# *PERIODIC SAFETY UPDATE REPORT FOR:*

## MIFEGYNE®

## MIFEPRISTONE

**EXELGYN LABORATORY**
6 rue Christophe COLOMB
F- 75008 Paris

***June 1st, 2001 until May 31st, 2002***

PSUR n° 13 \ JUNE 2002

**June 30th, 2002**

(b) (4), (b) (6)

(b) (4), (b) (6)

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# 1 - INTRODUCTION

This is the thirteenth Periodic Safety Update Report (PSUR N°13) on *Mifepristone*, compiled for regulatory authorities since January 1991.
It summarises safety data received by the Medical Department of Exelgyn from worldwide sources, during the period from June 1, 2001 to May 31, 2002.

*Mifepristone* (RU 486) is a potent antiprogestin, available as 200mg tablets for oral administration. Mifepristone is marketed by Exelgyn and was developed by Roussel Uclaf. The Population Council (USA) also has rights to mifepristone under a special agreement.

The initial and main indication for *Mifepristone* is medical termination of early intra-uterine pregnancy (first approval in France in December 1988), in combination with a prostaglandin analogue (misoprostol or gemeprost). This combination leads to successful pregnancy termination in more than 95% of cases.

*Mifepristone* is also approved for therapeutic termination of pregnancy beyond the first trimester in combination with prostaglandin analogues, softening and dilatation of the cervix uteri prior to surgical pregnancy termination and induction of labour for fœtal death in utero.

This report is compiled in the format proposed by ICH3 Topic E2C (Step 4 Document issued in November 1996).

# 2 - WORLDWIDE MARKET AUTHORISATION STATUS

The cumulative worldwide market authorisation status of *Mifepristone*, specifying the respective dates of approval and dates of launch is presented in Appendix 11.1.

During the period covered by the PSUR:

- New marketing authorisations were obtained through national procedure in the following countries: Azerbaijan, New Zealand and Uzbekistan.

# 3 - UPDATE OF REGULATORY OR MANUFACTURER ACTIONS TAKEN FOR SAFETY REASONS

## 3.1. Action taken by the Marketing Authorisation Holder (MAH)

The action taken for safety reasons during the covered period are described hereunder

- In Sweden, a type II variation was submitted on December 4th, 2001 in order to harmonise the section "4.1. Therapeutic indication" of the Swedish SmPC, with the European SmPC. In this context, the following new indications were submitted and are still outstanding :
  - Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.
  - Preparation for the action of prostaglandin analogues in the termination of pregnancy for second trimester.
  - Labour induction in foetal death in utero, in patients where prostaglandin and oxytocin cannot be used.

- In UK, type II variations mentioned in the previous report was approved and all amendments concerning the indication is now in the SmPC.

## 3.2. Action taken by the Regulatory Authorities

During the period of review, there was no specific action taken for safety reasons by the regulatory authorities.

There was no marketing authorisation rejection, no suspension or withdrawal, no restriction of distribution, no clinical trial suspension, no dosage or formulation modification, and no change in target population or indications.

# *4 – CHANGES TO REFERENCE SAFETY INFORMATION*

The Master Data Sheet (MDS) which includes the Core Safety Information has been used as a reference document for the preparation of the present PSUR (see Appendix 11.2.1).

Although there is no major change, the Master Data Sheet was revised in 1998 to be in line with the document proposed in the mutual recognition procedure. Since the last report, there is no major modification in the MDS and in the SmPC.

However in Sweden harmonisation of SmPC in section "4.1. Therapeutic indication" was submitted to be in line with the European SmPC

In UK, the type II variation concerning two modifications in the indications are now mentioned in the SmPC.

# *5 - PATIENT EXPOSURE*

A crude estimate of the number of patients treated with *Mifepristone* has been calculated from the sales volumes, in units, of drug sold in the period from June 1, 2001 to May 31, 2002. It has been assumed that each patient has received the standard dose of 600mg (3 tablets). This may underestimate the number of patients exposed to the drug. Indeed, in the UK, many physicians use a lower dose of 200mg. Also, since the approval of the indication "Softening and dilatation of the cervix" at the dose of 200mg in France, a number of patients received only one tablet.

## 5.1. CLINICAL TRIALS

From information obtained by Exelgyn Laboratories, it is estimated that (b) (4) patients, included in ongoing clinical trials during the period of review, received *Mifepristone*.

For all these trials, the medication is provided by Exelgyn only.

Information regarding these studies is presented in Appendix 11.3.1 and 11.3.2.

## 5.2. MARKET EXPERIENCE

During the period covered by this review (from June 1, 2001 to May 31, 2002), *Mifepristone* sales amount to (b) (4) units (on May 2002). Assuming one unit represents one treatment course, this would correspond to (b) (4) women who received mifepristone.

## 5.3. TOTAL EXPOSURE

(b) (4)

Clinical trials
Worldwide sales
Total

Thus it is estimated that over (b) (4) patients received *Mifepristone* in the period covered by this safety update report.

# *6 - INDIVIDUAL CASE HISTORIES*

All spontaneous and clinical trial reports, published and unpublished, meeting the criteria defined below, and received by the Medical Department of Exelgyn, from worldwide sources during the review period, are presented in Appendix 11.4.
The cases have been classified by body system and the details tabulated in a line-listing format. When reports of events affecting more than one body system were received, the most clinically serious event has been assigned to the corresponding body system and the other events listed with it.

## 6.1. SPONTANEOUS REPORTS

All serious (irrespective of labelling), and non serious, spontaneous reports received by Exelgyn, and medically unsubstantiated consumer reports mentioned in this section, are presented in a line-listing format in the attached documents: Appendix 11.4. is a listing with information on each individual case as recommended in the ICH guidelines.

During the period of review, the Medical Department of Exelgyn recorded from health professionals and authorities **23 spontaneous reports** (of which **12 cases of serious adverse events, 11 non serious adverse events** and **no case from clinical trials**) in association with *Mifepristone*.

- The 12 cases of serious adverse events reported during the period of review are classified as follows:
  - 3 serious unlabelled, in which 1 case of unintended pregnancy with fetal malformation, 1 case of death and 1 case of thoracic pain (ischaemic accident).
  - 9 serious labelled with 5 cases of unintended pregnancy, 2 cases of allergic reaction, 1 excessive bleeding and 1 septicaemia to *Streptococcus*.
- Among the 11 non serious cases, 9 cases of unintended pregnancy and 2 cases of rash were reported.

The outcome of the cases **S20000024S/MIF2** (previously reported as case S20000024S/MIF1 in PSUR n°11) and **S2000017UK/MIF1** (from PSUR n°12), are normal pregnancy with healthy baby (date of birth: (b) (6) and spontaneous abortion in the second case.

## 6.2. STUDY REPORTS

Unlabelled, serious, attributable adverse event reports are included. An unlabelled event is defined, as any particular untoward medical happening experienced by a patient that is not described in the Master Data Sheet. A serious event is one that is fatal, life-threatening, disabling, incapacitating, results in hospitalisation or prolongs hospitalisation, overdose, cancer or congenital anomaly. For the purpose of this report an event is considered to be attributable if the investigator or the company has rated the causality relationship with mifepristone as possible or more than possible.

No case was reported from clinical trials during the period of review.

Other studies are conducted by independent investigators or organisations and are listed in Appendix 11.3.1, the products used in these trials are provided by Exelgyn.

# 7 – STUDIES

## 7.1. NEWLY ANALYSED AND PUBLISHED STUDIES (References list Appendix 11.5.)

There is no newly analysed study.

## 7.2. TARGETED NEW STUDIES

There are no targeted new studies during the period of review.

## 7.3. PUBLISHED SAFETY STUDIES

**SETTING UP A ONE-STOP MIFEPRISTONE-MISOPROSTOL MEDICAL TERMINATION OF PREGNANCY SERVICE FOR ALL GESTATION FROM 5 TO 23 WEEKS – A REVIEW OF 482 CASES.**
**J. I. Ojidu, S. D. Sabharwal.**
J. Obstet. Gynaecol., 2001, Vol/Iss/Pg.21/4 (386-388)

Mifepristone–misoprostol combination is increasingly being utilised for medical termination of pregnancy on account of its reported efficacy, safety and lower cost. Experience with this modality of effecting termination of pregnancy from 9 to 13 weeks' gestation is scanty. At the Scunthorpe General Hospital in the United Kingdom, we established a nurse-led, one-stop medical termination of pregnancy service using ***mifepristone*** and misoprostol for all gestations from 5 to 23 weeks. A review of the case records of 482 women who had medical termination of pregnancy at all gestations from 5 to 23 weeks from December 1997 to May 1999 was undertaken in order to assess the effectiveness and complication associated with the ***mifepristone***-misoprostol protocol. Complete abortion was achieved in 406 (84 %) women. Surgical evacuation was required to complete the abortion in 74 (16 %) women. The complete abortion rate was similar across the spectrum, i.e. 87 % in the 5-8-weeks group; 79 % in the 9-13-weeks group; and 87 % in those of greater-than or equal to 14 weeks. Two failures occurred: one of them proceeded to surgical evacuation after three courses of misoprostol, while the over continued with her pregnancy after one course. Three women (0.6 %) required blood transfusion for haemorrhage, while two others were treated for infection. Oral ***mifepristone*** with or without vaginal misoprostol is an effective and safe regimen for termination of all pregnancies from 5 to 23 weeks' gestation.

## FIRST TRIMESTER ABORTION WITH MIFEPRISTONE AND VAGINAL MISOPROSTOL.

**U. B. Knudsen**
Contraception 2001; 63/5: 247-250.

This study assessed the efficacy and side effects of first trimester medical abortion using ***mifepristone*** and vaginally administered misoprostol. Medical abortion was first in Denmark in December 1997, and the acceptability of this new approach in a Danish population was evaluated. This study included the first 100 women seeking medical abortion. The gestational age was from 33 to 56 days. All received 600 mg ***mifepristone (RU 486)*** orally followed 2 days later by vaginally administered misoprostol 400 µg. Success was defined as achieving complete abortion without the need for surgical evacuation. Ninety-three percent achieved a successful medical termination of pregnancy. Side effects were few, and the acceptability was high. Ninety percent of the women would prefer medical abortion in case of a new unwanted pregnancy. The combination of ***mifepristone*** and vaginally administered misoprostol is effective, safe, has few side effects and in well accepted by Danish women.

## SECOND TRIMESTER MEDICAL ABORTION WITH MIFEPRISTONE AND GEMEPROST.

**O. S. Tang, K. J. Thong, D. T. Baird**
Contraception 2001; 64/1: 29-32

The treatment outcomes of 956 women undergoing second trimester termination of pregnancy with ***mifepristone*** and gemeprost were studied. The median gestational age was 16 weeks (range: 12-24 weeks). All women were treated with 200 mg ***mifepristone*** orally, followed 36 h later with 1 mg vaginal gemeprost administered every 6 h to maximum of 4 doses in the first 24 h. A second course of 1 mg vaginal gemeprost was given 3-hourly in the next 12 h, if abortion had not occurred. Overall, 96.4 % and 98.8 % of the women aborted within 24 and 36 h, respectively. The median induction-to-abortion interval was 7.8 h (range: 0.5-109.9h). The induction-abortion interval was longer in nulliparous women (7.3%; $p<0.001$). Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. In conclusion, a combination of ***mifepristone*** and gemeprost is a safe, effective, and non-invasive method of medical abortion for second trimester pregnancy.

## A RANDOMIZED COMPARISON OF MEDICAL ABORTION AND SURGICAL VACUUM ASPIRATION AT 10-13 WEEKS GESTATION

**P. W. Ashok, A. Kidd, G. M.M.Flett, A. Fitzmaurice, W. Graham and A. Templeton**
Human Reproduction, 2002, Vol.17/1: 92-98

A patient-centred, partially randomised, controlled trial was carried out. Those who expressed a strong preference for either medical (n = 15) or surgical (n = 62) abortion were allocated to that method. The remainder agreed to be randomized.

The medical method (n = 188) was mifepristone 200 mg followed by misoprostol up to 3 doses, and surgery (n = 180) was by vacuum aspiration under general anaesthesia. Outcome measures included efficacy rates, medical complications within 8 weeks of the procedure, patient preferences and acceptability.
Among women who underwent medical abortion, 5.4% required a second procedure compared with 2.1% who had surgery, although this difference was not statistically significant. Side effects experienced were higher in women who underwent medical abortion compared with those who underwent surgery. There were no significant differences in the rates of major complications up to 8 weeks. Prior to termination, 80% of women had a preference for a method, with 72% preferring medical and 28% preferring surgical abortion. Following abortion, 70% of those who underwent medical termination and 79% who underwent surgery would opt for the same method in the future.
Medical abortion is safe and effective at 10-13 weeks gestation and should be considered an option for those women who wish to avoid surgery and anaesthesia.

# *8 - OTHER INFORMATION*

## 8.1. EFFICACY-RELATED INFORMATION

No information was received during the period of review involving relevant lack of efficacy, which might represent a significant hazard to the treated population.

## 8.2. LATE-BREAKING INFORMATION

There is no information received since the data lock point, which might alter the risk benefit profile of mifepristone.

# *9 - OVERALL SAFETY EVALUATION*

## 9.1.OVERVIEW

From the data presented in this safety update and cumulative experience to date, it is considered that no further amendment to the Master Data Sheet is required at present, with respect to the reported listed adverse reactions, and especially those qualified as serious. No significant increase in the frequency of reports for any category of known toxicity was identified.

From the cumulative experience on mifepristone, it is considered that the statements given in the Core Safety Information of the last version of the Master Data Sheet are adequate with respect to mifepristone use in all its approved indications.

However type II variation for harmonisation of Swedish SmPC (section 4.1. Therapeutic indication) was submitted on December 4th, 2001 to be on line with the European SmPC.

## 9.2. DRUG INTERACTIONS

No information concerning interaction has been identified during the period of review.

## 9.3. OVERDOSE OR MISUSE

One case of misuse was reported. This case from France (S2001020F/MIF1) concerns a 22-year-old female patient who received 200 mg of mifepristone (instead of 600 mg as mentioned in SmPC) for medical termination of pregnancy at 12 weeks gestation. The patient experienced incomplete abortion with excessive bleeding.

## 9.4. DRUG ABUSE

There is no potential of drug abuse with mifepristone, as prescription is restricted to hospital (only one dose).

## 9.5. EXPERIENCE IN PREGNANCY

**Twelve new cases** of developing pregnancy were recorded during the period of review. In the majority of these cases of continuing pregnancies, women changed their mind either after mifepristone intake, before prostaglandin administration, or after exposure to both drugs.
Some cases were reported prospectively. The outcome was the following:

- seven cases of surgical termination of pregnancy,
- continuing pregnancy in five patients.

All cases are presented in the consecutive PSURs. The tables have been updated since PSUR n° 12 and are presented in Appendix 11.6.

The outcome of two previous pregnancies (case # S2000024S/MIF1 from PSUR n°11 and S2000017UK/MIF1 from PSUR n°12) were reported, normal birth in one patient and spontaneous abortion in the other patient.

Since the first marketing in 1989, **146** cases of ongoing pregnancies were identified either as spontaneous cases reported to or solicited by the company, or included in the listing even if the case was insufficiently documented. Ten of these cases were reported with various malformations.

The manufacturer recommends in the Master Data Sheet, "the woman must be informed that in the event of the failure of the method, the pregnancy is liable to continue to develop. The foetus may then be exposed to a risk of malformation".

## 9.6. EXPERIENCE DURING LACTATION

No new information concerning experience during lactation has emerged during the period of review.

## 9.7. LONG-TERM TREATMENT

The currently approved indications of mifepristone require one single dose, or two doses in case of foetal death in utero.

However some patients have received long-term daily treatment with mifepristone in non-registered indication such as unresectable meningiomas, leiomyosarcomas, Cushing syndrome. The two main adverse reactions identified during long-term use are reversible amenorrhea in premenopausal women and sub-acute adrenal failure symptoms. In addition, endometrial hyperplasia might be a potential adverse reaction of long-term mifepristone administration, possibly related to continued unopposed estrogen action.

## 9.8.EXPERIENCE IN SPECIAL PATIENT GROUPS

There is no information concerning the experience in special patient groups.

