 IU). Relative risk (RR) and 95% confidence intervals (CI) were calculated comparing the two misoprostol groups as well as using the oxytocin group as the reference group.

The trial was approved by the ethics committees of the two participating hospitals and by the Scientific and Ethical Review Group (SERG) of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland.

RESULTS

One hundred and ninety-nine women were randomised to the 600 μg misoprostol group, 198 women to the 400 μg misoprostol group, and 200 women to the oxytocin group. Eight women did not comply with the treatment in the oxytocin group: six because of emergency caesarean

section, one was human immunodeficiency virus (HIV) positive (mistakenly excluded despite HIV sero-positivity not being an exclusion criterion), and in another case the ampoule could not be located in the treatment pack. There was one woman in the misoprostol 600 μg group who did not comply with the treatment, because the tablets could not be located after the treatment pack was opened. Finally, in the misoprostol 400 μg group, one woman had an emergency caesarean section after the treatment pack was opened and could not receive the allocated treatment. The three groups were similar at trial entry and at delivery in all the studied variables except for low birthweight, which was higher in the misoprostol 600 μg group (Table 1).

Shivering was more prevalent in the misoprostol 600 μg group and a clear dose-effect relationship was observed (56/199, 38/198 and 25/200 in the misoprostol 600 μg, misoprostol 400 μg and oxytocin groups, respectively) (Fig. 1). The relative risk of shivering with 600 μg misoprostol was 1·5 (95% CI 1·0 to 2·1) when compared with 400 μg misoprostol, and 2·3 (95% CI 1·5 to 3·5) when compared with the oxytocin group. Comparing misoprostol 400 μg to oxytocin, the relative risk of shivering was 1·54 (95% CI 0·96 to 2·44). Increased shivering in the misoprostol 600 μg group was mostly due to a higher rate of 'moderate' shivering (Fig. 1).

The relative risk of pyrexia (temperature > 38°C) within one hour in the misoprostol 600 μg group was 3·7 (95% CI 1·3 to 10·9) when compared with misoprostol 400 μg, and 2·5 (95% CI 1·0 to 3·6) when compared with oxytocin (15/199, 4/195 and 6/199 in the misoprostol 600 μg, misoprostol 400 μg and oxytocin groups, respectively). When misoprostol 400 μg was compared with oxytocin, the relative risk of pyrexia was 0·68 (95% CI 0·19 to 2·37) (Fig. 2). However, there were only three women (two in misoprostol 600 μg and one in misoprostol 400 μg groups) with a temperature higher than 39°C, and none of the participants had a temperature above 40°C.

Only eight women received epidural anaesthesia, which prevented us from exploring the possible effect of epidural anaesthesia in modifying the rate of shivering associated with misoprostol suggested in earlier observational studies.

Among women receiving any dose of misoprostol, pyrexia was observed in 9·6% (9/94) of those who had shivering, compared with only 3·3% (10/299) of women who did not have shivering (RR 2·86, 95% CI 1·20 to 6·83). In the oxytocin group, none of the 25 women who experienced shivering had pyrexia, and 3·5% (6/173) of women who did not experience shivering had pyrexia.

Gastrointestinal side-effects (nausea, vomiting, diarrhoea) were infrequent in all three groups. There were four cases of diarrhoea (2·0%) and one case of nausea with 600 μg misoprostol, and one case of nausea and vomiting with oxytocin. No side-effects occurred with 400 μg misoprostol. There was no increase in the proportion of completed adverse event forms by groups (three cases in the misoprostol 400 μg group and one case each in the misoprostol 600 μg and oxytocin groups).

The two misoprostol groups and the oxytocin group had approximately similar mean blood loss after delivery (341 mL, standard deviation (SD) = 295 in the misoprostol 600 μg group; 371 mL, SD 327 in the misoprostol 400 μg group; and 353 mL, SD 310 in the oxytocin group). However, it must be emphasised that this pilot study was not designed to evaluate the clinical effectiveness of misoprostol and oxytocin on the occurrence of postpartum haemorrhage.

DISCUSSION

The purpose of this pilot trial was to determine the dose of misoprostol and finalise the preparations for the main trial. The Steering Committee of the trial was confronted with the dilemma of compromising on effectiveness to increase the acceptability of the drug, or aiming for maximum effectiveness despite the possibility of a relatively high incidence of unpleasant effects. A three-arm main trial with the interventions tested in this pilot study was considered but rejected because of

Table 1. Characteristics of women and infants at trial entry and delivery. Values are given as mean (SD) or *n* [%].

Characteristics	Misoprostol 600 μg (*n* = 199)	Misoprostol 400 μg (*n* = 198)	Oxytocin (*n* = 200)
Age	26·3 (5·1)	25·9 (5·5)	26·4 (5·8)
Gestational age	38·1 (2·5)	38·3 (2·2)	38·4 (2·0)
Oxytocin before delivery	66 [33]	65 [33]	79 [40]
Spontaneous vaginal delivery	177 [89]	182 [92]	180 [90]
Randomisation: delivery interval (min)	20·7 (43·5)	22·3 (57·3)	19·9 (35·9)
Perineal suturing	149 [74·9]	147 [74·2]	136 [68·0]
Low birthweight*	23 [11·6]	18 [9·1]	11 [5·5]
Birthweight	2994 (486·2)	3039 (482·5)	3101 (457·7)

*Defined as birthweight < 2500 g.

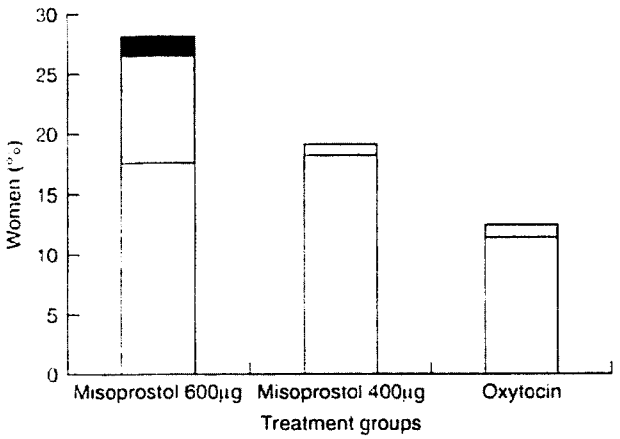

Fig. 1. Rates and grading of shivering in the study groups (56/199, 38/198 and 25/200 in misoprostol 600 μg, misoprostol 400 μg and oxytocin groups, respectively). Relative risk and 95% CI; misoprostol 600 μg *vs* misoprostol 400 μg 1·5, 1·0 to 2·1; misoprostol 600 μg *vs* oxytocin 2·3, 1·5 to 3·5; misoprostol 400 μg *vs* oxytocin 1·54, 1·3 to 10·9. □ = mild; ■ = moderate; ■ = severe.

the logistical complexities and the resulting increase in sample size. This pilot trial was then decided upon, to be conducted only in centres who were prepared to start enrolment without delay.

This pilot study confirms previous suggestions[6,8,9] that both pyrexia and shivering occur when misoprostol is used during the third stage of labour. Pyrexia is a centrally mediated prostaglandin E_1 effect[11]. In clinical studies, the temperature increase following prostaglandin E_1 or misoprostol administration is relatively common[4]. Creinin *et al.*[12] reported fever or chills in 31% of women undergoing first trimester abortion after vaginal misoprostol. Herabutya and O-Prasertsawat[13] reported pyrexia in 28% of women with 600 μg, 2% with 400 μg and none with 200 μg misoprostol, in a trial of second trimester abortion. Pyrexia during labour after misoprostol administration for induction of labour has been reported in a small proportion (< 3%) of women in some studies[14,15] and not reported in others[16,17]. However, the doses used for this purpose are considerably lower, and pyrexia may have been overlooked if not sought specifically.

