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An effective regimen for early medical abortion: a report of 2000 consecutive cases

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A combination of the anti-progesterone mifepristone and gemeprost provides an effective non-surgical method for the induction of abortion at gestations up to 63 days, achieving complete abortion rates of over 95%. We report our experience with an alternate regimen, comprising a reduced dose of mifepristone in combination with vaginal misoprostol. A consecutive series of 2000 women requesting early medical abortion at gestations up to 63 days was studied retrospectively. Each woman received mifepristone 200 mg orally, followed 36–48 h later by misoprostol 800 μg vaginally. Of the 2000 women, 39 (2.0%) aborted completely following administration of mifepristone alone and a further 1912 experienced complete abortion following administration of misoprostol (a complete abortion rate of 97.5%). Surgical intervention was required in 49 women (2.5%): for incomplete abortion in 27 (1.4%), for missed abortion in seven (0.4%), for continuing pregnancy in 11 (0.6%) and to exclude ectopic pregnancy in four (0.2%). The surgical intervention rate was significantly higher among women at gestations ⩾49 days than among those at ⩽49 days (3.3 versus 1.5%, $P = 0.0193$). The regimen appears as effective, in terms of high complete abortion rate and low continuing pregnancy rate, as any published alternative. This regimen has the benefit of being less costly as the dose of mifepristone is 67% lower and misoprostol is substantially less expensive than gemeprost. Additionally, misoprostol does not require special transport or storage requirements. As such, the combination of mifepristone and misoprostol may be preferable to mifepristone and gemeprost.

Key words: induced abortion/mifepristone/misoprostol

Introduction

The use of the anti-progesterone, mifepristone, plus a prostaglandin analogue for medical abortion at gestations up to 63 days of amenorrhoea has been licensed in France and China since 1988, in the UK since 1991 and in Sweden since 1992. The manufacturer's recommended regimen comprises 600 mg of mifepristone followed by 1 mg of the prostaglandin E_1 analogue, gemeprost, at an approximate drug cost of £66 per patient (BMA, 1995). The World Health Organization has advocated a reduced dose of 200 mg of mifepristone as being of equal efficacy to a dose of 600 mg, and previous work from our own group and others has shown the alternative E_1 analogue, misoprostol, to be effective and acceptable to women as an early pregnancy abortifacient (Norman *et al.*, 1991; El-Refaey and Templeton, 1994; Aubeny *et al.*, 1995; El-Refaey *et al.*, 1995). Moreover, it has been shown that misoprostol is more effective when administered vaginally, rather than orally (El-Refaey *et al.*, 1995). This series is a continuum to our previously reported experience with a regimen comprising 200 mg mifepristone followed by vaginal administration of 800 μg of misoprostol (Penney *et al.*, 1995), a combination which has an approximate drug cost of £15 per patient (BMA 1995).

We now present our experience with a consecutive series of 2000 women managed using this low cost regimen.

Materials and methods

A consecutive series of 2000 women with pregnancies of up to 63 days of amenorrhoea undergoing induced abortion under the terms of the 1967 Abortion Act in one Scottish NHS gynaecology unit was studied. All women had chosen to undergo abortion by medical, rather than surgical, means. The assessment of gestational age was based on ultrasound measurement (crown–rump length) in 1864 women (93.2%) and on menstrual history alone in 136 (6.8%).

Following appropriate counselling, each woman received a single tablet of 200 mg of mifepristone, swallowed under nursing supervision. Unless abortion occurred following administration of mifepristone alone, which was confirmed by ultrasound scan on patients who gave a history of heavy bleeding prior to misoprostol administration, women were admitted as a day case to the gynaecology unit 36–48 h later. On admission, four tablets (a total of 800 μg) of misoprostol were inserted into the posterior vaginal fornix by a trained nurse. Following administration of prostaglandin, women were observed in the ward for a minimum of 6 h and given oral (paracetamol 500 mg plus dihydrocodeine 10 mg) or parenteral (morphine 10 mg) analgesia every 4–6 h, as required.

Following misoprostol administration, pulse, blood pressure, temperature and systemic symptoms were monitored hourly. If passage of products of conception had not been observed by nursing staff within 6 h, a speculum examination was undertaken and any products of conception in the vagina or cervical os were removed. Women were discharged home following abortion or after 8 h if abortion had not occurred and did not appear imminent.

All women were offered a follow-up appointment within 2 weeks of the termination, at the hospital or with the referring doctor. Those few women who were discharged without passage of products of conception being confirmed were given a hospital follow-up

appointment and a telephone number for contacting staff if they were concerned at any time. Follow-up of these women included ultrasound assessment.