# *10 - CONCLUSION*

**No area of safety concern has been identified during the period of review. The data presented in this report are consistent with the cumulative experience to date and provide no information, which could alter the risk-benefit ratio of mifepristone.**

**Exelgyn Medical Department will continue to monitor reports of adverse experiences received worldwide and will revise the SmPC when an evaluation of surveillance data yields significant new information.**

# 11. APPENDICES

# *APPENDIX 11.1*

# CUMULATIVE REGULATORY APPROVAL / DECISION DATES

# *APPENDIX 11.1.1.*

## REGISTRATION STATUS UP TO 1998

# MIFEGYNE®
## REGISTRATION STATUS AS OF NOVEMBER 1998

| COUNTRY | DOSAGE PER TABLET | DATE OF | | | INDICATIONS (and POSOLOGY) |
|---|---|---|---|---|---|
| | | APPROVAL | LAUNCH | TRANSFER OF MARKETING AUTHORIZATION | |
| FRANCE | 200mg | December 28th, 1988<br><br>July 17th, 1992<br><br>November 6th, 1998 | September 1989 | 8/8/97<br><br>CIP N°556 473.0 | • Medical alternative to surgical termination of intra-uterine pregnancy of up to 49 days amenorrhea (600mg single dose)<br>• Preparation for the prostaglandin action in therapeutic pregnancy termination (600mg single dose)<br>• Fœtal death in utero (600mg x 2 days)<br>• Softening and dilatation of the cervix uteri prior to voluntary pregnancy termination by vacuum aspiration during the first quarter (200mg single dose) |
| U.K. | 200mg | July 1st, 1991<br><br>August 4th, 1995 | July 1991 | 24/09/97<br><br>PL 16152/0001 | • Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose)<br>• Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination (600mg single dose)<br>• Termination of pregnancy between 13 and 20 weeks gestation in combination with gemeprost (600mg single dose) |
| SWEDEN | 200mg<br><br>600mg | September 4th, 1992<br><br>August 2nd, 1995 | October 1992 | 1/10/97<br>ASP 91-0246<br><br>ASP95-0005 | • Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose)<br>• Termination of pregnancy in the second trimester (600mg single dose)<br>Same indications as for 200mg tablets |

# APPENDIX 11.1.2.

## NEW REGISTRATION AND LAUNCH DATES

## MIFEGYNE® REGISTRATION STATUS AS OF MAY 31, 2002

| COUNTRY | DATE OF SUBMISSION | DATE OF APPROVAL | PLANNED / ACTUAL DATE OF LAUNCH | LICENSE NUMBER |
|---|---|---|---|---|
| | | E U R O P E | | |
| **Mutual Recognition Procedure** | **April 6th, 1999** | **July 6th, 1999** | | **FR/H/137/01** |
| AUSTRIA | **April 6th, 1999** | September 21st, 1999 | Marketed December 1999 | 1-23220 |
| BELGIUM | **April 6th, 1999** | November 22nd, 1999 | July 3rd, 2000 | 2 532 IE 1 F3 |
| DENMARK | **April 6th, 1999** | August 27th, 1999 | Marketed $Q_1$ 2000 | 30 741 |
| FINLAND | **April 6th, 1999** | December 20th, 1999 | Marketed $Q_1$ 2000 | MTnr 14064 FIN |
| *FRANCE* | - | December 28th, 1988<br>Update December 15th, 1999 | Marketed 1989 | 556 473.0 |
| GERMANY | **April 6th, 1999** | August 19th, 1999 | Marketed November 1999 | 46 038 .00.00 |
| GREECE | **April 6th, 1999** | October 10th,1999 | $Q_4$ 2001 | 2455001 |
| LUXEMBOURG | **November 26th, 1999** | December 11th, 2000 | January, 2001 | 1181/00/11/0052 |
| NETHERLANDS | **April 6th, 1999** | August 25th, 1999 | Marketed January 2000 | RVG 24 206 |
| SPAIN | **April 6th, 1999** | October 21st, 1999 | Marketed February 2000 | 62.278 |
| *SWEDEN* | — | September 4th,1992 | Marketed $Q_3$ 1992 | 11642 |
| *UK* | — | July 1st, 1991<br>Updated August 4th, 1999<br>Updated August 8th, 2001 | Marketed $Q_3$ 1991 | PL 16152 / 0001 |
| | | O T H E R S | | |
| AZERBAIJAN | | April 20th, 2001 | **2002** | SN-004 00254 |
| GEORGIA | **September 13th, 2000** | December 11th, 2000 | **March, 2001** | R-0000075 |
| ISRAEL | **February 7th, 1999** | August 10th, 1999 | Marketed September 1999 | 115 52 29641 00 |
| NEW ZEALAND | **2000** | August 30th, 2001 | September 2001 | - |
| NORWAY | **March 29th, 1999** | December, 2000 | May 1st, 2001 | 99.1943 |
| OUZBEKISTAN | | June 8th ,2001 | **2002** | 6-250-95 |
| RUSSIA | **November 22nd, 1998** | April 14th, 1999 | Marketed September 1999 | P-8-242 N°01 1033 |
| SOUTH AFRICA | **April 9th, 1999** | **Pending** | **$Q_3$ 2001** | NA |
| SWITZERLAND | **February 10th, 1999** | July 14th, 1999 | Marketed October 99 | 55205 |
| TAIWAN | **1999** | **Pending** | **$Q_3$ 2001** | NA |
| TUNISIA | **August 8th, 1999** | November 15th, 2000 | **2002?** | 4303011H |
| UKRAINIA | **May, 1999** | June 23rd, 2000 | **January, 2001** | P.0600/01921 |

# *APPENDIX 11.1.3.*

## DIFFERENCES IN THE LABELING OF THE EUROPEAN SMPC AND OTHERS COUNTRIES

# APPROVED EUROPEAN SPC
# JULY 6, 1999

* * * * *

## Therapeutic indications & Posology

**The European SPC has used the following wording. Consequently, the initial wording used in France and referred to in Appendix 11.1.1. has been modified to reflect the harmonized EU SmPC.**

**The following countries have been included in the procedure of Mutual Recognition: Austria, Belgium, Denmark, Finland, France (Reference Member State), Germany, Greece, the Netherlands, Spain.**

- **Medical termination of developing intra-uterine pregnancy.**
  In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

  600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally, or gemeprost 1mg per vaginum.

- **Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.**

  200mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

- **Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*.**

  600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

**4- Labour induction in foetal death in utero.**

In patients where prostaglandin or oxytocin cannot be used.
600mg of mifepristone (e.g. 3 tablets of 200mg each) in a single oral daily dose, for two consecutive days.

**In the other countries** where the product has been approved the wording is the following:

## Israel

- **Medical alternative to uterine suction for termination of intra-uterine pregnancy:**
  - up-to-and no later than 49 days of amenorrhea (seven weeks).
  - In sequential use with a prostaglandin analogue, misoprostol 400µg per os administered 36 to 48 hours after mifegyne® intake.

  Only this indication has been approved at the moment.

## Russia

- **Medical termination of pregnancy up to 42 days of amenorrhea:**
- 600mg of mifepristone in a single dose.
- **Medical termination of pregnancy up to 63 days of amenorrhea in association with a prostaglandin analogue (misoprostol, gemeprost):**
- 600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg per vaginum.
- **Dilatation of the cervix uteri prior to a surgical termination of pregnancy up to 12 weeks:**
- 600mg of mifepristone in a single dose.
- **Preparation to the action of prostaglandin for termination of pregnancy between 13 and 20 weeks gestation for medical or social reasons:**

  600mg of mifepristone followed 36 to 48hours later by gemeprost 1mg p.v., repeated every three hours until complete expulsion.

The indication Labour induction for foetal death in utero has not been approved in Russia.

## Sweden

- **Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea** (600 mg single dose).
- **Termination of pregnancy in the second trimester** (600 mg single dose).

## Switzerland

The same text as in the EU has been approved for indications and posology with a slight difference in the wording of one indication: **Medical termination of intra-uterine pregnancy.**

## UK

- **Medical termination of intra-uterine pregnancy** of up to 63 days gestation.
- **Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination.**
- **For use in combination with gemeprost for termination of pregnancy between 13 and 24 weeks gestation.**
- **Labour induction in fetal death in utero.**

# Contra-indications

**For the above-mentioned countries the section Contra-Indications include the following:**

**In all indications:**

- chronic adrenal failure
- known allergy to mifepristone or to any component of the product
- severe asthma uncontrolled by therapy

**For countries included in the Mutual Recognition Procedure and for the UK, the following contra-indication has been added in all indications:**

- **Inherited porphyria**

**In the indication: medical termination of developing intra-uterine pregnancy:**

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- suspected extra-uterine pregnancy
- contra-indication to the prostaglandin analogue selected

**In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:**

- pregnancy not confirmed by ultrasound scan or biological test
- pregnancy of 84 days of amenorrhea and beyond (according to legal requirements)
- suspected extra-uterine pregnancy

**Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester):***

- contra-indication to the prostaglandin analogue selected

**Labour induction in foetal death in utero:**

Should prostaglandin combination be required, refer to Contra-Indications to the selected prostaglandin analogue.

In Israel, the section on Contra-Indications is different and include the following items:

1. Known allergy to mifepristone or to any component of the product.
2. Suspected extra-uterine pregnancy.
3. Pregnancy not confirmed by ultrasound scan.
4. Chronic adrenal failure.
5. Hemorrhagic disorders.
6. Long-term corticosteroid therapy.
7. Severe asthma uncontrolled by corticosteroid therapy.
8. Cardiac disease.
9. Hyperlipidemia.
10. Diabetes.
11. Patients with antipsychotic drug therapy.
12. Pregnancy beyond 49 days of amenorrhea.
13. As a special precaution, the medical method is not recommended for use in women over 35 years of age or who smoke more than 10 cigarettes/ day.
14. Know allergy to prostaglandins.
15. Patients with or history of cardiovascular disease.

**In the UK,** the following items are included in the Contra-Indication section of the UK data sheet:

1. Known allergy to mifepristone or to any component of the product.
2. Suspected extra-uterine pregnancy.
3. Pregnancy not confirmed by ultrasound scan or biological tests.
4. Chronic adrenal failure.
7. Severe asthma uncontrolled by corticosteroid therapy.
16. Inherited porphyria

Items 5, 6, 13 have been moved into the precautions section of the EU SmPC and item 13 is worded "... women over 35 years of age **and** who smoke more than 10 cigarettes/day". Item 9 and 11 do not exist in any of the master data sheet, EU, UK of Swedish information. Item 10 is included in the Precaution for use of the Master Data Sheet.

In addition, the following conditions have been considered in the warnings section: hepatic failure, renal failure, and malnutrition.

# *APPENDIX 11.2.*

## UPDATED LABELINGS

# *APPENDIX 11.2.1.*

## MASTER DATA SHEET

**Exelgyn Laboratories**
**6, rue Christophe Colomb**
**F-75008 Paris**

# MIFEGYNE®
# 200mg
# Mifepristone

## Master Data Sheet

**November 2001**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. TRADE NAME OF THE MEDICINAL PRODUCT

- MIFEGYNE® 200mg, tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(b) (4)

[redacted]

## 3. PHARMACEUTICAL FORM

- Light yellow, cylindrical, bi-convex tablets, for oral administration.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- **Medical alternative to surgical termination of intra-uterine pregnancy.**

  In sequential use with a prostaglandin analogue, administered 36 to 48 hours after MIFEGYNE® intake (see Posology and Method of Administration):
  - misoprostol 400µg orally (for pregnancies up to 49 days of amenorrhea),
  - or gemeprost 1mg, vaginal pessary (for pregnancies up to 63 days of amenorrhea).

  Under these conditions, the association of mifepristone and prostaglandins leads to a success rate of about 95 per cent of the attempted pregnancy terminations.
  (See Warnings and Precautions for use)

- **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination.**

  Pre-treatment with mifepristone facilitates the surgical step of the mechanical dilatation.

- **Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.**

  The use of MIFEGYNE® allows a significant reduction of the prostaglandins doses required for the expulsion.

- **Labour induction in fetal death in utero.**

  MIFEGYNE® administered alone leads to expulsion in about 60%, allowing avoidance, or reduction in the dose of prostaglandins. Therefore, it is indicated especially when prostaglandins are contra-indicated.

4.2 Posology and method of administration

1) **Medical alternative to surgical termination of intra-uterine pregnancy.**

MIFEGYNE® must not be administered if there is doubt as to the existence and age of the pregnancy, or in case of extra-uterine pregnancy. The prescribing doctor should in any case perform an ultrasound scan and/or measure ß-hCG before administration.

The method of administration which will be prescribed by the physician and applied in the presence of the practitioner or of a health professional will be as follows:

- 600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by

- 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally (pregnancies up to 49 days of amenorrhea), or gemeprost 1mg vaginally (pregnancies up to 63 days of amenorrhea).

2) **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination.**

- 200mg of mifepristone (one tablet) in the presence of the physician or of a health professional, followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

**3) Preparation for the action of prostaglandin analogs in the termination of pregnancy for medical reasons.**

600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, in the presence of the physician or of a health professional, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

**4) Labour induction for expulsion of a dead fetus (fetal death in utero).**

- 600mg of mifepristone, e.g. 3 tablets of 200mg each, in a single oral daily dose, for two consecutive days

Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.

4.3 Contra-Indications

This product SHOULD NEVER be prescribed in the following situations.

- Chronic adrenal failure.
- Known allergy to mifepristone or to any component of the product.
- Severe asthma uncontrolled by corticosteroid therapy.
- Inherited porphyria.

**In the indication: medical alternative to surgical termination of intra-uterine pregnancy.**

- Pregnancy not confirmed by ultrasound scan or biological tests.
- Pregnancy beyond 49 days of amenorrhea with misoprostol or beyond 63 days of amenorrhea with gemeprost.
- Suspected extra-uterine pregnancy.
- Contra-Indications due to the prostaglandins:
  - Known allergy to prostaglandins.
  - Patients with or history of cardiovascular disease (angina, Raynaud's syndrome or disease, cardiac arrhythmias, cardiac failure, severe hypertension).
    (See Precautions for use)

**Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.**

- Contra-indications to prostaglandins where relevant.

**Labour induction for expulsion of a dead fetus (fetal death in utero).**

- Should prostaglandins combination be required, refer to contra-indications to the selected prostaglandin analogue.

4.4 Warnings and Precautions for use

***Warnings***

Specific national legal requirements

MIFEGYNE® and the prostaglandin analogues can only be prescribed and administered in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter by the patient would certify that she has been fully informed about the method and its risks, except in the cases of preparation to the action of prostaglandins for pregnancy termination for medical reasons as well as for the labour induction for expulsion of a dead fetus (Fetal Death in Utero).

1) **Medical alternative to surgical pregnancy termination of intra-uterine pregnancy**

Failures

Unless abortion has already been completed, the use of MIFEGYNE® must be followed, 36 to 48 hours later, by a prostaglandin analogue administered either vaginally or orally, as mifepristone alone given without prostaglandins would lead to a failure rate of the method of at least 20 per cent.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analogue, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (about 9 days after MIFEGYNE® intake) which may be heavy.

Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place mandatorily within a period of **10 to 14 days** after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, Beta-hCG measurement, ultrasound scan, etc...) that expulsion has been completed and that vaginal bleeding has stopped (apart from light bleeding the disappearance of which should be checked within a few days).

Persistence of vaginal bleeding at this point could indicate incomplete abortion, or an unnoticed extra-uterine pregnancy, and an appropriate treatment should be considered.

Since heavy bleeding requiring hemostatic curettage occurs in up to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemorrhagic disorders with hypocoagulability, or with anemia.

The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anemia.

2) **Softening and dilatation of the cervix uteri prior to surgical pregnancy termination**

For the full efficacy of therapy, the use of MIFEGYNE® must mandatorily be followed, 36 to 48 hours later and not beyond, by surgical termination.

The woman must be informed of the risk of bleeding, which may be heavy, following mifepristone intake. She will be informed of the rare occurrence (0.9%) of expulsion prior to the surgical termination.

She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

3) **Preparation for the action of prostaglandin analogs for termination of pregnancy for medical reasons**

The administration of prostaglandins carries some risks; however pre-treatment with MIFEGYNE® has been shown to reduce the total dose of prostaglandins required. Moreover, the risks of other (mechanical) methods of termination for advanced pregnancies, beyond 12 weeks, have to be considered.

***Precautions for use***

1) **In all instances**

- The use of MIFEGYNE® requires blood group and rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any pregnancy termination.

- In case of suspected acute adrenal failure, dexamethasone administration is recommended.

- Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE® 's intake. Therapy should be adjusted.

  In the event of inhaled corticosteroid therapy, particularly in patients with asthma, it is recommended to adjust the treatment by doubling the dose during the 48 hours preceeding mifepristone's administration and for about one week duration.

- In patients with insulin-dependent diabetes, the occurrence of gastro-intestinal disorders induced by the pregnancy itself or by the treatment, would require an adjustment of insulin therapy.

- During clinical trials, pregnancies occurred between fetal expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

- As a precaution and in the absence of specific studies, mifepristone should not be used in patients with:
  - Renal failure
  - Liver failure
  - Malnutrition

2) **Medical alternative to surgical termination of intra-uterine pregnancy.**

In any case of a pregnancy occurring on an intra-uterine device, this device must be removed before administration of MIFEGYNE®.

During the initial clinical trials, rare serious cardiovascular accidents similar to coronary spasms have been reported following the administration of a $PGE_2$ analogue (intra-muscular sulprostone). These events were reported in women over 30 years of age and smoking more than 10 cigarettes a day.

No such cases have been reported, since analogues of $PGE_1$ (gemeprost or misoprostol) have been used. The present experience is based upon (b) (4) treatments of which about (b) (4) used misoprostol and about (b) (4) used gemeprost.

Therefore, as a special precaution, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

In any case, the risk of cardiovascular events must be taken into consideration when prostaglandins are used in association with mifepristone.

Method of prostaglandins administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be fitted with the appropriate cardiovascular monitoring and resuscitation equipment.

3) **For the sequential use of MIFEGYNE® - Prostaglandins, whatever the indication.**

The precautions related to the prostaglandins used should be followed if relevant.

4.5 Interaction with other drugs and other types of interactions.

Associations to be avoided

- Non steroidal anti-inflammatory drugs (NSAIDs) including aspirin. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of NSAIDs. Use preferably non-NSAIDs analgesics.

4.6 Pregnancy and lactation

Patients must be informed that in the event of failure of the methods, the pregnancy is liable to continue to develop. The fetus may then be exposed to a risk of malformation.

In studies performed in animals, fetal anomalies have been observed in rabbits (skull lesions), but not in rats and mice. No teratogenicity was observed after in vitro exposure of monkey embryos to mifepristone. When the pregnancy continued after mifepristone alone or with prostaglandins, uncommon cases of malformations have been reported in the fetus or the infant. Malformations have also been reported after the use of prostaglandins alone.

The exact role of mifepristone, prostaglandin analogue, or coincidental event cannot be established.

**It is essential that termination of pregnancy by another method be undertaken at a follow-up visit, in the event of such failure.**

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects or ability to drive and to use machines

Unknown.