Shivering after delivery occurs frequently[18] and perhaps misoprostol administration increased the incidence by lowering the threshold for physiological shivering. Nevertheless, the shivering rates with 600 μg in this trial (28%) were lower than the previously reported rates of 62% in an uncontrolled study[6] and 41% in a randomised controlled trial[9]. Half of the study population in this trial were recruited in the same hospital by the same investigators who had reported a shivering rate of 41% previously. Possible explanations for the differences in the rates could be the effect of staff being aware of side-effects of misoprostol, unblinded assessments or insecure blinding leading to assessment bias in the previous studies, differences in strength of active medications (local *versus* US made) or chance.

A change in feto-maternal temperature gradient during labour may, in theory, affect the fetus inadvertently as the maternal tissues are the main route of heat dissipation for the fetus[19,20]. Also, although of limited clinical concern, in some settings if pyrexia is detected during the third stage of labour, it can raise the suspicion of infection and cause unnecessary tests and administration of antibiotics or other medications.

Detection and grading of shivering is to a large extent subjective. Although the detection of pyrexia is more objective, the differences between the previous South African trial[9] and our current pilot trial persisted. In the South African trial the prevalence of pyrexia was 27% with 600 μg misoprostol, 14% with 400 μg misoprostol and 2·5% with placebo, whereas the corresponding percentages in the current WHO trial were 7·5, 2·0 and 3·0%, respectively. As mentioned above with regard to shivering, these differences in rates may be due to bias as well as to the other factors.

Misoprostol is an attractive drug for preventing postpartum haemorrhage because of its low cost, oral applicability and longer shelf-life at room temperature, features which are especially important for developing countries. Although shivering is more of a nuisance than a clinically serious morbidity, it could adversely affect the use and acceptability of misoprostol if the drug is shown to be effective in the prevention of postpartum haemorrhage in the main WHO trial. It is reassuring, however, that despite the higher incidence of observed/reported shivering with 600 μg compared with 400 μg misoprostol, the difference was modest (15%) and

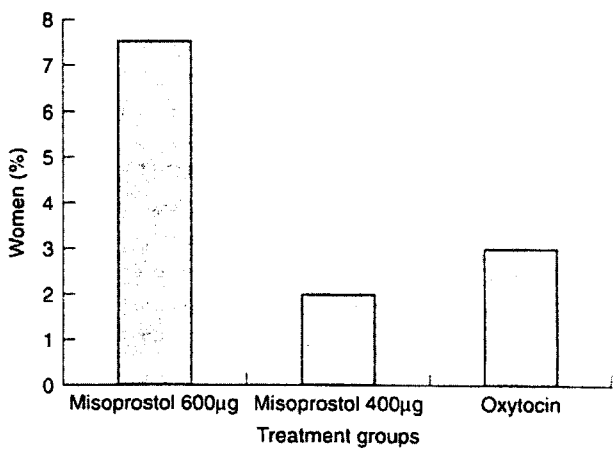

Fig. 2. Rates of pyrexia (temperature > 38°C) in the study groups (15/199, 4/195 and 6/199 in misoprostol 600 μg, misoprostol 400 μg and oxytocin groups, respectively). Relative risk and 95% CI; misoprostol 600 μg *vs* misoprostol 400 μg 3·7, 1·3 to 10·9; misoprostol 600 μg *vs* oxytocin 2·5, 1·0 to 3·6; misoprostol 400 μg *vs* oxytocin 0·68, 0·19 to 2·37.

mostly due to mild shivering, and there was no increase in either shivering or any other side effect necessitating any treatment with the larger dose of misoprostol. Also reassuring was the fact that only two women who received 600 μg misoprostol had a temperature above 39°C and neither was above 40°C.

Based on the findings of this pilot trial, the Trial Steering Committee decided that the main trial should aim to achieve maximum effectiveness with misoprostol and thus compare 600 μg misoprostol with 10 IU of oxytocin. However, as a safety measure, women with pyrexia at enrolment will not be eligible to participate in the trial. The primary outcome of the main trial is the rate of severe postpartum haemorrhage (defined as blood loss > 1000 mLs in the third stage of labour). The main trial is to be conducted in nine countries in Africa, Latin America, Europe and South East Asia and will enrol approximately 20,000 women. Recruitment started on 1 April 1998, and data collection is expected to be completed by July 1999.

Acknowledgements

WHO is grateful to Searle, Novartis Pharma AG and Becton Dickinson International, who donated the active and placebo tablets, ampoules, syringes and swabs included in the treatment packs in this trial. Special thanks are due to Mrs C. Nikodem, Ms P. Chouwajàroen and Ms J. Wachirapakorn who co-ordinated the recruitment in South Africa and in Thailand. WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour Group members: Dr H. Abdel-Aleem (Assiut, Egypt), Dr L. Adetoro (Sagamu, Nigeria), Mrs S. Boccard (Geneva, Switzerland), Dr G. Carroli (Rosario, Argentina), Dr L. Cheng (Shanghai, China), Dr D. Elbourne (Chair of the Trial Steering Committee, London, UK), Dr H. El-Refaey (London, UK), Dr R. Guidotti (Geneva, Switzerland), Dr M. Gülmezoglu (Geneva, Switzerland), Dr J. Hofmeyr (Johannesburg, South Africa), Dr P. Lumbiganon (Khon Kaen, Thailand), Dr N. Thi Ngoc (Hochiminh City, Vietnam), Dr G. Piaggio (Geneva, Switzerland), Mr A. Pinol (Geneva, Switzerland), Dr W. Prendiville (Dublin, Ireland), Dr C. Rodeck (London, UK), Dr K. Schulz (North Carolina, USA), Dr C. Unger (Zurich, Switzerland), Dr J. Villar (Trial Coordinator, Geneva, Switzerland), Dr P. Van Look (Geneva, Switzerland), Dr H. von Hertzen (Geneva, Switzerland).

References

1 Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991; **338**: 1233–1236.

2 Neto CM, Delbin AL, Junior RDV. Padrão tocográfico desencadeado pelo misoprostol [Tocographic pattern induced by misoprostol]. *Rev Paul Med* 1988; **106**: 205–208.

3 Aubény E, Bealieu EE. Activité contragestive de l'association au RU486 d'une prostaglandine active par voie orale. *CR Acad Sci (III)* 1991; **312**: 539–546.

4 El-Refaey H, Templeton A. Early induction of abortion by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception* 1994; **49**: 111–114.

5 Hofmeyr GJ. Misoprostol administered vaginally for cervical ripening and labour induction with a viable fetus. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ, editors. Pregnancy and Childbirth Module of *The Cochrane Database of Systematic Reviews* [updated December 1997]. *The Cochrane Library*. The Cochrane Collaboration; Issue 1. Oxford: Update Software, 1997.

6 El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997; **104**: 336–339.

7 Chong YS, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of the third stage of labour? A preliminary study of its effect on the postpartum uterus [abstract]. The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists Combined Scientific Meeting, Brisbane, 28 April–2 May, 1997; 61.

8 Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynaecol* 1998; **105**: 971–975.

9 Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A, Gelbart B. Oral misoprostol for labour third stage management: randomised assessment of side-effects. 17th Conference on Priorities in Perinatal Care in Southern Africa, Aldam, Free State, 3–6 March 1998.

10 Misoprostol in the management of third stage of labour [protocol]. Trial 97901 protocol. *Lancet* 1998. Available from URL: http://www.thelancet.com/newlancet/sub/author//menu_NOD7.html.

