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CLINICAL ARTICLE

Mifepristone and misoprostol in the induction of labor at term

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Abstract

Objective: To assess the ability of mifepristone to prime the cervix adequately and induce labor in pregnant women at term; and when mifepristone alone proves insufficient, to determine whether oral misoprostol taken 48 h following mifepristone administration is effective in inducing labor. *Methods:* In this prospective study 50 pregnant women at term with an unfavorable cervix were given 400 mg of mifepristone orally and allowed to return home. If labor did not start within 48 h, the women were admitted and induction was continued with 50 μg of misoprostol, a prostaglandin (PG) E1 analogue, taken orally every 4 h. The 50 controls, who were matched prospectively for parity and pregnancy duration, underwent labor induction according to the routine administration of 3-mg tablets of PGE2 vaginally. *Results:* In the study group, 66% of the women entered labor spontaneously or had a sufficiently ripened cervix within 48 h of taking mifepristone. However, there was no difference in time between prostaglandin administration and delivery between the control group and the 34% of women who required misoprostol in the study group. In the study group, the cesarean section rate was significantly lower among the women whose labor was induced with mifepristone alone than among those who required misoprostol. There were no differences overall in obstetric or neonatal outcomes between the study and control groups. *Conclusions:* In this pilot sample, 400 mg of mifepristone was effective in inducing cervical changes and labor. Although there were no adverse effects using oral misoprostol in combination with mifepristone, labor was more difficult to induce in the women who did not respond to mifepristone alone, and these women had a higher operative delivery rate.

1. Introduction

The sequential use of mifepristone, an antiprogesterone agent that has been shown to mature and dilate the cervix in

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pregnant women, and a prostaglandin has been extensively researched for termination of pregnancy in all trimesters, for cervical preparation prior to surgical termination of pregnancy, and for induction of labor in late pregnancy in cases of intrauterine death [1–5].

The role of mifepristone in inducing labor when the fetus is viable is being evaluated [6–10]. Mifepristone in doses of 200 to 400 mg has been shown to improve cervical ripening and rates of "spontaneous" labor, with no apparent maternal or neonatal adverse effects. In these studies, if ripening with a prostaglandin was required after cervix priming with mifepristone, either misoprostol, a prostaglandin (PG) E1 analogue, or PGE2 was administered vaginally.

The antiglucocorticoid properties of mifepristone have not been found to be of clinical significance in adult women, even at the dose of 2 g per day [11], and no cases of significant neonatal hypoglycemia have been reported so far.

The aims of this study were to explore cervical ripening in outpatients, and to determine whether (1) mifepristone alone initiated labor in a significant number of women while enabling them to remain at home until labor began, and (2) oral misoprostol was effective when labor was not initiated by mifepristone alone.

2. Patients and methods

This study was conducted at Aberdeen Maternity Hospital after approval from the local ethics committee. Exemption certificates for the use of mifepristone and misoprostol in combination for an unlicensed indication were obtained from the Medicines Control Agency of the Department of Health.

Women with an ultrasonographically confirmed singleton pregnancy of 37 to 42 weeks' duration, cephalic presentation, and no contraindications for a vaginal delivery were approached to participate in the study if (1) labor induction was indicated; (2) induction could be postponed for 48 h; and (3) the cervical Bishop score was 7 or less prior to induction. Parity greater than 5, previous cesarean delivery, known hypersensitivity to prostaglandins or mifepristone, or impaired renal, adrenal, or hepatic function were exclusion criteria, as well as any concerns about the well-being of the fetus.

Women attending the antenatal clinics who met the inclusion criteria were given written and verbal information about the study by the principal investigator, who was present at the clinics each week on 3 fixed days. Those who expressed a desire to participate in the study were seen on the induction unit on a scheduled date to determine their cervical score and to perform a cardiotocographic assessment of fetal well-being. A total of 50 consecutive women who met all conditions and gave informed consent received two 200-mg tablets of oral mifepristone (Exelgyn Laboratories, Paris, France).

After administration of mifepristone, the women were allowed home and asked to return for a check after 24 h, but to contact the labor ward if labor started or if they had any concerns. After the check, they were allowed home again if there were no fetal concerns on CTG and the Bishop score remained less than 8, and asked to report back to the labor ward if labor did start.

If labor had not started within 48 h of mifepristone administration, the women were admitted to the induction unit. If the Bishop score was 8 or greater, they were transferred to the labor ward where artificial rupture of membranes (ARM) was performed and an oxytocin drip started, if required. If the cervical score was less than 8, 50 μg of misoprostol (half of a 100-μg tablet) was administered orally (Cytotec; Searle Pharmaceuticals, Ontario, Canada) every 4 h to a maximum of 5 doses. A vaginal examination and CTG were performed prior to administering each dose. If at any of these examinations the Bishop score was 8 or greater, the participant was transferred to the labor ward for ARM and possible oxytocin infusion. If after 4 doses of misoprostol the Bishop score had not changed, the induction attempt was categorized as failed.

The inclusion and exclusion criteria were the same for the control group as for the study group. The women in the control group were selected prospectively from the booked induction list in the days preceding labor induction, and their actual recruitment took place in the induction unit on the day of induction. The women in this group received in the posterior fornix a pessary containing 3 mg of PGE2. The procedure could be repeated up to 5 times at 6-h intervals at the discretion of the attending obstetrician, if the cervix remained unfavorable according to the attending obstetrician; after 5 unsuccessful attempts, labor induction was categorized as failed and a cesarean section was performed. Uterine hyperstimulation was defined as tachysystole (6 or more contractions in 10 min) or hypertonus (single contractions lasting for at least 2 min), and an abnormal fetal heart tracing prompted intervention either with salbutamol (intravenously or by inhalation) or cesarean section.

Apgar scores at 1 and 5 min, cord blood pH, and base deficit were recorded, as is the usual practice. In the study group, neonatal blood glucose estimations were done at least twice before feeding, approximately 12 and 24 h postdelivery, using basal metabolic sticks following a heel prick (<2.6 mmol was managed as hypoglycemia).

After delivery, all women were given a questionnaire to assess the acceptability of the 2 methods of labor induction.

The 2 main outcome measures were the number of women going into "spontaneous" labor within 48-h of mifepristone administration; and in those who did not experience "spontaneous" labor, whether cervical priming with mifepristone significantly reduced the time from misoprostol administration to delivery compared with the use of PGE2 alone in the control group. Secondary outcome measures included the amounts of

Table 1 Maternal characteristics*

Characteristic	PGE2 group ($n=50$)	Mifepristone/misoprostol group ($n=50$)
Age, y	29±5.4	30.1±6.9
Height, cm	164±5.6	163±6.1
Weight, kg	68.5±13.5	73.6±18
Parity	0 (0–2)	0 (0–3)
Primigravidas	36 (72)	36 (72)
Gestation, d	289±3.9	288±1.8
Cervical score pre-induction	3.2±1.8	3.6±1.8
Indication for induction		
Prolonged pregnancy	44 (88)	46 (92)
Hypertension/PET	3 (6)	3 (6)
Other	3 (6)	1 (2)

Abbreviations: PET, pre-eclampsia; PGE2, prostaglandin E2.
*Values are given as number (percentage), mean±SD, or median (range).