4.8 Undesirable effects

| | | | |
|---|---|---|---|
| Very common | | | >1/10 |
| Common | >1/100 | and | <1/10 |
| Uncommon | >1/1000 | and | <1/100 |
| Rare | >1/10,000 | and | <1/1000 |
| Very rare | <1/10,000 | | |

– Urogenital

- Bleeding

  Bleeding occurs in almost all women and increases with the age of pregnancy at the time of termination.

  Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.

- Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
- Uterine rupture has been uncommonly reported after prostaglandin intake for induction of second trimester termination of pregnancy of labour induction for fetal death in utero during the third trimester.

  The reports occurred particularly in multiparous women or in women with a cesarean section scar.

– Gastrointestinal

Nausea, vomiting, diarrhea, are very common after prostaglandin intake.

– Cardiovascular

Uncommon hypotension (0.25%).

– Hypersensitivity and skin

Uncommon skin rashes (0.2%). Single cases of urticaria, of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

– Other systems

Rare cases of headaches, malaise, common vagal symptoms (hot flushes, dizziness, chills), and uncommon fever have been reported .

## 4.9 Overdose

Dose-ranging studies have shown that administration of single doses of mifepristone up to 2 g caused no unwanted reaction.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Any suggestion of acute intoxication, therefore, requires treatment in a specific environment, and with dexamethasone administration if relevant.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandins. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 % of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results slightly vary.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches to 98.7% up to 49 days of amenorrhea and to 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate may vary. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of fetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

## 5.2 Pharmacokinetic properties

After oral administration of a single dose of 600mg mifepristone is rapidly absorbed. The peak concentration of 1.98mg/l is reached after 1:30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

## 5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Anhydrous colloidal silica, maize starch, povidone, microcrystalline cellulose, magnesium stearate.

### 6.2 Incompatibilities

None known.

### 6.3 Shelf-life

3 years.

### 6.4 Special precautions for storage

None.

### 6.5 Nature and contents of container

Blister pack (PVC and Aluminium foil and carton) containing 3 tablets.

### 6.6 Instructions for Use/Handling

The treatment procedure should be fully explained and completely understood by the patient.

## 7. MARKETING AUTHORISATION HOLDER

## 8. MARKETING AUTORISATION NUMBER

## 9. DATE OF FIRST AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

November 2001.

# *APPENDIX 11.2.2.*

## EUROPEAN SMPC APPROVED JULY 6TH, 1999
## UPDATED NOVEMBER, 2000

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

MIFEGYNE® 200mg tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.

## 3. PHARMACEUTICAL FORM

Tablet.
Light yellow, cylindrical, biconvex tablets marked "167 B" on one side.

## 4. CLINICAL PARTICULARS

For termination of pregnancy, MIFEGYNE® and the prostaglandin can only be prescribed and administered in accordance with the countries laws and regulations.

As a consequence, they can only be prescribed by a medical doctor and in public or private hospital or centre (having approval to undertake termination of pregnancy). The product will be administered in the presence of the medical practitioner or of a delegated health professional.

If required by the afore mentioned laws and regulations, the patient should sign a letter of informed consent to certify that she has been fully informed about the method and its risks.

This timing of the first visit should take into account the requirement of some countries for a period of reflection prior to the abortion procedure.

### 4.1 Therapeutic indications

**1- Medical termination of developing intra-uterine pregnancy.**

In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

**2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.**

**3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester).***

**4- Labour induction in foetal death in utero.**

In patients where prostaglandin or oxytocin cannot be used.

## 4.2 Posology and Method of Administration

### 1- Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

600mg of mifepristone (i.e. 3 tablets of 200mg each) is taken in a single oral dose, followed by 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400µg orally, or gemeprost 1mg per vaginum.

### 2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester

200mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

### 3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons

600mg of mifepristone (i.e. 3 tablets of 200mg each) taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

### 4- Labour induction in foetal death in utero

600mg of mifepristone (e.g. 3 tablets of 200mg each) in a single oral daily dose, for two consecutive days.

Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.

## 4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

**In all indications**

- Chronic adrenal failure
- Known allergy to mifepristone or to any component of the product
- Severe asthma uncontrolled by therapy
- **Inherited porphyria**

**In the indication: medical termination of developing intra-uterine pregnancy**

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- suspected extra-uterine pregnancy
- contra-indication to the prostaglandin analogue selected

**In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:**

- pregnancy not confirmed by ultrasound scan or biological test
- pregnancy of 84 days of amenorrhea and beyond (according to legal requirements)
- suspected extra-uterine pregnancy

**Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)***

- contra-indications to the prostaglandin analogue selected

**Labour induction in foetal death in utero**

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

## 4.4 Special warnings and special precautions for use

### Warnings

*In the absence of specific studies, MIFEGYNE® is not recommended in patients with:*

- *Renal failure*
- *Hepatic failure*
- *Malnutrition*

### 1- Medical termination of developing intra-uterine pregnancy

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with prostaglandin to be administered at a second visit,
- the need for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake in order to check for complete expulsion,
- The possible failure of the method, leading to a pregnancy termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of MIFEGYNE®.

The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

- Risks related to the method

  - Failures

    The non-negligible risk of failure, which occurs in 1.3 to 7.5 % of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

  - Bleeding

    The patient must be informed of the occurrence of prolonged vaginal bleeding (up to 12 days after MIFEGYNE® intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place within a period of 10 to 14 days after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, ultrasound scan, and Beta-HCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

Since heavy bleeding requiring hemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

**2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination**

For the full efficacy of therapy, the use of MIFEGYNE® must be followed,
36 to 48 hours later and not beyond, by surgical termination.

- Risks related to the method

  - Bleeding

    The woman will be informed of the risk of vaginal bleeding which may be heavy, following MIFEGYNE's intake. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

- Other risks

They are those of the surgical procedure.

**3- In all instances**

The use of MIFEGYNE® requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

## Precautions for use

**1- In all instances**

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1mg of dexamethasone antagonises a dose of 400mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following MIFEGYNE's intake. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Use preferably non-NSAI analgesics.

**2- Medical termination of developing intra-uterine pregnancy**

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of $PGE_1$ (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

**3- For the sequential use of MIFEGYNE® - Prostaglandin, whatever the indication**

The precautions related to the prostaglandin used should be followed where relevant.

## 4.5 Interaction with other medicinal products and other forms of interactions

No studies to investigate possible interactions between mifepristone and other drugs have been carried out.

## 4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit *(viable ongoing pregnancy)*, and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultra-sonographic monitoring of the pregnancy will be established.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

## 4.7 Effects on ability to drive and to use machines

Not known.

## 4.8 Undesirable effects

Most frequently reported undesirable effects

- Urogenital
  - Bleeding
    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.

- Gastrointestinal
  - Cramping, light or moderate.
  - Nausea, vomiting.

- Undesirable effects related to prostaglandin use: nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

Other undesirable effects

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

- Other systems
  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

## 4.9 Overdose

After extensive clinical use, no reports of acute intoxication have been reported.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/
ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies

- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

## 5.2 Pharmacokinetic properties

After oral administration of a single dose of 600mg mifepristone is rapidly absorbed. The peak concentration of 1.98mg/l is reached after 1.30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

### 5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Colloidal silica anhydrous, maize starch, povidone, magnesium stearate, microcrystalline cellulose.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

3 years.

### 6.4 Special precautions for storage

None.

### 6.5 Nature and contents of container

3 tablets in blister (PVC / Aluminium).

### 6.6 Instructions for use and handling

Not applicable.

## 7. MARKETING AUTHORISATION HOLDER

EXELGYN
6, rue Christophe Colomb
75008 PARIS
France

## 8. MARKETING AUTHORISATION NUMBER

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

November 2000.

# *APPENDIX 11.3.*

# STATUS OF CLINICAL TRIALS

# *APPENDIX 11.3.1*

# CLINICAL TRIALS IN PROGRESS

## ONGOING CLINICAL TRIALS NOT SPONSORED BY THE COMPANY BUT FOR WHICH EXELGYN PROVIDED THE ACTIVE AND PLACEBO TABLETS

| PRINCIPAL INVESTIGATOR and TRIAL CODE | COUNTRY | TITLE | N PATIENTS | | SINGLE DOSE (mg) | Report |
|---|---|---|---|---|---|---|
| | | | ENROLLED | EXPECTED | | |
| (b) (4) | | | | | | |

# *APPENDIX 11.3.2.*

# NAMED-PATIENTS STUDIES

# NAMED PATIENTS

## Named-patients studies
## May 31st, 2002

| | |
|---|---|
| 41 | with unresectable meningioma |
| 1 | with leiomyosarcoma |
| 1 | with adrenal tumors (Cushing syndromes) |
| 1 | with paraganglioma |
| 1 | with paraneoplastic syndrome |
| 2 | with psychotic depression |
| 1 | with neurofibromatosis type II |
| 1 | with ovarian cancer |
| **49** | **Patients** |

# *APPENDIX 11.4*

# LINE LISTINGS OF INDIVIDUAL CASE HISTORIES

# CIOMS LISTING

**MIFEPRISTONE**

| Company number | Reaction term | | | | |
|---|---|---|---|---|---|
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

## SERIOUSNESS Yes

## REPRODUCTIVE DISORDERS, FEMALE

S2002003F/MIF1 **PREGNANCY UNINTENTED**
F spontaneous N TERMINATION OF PREGNANCY Fetal malformation

UNINTENTED PREGNANCY, FETAL MALFORMATION:

This case from France involved a 25-year-old woman who received mifepristone 600 mg on (b) (6) followed by misoprotol 400 µg on (b) (6) for medical termination of pregnancy at 7 weeks gestation. She did not return for the control 2 weeks later.
On (b) (6) she came back to the hospital for an amenorrhea. An ultrasound examination showed a viable intra-uterine pregnancy corresponding to 15 weeks gestation and revealed embryo (LCC: 90 mm) with a cephalic abnormality (encephalocele).
On (b) (6) therapeutic termination of pregnancy was decided and performed. Post-abortum examination revealed a 92 g fetus which was malformed with meningo-encephalocele, finger defects on the left hand (oligodactylia) and feet (monodactylia) and dysmorphia.

Company comments:
There were no reported cases of malformation associated with use of misoprostol when used with mifepristone.

S2001020F/MIF1 **EXCESSIVE BLEEDING**
(b) (6) F spontaneous Y TERMINATION OF PREGNANCY Recovered

INCOMPLETE ABORTION, EXCESSIVE BLEEDING:

This case from France (Regional Centre of Pharmacovigilance) involved a 22-year-old woman. She received mifepristone 200 mg for medical termination of pregnancy at 12 weeks gestation, on (b) (6)
She changed her mind, decided to keep her pregnancy and did not take misoprostol. One day later on (b) (6) she experienced excessive bleeding and came to the emergency room. An incomplete abortion was diagnosed and curettage was performed. The patient recovered with sequelae.

Company comments:
Case of misuse. Non conformed uses with respect to the SmPC of Mifegyne®. Improper posology. Mifepristone incorrectly administered (medical TOP at 12 weeks of amenorrhea).

S2001025F/MIF1 **PREGNANCY UNINTENDED**
☐ F spontaneous Y TERMINATION OF PREGNANCY Recovered

UNINTENDED PREGNANCY:

This case from France involved a 32-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

***SERIOUSNESS*** ***Yes***

## REPRODUCTIVE DISORDERS, FEMALE

S2001026F/MIF1 **PREGNANCY UNINTENDED**

| | | | | | |
|---|---|---|---|---|---|
| ☐ | F | spontaneous | Y | TERMINATION OF PREGNANCY | Recovered |

UNINTENDED PREGNANCY:

This case from France involved a 29-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001027F/MIF1 **PREGNANCY UNINTENDED**

| | | | | | |
|---|---|---|---|---|---|
| ☐ | F | spontaneous | Y | TERMINATION OF PREGNANCY | Recovered |

UNINTENDED PREGNANCY:

This case from France involved a 23-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001028F/MIF1 **PREGNANCY UNINTENDED**

| | | | | | |
|---|---|---|---|---|---|
| ☐ | F | spontaneous | Y | TERMINATION OF PREGNANCY | Recovered |

UNINTENDED PREGNANCY:

This case from France involved a 28-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

S2001029F/MIF1 **PREGNANCY UNINTENDED**

| | | | | | |
|---|---|---|---|---|---|
| ☐ | F | spontaneous | Y | TERMINATION OF PREGNANCY | Recovered |

UNINTENDED PREGNANCY:

This case from France involved a 32-year-old woman who received mifepristone 600 mg on (b) (6) and misoprostol 400 µg 2 days later for termination of pregnancy. The treatment failed and the patient requested surgical termination of pregnancy on (b) (6)

Company comments:

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

## *SERIOUSNESS* *Yes*

## BODY AS WHOLE-GENERAL DISORDERS

| | | | | | |
|---|---|---|---|---|---|
| S2002004UK/MIF1 | | DEATH | | | |
| (b) (6) | UK | spontaneous | N | TERMINATION OF PREGNANCY | |

DEATH:

This case from UK involved a young woman who received mifepristone 200 mg on (b) (6) followed by misoprotol 800 µg two days later for medical termination of pregnancy at 7.5 weeks gestation. She was treated also by codeine and paracetamol for pain relief and azithromycin 1 mg antibiotic as prophylaxis of infection. The procedure went well and the patient was discharged home.
On (b) (6) evening, the patient started to feel unwell and reported pain in her leg, headache and racing heart. She reported to the hospital accident and emergency department but she collapsed and she died in the ambulance before her arrival at the hospital.
No information available at the moment of the time scale involved nor the details of her symptoms at the time of death.
Preliminary information from post-mortem indicates that one litre of blood was found in the stomach and gastric ulceration was identified.

Company comments:
The cause of the death is still unknown. Further details are requested. Results of the toxicology tests and the Coroners findings are still not available.

| | | | | | |
|---|---|---|---|---|---|
| S2002001F/MIF1 | | CHEST PAIN | | | |
| (b) (6) | F | spontaneous | N | FETAL DEATH IN UTERO | Recovered |

THORACIC PAIN, ISCHEMIC ACCIDENT:

This case from France involved a 29-year-old female patient without relevant medical history. She received mifepristone 600 mg on (b) (6) (b) (6) for fetal death in utero at 22 weeks gestation.
On (b) (6), another dose of mifepristone 600 mg was given, and the same day the patient experienced thoracic pain. She came to the emergency room, an ECG was performed and showed a subepicardial anteseptal ischemia. The patient was hospitalised in cardiology unit. Biological complementary exams were performed and showed very high level of antiphospholipid antibodies. This result together with the symptoms (Fetal Death in Utero + ischemia) allowed the physician to make the diagnosis of antiphospholipid Syndrome (systemic disease).
On (b) (6), cervical dilatation with laminarias was performed to induce dead foetus evacuation.
On (b) (6) expulsion occurred under peridural anaesthesia without any cardiovascular symptom. She was transferred to the intensive care unit and monitored during 24h. The patient recovered and had no additional complications.
Complementary exams were requested by the physician to confirm the diagnosis of systemic disease.

Company comments:
There is no known effect of mifepristone on the vessels. The relationship to Mifegyn® is unlikely in view of the fact that the patient was suffering from a latent systemic disease.

# CIOMS LISTING

**MIFEPRISTONE**

| Company number | Reaction term | | | | |
|---|---|---|---|---|---|
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

***SERIOUSNESS*** ***Yes***

## BODY AS WHOLE-GENERAL DISORDERS

S2001022F/MIF1 **EDEMA**
(b) (6) F spontaneous Y TERMINATION OF EARLY PREGNANCY Recovered

ALLERGIC REACTION, PALPEBRAL EDEMA:

This case from France involved a 19-year-old woman who received mifepristone 600 mg on (b) (6) for medical termination of pregnancy.
On (b) (6), she received at 6:45 a.m. misoprostol, Temgesic® (buprenorphine), Monocline® (doxycycline) and Primperan® (metoclopramide). At 8a.m., she received Pro-Dafalgan® (propacétamol) and Profenid® (kétaprofène). She vomited immediately and experienced bilateral palpebral edema without any cardiovascular and pulmonary symptom. The hemodynamic situation was correct. She was treated immediately with Celesten® (betaméthasone) and she left the hospital the same day. Cutaneous tests were performed for Cytotec® (misoprostol), Temgesic®, Monocline®, Pro-Dafalgan®, Profenid® and Monocline®. All were negative.

Company comments: Expected and listed adverse event

S2001030F/MIF1 **ALERGIC REACTION**
(b) (6) F spontaneous Y TERMINATION OF EARLY PREGNANCY Recovered

CYTOTEC ALLERGIC REACTION:

This case from France involved a patient who received mifepristone and misoprostol for medical termination of pregnancy on (b) (6).
The patient developed allergic reaction 2 hours after taking misoprostol, she had pallor, tachycardia, hypotension. The patient was hospitalized and treatment was given. The medical termination of pregnancy failed and the patient requested surgical termination of pregnancy which was performed. Cutaneous allergic tests were performed for misoprostol, mifepristone and trinordiol. The tests were negative for mifepristone and trinordiol. Misoprostol test was strongly positive and the drug became contra-indicated for the patient.