11 Stobie-Hayes KM, Fewell JE. Influence of pregnancy on the febrile response to intracerebroventricular administration of PGE1 in rats. *J Appl Physiol* 1996; **81**: 1312–1315.

12 Creinin MD, Vittinghof E, Schaff E, Klaisle C, Darney PD, Dean C. Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90**: 611–616.

13 Herabutya Y, O-Prasertsawat P. Second trimester abortion using intravaginal misoprostol. *Int J Gynecol Obstet* 1998; **60**: 161–165.

14 Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: an effective agent for cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; **172**: 1811–1816.

15 Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E2 gel for preinduction cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; **172**: 1804–1810.

16 Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. *Obstet Gynecol* 1996; **87**: 923–926.

17 Wing DA, Ortiz-Omphroy G, Paul RH. A comparison of intermittent vaginal administration of misoprostol with continuous dinoprostone for cervical ripening and labor induction. *Am J Obstet Gynecol* 1997; **177**: 612–618.

18 Berry D, Giannino G, Abadejos P, Moise K. Evaluation of postpartum shivering in term pregnancies. *Am J Obstet Gynecol* 1997: **176**: S176.

19 Macaulay JH, Randall NR, Bond K, Steer PJ. Continuous monitoring of fetal temperature by noninvasive probe and its relationship to maternal temperature, fetal heart rate, and cord arterial oxygen and pH. *Obstet Gynecol* 1992; **79**: 469–474.

20 Rudelstorfer R, Simbruner G, Szalay S, Janisch H. Heatflux from the fetus during delivery. *J Perinat Med* 1981; **9**: 311–313.

Received 5 June 1998
Returned for revision 25 September 1998
Accepted 23 November 1998

Articles

WHO multicentre randomised trial of misoprostol in the management of the third stage of labour

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Summary

Background Postpartum haemorrhage is a leading cause of maternal morbidity and mortality. Active management of the third stage of labour, including use of a uterotonic agent, has been shown to reduce blood loss. Misoprostol (a prostaglandin E1 analogue) has been suggested for this purpose because it has strong uterotonic effects, can be given orally, is inexpensive, and does not need refrigeration for storage. We did a multicentre, double-blind, randomised controlled trial to determine whether oral misoprostol is as effective as oxytocin during the third stage of labour.

Methods In hospitals in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam, we randomly assigned women about to deliver vaginally to receive 600 μg misoprostol orally or 10 IU oxytocin intravenously or intramuscularly, according to routine practice, plus corresponding identical placebos. The medications were administered immediately after delivery as part of the active management of the third stage of labour. The primary outcomes were measured postpartum blood loss of 1000 mL or more, and the use of additional uterotonics without an unacceptable level of side-effects. We chose an upper limit of a 35% increase in the risk of blood loss of 1000 mL or more as the margin of clinical equivalence, which was assessed by the confidence interval of the relative risk. Analysis was by intention to treat.

Findings 9264 women were assigned misoprostol and 9266 oxytocin. 37 women in the misoprostol group and 34 in the oxytocin group had emergency caesarean sections and were excluded. 366 (4%) of women on misoprostol had a measured blood loss of 1000 mL or more, compared with 263 (3%) of those on oxytocin (relative risk 1·39 [95% CI 1·19–1·63], p<0·0001). 1398 (15%) women in the misoprostol group and 1002 (11%) in the oxytocin group required additional uterotonics (1·40 [1·29–1·51], p<0·0001). Misoprostol use was also associated with a significantly higher incidence of shivering (3·48 [3·15–3·84]) and raised body temperature (7·17 [5·67–9·07]) in the first hour after delivery.

Interpretation 10 IU oxytocin (intravenous or intramuscular) is preferable to 600 μg oral misoprostol in the active management of the third stage of labour in hospital settings where active management is the norm.

Lancet 2001; **358:** 689–95
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Introduction

Postpartum haemorrhage is a leading cause of severe maternal morbidity and death, in more developed and less developed countries. In Zimbabwe, one study found that obstetric haemorrhage was responsible for 25% of maternal deaths, with a cause-specific maternal mortality rate of 40 per 100 000 livebirths.[1] Similarly, in Nigeria, postpartum haemorrhage was found to have a case-fatality rate of 2·2% at a teaching hospital.[2] The use of uterotonic agents in the management of the third stage of labour reduces the amount of bleeding and the need for blood transfusion, but is associated with side-effects, especially when ergot alkaloids are used.[3] Furthermore, these agents are given by injection, and ergot preparations require refrigeration and protection against light to preserve their effectiveness. Some prostaglandins such as prostaglandin F2α and synthetic prostaglandin E2 derivatives have been found to prevent postpartum haemorrhage in the third stage of labour,[4] but these agents are expensive, and also have to be given by injection and are associated with side-effects.

Misoprostol—a prostaglandin E1 analogue registered for the prevention and treatment of peptic-ulcer disease—has attracted widespread attention because of its strong uterotonic effects and ease of administration. These

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effects have been studied in early pregnancy, orally and vaginally after mifepristone for medical abortion,[5,6] for cervical ripening before surgical termination of pregnancy,[7] and at term for induction of labour.[8] El-Refaey and colleagues reported the first use of oral misoprostol for the management of the third stage of labour in an observational study.[9,10] 600 μg misoprostol were given orally to 237 women after vaginal delivery. Estimated blood loss of 500 mL or more occurred in 6% of women, and a further 5% needed therapeutic uterotonics. Shivering was noted in 62%, and there was a mean increase of 0·5°C in body temperature after misoprostol administration. In a randomised controlled trial from South Africa,[11] shivering was reported in 41% of women receiving 600 μg misoprostol, 37% of those who received 400 μg, and 15% of those who received placebo. We confirmed these side-effects in a dose-finding trial.[12]

We present here the results of a trial to test the hypothesis that misoprostol use in the active management of the third stage of labour is equivalent to that of oxytocin in terms of measured blood loss of 1000 mL or more and the use of additional uterotonics without an unacceptable level of side-effects.

Methods

Participants

We assessed women on admission to labour wards in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam. Women were not eligible if they had asthma or other severe chronic allergic conditions, if the delivery was regarded as an abortion, if caesarean section was already planned, if they had a body temperature of greater than 38°C, or if they were not willing or able to give informed consent. We excluded from the analysis of outcomes the women who had an emergency caesarean section after randomisation because these women were not eligible to receive the interventions and did not have the outcomes measured.

The trial was approved by the ethics committees of the participating hospitals and by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland.

Procedures

The random allocation schedule was generated centrally at WHO, Geneva, Switzerland, by computer-generated random numbers and was stratified by country. Within the strata, women were individually randomised into one of two intervention groups with randomly varying block sizes of 4–6 women.

Specially designed, treatment-pack dispensers holding 25 treatment packs were placed in a central location close to delivery beds in the labour wards. The treatment packs were sealed, numbered sequentially, and could only be taken from the dispenser consecutively. Randomisation took place during the second stage of labour, when there was reasonable certainty that vaginal delivery would occur. The researcher took the next treatment pack from the dispenser and immediately wrote the woman's name on the pack and in the trial participants' list. At this point, the woman was considered to have entered the trial. If, for any reason, the contents of the pack were not used, the pack was returned to the WHO coordination centre in Geneva.

Each treatment pack contained three tablets, one ampoule, one syringe, and needle and swabs for injection. The treatment packs and their contents were identical in shape, colour, weight, and feel. Each woman received an injection and three tablets. The injection was given intramuscularly or intravenously according to the routine practice of the trial centres.

Misoprostol was provided in 200 μg tablets (Searle, Skokie, IL, USA) and oxytocin in 10 IU ampoules (Novartis Pharma, Basel, Switzerland). 18 975 treatment packs were prepared and distributed to the centres; 445 of these were not used by the closure of recruitment. Three random checks were made on the treatment packs to see whether the packing was error-free and all contents included. Additional quality control was done by the manufacturers to check whether we included correct active or placebos in the packs.