For each woman, the outcome of the medical abortion regimen was classified into one of four categories: (i) complete abortion (requiring no further treatment), (ii) incomplete abortion (products of conception passed but clinical or ultrasound signs of incomplete abortion), (iii) missed abortion (no products passed and ultrasound evidence of retained gestation sac but no cardiac activity) and (iv) continuing pregnancy (no products passed and cardiac activity present on ultrasound). Women with treatment outcomes in the final three categories were further managed by surgical evacuation of the uterus. The categorization of treatment outcome was agreed following independent review of patients' records by three of the co-authors (P.A., G.P. and G.F.).

In presenting the results, continuous variables are presented as means with standard deviations and ranges. Comparisons between groups were made using the Fisher exact or χ^2 tests as appropriate. Differences were regarded as statistically significant if $P < 0.05$.

Results

Patient characteristics

The mean ± SD age of the 2000 women was 26.0 ± 5.3 years (range 14–47 years). Of 1942 for whom parity was documented, 923 (47.5%) were primiparous and 1019 (52.5%) had one or more previous pregnancies. The mean gestation, by best estimate at the time of mifepristone administration, was 49.9 ± 7.6 days of amenorrhoea (range 28–63 days). Of the 2000 women, 928 (46.4%) were at gestations of ⩽49 days and 1072 (53.6%) were at gestations of >49 days at the time of commencing treatment.

Treatment outcome

Of the 2000 women, 48 complained of heavy bleeding within 48 h of mifepristone administration alone and complete abortion was confirmed in 39 (2.0%) on ultrasound scan. These women received no further treatment. Among the 1961 women who went on to receive misoprostol, complete abortion, with no need for surgical intervention, occurred in 1912. Thus, the overall, complete abortion rate was 1951/2000 (97.6%).

The remaining 49 women (2.5%) required surgical intervention for one of the three adverse treatment outcomes. Overall, 27 surgical evacuations were undertaken because of incomplete abortion, seven because of missed abortion and 11 because of continuing pregnancy. The remaining four women underwent evacuation as an adjunct to (negative) laparoscopy undertaken to exclude ectopic pregnancy. Treatment outcomes are summarized in Table I for women in the two gestation groups, ⩽49 days and >49 days. Women in the lower gestation band were significantly more likely to abort after mifepristone alone and to abort completely following the full regimen. Of the 49 women who required surgical intervention, seven had surgery on the day of misoprostol treatment (four to achieve haemostasis, one as an adjunct to a negative laparoscopy for suspected ectopic pregnancy and two because of patient preference following failure to abort on the day of treatment). The remaining 42 women underwent surgical intervention at intervals of 1 day to > 1 month following the medical regimen. Most evacuations (36, 73.5%) were undertaken within 14 days of the regimen and a total of seven evacuations was required to achieve haemostasis.

Induction–abortion interval

Of the 1961 women who received the full mifepristone/misoprostol regimen, 1827 (93.7%) were observed to pass products of conception while in the ward. Of the 106 women who failed to abort while under observation, 105 subsequently had complete abortion confirmed by ultrasound examination at a hospital follow-up visit. Only one woman who had not aborted in the ward failed to attend for follow-up. The passage of products of conception at home was subsequently confirmed by this patient's general practitioner.

The induction–abortion interval could be accurately determined for 1633 women (93.7% of those who aborted while under ward observation and 82% of the total). Of these, 1407 (86.2%) aborted within 6 h of receiving misoprostol. The median induction–abortion interval was 4.15 h (range among those observed: 0.30–13.25 h).

Analgesia requirements

Data on analgesic use were recorded for the 1055 (52.8%) consecutive women studied since the later part of 1995. Of these, 443 (42%) required no analgesia (including 39 women who aborted following mifepristone alone), 487 (46.2%) required oral analgesia only and 125 (11.9%) required parenteral opiate analgesia.

Complications

As outlined above, a total of seven women (0.35%) required haemostatic uterine evacuation. In addition, 30 women (1.5%) received oxytocics at the time of abortion because of heavy bleeding. Only three women (0.15%) required blood transfusion in association with the termination procedure. All three women were over 49 days gestation and were admitted with a history of heavy bleeding (within 2 weeks following the procedure), two of whom required surgical evacuation of the uterus for incomplete abortion and one woman was found to have a haemoglobin concentration of 7 g/dl. The management of 1931 of the 2000 women (97%) was completed on a day-case basis, with only 61 women (3.0%) requiring an overnight stay. Of those who required an overnight stay, 12 had surgical evacuation of the uterus, nine were admitted overnight prior to misoprostol administration with bleeding, four passed products of conception late at night, 10 complained of pain and bleeding following the procedure and stayed overnight for observation, four had significant side-effects in relation to prostaglandin, four stayed in for other medical reasons unrelated to the termination procedure, 10 required an overnight stay for social/geographic reasons and in a further eight, the reason for an overnight stay was not known. A total of 1322 women (88.8% of those invited) attended the hospital (rather than the referring doctor) for follow-up. Among these women, the most common problems reported were continued pain, vaginal bleeding and offensive discharge. In all, 61 women with symptoms of this type (4.6% of those seen for hospital follow-up) were prescribed antibiotics for presumed genital tract infection. There are no