Company comments: Expected and listed adverse event

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

## SERIOUSNESS Yes

## RESISTENCE MECHANISM DISORDERS

| | | | | | |
|---|---|---|---|---|---|
| S2001019F/MIF1 | | SEPTICEMIA | | | |
| (b) (6) | F | spontaneous | Y | TERMINATION OF EARLY PREGNANCY | Recovered |

STREPTOCOCCUS SEPTICEMIA, ENDOMETRITIS, ARTHRITIS, ICTERUS, ANEMIA:

This case from France involved a 29-year-old woman who was given mifepristone 400 mg on (b) (6) for medical termination of pregnancy while she was at 7.3 weeks of amenorrhea. She received misoprostol (400 µg x 2) two days later on the (b) (6) The patient did not bleed very much during the three hours observation period and the expulsion did not occur. She went home with a prescription for an ultrasound examination, analgesics and oral contraception.
On (b) (6), the patient experienced fever (40°C), vomiting and diarrhea. After examination, the doctor diagnosed febrile arthritis of the left knee. The patient came to emergency room with icterus, important metrorrhagia and pelvic pain at the gynaecological examination. An ultrasound was done and showed a normal uterus with a normal size. Hemoglobin level was 8.7 g/l, SGPT 69 and SGOT 96, bilirubin level was 66 µmol/l and βHCG were 47,000 mUI/ml.
She was hospitalised and the diagnosis of endometritis with secondary localisation at left knee was done. She was treated with amoxicillin-clavulanic acid, netilmicin and oxytocin.
On (b) (6), at 1 a.m., vacuum aspiration was performed because of heavy bleeding and low hemoglobin level (6.9 g/l). The same day, at 6 a.m. the hemoglobin level decreased to 4.9 g/l and blood transfusion was performed. Hemocultures and bacteriological test of vaginal fluid were done and revealed a *Streptococcus dysgalactiae penicillin sensible*. The treatment was changed to amoxicillin and metronidazole.
On (b) (6) puncture of the knee showed 1,000 white blood cells (95% sterile polynuclear).
On an arthroscopy was performed and βHCG were 4,800 mUI-ml. Apyrexia was obtained after 72h of antibiotherapy.
On , gynaecologic problems were resolved, the outcome was favorable with a good status of the patient and normal clinical examination.

Company comments:
The dose of mifepristone (400 mg) was less than the recommended one (600 mg).

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

## SERIOUSNESS No

## REPRODUCTIVE DISORDERS, FEMALE

S20000024S/MIF2 PREGNANCY UNINTENDED

| | | | | | |
|---|---|---|---|---|---|
| ☐ | S | spontaneous | Y | TERMINATION OF PREGNANCY | Normal baby |

UNINTENDED PREGNANCY, NORMAL BABY:

This case from Sweden involved 20-year-old woman who was treated with mifepristone 600 mg followed by gemeprost 1mg at 8-9 weeks gestation . She came back to the hospital, after 4 weeks for control by urinary pregnancy test. The result was negative. She came back again later to the hospital and a 23 weeks pregnancy was shown by ultrascan. Application for late abortion was made but the authority did not approve (this case was reported in PSUR n°10: S2000024S/MIF).
The pregnancy was normal and a totally healthy baby girl was born on (b) (6)

Company comments:
This case has been reported retrospectively.

S2001031UK/MIF1 PREGNANCY UNINTENDED

| | | | | | |
|---|---|---|---|---|---|
| ☐ | UK | spontaneous | Y | TERMINATION OF PREGNANCY | Ongoing |

UNINTENDED PREGNANCY:

This case from UK involved 21-year-old woman who received mifepristone 200 mg at 17 weeks gestation for termination of pregnancy. She changed her mind and wanted to keep her pregnancy. More information is requested.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

S2001032UK/MIF1 PREGNANCY UNINTENTED

| | | | | | |
|---|---|---|---|---|---|
| ☐ | UK | spontaneous | Y | TERMINATION OF PREGNANCY | Ongoing |

UNINTENTED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg and misoprostol 800 µg vaginally for termination of early pregnancy. She changed her mind and decided to keep her pregnancy. More information is requested.

Company comments:
No other information, follow-up has been required. This case has been reported prospectively.

# CIOMS LISTING

**MIFEPRISTONE**

| Company number | Reaction term | | | | |
|---|---|---|---|---|---|
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

***SERIOUSNESS*** ***No***

## REPRODUCTIVE DISORDERS, FEMALE

S2001033UK/MIF1 **PREGNANCY UNINTENDED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENDED PREGNANCY:

This case from UK involved a woman who received mifepristone 600 mg for termination of pregnancy at 18 weeks of gestation. She changed her mind and decided to keep her pregnancy. More information is requested.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

S2001034UK/MIF1 **PREGNANCY UNINTENTED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENTED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg at 9 weeks gestation for termination of pregnancy. She changed her mind and wanted to keep her pregnancy. More information is requested.

Company comments:
No other information, follow-up has been required. This case has been reported prospectively.

S2001035UK/MIF1 **PREGNANCY UNINTENDED**
☐ UK spontaneous Y TERMINATION OF PREGNANCY Ongoing

UNINTENDED PREGNANCY:

This case from UK involved female patient who received mifepristone 200 mg and misoprostol 600 µg vaginally followed by misoprostol 400 µg per os for termination of pregnancy at 10 weeks gestation.. The treatment failed and the patient decided to keep her pregnancy.

Company comments:
No other information, a follow-up has been required. This case has been reported prospectively.

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

## SERIOUSNESS No

## REPRODUCTIVE DISORDERS, FEMALE

S2001024D/MIF1 PREGNANCY UNINTENDED
☐ D spontaneous Y TERMINATION OF PREGNANCY

UNINTENDED PREGNANCY:

This case from Germany involved female patient who received mifepristone 600 mg on (b) (6) followed by misoprostol 400 µg 36 hours later for termination of pregnancy at less than 6 weeks amenorrhea.
She came back for control on (b) (6) She was bleeding and the ultrasound showed continuing intra-uterine pregnancy. The patient requested a surgical termination of pregnancy which was performed.

Company comments:

S2001023D/MIF1 PREGNANCY UNINTENDED
☐ D spontaneous Y TERMINATION OF PREGNANCY

UNINTENDED PREGNANCY:

This case from Germany involved a 24-year-old woman who received mifepristone 600 mg on (b) (6) followed by misoprostol 400 µg 2 days later for medical termination of pregnancy.
She came back for control on (b) (6) An ultrasound was performed and showed continuing intra-uterine pregnancy. Surgical termination of pregnancy was performed.

Company comments:

S2001017UK/MIF2 PREGNANCY UNINTENDED
☐ UK spontaneous Y TERMINATION OF PREGNANCY fetal death

UNINTENDED PREGNANCY, FETAL DEATH IN UTERO:

This case from UK involved a 22-year-old woman who received mifepristone 200 mg on (b) (6) followed by misoprostol 400 µg two days later for medical termination of pregnancy in the first trimester. The treatment failed and the patient decided to keep her pregnancy (this case was reported in PSUR n° 12, case # S2001017UK/MIF)
She came back for control on (b) (6) An ultrasound was performed and showed fetal death in utero with no fetal abnormality and a large placenta abruption. The abortion occurred on (b) (6)

Company comments:
Fetal death in utero is probably related to the large placenta abruption and not related to the early administration of mifepristone.

# CIOMS LISTING

| MIFEPRISTONE | | | | | |
|---|---|---|---|---|---|
| Company number | Reaction term | | | | |
| Date | Country | Type of report | labelled | Indication | Outcome |
| Reaction / event description | | | | | |
| Case comments | | | | | |

***SERIOUSNESS*** ***No***

## BODY AS WHOLE-GENERAL DISORDERS

| | | | | | |
|---|---|---|---|---|---|
| S2001021F/MIF1 | | RASH | | | |
| (b) (6) | F | spontaneous | Y | UNRESECTABLE MENINGIOMA | Recovered |

GENERALISED RASH, TOXIDERMA:

A 71 year-old female patient with relevant medical and surgical histories of unresectable meningioma, ovarian and uterine surgery and arterial hypertension. She received since (b) (6) mifepristone 200 mg.
On (b) (6) she experienced generalised macular rash.
In the investigator judgement the event is related to the drug mifepristone. The treatment was stopped and the patient recovered totally with an anihistaminic treatment (Zyrtec®).

Company comments:
Expected and listed adverse event.

| | | | | | |
|---|---|---|---|---|---|
| S2002002D/MIF | | ALLERGIC REACTION | | | |
| (b) (6) | D | spontaneous | Y | TERMINATION OF EARLY PREGNANCY | Recovered |

ALLERGIC REACTION:

This case from Denmark involved female patient who received mifepristone 600 mg on (b) (6) for a medical termination of pregnancy. Five hours later, she begun to have exhantem on her arm and later over on the whole body.
She also experienced pressure over the breast and tendency for fainting. She was treated with antihistaminic agent and solumedrol 80 mg. The event disappeared and the patient totally recovered.

Company comments:
Expected and listed adverse event

# *APPENDIX 11.5*

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**REFERENCE 1**

J.I. Ojidu, S.D. Sabharwal

**Setting up a one-stop mifepristone-misoprostol medical termination of pregnancy service for all gestation from 5 to 23 weeks – a review of 482 cases.**

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GYNAECOLOGY

# Setting up a one-stop mifepristone—misoprostol medical termination of pregnancy service for all gestations from 5 to 23 weeks—a review of 482 cases

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*Summary*
Mifepristone—misoprostol combination is increasingly being utilised for medical termination of pregnancy on account of its reported efficacy, safety and lower cost. Experience with this modality of effecting termination of pregnancy from 9 to 13 weeks' gestation is scanty. At the Scunthorpe General Hospital in the United Kingdom, we established a nurse-led, one-stop medical termination of pregnancy service using mifepristone and misoprostol for all gestations from 5 to 23 weeks. A review of the case records of 482 women who had medical termination of pregnancy at all gestations from 5 to 23 weeks from December 1997 to May 1999 was undertaken in order to assess the effectiveness and complications associated with the mifepristone—misoprostol protocol. Complete abortion was achieved in 406 (84%) women. Surgical evacuation was required to complete the abortion in 74 (16%) women. The complete abortion rate was similar across the spectrum, i.e. 87% in the 5–8-weeks group; 79% in the 9–13 weeks group; and 87% in those of ≥14 weeks. Two failures occurred: one of them proceeded to surgical evacuation after three courses of misoprostol, while the other continued with her pregnancy after one course. Three women (0·6%) required blood transfusion for haemorrhage, while two others were treated for infection. Oral mifepristone with or without vaginal misoprostol in an effective and safe regimen for termination of all pregnancies from 5 to 23 weeks' gestation.

## Introduction

The medical option for termination of pregnancy is increasingly being utilised. The efficacy of mifepristone and misoprostol in this regard has been established (UK Multicentre Study, 1997; Ashok and Templeton, 1999; Gouk *et al.*, 1999). The other option, surgical evacuation of the uterus, although safe and effective, requires skilled personnel (Grimes and Cates, 1997). In addition, the medical option offers patients choice and is cheaper (Cameron *et al.*, 1996). Various regimens utilising mifepristone and misoprostol for terminating pregnancies at all possible gestations have been used (El-Refaey *et al.*, 1995; Ashok *et al.*, 1998; Ashok and Templeton, 1999).

Although the manufacturers of mifepristone recommend the use of a 600-mg dose pretreatment and gemeprost as the prostaglandin of choice, for termination of pregnancy, 200 mg of mifepristone and misoprostol (although not licensed for this indication) can be as effective (WHO, 1993; Webster *et al.*, 1996; Dickenson *et al.*, 1998). These have cost-saving implications. Using low-dose mifepristone and misoprostol as described in this text could save £157 per case compared to the manufacturer's recommendation (Table I).

Table I. Cost per termination of pregnancy by method

| *Method* | *Cost per case* |
|---|---|
| Surgical | £226 |
| Gemeprost | £175 |
| Mifepristone/misoprostol | £18 |

Mifepristone is recommended for use at gestations of ≤8 and ≥13 weeks, but not from 9 to 12 weeks. It is in the latter area that experience is scanty. In this unit, prior to June 1997, most early pregnancy terminations were performed surgically while late termination involved using gemeprost. In June 1997, a medical termination of pregnancy clinic using mifepristone/misoprostol for all gestations from 5 to 23 weeks was established. This review was undertaken to assess the effectiveness of and problems associated with this method as the sole means of termination of pregnancy.

## Methods

This service is provided by a specially dedicated termination of pregnancy clinic based exclusively on a day-case ward. It is led by specially trained nurses (additional qualifications include certificate in counselling) and supported by nursing and medical personnel, and the ultrasound department. We aim to see and treat patients within 2 weeks of referral (this target has been achieved in 90% of cases).

When a patient is referred, she first has an ultrasound examination to establish viable intrauterine pregnancy and gestational age. An occasional asymptomatic ectopic gestation is picked up at this stage. She then moves into the counselling room, during

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which time her wish to terminate her pregnancy is confirmed. She is assured of support, medical and surgical options for termination of pregnancy are discussed with her as well as future contraception.

If she elects to proceed with medical termination, the medications are usually commenced on the same day or the next day according to patient preference. Medication consists of mifepristone 200 mg orally. She is observed for 2 hours to ensure that she does not vomit and that the medication is retained. She goes home and returns 36–48 hours later when 800 mcg of misoprostol is administered vaginally. Those who are ≤8 weeks' gestation are observed for 6 hours and discharged. Most in this group (73%) expel the products of conception at this stage. Those who are ≥9 weeks' gestation receive further doses of misoprostol at 400 mcg orally 3-hourly for three doses if they had not expelled products of conception. This group may be observed overnight in hospital if necessary. In the occasional case in which the product of conception is not expelled, a repeat course of misoprostol is administered 24 hours later. The clinic staff check all products of conception for completeness. Contraception is commenced soon after abortion is complete.

When the patients go home, they are in contact with clinic staff and their GP by telephone. They are advised to report if unwell, if there is excessive bleeding, or offensive vaginal discharge. They are seen 2 weeks later to ensure that all is well. An ultrasound scan is performed in those women in whom the clinic staff did not visually confirm expulsion of products of conception, so as to ensure that abortion had occurred and was complete.

## Results

The case records of 482 women who had mifepristone/misoprostol termination of pregnancy from June 1997 to May 1999 was reviewed. This represented 76% of all terminations of pregnancy during this period. This is compared to 27% in the period before June 1997 (Figure 1) The women were aged from 12 to 42 years with a mean of 24·2 years. Multiparous women made up 57·5% while 42·5% were nulliparous.

A total of 406 (84%) women had complete expulsion of the products of conception without any need for surgical intervention (made up of 403 women who succeeded after one course and three women who required repeat medication to succeed) (Figure 2). Seventy-four women did expel products of conception but required surgical evacuation to complete the process. Two women did not expel any products of conception—one was an 8 weeks' pregnancy that continued after one course of medication while the other was a 16 weeks' pregnancy which remained intact and had to have a surgical termination. A breakdown of the outcome into gestational age groups showed that complete success was achieved in 86·9% of those of ≤8 weeks' 79% in the 9–13 weeks' group, and 86·8% in the ≥14 weeks' group (Table II). Outcome was similar in multiparous and nulliparous groups with success rates of 84·9% and 83·6%, respectively.

The time from the administration of vaginal misoprostol to expulsion of the products of conception (misoprostol—abortion interval) ranged from 30 minutes to 29·5 hours across the board. Subdivided into gestational age groups, the mean misoprostol—abortion interval was 4·9 hours in the ≤8 weeks' 7·5 hours in the 9–13 weeks' group and 9·5 hours in the ≥14 weeks' group (Figure 3).

Haemorrhage requiring blood transfusion occurred in three patients (0·6%) and two (0·4%) patients were treated for infection.

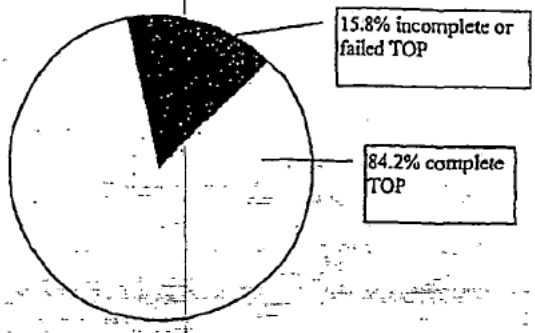


Figure 2. Overall outcome of mifepristone/misoprostol termination of pregnancy.

Table II. Outcome following mifepristone/misoprostol therapy

| | Gestation | | |
|---|---|---|---|
| | ≤8 weeks (n=236) | 9–13 weeks (n=169) | ≥14 weeks (n=76) |
| Complete | 205 (86·9%) | 134 (79·2%) | 67 (87%) |
| Incomplete | 30 (12·7%) | 35 (20·7%) | 9 (11·6%) |
| Failed | 1 (0·4%) | 0 | 1 (1·3%) |

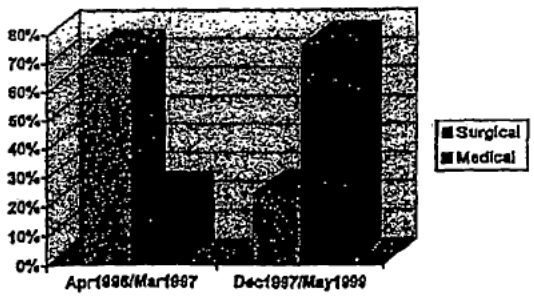


Figure 1. Proportion of termination of pregnancy performed surgically and medically before and after June 1997.

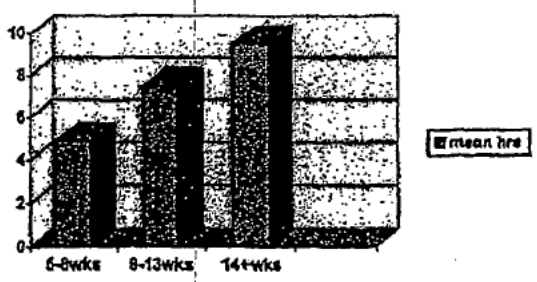


Figure 3. Mean misoprostol–abortion interval.