Each woman received either misoprostol 600 μg (3×200 μg tablets), or 10 IU oxytocin plus the corresponding placebo immediately after the baby was delivered and the cord was clamped and cut. If the women already had an intravenous line in place (eg, for epidural analgesia or augmentation of labour) or if the hospital's routine practice was to give oxytocin intravenously, the oxytocin (or placebo) was given via this route as a bolus injection. The routine management of the third stage of labour was ascertained before the trial through a survey of all centres. During the trial the third stage of labour was managed actively, as routinely practised in the participating hospitals. The active management consisted of the use of a uterotonic, clamping and cutting of the umbilical cord immediately after delivery of the infant, and either fundal or suprapubic pressure with cord traction after signs of placental separation. All centres followed their standard procedures in cases for which haemorrhage was regarded as abnormal.

The two prespecified primary outcomes were: measured postpartum blood loss of 1000 mL or more and the use of additional uterotonics. Secondary outcomes were: measured blood loss of 500 mL or more, blood transfusion, manual removal of placenta, any clinically diagnosed postpartum haemorrhage beyond the first hour after delivery, and additional measures required to treat clinically diagnosed haemorrhage (examination under general anaesthesia, bimanual compression, hysterectomy, suturing of cervical tears, and maternal admission to intensive-care unit).

Blood loss was measured from the time of delivery of the baby until the mother was transferred to postnatal care. Immediately after the cord was clamped and cut, the blood collection was started by passing a flat bedpan under the buttocks for women delivering in beds or putting in place an unsoiled receiver for women delivering on gynaecological tables. Blood collection continued in the immediate postdelivery period until the third stage of the labour was completed; the woman was then transferred to the postnatal ward. This period usually lasted up to 1 h postpartum. The collected blood was poured into a standard measuring jar provided by WHO, and its volume measured. To simplify the procedure for measurement of blood loss, small gauze swabs soaked with blood were put into the measuring jar and included in the measurement together with the blood and clots. We did a validity study before the trial to assess the effect of gauze swabs on estimation of blood loss and found that it was likely to result in about a 10% increase in the measurements.

Shivering was assessed by direct observation or indirect questioning (ie, "Do you have any complaints?"). If shivering was detected or reported, the woman was asked whether she would regard her

experience as mild, moderate, or severe. Any side-effect necessitating treatment was recorded as severe, and a special form with details of the event was completed. Body temperature was assessed with the standard thermometers routinely used in each centre. High body temperature was defined as an axillary temperature greater than 38°C. Shivering and pyrexia were both assessed within 1 h of delivery.

The trial data safety and monitoring committee met twice, after about 6000 and 12 000 women were recruited. The steering committee was advised to continue with recruitment after both interim analyses.

Statistical analysis

The question guiding the sample-size calculation of this equivalence trial was, "What level of (weaker) efficacy of oral 600 μg misoprostol would be clinically acceptable as equivalent to the standard regimen of 10 IU oxytocin?" The sample-size calculation was based on the occurrence of measured (not estimated) blood loss of 1000 mL of more. An increase in relative risk of up to 35% with misoprostol was regarded as acceptable. 20 246 women were needed to provide 90% power for a two-sided, 5% level test to detect a proportional change of 35% or more if the rate of blood loss of 1000 mL or more was 2% with oxytocin. Similarly, 13 338 women were needed if the rate of blood loss of 1000 mL or more was 3% with oxytocin.

Relative risks with 95% CI were used to measure the treatment effect for the main outcomes. Crude relative risks were calculated first, and these were adjusted for centres by means of the Mantel-Haenszel weighted relative risk and the Greenland and Robbins 95% CI. The Breslow and Day χ^2 test for homogeneity across centres was used. Risk differences and 95% CI were also calculated for the primary outcomes by the "traditional" method with crude proportions.[13] From these risk differences and 95% CI, the number needed to treat (and its 95% CI) with oxytocin to prevent an extra case of blood loss greater than or equal to 1000 mL was calculated.[13]

Effect modification for the primary outcomes was assessed by subgroup analyses specified a priori with the following variables: parity, use of epidural analgesia, and use of oxytocin or prostaglandin before delivery.

Results

Of the 29 295 women screened for eligibility between April, 1998, and November, 1999, 19 025 were eligible. 18 530 of these eligible women were enrolled into the trial. The most common reasons for not being eligible were no consent given or obtained (6203 [60·4%]) and planned caesarean section (5381 [52·4%]). 495 eligible women were not randomised either because the attending health worker refused or because the women delivered too quickly. 9264 women were randomly assigned misoprostol and 9266 oxytocin (figure 1). 2734 women were recruited in Argentina, 2195 in China, 3436 in Egypt, 449 in Ireland, 1570 in Nigeria, 2819 in South Africa, 356 in Switzerland, 1819 in Thailand, and 3152 in Vietnam.

Among randomised women, 37 in the misoprostol group and 34 in the oxytocin group had an emergency caesarean section. These women neither received the interventions nor had the outcomes measured, and were therefore excluded from the analysis of outcomes. A further small group of women had some missing outcome data and could not be included in the corresponding analyses (figure 1).

The two groups were similar with regard to baseline characteristics and risk factors associated with the primary outcomes (table 1). 39 (0·4%) of 9227 women in the misoprostol group and 20 (0·2%) of 9232 women in the oxytocin group did not receive the allocated treatment. These women were included in the analysis in the groups as randomised. In both groups, more than 96% of women were randomised less than 2 h before delivery. 137 (1·5%) women in the misoprostol group and 138 (1·5%) in the oxytocin group were randomised immediately after delivery because of shortage of staff or unexpectedly speedy delivery. All of these women had given consent earlier, but packs were drawn and the women's names were recorded after delivery.

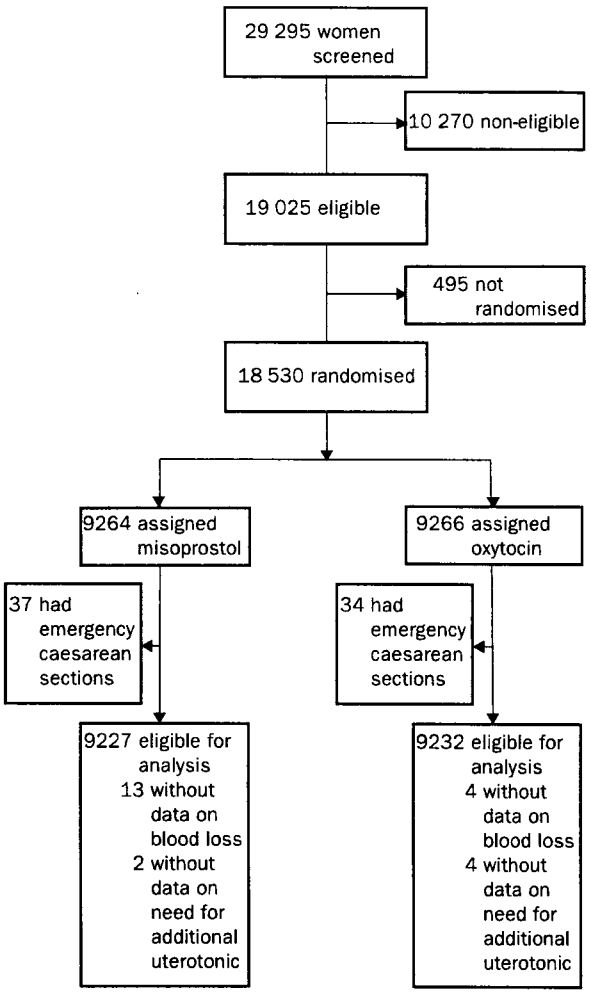

Figure 1: **Trial profile**

	Misoprostol (n=9264)	Oxytocin (n=9266)
Mean (SD) maternal age (years)	26·5 (5·5)*	26·3 (5·4)†
Parity=0	4153 (45%)	4245 (46%)
Parity ≥5	482 (5%)	482 (5%)
Mean (SD) gestational age (weeks)	38·7 (2·3)‡	38·7 (2·2)§
Gestational age <37 weeks	1126 (12%)	1082 (11%)
Low birthweight (<2500 g)	684 (7%)	709 (8%)
Oxytocin or prostaglandin before birth of baby	3517 (38%)	3503 (38%)
Epidural analgesia	572 (6%)	557 (6%)
Assisted vaginal delivery	843 (9%)	764 (8%)
Perineal suturing	6152 (66%)	6129 (66%)

*Data available for 9248 women only. †Data available for 9238 women only. ‡Data available for 9261 women only. §Data available for 9262 women only.