Table I. Treatment outcomes and indications for surgical evacuation by gestation

	Gestation no. (%)	Aborted on mifepristone alone	Complete abortion	Total surgical	Indication for uterine evacuation		
					Incomplete	Missed	Continuing
⩽ *49 days*	928 (46.4%)	30 (3.2)	914 (98.5)	14 (1.0)	9 (1.0)	1 (0.1)	2 (0.2)
> *49 days*	1072 (53.6%)	9 (0.8)	1037 (96.7)	35 (3.3)	19 (1.8)	6 (0.6)	9 (0.8)
Total	2000 (100%)	39 (2.0)	1951 (97.5)	49 (2.5)[a]	27 (1.4)	7 (0.4)	11 (0.6)
P value[b]		0.0001	0.0131	0.0193	0.0750	0.1336	0.1814

[a]The total of 49 interventions includes four cases where the principal procedure was laparoscopy to exclude ectopic pregnancy. These cases are not included in the breakdown of indications for uterine evacuation.
[b]*P* value for difference between gestation groups.
Values in parentheses are percentages.

data available regarding the length of bleeding following the procedure.

Discussion

To our knowledge, this study of 2000 women represents the largest reported series of a regimen for early medical abortion undertaken in a single centre. The UK multicentre study (1995) of the conventional regimen of 600 mg mifepristone followed by 1 mg of gemeprost involved 1018 women, the multicentre study of mifepristone in combination with various doses of oral misoprostol conducted by Aubeny *et al*. (1995) involved 1108 women and the WHO Multicentre Study (WHO Task Force, 1993) comparing different doses of mifepristone in combination with 1 mg of gemeprost involved 1182 women. The overall complete abortion rate of 97.6% achieved in our study compares well with the rates of 94.8% reported in the UK study of the conventional regimen (UK Multicentre Study, 1995) and of 92.9% reported in Aubeny's series using oral misoprostol (Aubeny *et al*., 1995).

In our series, 11 women (0.6%) had continuing, viable pregnancies following the medical regimen. In all cases, the continuing pregnancies were recognized and appropriately managed. The continuing pregnancy rate is similar to that of 0.4% reported in the WHO multicentre study (WHO Task Force, 1993) and lower than the 3% reported with oral misoprostol regimens (Thong and Baird, 1992).

The UK Multicentre Study (1995) using the mifepristone and gemeprost regimen revealed no relationship between treatment outcome and gestational age. Our own findings suggest lower efficacy at increased gestation, in line with the findings of Aubeny *et al*. (1995) in their studies using oral misoprostol. Nevertheless, our complete abortion rate of 96.7% among women in the 7–9 week gestation band is still as high as any overall rate reported elsewhere. This is probably due to a higher dose of misoprostol and the vaginal route of administration.

Although the induction abortion interval in our series was 4.15 h, with a range among those observed of 0.30–13.25 h, 106 women aborted at home, which was up to 2 weeks following the procedure. However, abortion was confirmed on ultrasound scan in all but one in whom the GP confirmed a history of passing products of conception at home. A follow-up appointment in hospital was given to 1489 women (of whom 88.8% attended), while the remaining 511 women were given an appointment with the referring doctor. There is no reason to believe that there were any significant unidentified problems in the latter group, since they were not referred back to hospital (on reviewing the data sheets and case notes).

The reported rate of inpatient care with the gemeprost regimen is up to 2% (UK Multicentre Study, 1995), with 61 (3%) women in our series requiring overnight stay. However, some of our patients lived far away and were kept in overnight for this reason.

Although misoprostol does not have a product licence for use for termination of pregnancy the EC Pharmaceutical Directive 89/341/EEC specifically permits doctors to use 'licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the licence' (Ferner, 1996). However, it is possible that its use could cause legal problems in certain countries, particularly in the unlikely event that the pregnancy continues, as there are reports of fetal malformations in these circumstances (Gonzalez *et al*., 1993).

The low drug costs coupled with the low requirement for inpatient care (3% of women) makes the regimen described here a cost-effective method for early pregnancy abortion, suitable for use in many settings. In particular, it is acknowledged that, in many instances, unsafe abortion is a consequence, not of illegality, but of lack of access to medical resources (Van Look and Von Hertzen, 1993). The availability of this low cost medical treatment using agents which do not require special cold storage and transport facilities may make the provision of safe abortion feasible in developing country settings where medical facilities are limited. Nevertheless, our findings confirm the small but finite risk of haemorrhage requiring oxytocics, surgical haemostasis or blood transfusion. Thus, early medical abortion should only be undertaken in settings where there is access to medical assistance for those few women requiring it.

In conclusion, 200 mg of oral mifepristone in combination with 800 μg of vaginal misoprostol represents a cost-effective regimen for the induction of abortion at gestations up to 9 weeks (63 days of amenorrhoea).

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