## Discussion

Termination of pregnancy services are increasingly adopting methods that reduce cost and provide choice for women. Setting up a one-stop termination of pregnancy service is one way of achieving this aim. Providing all the service in one ward helped patient uptake of the service. A recent audit (unpublished) showed that 97% of all terminations of pregnancy in this hospital are now performed using the protocol described, the remaining 3% by the surgical method.

Our results add to the growing body of evidence that low dose mifepristone and misoprostol regimen offers an effective modality for terminating pregnancy at all possible gestations, and this has been shown to be cheaper (Hinshaw, 1999). Based on local costing (Table I), a saving of £208 and £157 accrues for each case of pregnancy terminated using this mifepristone/misoprostol protocol compared to the surgical or gemeprost options, respectively. Mifepristone is licensed for termination of pregnancy at ≤8 weeks and at ≥13 weeks' gestation. In most hospitals, surgical methods are used almost exclusively to effect termination of pregnancy from 9 to 13 weeks' gestation. Our success rate of 79% at 9–13 weeks further attest to the feasibility of a medical approach at this gestation (Ashok *et al.*, 1998a; Gouk *et al.*, 1999). Before June 1997, all the 168 women who presented for medical termination would have gone to theatre for suction termination. But following the introduction of this protocol, 133 of them had their wish accomplished without surgical intervention.

Our overall success rate of 84% is within the range of success rates reported in the literature, for those methods that used a similar regimen (Spitz *et al.*, 1998; Ashok *et al.*, 1998b). The success rate of 79% at 9–13 weeks could improve now that we are at the top end of the 'learning curve' since introducing the protocol in June 1997. This has nevertheless transformed the provision of termination of pregnancy service from a predominantly surgical procedure to an almost exclusively low-cost medical procedure.

Major complications are rare. Our blood transfusion rate of 0·6% is within the literature range of 0·4–0·7% (UK Multicentre Study, 1997; Gouk *et al.*, 1999). The prophylactic antibiotic regimen utilised in this protocol follows the recommendation of Sawaya *et al.* (1996), and the RCOG (1997). This seem effective since only two (0·4%) women were treated for infection. The low dose mifepristone/misoprostol protocol for termination of pregnancy at all gestations from 5 to 23 weeks is effective and safe. It reduces cost, releases theatre slots and staff, resources which are usually under pressure, for use by other competing needs. In addition, it offers women choice, especially those of 9–13 weeks' gestation who in most hospitals have no choice but surgical evacuation of uterus.

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## *REFERENCE 2*

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**First trimester abortion with mifepristone and vaginal misoprostol.**

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# First trimester abortion with mifepristone and vaginal misoprostol

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**Abstract**

This study assessed the efficacy and side effects of first trimester medical abortion using mifepristone and vaginally administered misoprostol. Medical abortion was first introduced in Denmark in December 1997, and the acceptability of this new approach in a Danish population was evaluated. The study included the first 100 women seeking medical abortion. The gestational age was from 33 to 56 days. All received 600 mg mifepristone (RU 486) orally followed 2 days later by vaginally administered misoprostol 400 μg. Success was defined as achieving complete abortion without the need for surgical evacuation. Ninety-three percent achieved a successful medical termination of pregnancy. Side effects were few, and the acceptability was high. Ninety percent of the women would prefer medical abortion in case of a new unwanted pregnancy. The combination of mifepristone and vaginally administrated misoprostol is effective, safe, has few side effects and is well accepted by Danish women. 

*Keywords:* Early medical abortion; Vaginal misoprostol; Vaginal $PGE_1$; Danish population

## 1. Introduction

Medical abortion during the first 49–63 days of gestation is generally successful after using pretreatment with the progesterone antagonist mifepristone (Mifegyne®) followed by a prostaglandin E-1 analog [1–3]. Several medical regimens have been used, where the most common prostaglandin E-1 preparation in Europe is gemeprost (Cervagem®). Recently, the prostaglandin-E-1 misoprostol (Cytotec®) has been introduced. Most reports have been based on oral administration, but vaginal administration is associated with fewer side effects and improved efficacy [2,4–6].

Medical abortion is a new approach in Denmark, and the purpose of this study was to assess the efficacy, side effects and the acceptability of mifepristone followed by vaginal administration of 400 μg misoprostol 2 days later.

## 2. Materials and methods

The study was performed at the Department of Gynaecology, University Hospital of Aarhus, Denmark, from September 1998 to July 1999. During that period, 753 women underwent termination of pregnancy in the department. Women over the age of 18, requesting termination of pregnancy and with a gestation of less than 56 days, received written information about the methods offered before attending the clinic. They were all tested for chlamydia by their general practitioner and, if positive, treated with antibiotics prior to the day of attendance. All women underwent a transvaginal ultrasound scan to evaluate the gestational age. Two-hundred-eighty women (34.5%) were less than 56 days pregnant. If no medical contraindications to the mifepristone-misoprostol regimen were found, the woman was offered the choice between termination by vacuum aspiration or medical termination.

At the first visit, including ultrasound scan, a further 25 women did not fulfill inclusion criteria and were excluded. A total of 100 (39.2%) chose the medical abortion method and thus constitute the patients entered into the study.

Oral mifepristone 600 mg was administered either on the same day as the first visit to the clinic or within the following 4 days (day 1), and the women were allowed to go home 30 min later. They were informed that in some cases abortion might occur at home following the mifepristone administration, and an emergency telephone number was given. Thirty-six to 48 h later, they returned in the morning to the outpatient clinic (day 3). Here, vaginal misoprostol 400 μg was given (self administration) and 2 tablets containing 400 mg paracetamol and 28.7 mg codeinphosphat, administered

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Table 1
Data of the first 100 women undertaking medical abortion

| | | |
|---|---|---|
| Age (years; median; range) | 29 | [18–46] |
| Gestational age (days; median; range) | 48 | [33–56] |
| Nullipara | 45 | |
| Previous termination of pregnancy[a] | 30 | (32 %) |

[a] n = 93.

orally. The patients were observed by the nurses for bleeding and pain over the next hours, permitting further administration of analgesic or antiemetic agents if necessary. If abortion had not taken place, evaluated by the amount of bleeding within the first 3 h, a further 400 μg misoprostol was administered vaginally. They were allowed to leave the hospital if bleeding and pain were acceptable 2–5 h after the last misoprostol administration. The nurses telephoned all patients on day 4. Two weeks later, the women had a vaginal ultrasound scan. If the thickness of the endometrium was less than 15 mm, with no sign of retained product, no further action was taken. If the thickness was more than 15 mm, β-hCG concentration was measured, and the woman was followed weekly by ultrasound scan until measurement of β-hCG was below detection level. Rhesus-negative women received anti-D (Rho) immunoglobulin at day 3.

All women were asked to fill in a daily chart concerning bleeding, pain, nausea, vomiting, diarrhea, and whether they had gone to work/done as usual over the next fortnight from day 1. The amount of bleeding was estimated by a visual analog score (VAS-scale) with a line (12 cm long) ranging from "no bleeding" to "heavy bleeding" at the ends, with the mark "like your period" in the middle. Likewise, the severity of pain was measured on a VAS-scale ranging from "no pain" to "severe pain," with the mark "moderate pain" in the middle. The satisfaction with the method was estimated on a VAS-scale ranging from "dissatisfied" to "very satisfied" (range 0 to 12) with "satisfied" in the middle. All medical records were reviewed 2 months after entry to the study to evaluate the success rate and complication.

## 3. Results

One hundred women (39.2%) chose the medical abortion method, and demographic data can be seen in Table 1. Five

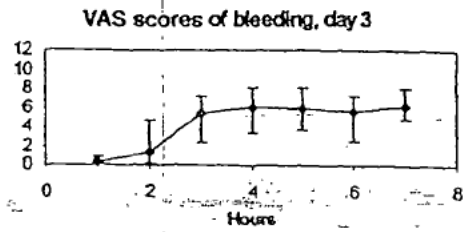


Fig. 1. Bleeding after misoprostol administration (day 3 after mifepristone administration). X-axis: hours after misoprostol administration; y-axis: score on VAS-scale. Median, 5 and 95-percentiles.

women did not attend the follow-up 14 days later, in spite of several letters/telephone calls. When contacted by telephone, all 5 reported cessation of bleeding and symptoms of pregnancy.

Side effects are presented in Table 2. After administration of mifepristone, 59% started to bleed with a median of 0.6 on a scale from 0–12 (range 0–11.6). Almost 4 of 5 women experienced pain with a median pain score of 1.1 (75 percentile: 2.6, total range 0–9) on a scale from 0 to 12, and 23 took paracetamol for the pain. The VAS scores of bleeding and pain after misoprostol administration (day 3 after mifepristone administration) are presented in Figs. 1 and 2.

Eighty-seven percent of the pregnancies were aborted at the hospital. Nine women believed they had aborted on day 2, and 4 that they had aborted on day 4. The nurses recorded when the women had been bleeding more heavily and probably aborted. A fixed time for abortion could be recorded for 84 women, and the time from administration of vaginal misoprostrol to abortion was a median of 3 h (75 percentile: 3 h and 30 min). An additional dose of misoprostol (400 μg) was administered to 9 women 3 h after the initial dose, as the bleeding was less than expected for an abortion to have taken place. Twenty women had extra analgesics, mainly paracetamol (1 g), and only one patient received an injection of pethidine. No other drugs were administered.

Figures 3 and 4 show the VAS scores of bleeding and pain from day 4 to 13.

At the follow-up 14 days after mifepristone administration, 66% were still bleeding, although it was mainly spotting (median 0.4 on the VAS-scale), and only 4% indicated that it was more than a period. Two patients marked pain of

Table 2
Side effects (percents and n in parentheses)

| | Prior to abortion | After mifepristone administration (day 1) (n = 100) | After misoprostol administration (day 3) (n = 99) | Day 14 (n = 94) |
|---|---|---|---|---|
| Nausea | 65% (65) | 72% (72) | 51% (50) | 0 |
| Vomiting | 12% (12) | 12% (12) | 18% (18) | 0 |
| Diarrhea | – | – | 3% (3) | 0 |
| Bleeding | – | 59% (59) | 100% (99) | 66% (62) |
| Pain | – | 79% (79) | 98% (97) | 5% (5) |

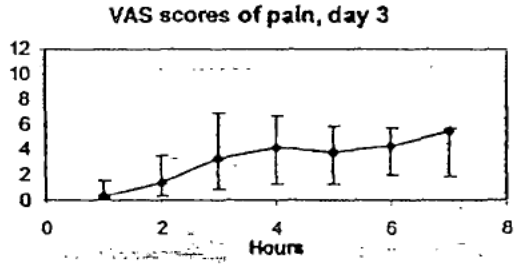


Fig. 2. Pain experienced after misoprostol administration (day 3 after mifepristone administration). X-axis: hours after misoprostol administration; y-axis: score on a VAS-scale. Median, 5 and 95 percentiles.

more than 5 on the VAS on day 14. None required analgesic at this time.

The endometrium was measured by ultrasound on day 14, and the median thickness was 9.2 mm (range: 3–18 mm, n = 87) (from edge to edge).

The overall success rate, defined as termination without use of evacuation, was 93% after 2 months of follow-up. No ongoing pregnancies were found at the 2-week follow-up. Four women were evacuated due to bleeding 7 to 9 weeks after administration of mifepristone, 2 had an evacuation due to infection (pyrexia, pain, discharge) at day 15 and 23, respectively, and one was evacuated due to severe headache occurring after administration of mifepristone; this patient did not receive misoprostol on day 3. Six of the 7 patients who had an evacuation had a gestation of more than 49 days.

Two patients were admitted to the ward due to bleeding and discharged the following day. Three women were given ergometrine tablets (Methergin®) orally for the next 3 days due to heavy bleeding, but none necessitating transfusion. No prophylactic antibiotics were given, and only the two women with clinical signs of infection received antibiotics.

All 100 women who had entered the study were asked to fill out a questionnaire on day 14. Approximately 14% felt that the bleeding had been more than expected. Likewise around 15% felt the pain and the nausea (16%) had been worse than expected. On the VAS-scale, satisfaction with

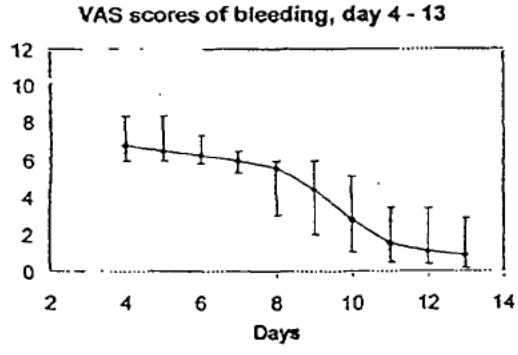


Fig. 3. Bleeding on day 4 to 13 after mifepristone administration. X-axis: days after mifepristone administration; y-axis: score on VAS-scale. Median, 5 and 95 percentiles.

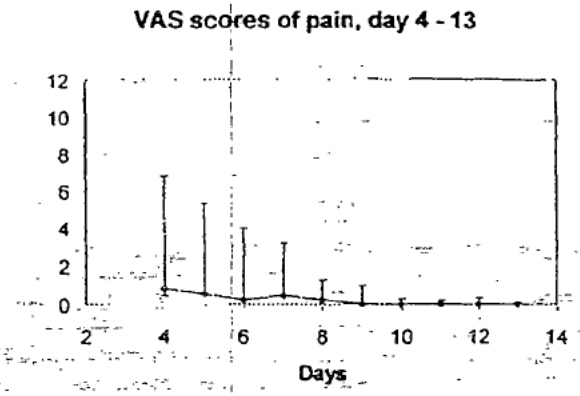


Fig. 4. Pain experienced on day 4 to 13 after mifepristone administration. X-axis: days after mifepristone administration; y-axis: score on VAS-scale. Median, 5 and 95 percentiles.

the method was a median of 12 (on a scale from 0 to 12; range 0–12). If they had to go through an abortion again, 90% would choose this method again. Of those who previously had experienced a surgical abortion (n = 26), 21 (81%) would choose the medical abortion.

Table 3 shows the influence of medical abortion on social life or working life. Sixty-two percent did go to work/did as usual on day 2, 68% on day 4, and only 1 or 2 women per day did not attend to their usual tasks from day 5 to 13 (n = 89).

## 4. Discussion

This study demonstrates that medical abortion using 600 mg mifepristone orally and 400 μg misoprostol vaginally is a well accepted, effective method of pregnancy termination for gestations less than 56 days. The success rate of 93% after 2 months of follow-up is similar to other studies for gestations less than 63 days [2,5,7–8]. In many studies the length of the follow-up period and the completeness of follow-up is difficult to evaluate. In this study, all medical records of the 100 women were evaluated 2 months after the medical abortion.

Thirty-nine per cent of the women who had the opportunity chose medical abortion. This is somewhat lower than reported in other countries [3,9–10,13], and could be due to the fact that medical abortion is a new method in Denmark; only 2 other hospitals had started the program at the time these data were collected. Moreover, as it has been shown

Table 3
Effect of medical abortion on attending work or social life

| | Day 2 (n = 100) | Day 4 (n = 89) | Day 5–13 (n = 89) |
|---|---|---|---|
| Unaffected work/social life | 62% (62) | 68% (61) | 98% (87) |

that the attitude of the advising medical staff influences a woman's choice [3], we expect more women to choose medical abortion in the future, as the staff becomes more familiar with the method. The very fact that women have a choice in method is important, hence she is more likely to be satisfied with the treatment [11].

The few gastrointestinal side effects seen in our study are as expected after vaginal administration compared to oral administration [2]. Twenty per cent of our population required more analgesics (mainly paracetamol), than those given at the time of administration of misoprostol, but only one received intramuscular opiate analgesia. Reported analgesic requirements for early medical termination of pregnancy vary greatly between centres, ranging from 12.5% [1] to 68% [8]. In a Danish study using gemeprost 55% received pethidine [12]. In addition, the price of misoprostol is substantially less: DKK 5 (USD 0.6), less than 2% of the DKK 290 (USD 34.4) that gemeprost costs.

This study has shown that mifepristone and misoprostol vaginally for early medical abortion is well tolerated and effective with an overall success rate of 93%. No antiemetic agents were needed, analgesic requirements were minimal and few side effects were reported.

## Acknowledgments

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***REFERENCE 3***

**O.S. Tang, K.J. Thong, D.T. Baird**

**Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases.**

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# Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases

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**Abstract**

The treatment outcomes of 956 women undergoing second trimester termination of pregnancy with mifepristone and gemeprost were studied. The median gestational age was 16 weeks (range: 12–24 weeks). All women were treated with 200 mg mifepristone orally, followed 36 h later with 1 mg vaginal gemeprost administered every 6 h to a maximum of 4 doses in the first 24 h. A second course of 1 mg vaginal gemeprost was given 3-hourly in the next 12 h, if abortion had not occurred. Overall, 96.4% and 98.8% of the women aborted within 24 and 36 h, respectively. The median induction-to-abortion interval was 7.8 h (range: 0.5–109.9 h). The induction-abortion interval was longer in nulliparous women and women with a gestation age 17 weeks or above. Surgical evacuation of the uterus was performed in 11.5% of women for incomplete abortion or retained placenta. More multiparous women (16.7%) required surgical evacuation of uterus than did nulliparous women (7.3%; $p < 0.001$). Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. In conclusion, a combination of mifepristone and gemeprost is a safe, effective, and noninvasive method of medical abortion for second trimester pregnancy. 

*Keywords:* Second trimester; Abortion; Mifepristone; Misoprostol

## 1. Introduction

Since the introduction of prostaglandin analogs for medical abortion more than two decades ago, medical methods have provided a safe alternative to surgical termination of pregnancy [1]. Although dilatation and evacuation is widely used in the United States, a combination of mifepristone and prostaglandin is the preferred method in the United Kingdom.