Table 1: **Baseline characteristics**

	Misoprostol	Oxytocin	Relative risk (95% CI)	p
Primary outcomes				
Blood loss ≥1000 mL*	366/9214 (4%)	263/9228 (3%)	1·39 (1·19–1·63)	<0·0001
Use of additional uterotonics*	1398/9225 (15%)	1002/9228 (11%)	1·40 (1·29–1·51)	<0·0001
Secondary outcomes				
Blood loss ≥500 mL	1793/9213 (20%)	1248/9227 (14%)	1·44 (1·35–1·54)	<0·0001
Need for blood transfusion	72/9221 (0·8%)	97/9226 (1%)	0·74 (0·55–1·01)	0·06
Manual removal of placenta	219/9225 (2%)	215/9228 (2%)	1·02 (0·85–1·23)	0·88
Delayed postpartum haemorrhage	37/9226 (0·4%)	31/9229 (0·3%)	1·19 (0·74–1·92)	0·54
Bimanual compression	84/9224 (0·9%)	80/9231 (0·9%)	1·05 (0·77–1·43)	0·81
Exploration under general anaesthesia	70/9224 (0·8%)	61/9231 (0·7%)	1·15 (0·82–1·62)	0·48
Hysterectomy	4/9224 (0·04%)	8/9231 (0·09%)	0·50 (0·15–1·66)	0·39
Admission to intensive care	4/9224 (0·04%)	5/9231 (0·05%)	0·80 (0·22–2·98)	1·00†
Maternal death	2/9225 (0·02%)	2/9230 (0·02%)	1·00 (0·14–7·10)	1·00†

*Excluding 37 and 34 women with emergency caesarean section and 13 and 4 women lost to follow-up in misoprostol and oxytocin groups, respectively, for blood loss ≥1000 mL, and two and four women without information on the need for additional uterotonics. †Fisher's exact test used.

Table 2: **Primary and secondary outcomes according to treatment group**

Centre	Misoprostol	Oxytocin
Argentina	96/1358 (7%)	49/1361 (4%)
China	18/1093 (2%)	10/1098 (0·9%)
Egypt	3/1708 (0·2%)	6/1703 (0·4%)
Ireland	15/221 (7%)	9/225 (4%)
Nigeria	36/785 (5%)	40/783 (5%)
South Africa	56/1405 (4%)	51/1409 (4%)
Switzerland	17/173 (10%)	16/177 (9%)
Thailand	57/900 (6%)	24/899 (3%)
Vietnam	67/1570 (4%)	57/1572 (4%)

Table 3: **Rate of blood loss of 1000 mL or more by centre**

A higher proportion of women in the misoprostol group than the oxytocin group had measured blood loss of at least 1000 mL and use of additional uterotonics (table 2). The additional uterotonic was oxytocin in most cases in the misoprostol group (77%) and in the oxytocin (80%) group. The crude overall difference in the rate of blood loss of 1000 mL or more between misoprostol and oxytocin was 1·1% (95% CI 0·6–1·6), which ranged from −0·2 to 3·7% between centres. After adjusting for centre characteristics, we obtained the same relative risks and almost identical 95% CIs (1·20–1·63 and 1·30–1·51 for blood loss and additional uterotonics, respectively). The number of women who needed to receive oxytocin rather than misoprostol to prevent one extra case of blood loss of at least 1000 mL was 89 (61–167), and the number who needed to receive oxytocin rather than misoprostol to prevent one extra case of the use of additional uterotonics was 23 (19–30).

There was statistical heterogeneity between centres for measured blood loss of 1000 mL or more (p=0·02) and for the use of additional uterotonics (p<0·0001). The relative risk of having measured blood loss of 1000 mL for a woman receiving misoprostol ranged from 0·50 to 2·37 across centres (table 3). We did not collect individual data on route of administration of oxytocin, but used the presence of an intravenous line as a proxy for intravenous oxytocin administration. Regarding this variable as a possible effect modifier did not influence the pattern of the results.

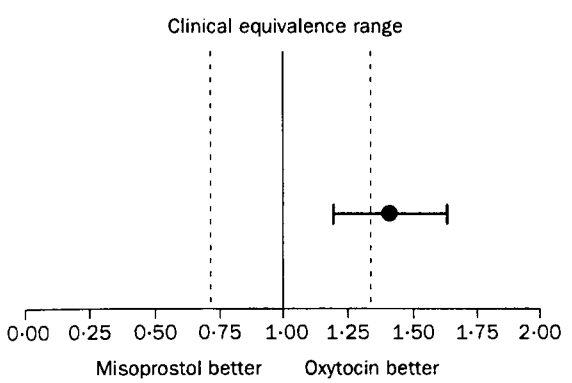

Figure 2: **Relative risk of blood loss of 1000 mL or more with misoprostol compared with oxytocin**
Vertical dotted lines represent margins of clinical equivalence determined a priori. Solid line represents null effect.

Figure 2 is a graphical presentation of the CI for the relative risk of having a measured blood loss of 1000 mL or more with misoprostol. The dotted vertical lines represent the margins of clinical equivalence[14] between misoprostol and oxytocin expressed as a 35% increase in the rate of blood loss of 1000 mL or more as defined before the start of the trial. The whole 95% CI for the relative risk was not fully inside the range defined by the two dotted lines and crossed the upper equivalence margin. The two drugs were therefore not shown to be clinically equivalent, although this possibility cannot be completely discarded.

The misoprostol group also had a consistently higher risk than the oxytocin group of blood loss of 500 mL or more in all centres (range of relative risks 1·0–2·6). There were no significant differences between misoprostol and oxytocin with regard to other secondary outcomes such as delayed postpartum haemorrhage or manual removal of the placenta, and consequences of severe bleeding such as exploration under general anaesthesia, bimanual compression, hysterectomy, or admission to intensive care (table 2). However, we had insufficient power to detect clinically relevant differences in effects on such rarer outcomes. Fewer women in the misoprostol group needed postpartum blood transfusion (table 2).

Misoprostol was associated with a significantly higher rate of any and severe shivering, body temperature higher than 38°C, and other prostaglandin-related side-effects such as nausea, vomiting, and diarrhoea (table 4). Few women had a body temperature of greater than 40°C during the first hour post partum. For every seven to nine women treated with misoprostol, one additional woman will have "any shivering", and for every 17–21 women, one additional woman will have a temperature greater than 38°C (table 4).