Different types of prostaglandin analogs have been used in the past 20 years for second trimester medical abortion. Currently, gemeprost (Cervagem, Farillon, Dagenham, UK) and misoprostol (Cytotec, Searle, Bucks, UK) are the two most common prostaglandin analogs used for this purpose. Both have been shown to be safe and effective when combined with mifepristone for second trimester abortion [2–4]. Although misoprostol is cheaper and stable at room temperature when compared with gemeprost, only the latter is licensed for the purpose of medical abortion.

Mifepristone (Exelgyn, UK) is a progesterone receptor blocker that increases the sensitivity of the uterus to prostaglandin analogs when administered to pregnant women [5]. The administration of 600 mg of mifepristone 36–48 h before gemeprost has been shown to shorten the induction-to-abortion interval [6]. Recently published data suggested that 200 mg is as effective as 600 mg for second trimester abortion [7].

The regimen used in present study was previously reported in a study of 100 women [2], and the purpose of this study was to report the effectiveness and safety of the same regimen in clinical practice over a period of 6 years.

## 2. Materials and methods

Nine hundred fifty-six consecutive women admitted to the Edinburgh Royal Infirmary for second trimester abortion from January 1994 to July 2000 were studied. Abortion was carried out under the conditions of the 1967 United Kingdom Abortion Act.

The gestational age was determined by menstrual history and clinical examination, and ultrasound was performed only if it was necessary as judged by the attending doctor. After the decision for termination of pregnancy was made, the women were referred to the Simpson Memorial Maternity Pavilion medical abortion unit where they were coun-

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Table 1
Characteristics of the 956 women who underwent midtrimester abortion

| Characteristics | Gestation age | | Parity | | Total |
|---|---|---|---|---|---|
| | 12–16 weeks n = 652 | 17–24 weeks n = 304 | Nulliparous n = 531 | Multiparous n = 425 | n = 956 |
| Median age in years (range) | 21 (14–44) | 22 (13–44) | 19 (13–44) | 26[a] (14–44) | 22 (13–44) |
| Median gestation age in wks (range) | — | — | 16 (12–24) | 15.5 (12–21) | 16 (12–24) |
| Parous (%) | 44.9 | 43.4 | — | — | 44.5 |

[a] Significant difference by Mann–Whitney test, $p < 0.001$.

seled by a doctor and a nurse. The women were then given a date for administration of a single dose of 200 mg oral mifepristone in the medical abortion unit. The women were admitted to the unit 36 h later. One milligram of gemeprost was inserted to the posterior vaginal fornix every 6 h for a maximum of four doses over the first 24 h. If abortion had not occurred within the first 24 h, 1 mg of vaginal gemeprost was inserted every 3 h to a maximum of five doses over the next 12 h. Intravenous (iv) oxytocin in incremental dosage of up to 111 mU/min was started 36 h from the first pessary, if abortion had not occurred after the second course of gemeprost.

Analgesia [paracetamol 1 g, dihydrocodeine 30 mg, or intramuscular (im) diamorphine 7.5 mg] and antiemetic (im cyclizine 50 mg) were administered as required.

Intramuscular syntometrine (5 IU oxytocin and 0.5 mg ergometrine maleate; Alliance, UK) was administered following expulsion of the fetus and placenta. The product of conception was examined by the attending doctor for completeness. Surgical evacuation of the uterus was carried out if there was evidence of retained placenta or clinical suspicion of incomplete abortion.

SPSS for Windows Statistical Package was used for statistical analysis. Continuous variables were compared by Mann–Whitney test. Differences in proportions were analyzed with the chi-square test or Fisher's exact test as appropriate. A $p < 0.05$ was considered significant.

## 3. Results

Table 1 shows the characteristics of the 956 women who underwent second trimester abortion. The median gestation age was 16 weeks (range: 12–24 weeks), and 31.2% of them were above 16 weeks. Multiparous women were older than nulliparous women (median 26 years versus 19 years, $p < 0.001$). Table 2 shows the treatment outcomes of these 956 women. The median dose of gemeprost required was two, and the median induction-to-abortion interval was 7.8 h. Two (0.2%) women aborted after mifepristone without gemeprost. One of them was a nulliparous woman at 14 weeks of gestation, and the other woman, at 16 weeks of gestation, had three previous vaginal deliveries. Both of the women aborted at home and there was no excessive bleeding after abortion. Following insertion of gemeprost, 32.8% and 53.1% of women aborted within 6 and 8 h, and 80.5% and 96.4% aborted within 12 and 24 h, respectively. Overall, 98.8% of women aborted within 36 h (Fig. 1). The median induction-to-abortion interval was significantly longer in nulliparous (8.5 h) compared to multiparous women (6.7 h) ($p < 0.001$). Women with gestational age of 17 weeks or above had a significantly longer induction-abortion interval (8.8 h) than women less than 17 weeks (7.00 h; $p < 0.001$)

Overall, 110 (11.5%) women required surgical evacuation of the uterus for incomplete abortion. The rate of

Table 2
Treatment outcomes by parity and gestation age

| | Gestation age | | Parity | | Total |
|---|---|---|---|---|---|
| | 12–16 weeks n = 652 | 17–24 weeks n = 304 | Nulliparous n = 531 | Multiparous n = 425 | n = 956 |
| Median dose of gemeprost (range) | 1 (0–14) | 2[a] (1–14) | 2[a] (0–9) | 1 (0–14) | 2 (0–14) |
| Median induction, in hours (range) | 7.00 (1.3–48.2) | 8.8[a] (0.5–109.9) | 8.5[a] (0.5–57.3) | 6.7 (1.25–109.9) | 7.8 (0.5–1009.9) |
| Surgical evacuation of uterus for incomplete abortion (%) | 77 (11.8) | 33 (10.9) | 39 (7.3) | 71 (16.7)[b] | 110 (11.5) |
| Need for other therapy (%)[c] | 5 (0.8) | 5 (1.6) | 1 (0.2) | 9 (2.1)[d] | 10 (1.0) |

[a] Significant difference by Mann–Whitney test, $p < 0.001$.
[b] significant difference by chi-square test, $p < 0.001$.
[c] Therapies include oxytocin, surgical evacuation of uterus, and hysterotomy.
[d] significant difference by Fisher's Exact test, $p = 0.007$.

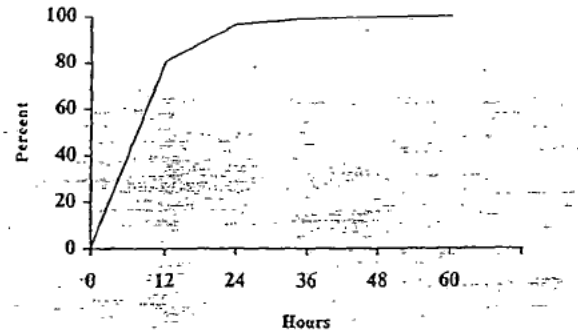


Fig. 1. Cumulative induction-to-abortion interval.

incomplete abortion was analyzed with respect to gestation, parity, and history of previous abortion. There was a trend ($p = 0.057$) toward a higher incidence of surgical evacuation in the 111 women with gestation of less than 14 weeks (17.1%) compared to women of greater than 14 weeks of gestation (10.8%). Women with a history of previous abortion had a significantly higher incidence of surgical evacuation (16.0%; $p = 0.001$) compared to women without a history of abortion (8.8%). Multiparous women had a significantly higher incidence of surgical evacuation (16.7%; $p < 0.001$) for incomplete abortion or retained placenta compared to nulliparous women (7.3%; Table 3).

Ten (0.1%) women failed to abort with gemeprost and required other methods for abortion. Seven (0.7%) women required an iv. infusion of oxytocin, two (0.2%) women at less than 14 weeks gestation needed surgical evacuation, and one (0.1%) woman underwent a hysterotomy. The woman who had a hysterotomy was 42 years old at 16 weeks of gestation. She failed to abort after nine doses of gemeprost and developed heavy vaginal bleeding requiring a blood transfusion during oxytocin infusion. An emergency hysterotomy was performed to terminate the pregnancy. Her hemoglobin concentration dropped from 11.9 g/dL to 7.5 g/dL prior to the hysterotomy. Three (0.3%) women were given more than nine doses of gemeprost. All of them were in the group of 10 women requiring other methods for abortion. The proportion requiring other methods for abortion was found to be higher in multiparous women.

Four patients (0.42%) stayed in hospital for more than 3 days. The woman who had a hysterotomy stayed for 5 days. The other three patients aborted after 48 h and also required surgical evacuation of the uterus for retained placenta. Blood transfusion was required only by the woman who had a hysterotomy. There was not a single case of cervical tear or cardiovascular complication.

## 4. Discussion

The results of the present series, which was larger than the previous study, of women who underwent second trimester termination of pregnancy confirms the efficacy of this combination regimen of mifepristone and gemeprost [2]. Out of the 956 women, 68.6% aborted within 10 h and could be managed as day-cases. The median induction-to-abortion interval (7.8 h) is comparable to previous studies using gemeprost or misoprostol in combination with mifepristone [2–4].

In this study, 11% of the women required evacuation of the uterus for retained placenta or incomplete abortion. Thirty percent of the women required evacuation of the uterus in our previous study using a similar regimen when pelvic ultrasound was used in addition to clinical judgment for the diagnosis of incomplete abortion or retained placenta [2]. In the past 6 years, our diagnosis of retained placenta or incomplete abortion has been based on clinical judgment alone, and this has reduced the proportion of women requiring surgical intervention. The surgical evacuation rate in the present study is comparable to the regimen using mifepristone and misoprostol (9.4%) [3].

The response of multiparous women was different from that of nulliparous women following treatment with the antiprogesterone, mifepristone and gemeprost. The induction-to-abortion interval of multiparous women (6.7 h) was significantly shorter than nulliparous women (8.5 h). This can be explained by the difference in the compliance of the cervix in the two groups of women. In contrast, multiparous women (16.7%) were found to have a significantly higher incidence of surgical evacuation of the uterus after medical abortion compared to nulliparous women (7.3%). Surgical

Table 3
Effect of obstetric history on the incidence of incomplete abortion

| | Obstetric history | | | | |
|---|---|---|---|---|---|
| | Nulliparous | | Multiparous | | |
| | No past history of previous abortion n = 390 | History of previous abortion n = 141 | No past previous history of abortion n = 209 | History of previous abortion n = 216 | Total n = 956 |
| Surgical evacuation for incomplete abortion (%) | 23 (5.9) | 16 (11.3)[a] | 30 (14.4) | 41 (19.0)[b] | 110 (11.5) |

[a] History of previous abortion versus no history of previous abortion in nulliparous women ($p = 0.053$ by chi-square test).
[b] History of previous abortion versus no history of previous abortion in multiparous women ($p = 0.251$ by chi-square test).

evacuation is usually performed for incomplete abortion based on the clinical diagnosis of retained placenta, incomplete placenta, or excessive hemorrhage. In this study, the incidence of surgical evacuation was found to be higher in women with a previous history of abortion. Thus, women with a history of previous pregnancy that ended either in an abortion or full-term delivery were more likely to have retained placenta or residual trophoblast. It was reported that more parous women bled greater than 500 mL during termination of second trimester pregnancy by gemeprost alone [8]. The reason why a higher proportion of multiparous women failed to abort completely with this regimen of mifepristone and gemeprost is not known but is similar to recent reports on medical abortion in the first trimester [9,10]. A more efficient establishment of the pregnancy at a very early stage was suggested by one of the author as the reason for a higher failure rate in multiparous women [9].

The choice of surgical versus medical termination of pregnancy poses a dilemma to clinicians in the management of women at 12–14 weeks gestation [11]. Twenty percent of multiparous women in this study required surgical evacuation for incomplete abortion. In addition, the proportion of multiparous women who failed to abort with gemeprost was higher. Dilatation of the cervix is usually easier in multiparous women, and it may be more convenient and cost-effective to perform a dilatation and evacuation in this group of women. In skilled hands, dilatation and evacuation may require a shorter stay in the hospital, and women may possibly experience less pain compared to termination using this regimen of mifepristone and gemeprost.

The results of this study demonstrated that gemeprost is comparable to misoprostol in terms of efficacy and safety [3]. Misoprostol is cheap and stable at room temperature when compared to gemeprost. Oral misoprostol is available in many countries for treatment of peptic ulcer. Although vaginal misoprostol is commonly used with mifepristone for second trimester medical abortion, it is not licensed for this purpose. Moreover, gemeprost is the prostaglandin that clinicians usually resort to when the women fail to abort using misoprostol for termination of pregnancy in the second trimester [3,12,13].

In conclusion, a combination of mifepristone and gemeprost is a safe, noninvasive, and effective method for termination of pregnancy in the second trimester.

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A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation.

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# A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation

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**BACKGROUND: Since 1991, mifepristone in combination with a prostaglandin analogue has been licensed for termination of pregnancy in the UK at up to 9 weeks amenorrhoea, and since 1995, beyond 13 weeks. Surgical methods are used almost exclusively at 10–13 weeks amenorrhoea. METHODS: A patient-centred, partially randomized, controlled trial was carried out. Those who expressed a strong preference for either medical ($n$ = 15) or surgical ($n$ = 62) abortion were allocated to that method. The remainder agreed to be randomized. The medical method ($n$ = 188) was mifepristone 200 mg followed by misoprostol up to 3 doses, and surgery ($n$ = 180) was by vacuum aspiration under general anaesthesia. Outcome measures included efficacy rates, medical complications within 8 weeks of the procedure, patient preferences and acceptability. RESULTS: Among women who underwent medical abortion, 5.4% required a second procedure compared with 2.1% who had surgery, although this difference was not statistically significant. Side effects experienced were higher in women who underwent medical abortion compared with those who underwent surgery. There were no significant differences in the rates of major complications up to 8 weeks. Prior to termination, 80% of women had a preference for a method, with 72% preferring medical and 28% preferring surgical abortion. Following abortion, 70% of those who underwent medical termination and 79% who underwent surgery would opt for the same method in the future. CONCLUSION: Medical abortion is safe and effective at 10–13 weeks gestation and should be considered an option for those women who wish to avoid surgery and anaesthesia.**

*Key words:* medical abortion/mifepristone/misoprostol/surgical vacuum aspiration

## Introduction

In England and Wales the majority of abortions (72%) are carried out at 9–13 weeks gestation (Office for National Statistics, 1999), while in Scotland about one-third of all abortions are carried out at 10–13 weeks (Information and Statistics Division, 2000).

In the UK, mifepristone in combination with a prostaglandin analogue was licensed for the termination of pregnancy at up to 9 weeks amenorrhoea in 1991, and since 1995 has also been available for termination of pregnancy beyond 13 weeks. At present, surgical methods (vacuum aspiration) are used at 10–13 weeks amenorrhoea, and there is little published work on the use of medical methods (Ashok *et al.*, 1998a).

Vacuum aspiration is considered to be safe and effective but has been associated with major morbidity in up to 1% of women and minor morbidity in 10% (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985), the major determinants of morbidity being gestational age and the procedure used to terminate the pregnancy. In the first trimester the complication rate is lowest at 7–8 weeks gestation (0.26 per 100 abortions) and increases progressively to 1.37 per 100 abortions at 13 weeks (Grimes and Cates, 1979). Vacuum aspiration, usually performed under general anaesthesia, is currently the method of choice at 10–13 weeks gestation.

The manufacturer's recommended regimen for early medical abortion comprises mifepristone 600 mg in combination with the prostaglandin analogue gemeprost. A randomized controlled trial comparing medical abortion with vacuum aspiration at gestations up to 9 weeks showed that although both methods were highly acceptable to women, medical abortion was more painful and less effective with advancing gestation (Henshaw *et al.*, 1993, 1994a,b).

Since then, a number of developments in the drug regimen have occurred based on randomized controlled studies (McKinley *et al.*, 1993; World Health Organization Task Force, 1993; El-Refaey *et al.*, 1995) and these led to the development in 1994 of a new medical regimen consisting of a reduced dose of mifepristone (200 mg) and the vaginal use of the

prostaglandin analogue misoprostol (El-Refaey and Templeton, 1994; Ashok *et al.*, 1998b, 1999). This prostaglandin has a number of advantages over gemeprost in that it is easily stored and transported and of very low cost.

This paper compares the efficacy, early medical sequelae (up to 8 weeks following termination) and acceptability of medical and surgical abortion at 10–13 weeks gestation.

## Materials and methods

### *Study design*

The preferred design for evaluating a new treatment or management policy is a randomized controlled trial, and this was adopted for the study. The partially-randomized patient preference (PRPP) design has been recommended for use in trials where motivational factors may produce bias in outcomes (Brewin and Bradley, 1989). In this study, a conventional randomized trial was conducted, alongside an assessment of preferences in those who did not wish to be randomized to one method or the other.

### *Study participants*

The study was approved by the Grampian Research Ethics Committee and was conducted at Aberdeen Royal Infirmary. Women presenting for termination of pregnancy at 10–13 weeks amenorrhoea, gestation confirmed by transvaginal ultrasound, and fulfilling the requirements of the 1967 Abortion Act, were eligible for recruitment. They were also required to meet the following criteria: (i) eligible to undergo either surgical vacuum aspiration or medical abortion; (ii) singleton, viable intrauterine pregnancy; and (iii) ultrasonically estimated gestational age of 10–13 weeks at the time of termination. The exclusion criteria were: (i) suspected ectopic pregnancy; (ii) chronic adrenal failure; (iii) long term corticosteroid treatment; (iv) haemorrhagic disorder and treatment with anticoagulants; (v) known allergy to mifepristone; (vi) smokers >35-years-of-age with electrocardiogram abnormalities; and (vii) breast feeding.