We did prespecified, stratified analyses for primary outcomes and main side-effects by oxytocin or prostaglandin use before delivery and by parity. There was no evidence of effect modification of these variables on the primary outcomes or main side-effects. In three centres (in Argentina, Ireland, and Switzerland), epidural analgesia was frequently used, so we did a

Side-effects	Misoprostol	Oxytocin	Relative risk (95% CI)	NNH (95% CI)
Any shivering	1620/9227 (18%)	466/9232 (5%)	3·48 (3·15–3·84)	8 (7–9)
Severe shivering	120/9227 (1%)	14/9232 (0·2%)	8·58 (4·93–14·91)	87 (72–111)
Body temperature >38°C	559/9198 (6%)	78/9205 (0·8%)	7·17 (5·67–9·07)	19 (17–21)
Body temperature >40°C	5/9198 (0·1%)	0/9205	Infinity	..
Nausea	77/9227 (0·8%)	34/9232 (0·4%)	2·27 (1·52–3·39)	214 (145–411)
Vomiting	66/9227 (0·7%)	25/9232 (0·3%)	2·64 (1·67–4·18)	225 (155–412)
Diarrhoea	35/9227 (0·4%)	8/9232 (0·1%)	4·38 (2·03–9·43)	342 (232–651)

NNH=number needed to harm.

Table 4: **Shivering, body temperature greater than 38°C, and other side-effects according to treatment group**

	Epidural	No epidural	Relative risk (95% CI; epidural effect)
Any shivering			
Misoprostol	195/522 (37%)	254/1244 (20%)	1·83 (1·57–2·14)
Oxytocin	46/505 (9%)	93/1263 (7·4%)	1·24 (0·88–1·73)
Relative risk (95% CI; utero-tonic effect)*	4·10 (3·05–5·52)	2·77 (2·22–3·47)	..
Temperature >38°C			
Misoprostol	75/518 (14%)	61/1221 (5%)	2·90 (2·10–4·00)
Oxytocin	6/499 (1%)	6/1244 (0·5%)	2·49 (0·81–7·69)
Relative risk (95% CI; utero-tonic effect)†	12·04 (5·29–27·41)	10·36 (4·49–23·87)	..

*Difference in relative risks p=0·04. †Difference in relative risks p=0·80.

Table 5: **Shivering and body temperature above 38°C according to treatment group and use of epidural analgesia during labour and delivery**

stratified analysis in this subgroup for the two main side-effects of misoprostol: shivering and raised body temperature. The low prevalence of diarrhoea, nausea, and vomiting did not allow a meaningful assessment of interaction for these side-effects. The relative risk of shivering with misoprostol compared with oxytocin was higher among women with epidural analgesia than among women without epidural analgesia (p=0·04, table 5), but there was no difference in relative risk for high body temperature in women with and without epidural analgesia (p=0·80).

Discussion

We have shown that oral misoprostol (600 μg) is associated with a higher rate of measured blood loss of 1000 mL or more and the use of additional uterotonics than oxytocin 10 IU. We are 95% confident that the increased risk of blood loss with misoprostol is between 20 and 60%. This result corresponds to an absolute risk of 2·9% in the oxytocin group and 4·0% in the misoprostol group (difference 1·1% [95% CI 0·6–1·6]). Similarly, we are 95% confident that the risk of using additional uterotonics with misoprostol is between 30 and 50% higher than with oxytocin. This corresponds to an absolute risk of 10·9% in the oxytocin group and 15·2% in the misoprostol group (difference 4·3% [3·3–5·3]).

The trial had sufficient statistical power to test the a priori hypothesis for the two primary outcomes, but it did not have sufficient power for other clinically relevant outcomes such as maternal mortality. There were four maternal deaths: two in each group. Similarly, few women had severe morbidity such as exploration under anaesthesia, bimanual compression, hysterectomy, and intensive-care admission.

Blood loss was measured in a standardised way in all centres rather than by clinical estimation, as used in many previous trials of the third stage of labour. Measurement of blood loss enabled a more objective and accurate assessment than clinical estimation, since this procedure underestimates blood loss, particularly when the blood loss is more than 1000 mL.[15] All outcomes were measured in the first hour after delivery because of the organisation of postpartum care in the participating hospitals. The measurement of some secondary outcomes and side-effects might have been influenced by this factor—eg, the temperature rise and return to normal might extend beyond this period, whereas shivering is most likely to occur within the first hour (based on substudies in some centres).

Double-blinding, including double placebos, ensured that ascertainment bias in the measurement of blood loss and use of additional uterotonics was unlikely. However, unblinding could have occurred because of the higher rate of shivering associated with misoprostol. A sensitivity analysis in which women with shivering were excluded showed a similar level of comparative effectiveness for oxytocin to that in the total population (relative risk 1·32 [1·11–1·56]). Exclusion of women with diarrhoea did not change the treatment effect either.

We used the highest dose of misoprostol (600 μg) regarded as effective without an unacceptable level of side-effects.[12] Considering the observed rate of side-effects in the present trial, higher doses should probably not be tested for the prevention of postpartum haemorrhage. Oral administration of misoprostol, despite having a rapid onset of action, does not have the continuous and long-lasting effect of vaginal administration early in pregnancy. Concentrations of orally administered misoprostol in plasma peak at 30 min when used in first trimester pregnancies,[16] which might explain the lower effectiveness. With regard to the route of oxytocin administration, pharmacokinetic studies indicate that the absorption times of intramuscular and intravenous oxytocin are both 1–2 min, and their effectiveness is likely to be similar.[17]

The trial was done in an ethnically heterogeneous population, which provides external validity to the results. However, all hospitals practised active management of the third stage of labour, restricting our recommendations to settings with this routine practice. The effectiveness might be different if the two drugs were compared without other components of active management—eg, Nordstroem and colleagues[18] found that oxytocin reduced the blood loss by 22% compared with placebo when the third stage of labour was managed expectantly.

To explain the statistical heterogeneity of effect with blood loss of 1000 mL or more, we did multivariate and sensitivity analyses, but could not explain the heterogeneity. One should be very cautious in using results from individual centres, because the probability of at least one centre showing an effect reversal in a multicentre trial with nine centres like ours can be around 80%.[19] Blood loss of 500 mL or more, on the other hand, was consistently higher in the misoprostol group in all centres.

We explored the combined effect of misoprostol and epidural analgesia for shivering and body temperature greater than 38°C, and found an interaction between misoprostol and epidural analgesia on any shivering (37·4% of women who receive both will shiver; table 5). There was also an epidural-independent increase in temperature to more than 38°C with the use of misoprostol in the third stage of labour, and an independent increased risk of raised body temperature among women with epidural analgesia, in agreement with previous epidemiological studies.[20]

We identified six other trials that compared oral misoprostol with other uterotonics (oxytocin, ergometrine, or both), and one trial that compared rectal misoprostol with other uterotonics.[4] Three used 600 μg misoprostol orally (2657 women in total),[12,21,22] one used 500 μg (1000 women),[23] and three used 400 μg (1662 women).[12,24,25] One trial[12] compared 600 or 400 μg misoprostol with oxytocin. The summary relative risks of blood loss of at least 1000 mL were 0·83 (0·42–1·65), 0·90 (0·37–2·19), and 1·38 (0·78–2·42) for the 600 μg, 500 μg, and 400 μg comparisons, respectively. None of these meta-analyses had the power to test the equivalence hypothesis between the two drugs. These promising findings of the meta-analyses were not corroborated by the largest trial reported here. This apparent difference highlights the importance of doing trials of adequate sample size, since meta-analyses of small trials can often disagree with the largest trial.[26]

We did not address the introduction of misoprostol to a level of care at which there is no active management, or the use of oxytocin during the third stage of labour where it is not feasible. In other words, we did not investigate whether misoprostol is better than placebo. We identified four randomised controlled trials that compared oral misoprostol with placebo and one that compared rectal misoprostol with placebo in a systematic review.[4] There is no clear evidence from these trials, which included 1900 women in total, to indicate that misoprostol reduces the risk of blood loss of 1000 mL or more when compared with placebo.[11,27–30]

In settings in which active management of the third stage of labour with oxytocin is the norm, we do not recommend a change in practice. Oxytocin is cheap, effective, and has been shown to retain its efficacy after 12 months at 30°C even if it is exposed to light and when stored at 42°C for one year.[31,32] In health facilities considering the introduction of active management of the third stage of labour, 10 IU oxytocin should be considered as the uterotonic of choice over oral misoprostol 600 μg, perhaps through prefilled syringes for increased safety of injections.