Eligible women were given a standardized information sheet describing medical and surgical methods of abortion and were asked if they were willing to be allocated to a method of abortion. Women were also informed of side effects and complications of each method. Women who agreed to be randomized were assigned to a method by opening consecutive sealed opaque envelopes containing a random number generated by computer. The randomization was prepared by the trial statistician using a randomized block design with blocks of 2, 4, 6 and 8, to ensure equal numbers in each group during the study.

The women who declined to be randomized were asked by the study nurse the reasons for their decision. Those not wishing to be randomized because they had a strong preference for a particular treatment were identified. The women willing to participate if they received their preferred treatment option constituted a non-randomized prospective cohort.

A total of 486 women were recruited (400 in the randomized arm) in order to achieve a 90% power of detecting at the 5% significance level a difference of 10% in the level of acceptability between the two termination methods. Eighty-six women were recruited to the preference arm of the trial. A further 93 women eligible to participate declined to take part in either the randomized or preference arm of the study. Analysis was by intention to treat, and women allocated to a method of treatment were attributed to that method for the purpose of analysis, whether or not they underwent their allocated procedure. Five women randomized to the medical group had surgical treatment by choice and three women who were randomized to surgery had medical treatment.

### *Intervention*

The two alternatives were medical or surgical abortion.

#### *Medical termination*

Women undergoing medical abortion were asked to attend the gynaecology ward and given 200 mg of mifepristone orally in hospital under nursing supervision. They were then admitted to the ward 36–48 h later, when misoprostol 800 µg was administered vaginally. If products of conception were not passed, a further two doses (400 µg) of misoprostol were given either orally or vaginally at 3 h intervals depending on vaginal bleeding. Women who had vaginal bleeding heavier than a normal period were given misoprostol orally. After products of conception were passed, women were observed in the ward for a further 4 h. Following administration of prostaglandin, pulse, blood pressure, temperature and systemic symptoms were monitored hourly. Women were given oral (paracetamol 500 mg plus dihydrocodeine 10 mg) or parenteral (morphine 10 mg) analgesia every 4–6 h as required.

If products of conception were not passed 3–4 h after the third dose of prostaglandin, a speculum examination was undertaken and any products of conception in the vagina or cervix were removed. If products of conception were not identified, an ultrasound scan was performed and surgical evacuation undertaken if necessary prior to discharge.

#### *Surgical termination*

Standard techniques were used to perform vacuum aspiration, under general anaesthesia. Women were admitted to the day surgery unit and were given 800 µg of misoprostol for cervical priming 3 h pre-operatively.

In all other respects (e.g. counselling, infection screening) there were no differences between the two groups. All women were screened for genital tract infection including *Chlamydia trachomatis* and treated if necessary.

Women who underwent medical termination were invited to return to the hospital 14–21 days after the termination of pregnancy for follow-up. At this visit, if vaginal bleeding had not ceased then an ultrasound scan was done and high vaginal and endocervical swabs taken if indicated. Patients were commenced on antibiotics or curettage performed if necessary. Those undergoing surgical termination of pregnancy were followed up by their referring doctor, usually at ~14 days post-procedure.

### *Outcome measures*

These included efficacy, major medical complications and relatively minor short-term physical symptoms. Patient preferences prior to termination and acceptability following the procedure were also assessed. These were measured by self administered questionnaires prior to the procedure following randomization, prior to discharge and at 2–3 weeks following termination.

#### *Efficacy and immediate medical complications prior to discharge*

The efficacy of the procedure was defined as complete uterine evacuation without the need for a second procedure [subsequent surgical (re)curettage or medical regimen] within 8 weeks of abortion.

Women were asked to complete a modified 'menstrual distress questionnaire' as well as a visual analogue scale for pain, after termination and prior to discharge. The former was used to assess symptoms such as nausea, vomiting, headache, hot flushes, dizziness, tiredness and diarrhoea on a five point scale (none to very severe) (Henshaw *et al.*, 1994c). Analgesia use in hospital was also documented.

#### *Medical sequelae at 2 weeks following the procedure*

Complications recorded at the follow-up visit and unscheduled visits to hospital were documented.

Table I. Characteristics of study subjects

| Group | n | Estimated gestation (days) | Age (years) | Body mass index | Primigravid n (%) | Previous induced abortion n (%) | Chlamydia-positive n (%) |
|---|---|---|---|---|---|---|---|
| Randomized medical | 188 | 71.8 (7.2) | 25.5 (6.9) | 23.4 (3.7) | 80 (42.6%) | 55 (29.3%) | 11 (5.9%) |
| Randomized surgical | 180 | 73.0 (7.0) | 24.8 (6.7) | 23.5 (3.8) | 82 (45.6%) | 54 (30.0%) | 15 (8.3%) |
| Preference medical | 15 | 71.9 (7.6) | 29.3 (7.0) | 23.1 (2.4) | 3 (20.0%) | 5 (33.3%) | 0 |
| Preference surgical | 62 | 74.0 (5.9) | 26.0 (6.4) | 23.3 (4.0) | 17 (27.4%) | 24 (38.7%) | 4 (6.5%) |
| Total | 445 | 72.0 (7.0) | 25.4 (6.8) | 23.4 (3.8) | 182 (40.9%) | 138 (31.0%) | 30 (6.7%) |

Values are mean (SD), except where n (%).

A further questionnaire was completed and returned by post 2–3 weeks following the procedure to assess the following: (i) duration and severity of vaginal bleeding recorded on a menstrual calendar (each day on the menstrual calendar was subdivided into five to indicate the severity of bleeding, none to flooding). The values were added to give the total vaginal bleeding score (TVBS); (ii) a visual analogue scale to assess pain and analgesia use following discharge; (iii) a record of the time taken off work and to return to normal activity.

*Medical sequelae at 8 weeks following the procedure*

A third questionnaire was completed by the family doctor at 8 weeks following termination and all medical problems attributable to the abortion were documented. Women experiencing more than one problem were classified for analysis according to the primary complaint.

Major and minor complications attributable to the termination up to 8 weeks following the procedure were assessed. Major complications were classified according to categories previously defined (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985). The minor complications are listed in Table V.

Unscheduled visits to hospital related to abortion were recorded and the termination database reviewed for complications related to abortion.

*Preference and acceptability of procedure*

Preference for a particular method was included in the questionnaire completed following randomization and prior to the procedure. Acceptability was assessed with regards to preferred future method by means of questions included in the 2–3 weeks questionnaire, returned by post.

*Statistical analysis*

The data were entered into a personal computer-held database and analysed using the Statistics Package for Social Sciences program. The principal analysis compared the outcomes in the two arms of the randomized controlled trial. Independent and paired *t*-tests were used for continuous variables with a normal distribution, and Mann–Whitney's *U*-test for ordinal or non-parametric continuous variables. The $\chi^2$ test or Fisher's Exact test, as appropriate, was used for independent nominal data and McNemar's test for paired data describing dichotomous variables. Confidence intervals (95% CI) were applied where appropriate. Comparisons were made between the randomized women and those entering the preference cohort with regard to their characteristics and outcomes.

## Results

A total of 486 women were recruited, 400 to the randomized and 86 to the preference arm of the trial. Thirty-four (7.0%) women who had agreed to participate in the study subsequently decided to continue with their pregnancy, seven withdrew (1.4%) and one (0.2%) woman failed to attend for termination and subsequently had a midtrimester medical termination of pregnancy. Thus, a total of 445 women were enrolled in the study, 368 in the randomized and 77 in the preference group. Figure 1 shows the numbers recruited and the study design.

The 445 women were allocated to four groups: those randomized to medical abortion [$n$ = 188 (51.1%)], those randomized to surgery [$n$ = 180 (48.9%)], those who had a strong preference for medical abortion [$n$ = 15 (3.4%)], and those with a strong preference for vacuum aspiration [$n$ = 62 (13.9%)]. Thus, a total of 203 (45.6%) underwent the medical method and 242 (54.4%) vacuum aspiration. There were no differences between the groups in any baseline physical or sociodemographic characteristics (Table I).

Women treated as day cases included 179 (88.2%) of those undergoing medical abortion and 222 (91.7%) undergoing surgical abortion.

For descriptive purposes, the data in certain sections have been combined for women who underwent a particular method either by choice or chance.

*Medical abortion*

Of the 203 women allocated to the medical group, 45 (22.2%) experienced some vaginal bleeding following mifepristone administration and prior to the administration of prostaglandin; nine (4.5%) women rated this to be heavier than a normal period. One (0.5%) woman aborted on mifepristone alone, prior to the administration of prostaglandin. The median time interval from administration of mifepristone to prostaglandin administration was 44.00 h (range 33.83–48.58).

The median number of doses of prostaglandin required was 2 (range 0–3). Products of conception were identified by inspection in 192 (94.6%) women. Twenty women (9.9%) also had abortion confirmed on ultrasound scan prior to discharge. Of the 203 women who underwent medical abortion 139 (68.5%) aborted within 6 h of prostaglandin administration. The median induction abortion interval was 5.00 h (range 2.00–27.58). Following the third dose of prostaglandin, 57 women (28.1%) did not pass products of conception within 3–4 h and required a speculum examination.

*Surgical abortion*

All 242 surgical terminations were carried out under general anaesthesia on a dedicated theatre list. The consultant responsible for patients carried out 159 (65.7%) of the vacuum aspirations. The median time interval between cervical priming and surgical evacuation was 2.42 h (range 0.17–7.00).

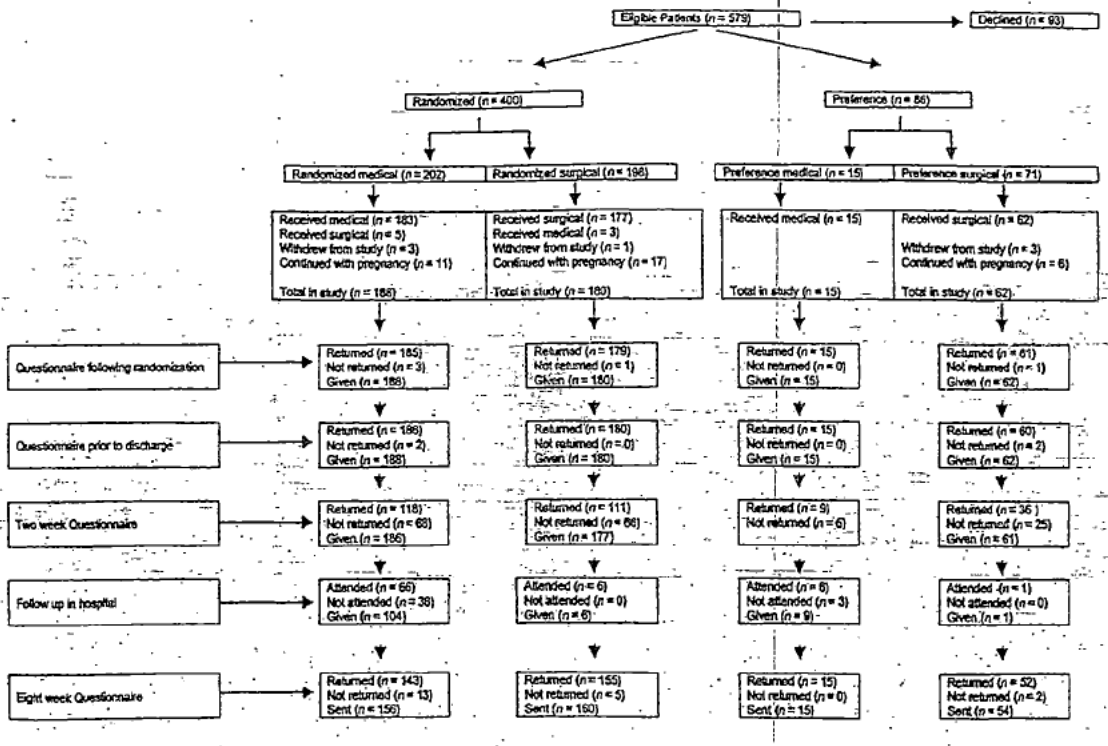


Figure 1. Study design and numbers recruited.

*Efficacy and immediate medical complications prior to discharge*

There were no significant differences in overall efficacy between medical abortion and vacuum aspiration. Gestation did not influence efficacy in either group (Table II). Of the 11 (5.4%) failures in the medical group who subsequently had surgery, three (1.5%) had a continuing pregnancy, one (0.5%) a missed abortion and seven (3.4%) had incomplete abortions. Surgical evacuation following failed medical abortion was undertaken prior to discharge in 10 (90.9%) women, and within 2 weeks of the procedure in one woman. Products of conception from five women were sent for histological examination and chorionic villi were identified in four of these. Of the five women (2.1%) who required a second procedure in the surgical group, medical treatment was undertaken following a failed attempt to dilate the cervix at vacuum aspiration in one woman (0.4%). Surgical (re)curettage was undertaken in the other four women (1.7%) for incomplete abortion within 4 weeks of the first procedure. Products of conception were identified in all three women where histological examination was requested.

Among women who were randomized, the overall pain score [median (range)] experienced by women who underwent medical abortion was 6.2 (0–10) and with vacuum aspiration 2.5 (0–10), indicating a significant difference between the two groups ($P < 0.0001$). Similarly, women who underwent the medical method [7.6 (0.6–9.9)] in the preference group experienced significantly more pain than those who underwent vacuum aspiration [2.1 (0–9); $P < 0.0001$). However, women who were randomized to the medical method had significantly lower pain scores [5.7 (0–10)] following analgesic administration compared with those randomized to surgery [7.7 (0–10); $P < 0.0001$). Such a significant difference was not seen in the pain scores following analgesia administration in the preference group ($P = 0.53$). The median (range) scores in the medical and surgical groups were 6.7 (0.3–9.3) and 6.8 (0.1–10.0) respectively.

Table II. Efficacy of abortion method according to gestation

| Gestation | Medical abortion *n* (%) *n* = 203 | Surgical Abortion *n* (%) *n* = 242 | *P*-value |
|---|---|---|---|
| 64–70 days | | | |
| Total number | 105 (51.7) | 108 (44.6) | NS |
| Failed | 3 (2.9) | 0 (0) | |
| Complete abortion | 102 (97.1) | 108 (100) | |
| 71–77 days | | | |
| Total number | 52 (25.6) | 57 (23.6) | NS |
| Failed | 4 (7.7) | 3[a] (5.3) | |
| Complete abortion | 48 (92.3) | 54 (94.7) | |
| 78–84 days | | | |
| Total number | 32 (15.8) | 63 (26.0) | NS |
| Failed | 4 (12.5) | 2 (3.2) | |
| Complete abortion | 28 (87.5) | 61 (96.8) | |
| 85–91 days | | | |
| Total number | 14 (6.9) | 14 (5.8) | – |
| Failed | 0 (0) | 0 (0) | |
| Complete abortion | 14 (100) | 14 (100) | |
| Overall | | | |
| Total number | 203 | 242 | NS |
| Failed | 11 (5.4) | 5 (2.1) | |
| Complete abortion | 192 (94.6) | 237 (97.9) | |

[a]In one woman medical treatment was undertaken following an attempt at surgery due to inability to dilate the cervix.
NS = not significant.

Table III. Side effects experienced by women in the ward

| | Randomized | | | Preference | | |
|---|---|---|---|---|---|---|
| | Medical abortion *n* (%) *n* = 186 | Surgical abortion *n* (%) *n* = 180 | *P*-value | Medical abortion *n* (%) *n* = 15 | Surgical abortion *n* (%) *n* = 60 | *P*-value |
| Nausea | 128 (69.2) | 50 (27.8) | < 0.0001 | 9 (60.0) | 11 (18.3) | 0.001 |
| Vomiting | 91 (49.2) | 15 (8.3) | < 0.0001 | 7 (46.7) | 3 (5.0) | < 0.0001 |
| Diarrhoea | 79 (42.5) | 8 (4.5) | < 0.0001 | 7 (46.7) | 0 (0) | < 0.0001 |
| Abdominal pain | 182 (97.8) | 163 (90.6) | 0.003 | 15 (100) | 53 (88.3) | NS |
| Vaginal bleeding | 178 (97.8) | 166 (94.3) | NS | 12 (80.0) | 53 (91.4) | NS |
| Tiredness | 159 (85.5) | 127 (70.9) | 0.001 | 10 (66.7) | 45 (75.0) | NS |
| Headache | 51 (27.6) | 28 (15.6) | 0.005 | 6 (40.0) | 4 (6.7%) | 0.001 |
| Hot flushes | 74 (40.0) | 21 (11.7) | < 0.0001 | 5 (33.3) | 5 (8.5) | 0.012 |
| Dizziness | 82 (44.3) | 39 (21.0) | < 0.0001 | 7 (46.7) | 10 (16.7) | 0.013 |

NS = not significant.

Table IV. Short-term medical sequelae (2–3 weeks following the termination)

| | Randomized | | | | Preference | | | |
|---|---|---|---|---|---|---|---|---|
| | Medical *n* = 118 | Surgical *n* = 111 | *P*-value | CI *n* = 9 | Medical *n* = 36 | Surgical | *P*-value | CI |
| Total number of days bleeding Mean (SD) | 14.21 (4.8) | 11.21 (5.9) | < 0.0001 | 1.59, 4.41 | 13.0 (4.1) | 10.8 (4.7) | NS | –1.47, 5.85 |
| Total vaginal bleeding score Mean (SD) | 37.63 (13.7) | 23.33 (14.8) | < 0.0001 | 10.58, 18.01 | 31.50 (8.96) | 22.42 (13.35) | NS | –0.84, 18.43 |
| Overall pain since termination Median (range) | 2.1 (0–9.5) | 1.6 (0–9.8) | NS | – | 0.4 (0.1–6.2) | 1.4 (0–6.0) | NS | – |
| Most severe pain since termination | 3.9 (0–10) | 2.5 (0–9.9) | NS | – | 1.5 (0.2–9.9) | 3.1 (0–9.2) | NS | – |

Median (range).
CI = confidence interval; NS = not significant.