Because of the large evidence gap for the treatment of postpartum haemorrhage, as opposed to prevention addressed in this paper, further research into treatment strategies is needed. For example, the pharmacokinetics of misoprostol might be more suitable for its use at higher doses, possibly with different routes, in the treatment of postpartum haemorrhage. Research on resolving the effective components of active management and auditing any introduction of active management in community settings is also required.

Contributors

José Villar, José Miguel Belizan, Sune Bergstroem, Olav Meirik, and Paul Van Look identified the research hypothesis and designed the study. Hazem El-Refaey and Charles Rodeck stimulated the WHO to select misoprostol as the prostaglandin to be tested for the prevention of postpartum haemorrhage. A Metin Gülmezoglu and José Villar prepared the protocol, selected the populations, and coordinated the implementation of the trial. Guillermo Carroli, Justus Hofmeyr, Gilda Piaggio, Alain Pinol, Diana Elbourne, Hazem El-Refaey, Walter Prendiville, Ken Schulz, and Paul Van Look made comments and contributed to the final trial protocol. Guillermo Carroli, Linan Cheng, Hany Abdel-Aleem, Walter Prendiville, Lekan Adetoro, Justus Hofmeyr, Christian Unger, Pisake Lumbiganon, and Nguyen Thi Nhu Ngoc implemented the trial in their respective countries and actively contributed to the overall execution of the trial. Diana Elbourne chaired the steering committee. Gilda Piaggio and Alain Pinol did the data analyses with input from José Villar, A Metin Gülmezoglu, Guillermo Carroli, and other members of the steering committee. A Metin Gülmezoglu, José Villar, Gilda Piaggio, and Guillermo Carroli wrote the paper. All the steering committee members read the report and made substantive suggestions on its content.

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Acknowledgments

We thank the women who participated in the trial and the many doctors, nurses, and midwives in the participating hospitals for making the project possible. We also thank Charles Rodeck, Albert Huch, and Renate Huch for their advice and support, and Olav Meirik, Sune Bergstroem, and Paul Van Look for their contributions to the initial hypothesis.

The trial was supported by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction of WHO. Searle (Skokie, IL, USA) and Novartis (Basel, Switzerland) donated the active and placebo medications used in the trial.

References

1 Fawcus S, Mbizvo M, Lindmark G, Nystrom L. A community-based investigation of maternal mortality from obstetric haemorrhage in rural Zimbabwe. *Trop Doct* 1997; **27**: 159–63.
2 Etuk SJ, Asuquo EE. Maternal mortality following post-partum haemorrhage in Calabar: a 6-year review. *West Afr J Med* 1997; **16**: 165–69.
3 Prendiville WJ, Elbourne D, McDonald S. Active versus expectant

management in the third stage of labour. In: Cochrane Library, issue 1. Oxford: Update Software, 2000.
4 Gülmezoglu AM, Forna F. Prostaglandins for prevention of postpartum haemorrhage. In: Cochrane Library, issue 3. Oxford: Update Software, 2001.
5 Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991; **338:** 1233–36.
6 El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995; **332:** 983–87.
7 Singh K, Fong YF, Prasad RN, Dong F. Vaginal misoprostol for pre-abortion cervical priming: is there an optimal evacuation time interval? *Br J Obstet Gynaecol* 1999; **106:** 266–69.
8 Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy. In: Cochrane Library, issue 1. Oxford: Update Software, 2000.
9 El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. *Lancet* 1996; **347:** 1257.
10 El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997; **104:** 336–39.
11 Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A. Side-effects of oral misoprostol in the third stage of labour: a randomised placebo controlled trial. *S Afr Med J* 2001; **91:** 432–35.
12 Lumbiganon P, Hofmeyr J, Gülmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour: WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour. *Br J Obstet Gynaecol* 1999; **106:** 304–08.
13 Altman DG, Machin D, Bryant TN, Gardner MJ. Statistics with confidence, second edn. London: BMJ Publishing, 2000.
14 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996; **313:** 3–4.
15 Andolina K, Daly S, Roberts N, Tolosa J, Wapner R. Objective measurement of blood loss at delivery: is it more than a guess? *Am J Obstet Gynecol* 1999; **180:** S69.
16 Danielson KG, Marions L, Rodriguez A, Spur BW, Wong P, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. *Obstet Gynecol* 1999; **93:** 275–80.
17 Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following intravenous and intramuscular administration of syntometrine. *J Obstet Gynaecol Br Commonwealth* 1972; **79:** 644–46.
18 Nordstroem L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. *Br J Obstet Gynaecol* 1997; **104:** 781–86.
19 Senn S. Statistical issues in drug development. Chichester: John Wiley and Sons, 1999: 187–206.
20 Lieberman E, Cohen A, Lang J, Frigoletto F, Goetzl L. Maternal intrapartum temperature elevation as a risk factor for cesarean delivery. *Am J Public Health* 1999; **89:** 506–10.
21 Ng PS, Chan ASM, Sin WK, Tang LCH, Cheung KB, Yuen PM. A multicentre randomized controlled trial of oral misoprostol and IM syntometrine in the management of the third stage of labour. *Hum Reprod* 2001; **16:** 31–35.
22 Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. *Br J Obstet Gynaecol* 1999; **106:** 1066–70.
23 El-Refaey H, Nooh R, O'Brien P, et al. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. *Br J Obstet Gynaecol* 2000; **107:** 1104–10.
24 Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled trial of misoprostol and oxytocin in the management of the third stage of labour. *Br J Obstet Gynaecol* 2000; **107:** 1111–15.
25 Cook C, Spurret B, Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. *Aust NZ J Obstet Gynaecol* 1999; **39:** 414–19.
26 Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. *Lancet* 1995; **345:** 772–76.
27 Hofmeyr GJ, Nikodem C, de Jager M, Drakely A, Gilbart B. Oral misoprostol for labour third stage management: randomised assessment of side effects (part 2). Proceedings of the 17th Conference on Priorities in Perinatal Care, South Africa, 1998: 53–54.
28 Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynaecol* 1998; **105:** 971–75.
29 Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. *Am J Obstet Gynecol* 1998; **179:** 1043–46.
30 Surbek DV, Fehr P, Hoesli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. *Obstet Gynecol* 1999; **94:** 255–58.
31 Hogerzeil HU, Walker GJA, de Goey M. Stability of injectable oxytocin in tropical climates. WHO/DAP/93.6. Geneva: WHO, 1993.
32 Chua S, Arulkumaran S, Adaikon G, Ratnam S. The effect of oxytocics stored at high temperatures on postpartum uterine activity. *Br J Obstet Gynaecol* 1993; **100:** 874–75.

23.

Effects of misoprostol on profuse blood loss after birth: an exploratory study of data from the WHO Randomised Trial of Misoprostol in the Third Stage of Labour

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Introduction

Misoprostol is an effective agent for the induction of abortion[1] and of labour,[2] though not without problems and risks.[3]

Earlier reports have suggested that oral misoprostol is as effective as standard uterotonic drugs in the prevention of postpartum haemorrhage[4,5.] We conducted the WHO Multicentre Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour to compare oral misoprostol 600 μg versus parenteral oxytocin 10 units for the routine management of the third stage of labour in terms of blood loss = 1000 ml after birth and the use of additional uterotonics.[6] Misoprostol was significantly less effective than oxytocin in these respects. Surprisingly, fewer women in the misoprostol group received blood transfusion (72/9221 vs 97/9226, RR: 0.74, 95% CI 0.55 to 1.01). Blood transfusion was one of several secondary outcomes, and the apparent beneficial effect of misoprostol could be the result of chance. To determine whether the lower rate of blood transfusion with misoprostol was consistent with blood loss patterns, we conducted an exploratory analysis using the rates of greater volumes of blood loss in the two groups as outcomes.

Methods

Details of the main trial are published elsewhere.[7] Briefly, the trial was conducted at hospitals in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland,

Thailand and Viet Nam. Women were approached on admission to labour ward for consent and to check if they were eligible for participation in the trial.

Randomization took place during the second stage of labour, when the researcher took the next in a series of consecutively numbered treatment packs. Each woman received oral misoprostol 600 μg or 10 IU of oxytocin intramuscularly or intravenously, plus the appropriate placebo. The third stage of labour was managed actively. Blood loss was measured from the time of delivery of the baby until the mother was transferred to postnatal care following standardised procedures. The blood was collected directly into a flat, plastic 'fracture bedpan' or other receiver slipped under the mother's buttocks after delivery, or a bowl attached to the delivery bed, and poured into a standard measuring jar and measured. Additional uterotonics were used at the discretion of the attending clinicians.

The protocol for the present exploratory analysis was written prior to this analysis being performed. The two randomised groups were compared for blood loss intervals of 250ml between 1000 and 2000ml, and greater than 2000ml. Comparisons were by means of relative risks and 95% confidence intervals.

The trial was approved by the ethics committees of the participating hospitals and by the Scientific and Ethical Review Group (SERG) of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland.

Results

There were 9264 women in the misoprostol and 9266 women in the oxytocin group. The groups were similar at trial entry and at delivery in all of the studied baseline variables variables[7].

The risk of haemorrhage for the intervals above 1750ml was somewhat lower in the misoprostol group, but the numbers of these outcomes were small, and the differences not statistically significant (Table).

Discussion

The somewhat lower risk of haemorrhage in the misoprostol group in catgories above 1750ml, while not statistically significant in itself, is consistent with the possibility that the lower use of blood transfusion in the misoprostol group was in fact related to lower rates of massive blood loss.

There are several possible explanations for the lower use of blood transfusion in the misoprostol group. Firstly, it could be due to chance. Secondly, there could be a synergistic pharmacological effect between misoprostol and conventional uterotonics, which were given to most women with increased blood loss. Many women in the misoprostol group thus received misoprostol as well as conventional uterotonics, whereas those in the oxytocin group received only conventional oxytocics. Another possible explanation may be related to the phamacokinetics of misoprostol. Misoprostol acid, the active metabolite of misoprostol, reaches its peak plasma levels 20-30 minutes after oral administration during pregnancy[8], whereas oxytocin has a more rapid effect.[9] The mean duration of the third stage of labour in this trial was 8.3 minutes (SD 14.6) in both groups. In many women, considerable bleeding may have occurred before misoprostol reached therapeutic blood levels. However, for the minority of women who continue to bleed after 20-30 minutes, misoprostol may have reduced further blood loss.

Our primary results indicate that misoprostol as a first-line uterotonic agent is less effective than oxytocin at preventing blood loss = 500 and 1000 ml and has more side effects[6], and therefore misoprostol should not replace oxytocin 10 units as the first line preventive measure. The data presented here raise the possibility that misoprostol may have a place in the secondary management of postpartum haemorrhage unresponsive to conventional uterotonics alone. This hypothesis remains to be established by appropriately designed trials.

References

1 El-Refaey H, Templeton A. Early induction of abortion by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception,* 1994;**49**:111-114.

2 Hofmeyr GJ, Gülmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review.*Br J Obstet Gynaecol.* 1999;**106**:798-803.

3 Hofmeyr GJ. Misoprostol in obstetrics and gynaecology – unregistered, dangerous and essential. *S Afr Med J* 1998; **88**: 535-536

4 El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. *Br J Obstet Gynaecol,* 2000;**107**:1104-1110.

5 Walley RL, Wilson JB, Crane JMG, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. *Br J Obstet Gynaecol* 2000; **107**: 111-115.

6 Lumbiganon P, Hofmeyr GJ, Gülmezoglu AM, Pinol A, Villar J. Misoprostol dose related shivering and pyrexia in the third stage of labour. *Br J Obstet Gynaecol*, 1999;**106**:304-308.

7 Gülmezoglu AM, Villar J, Ngoc NN, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr GJ, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, El-Refaey H, Schulz KF, for the WHO Collaborative Group to Evaluate Misoprostol in the Third Stage of Labour. The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the third stage of labour. Lancet 2001, in press.

8 Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol*, 1997; **90**: 88-92.

9 Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following intravenous and intramuscular administration of syntometrine. *J Obstet Gynaecol Br Commonwealth*, 1972;**79**:644-646.

Acknowledgements

This trial was supported by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction of WHO.

WHO is grateful to Searle (Searle, Skokie, IL, U.S.A.), Novartis Pharma AG (Novartis Pharma AG) and Becton Dickinson International who donated the active and placebo tablets, ampoules, syringes and swabs included in the treatment packs in this trial.

We would like to thank specially the women who participated in the trial and the many doctors, nurses and midwives in the participating hospitals for making the implementation of the project possible.

Table. Comparison of misoprostol versus oxtocin for postpartum blood loss categories >1000ml, expressed as relative risks (RR) and 95% confidence intervals (CI).

Blood loss in intervals						
Blood loss category (ml)	Misoprostol N = 9214		Oxytocin N = 9228		RR	95% CI
1000-1250	226	2.5%	151	1.6%	1.50	1.22-1.84
1250-1500	61	0.66%	45	0.49%	1.36	0.92-1.99
1500-1750	57	0.62%	37	0.40%	1.54	1.02-2.33
1750-2000	10	0.11%	14	0.15%	0.72	0.32-1.61
>2000ml	12	0.13%	16	0.17%	0.75	0.36-1.59

1 El-Refaey H, Templeton A. Early induction of abortion by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception,* 1994;**49**:111-114.

2 Hofmeyr GJ, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review.Br J Obstet Gynaecol. 1999;106:798-803.

3 Hofmeyr GJ. Misoprostol in obstetrics and gynaecology – unregistered, dangerous and essential. S Afr Med J 1998; 88: 535-536

4 El-Refaey H, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. *Br J Obstet Gynaecol,* 2000;**107**:1104-1110.

5 Walley RL, Wilson JB, Crane JMG, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. Br J Obstet Gynaecol 2000; 107: 111-115.

6 Lumbiganon P, Hofmeyr GJ, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose related shivering and pyrexia in the third stage of labour. Br J Obstet Gynaecol, 1999;106:304-308.

7 Gulmezoglu AM, Villar J, Ngoc NN, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr GJ, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, El-Refaey H, Schulz KF, for the WHO Collaborative Group to Evaluate Misoprostol in the Third Stage of Labour. The WHO multicentre double-blind randomized controlled trial to evaluate the use of misoprostol in the third stage of labour. Lancet 2001, in press.

8 Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol, 1997; 90: 88-92.

9 Abdel-Aleem H

10 Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following intravenous and intramuscular administration of syntometrine. J Obstet Gynaecol Br Commonwealth, 1972;79:644-646.