Of the 203 women who underwent medical abortion, 61 (30.0%) required no analgesia, 120 (59.1%) requested oral analgesia only, and 22 (10.9%) requested parenteral opiate analgesia. All women who underwent surgical termination were given diclofenac per rectally 100 mg or paracetamol per rectally 1000 mg in theatre following the procedure. However, a further 96 (39.7%) women required additional analgesia with 91 (37.6%) women requesting oral analgesia and 5 (2.1%) requesting parenteral opiates.

Side effects experienced by women on the ward are shown in Table III. Four (2.0%) women who had medical abortion required syntometrine to control bleeding. Two (0.8%) women in the surgical group had a blood loss >500 ml, one (0.4%) woman requiring a blood transfusion.

### *Medical sequelae at 2–3 weeks following the procedure*

Of the 386 women randomly allocated, 229 (60%) returned the questionnaire, 118 (64%) of whom underwent the medical method and 111 (62%) who had vacuum aspiration. Of the 76 in the preference group, 45 (60%) returned the questionnaire, 9 (60%) in the medical group and 36 (58%) in the surgical group.

Short-term sequelae 2–3 weeks following the two methods of termination are shown in Table IV. The duration and total vaginal bleeding score was greater in women randomized to medical abortion. The median (range) time taken to return to normal activity was 2.5 days (0–14) in women who underwent medical abortion and 2.5 days (0–20) in those who underwent vacuum aspiration with no significant difference between the two groups. There were no differences in median (range) time taken to return to work, 2.0 days (0–21) in the medical group and 2.0 days (0–21) in the surgical group.

At 2–3 weeks following the procedure there was no difference in the level of pain experienced by women between the medical and surgical groups, randomized or in the preference arm (Table IV). Following discharge from hospital, of the women who returned questionnaires, overall (both randomized and preference) 12 (9.4%) women who underwent medical abortion and 11 (7.5%) who underwent vacuum aspiration required analgesia with no significant difference between the two groups.

All (both randomized and preference) women who underwent medical abortion were invited to attend follow-up 2 weeks later in hospital. Of these, 113 (55.7%) agreed to attend for follow-up, of whom 72 (63.7%) attended. The remaining 41 (36.3%) women failed to keep their hospital appointment. The remaining 90 (44.3%) women who declined the initial invitation to attend hospital were followed up by their family doctor. Women undergoing surgical abortion were followed up by the family doctor, and only seven (2.9%) women followed up in hospital for medical reasons.

Table V. Medical sequelae assessed (at 8 weeks following the abortion)

| | Medical Abortion n (%) n = 158 | Surgical Abortion n (%) n = 207 | 95% Confidence interval for difference between proportion[a] | *P*-value |
|---|---|---|---|---|
| Contacted family doctor | 30 (19.0) | 43 (20.8) | −0.100, 0.065 | NS |
| Presumed pelvic infection requiring antibiotic treatment | 7 (4.4) | 17 (8.2) | −0.087, 0.011 | NS |
| Psychiatric and psychological morbidity | 10 (6.3) | 10 (4.8) | −0.033, 0.063 | NS |
| Abnormal abdomino-pelvic pain and or vaginal bleeding | 5 (3.2) | 8 (3.9) | −0.045, 0.031 | NS |
| Other morbidity | 8 (5.1) | 8 (3.9) | −0.036, 0.047 | NS |

[a]The confidence intervals include zero and hence the differences between the two groups are not significant at the 5% level.
NS = not significant.

Of the 72 women who underwent medical abortion and were followed up in hospital, six required oral antibiotics for suspected pelvic infection. All seven women who were followed up in hospital following vacuum aspiration required oral antibiotics for suspected infection.

*Medical sequelae at 8 weeks following the procedure*

Of the 445 women in the study, 385 (86.5%) agreed to the researchers contacting the family doctor at 8 weeks following the procedure to complete a questionnaire. Information was obtained from family doctors in 365 (94.8%) of these. Overall, 73 (20.0%) women consulted the family doctor with problems related to termination. There was no significant difference in the consultation rates between the medical and surgical group. Seven (4.4%) women who had medical and 17 (8.2%) who had surgical treatment were given oral antibiotic treatment by the family doctor for presumed pelvic infection (Table V).

There were no significant differences in the rates of major complications within 8 weeks of abortion. Two (0.8%) women in the surgical group and one (0.5%) woman in the medical group required i.v. antibiotics for presumed pelvic infection.

In total, 15 of the 445 women in the study had an unscheduled visit to hospital, six (3.0%) in the medical and nine (3.7%) in the surgical group. Of these, one (0.5%) women in the medical group and seven (2.9%) who had vacuum aspiration were re-admitted ($P = 0.04$).

Of the 41 women who underwent medical abortion but failed to keep their hospital appointment, information was obtained from the family doctor in 33. Thus, in only eight women was no follow-up information obtained.

*Preferences and acceptability*

Prior to termination and following randomization, 351 (80%) of 441 women who returned the questionnaire had a definite preference for a particular method. Of these, 253 women (72%) preferred the medical method and 98 (28%) preferred vacuum aspiration ($P < 0.0001$).

Following termination, 118 women who underwent the medical method and 111 women who had vacuum aspiration returned questionnaires, but only 67 (35.6%) women who had the medical method and 96 (53.3%) who underwent surgery answered the question regarding future preferred method. Forty-seven women (70%) who underwent medical termination would opt for the same method in future, and 76 women (79%) who underwent vacuum aspiration would opt for the same method in future—a statistically significant difference between the two groups ($P < 0.0001$).

## Discussion

This study is a robust comparison of medical and surgical abortion. A pilot study had previously shown the feasibility of medical abortion at 10–13 weeks gestation (Ashok *et al.*, 1998a). A large number of women were randomized in this study in a single centre in which all data were collected prior to discharge. Furthermore, the termination database and all hospital notes could be scrutinized for re-admission and complications related to termination. There was a very good response from family doctors with nearly 95% of those contacted responding to the questionnaire at 8 weeks following the procedure. None of the women in either group (medical or surgical) was discharged home prior to confirming interruption of the pregnancy. All women with a continuing pregnancy following the medical regimen were identified and had evacuation of products of conception prior to discharge.

Although the drop-out rate was higher than expected (short-term follow-up rate with regards to acceptability), which would directly affect the power calculation, the results achieved are believed to be a true reflection of differences between the groups. However, data regarding problems related to termination were obtained from family doctors and in only eight women who underwent medical abortion was no information obtained. All these women had passed products of conception prior to discharge.

Overall, 11.8% of women who underwent medical abortion and 8.3% who underwent surgery were managed as in-patients. The majority of women who required overnight admission had geographical reasons.

Following randomization but prior to termination, nearly 80% of women had a definite preference for a particular method. Of these, the majority preferred the medical method. Of those who underwent medical abortion, 70% would opt for the same method in future while 79% who underwent vacuum

aspiration would opt for the same in future—a statistically significant difference. Based on these results, it appears that medical abortion is less acceptable than surgery, although the response was from a small number of women who underwent either procedure (one-third of all women who underwent medical abortion and half of who underwent surgery returned the questionnaire), which highlights difficulties in post-termination surveys.

Medical abortion has proven to be a safe and effective alternative to vacuum aspiration in the early first trimester and for midtrimester termination of pregnancy (Ashok and Templeton, 1999). The efficacy is up to 97.5% overall and at gestations of 7–9 weeks ~97% (Ashok *et al.*, 1998b). Even when the efficacy falls to 94% at 9 weeks gestation, acceptability among women remains high, as demonstrated in a previous randomized study (Henshaw *et al.*, 1993). To demonstrate a significant difference of 2–3% in efficacy, as found in this study, would have required 1750 women, but the clinical relevance would have been doubtful given the level of acceptability.

There is now increasing experience of medical abortion in the late first and early second trimester of pregnancy in China (Cheng, 1999). Mifepristone in an oral 200 mg dose in combination with vaginal misoprostol of up to three doses has an efficacy of 94.0%. The vaginal administration of misoprostol was more effective than the oral route. In our study we used a combination of vaginal and oral misoprostol with success rates similar to the above study. It has been shown that in the second trimester, provided the first dose of misoprostol is administered vaginally, there is no advantage in the vaginal administration of subsequent doses (El-Refaey and Templeton, 1995).

Re-admission rates to hospital were lower than in previous studies with only 1.8% of women requiring re-admission (Henshaw *et al.*, 1994c). This may be associated with our current policy of pre-operative screening for pathogenic organisms. However, significantly more women in the surgical group were re-admitted following termination, although there were no significant differences between the two groups in family doctor consultation rates or in the requirement for antibiotics for presumed pelvic infection.

The current care provided to women undergoing medical abortion in the UK includes in-patient hospitalization on a day case basis. Medical abortion using mifepristone and home administration of misoprostol has been shown to be feasible in the USA at gestations up to 63 days (Schaff *et al.*, 2000). Schaff and colleagues showed no difference in efficacy in relation to gestation, with medical abortion being highly acceptable (91%). The feasibility of carrying out the procedure at home needs to be evaluated in different settings and in the context of further studies.

In summary, medical abortion is as safe and effective as vacuum aspiration at 10–13 weeks gestation. The introduction of a medical method of abortion at 10–13 weeks could have a considerable impact on the provision of medical services, as well as increasing women's choice of methods, particularly for those women who wish to avoid surgery and anaesthesia.

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**Mifepristone and misoprostol for early abortion when no gestational sac is present.**

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# Mifepristone and misoprostol for early abortion when no gestational sac is present

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**Abstract**

The study was conducted to determine whether the administration of mifepristone followed by vaginal misoprostol can induce an abortion in early pregnancy when no gestational sac is present on sonogram. This report presents a prospective, pilot study of 30 healthy adult women, pregnant and seeking an abortion, and with no gestational sac on sonogram. All women had a baseline serum chorionic gonadotropin (hCG) level measured prior to using mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 48 h later, and then returned up to 4 days later for a repeat sonogram and serum hCG level. Women with initial hCG levels > 2000 IU/L were evaluated for ectopic pregnancy. At the first follow-up visit, if the hCG decreased by >50%, the women were followed with home pregnancy (25 IU/L) tests weekly until negative. If the levels did not decrease by 50%, a second dose of misoprostol was given. Surgical intervention was indicated for persistent hCG levels or excessive bleeding. Of the 30 women enrolled, the mean number of days of amenorrhea was 40 (SD 9) days. Two women had surgical intervention for continuing pregnancy, 2 had ectopic pregnancies, and 1 was lost to follow-up. Complete medical abortions occurred in 25/30 (88%) women, but when recalculated, in 25/27 (93%) women who completed the protocol and who did not have an ectopic pregnancy. There was 1 adverse event in a woman with an ongoing pregnancy who then received methotrexate. She was hospitalized a day later with a complicated pelvic infection and likely methotrexate-induced pneumonitis. Twenty-three women had a decrease in hCG at first follow-up visit of >50%. All 27 women who completed the protocol found the overall regimen acceptable. Mifepristone followed at 48 h by vaginal misoprostol were effective and acceptable in inducing an abortion in very early pregnancy. There may be a higher incidence of failure in very early pregnancies. Documentation of a complete abortion by hCG level is necessary to ensure the pregnancy is neither ongoing nor ectopic. 

*Keywords:* Abortion; Mifepristone; Misoprostol

## 1. Introduction

Mifepristone for medical abortion was approved by the US Food and Drug Administration in September 2000. It is highly effective when combined with the prostaglandin misoprostol 2 days later for up to 7-week pregnancy, with efficacy rates ranging from 92–98% [1–6].

An intrauterine gestational sac on sonogram usually is first seen in a 5-week intrauterine pregnancy [7]. In recent US medical abortion trials, inclusion criteria have required a gestational sac to be present on sonogram [8,9]. In contrast, women in France do not routinely have a sonogram examination, but the mandatory 7-day waiting period prior to using mifepristone, would likely ensure that the pregnancy is beyond ≥5 weeks gestation. Consequently, there is little information about the effectiveness of mifepristone and very early pregnancy prior to a gestational sac present on sonogram.

The advantages of offering very early medical abortion are the following: 1) identifying an ectopic pregnancy in an asymptomatic phase by ultrasound and hCG levels; and 2) reducing the anxiety of waiting when a woman knows she wants an abortion. The disadvantages of offering an early mifepristone abortion when no gestational sac is present are: 1) treating an ectopic pregnancy with an inadequate regimen with mifepristone; and 2) over-treating a spontaneous miscarriage when mifepristone is not needed. Alternatively, women can wait until an intrauterine pregnancy is confirmed by sonogram thereby excluding an ectopic pregnancy or use methotrexate that is effective in inducing an early abortion or treating an early ectopic pregnancy [10–12].

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The objective of this pilot study was to determine whether women with no gestational sac on sonogram should be offered mifepristone for medical abortion.

## 2. Material and methods

This was a prospective study of 30 women at a single site. The study had institutional review board approval. Inclusion criteriad included: 1) age ≥ 18; 2) good health; 3) positive sensitive pregnancy test and wanting an abortion; 4) a normal bimanual examination; and 5) no gestational sac on vaginal probe sonogram. Additional inclusion and exclusion criteria have been previously reported [8,9]. On day 1, women had a medical history, a gynecologic examination and a vaginal probe sonogram. All women had Rh blood typing, a hemoglobin, and baseline serum human chorionic gonadotropin (hCG) level. Rh-negative women received Rh immune globulin. Women were administered mifepristone 200 mg orally in the office. If the initial or subsequent hCG levels were >2000 IU/L with no gestational sac visible on sonogram, the woman was evaluated for ectopic pregnancy. On day 3, women inserted 4, dry 200 μg tablets of misoprostol (total 800 μg) vaginally at home and returned to the office up to 4 days later for a repeat vaginal probe sonogram and hCG level. At this visit, if the hCG had deceased by >50% from baseline, the woman was followed by phone with home pregnancy tests weekly until negative. Otherwise, a second dose of misoprostol was administered vaginally and the woman returned at her option from 1 day later to day 15. If a third visit was needed and if the hCG had decreased by >50%, the woman was followed by phone with home pregnancy tests weekly until negative. Surgical intervention was indicated for persistent hCG level or excessive bleeding. Women reported by phone or postcard when their bleeding stopped. Women were considered lost to follow-up if there was no known outcome after repeated attempts by phone and certified letter.

The primary outcome measures were as follows: 1) efficacy of the regimen without surgical intervention; 2) side effects; 3) adverse outcome; and 4) woman's perception of the procedure.

Women were interviewed about symptoms and use of medications at all visits. After either a >50% decrease in hCG levels or a surgical intervention occurred, a final questionnaire was administered that rated the woman's agreement about her acceptability of: 1) overall procedure; 2) cramping pain; 3) bleeding; 4) side effects from the medications; 5) time waiting until the abortion was over; 6) willingness to use misoprostol at home; 7) willingness to recommend the procedure; and, 8) willingness to choose the procedure again. The Likert scale ranged from *strongly disagree*, *disagree*, *neutral*, *agree*, to *strongly agree*. *Agree* and *strongly agree* were combined in this analysis.

## 3. Results

Thirty women were enrolled from February through December 1999. Twenty-two (73%) were white, 4 (13%) African American, and 4 (13%) Hispanic. The mean age was 28.2 (SD 7.7) years. The initial mean gestational age by last menstrual period was 40.3 days (SD 9.0). The mean initial hCG level was 547 IU/L (SD 477), excluding the woman with an initial hCG of 16,922 IU/L who had an ectopic pregnancy.

Two women had surgical intervention for continuing pregnancy. One woman had an increase in her hCG level from 1000 IU/L to 5350 IU/L on day 4, a visible gestational sac on follow-up, and an uncomplicated aspiration curettage on day 12. The other woman's course was complicated. Her initial hCG was 385 IU/L which rose over the next 2 weeks to 1312 IU/L, and then to 1814 IU/L. She had no findings on sonogram. Although feeling well, she was considered a study failure and was given methotrexate to treat an early intrauterine pregnancy or an occult ectopic pregnancy. She presented 24 h later with acute abdominal pain and pelvic tenderness. Her white blood cell count was 18,500 with 93% neutrophils and 4% bands. She had a diagnostic aspiration curettage and an abdominal laparoscopic examination on day 29. Both procedures confirmed a pelvic infection despite negative cervical cultures for chlamydia and gonorrhea. Pathology from the curettings revealed an inflammatory exudate and trophoblastic tissue confirming an intrauterine pregnancy. On the first post-operative day, the woman was noted to have mild tachypnea, an oxygen saturation of 80%, and a chest film showing bilateral, nonspecific, patchy alveolar densities with small effusions consistent with fluid overload, mild acute respiratory distress syndrome possibly due to her pelvic infectious process, or mild pneumonitis from methotrexate [13]. After 24 h of antibiotics, oxygen therapy and diuretics, the oxygen saturation improved and the woman had an uncomplicated recovery. Her hCG levels decreased precipitously post curettage, also consistent with having had an intrauterine pregnancy.

Two women had ectopic pregnancies; one presented with 39 days of amenorrhea and an initial hCG level of 16,922 IU/L. A formal sonogram revealed a right adnexal mass and she underwent a salpingectomy without further complications. The other woman was gravid 10, para 3 with a history of a heterotopic ectopic pregnancy 2 years earlier. Her hCG levels rose from 1,326 IU/L on day 1 to 5,598 IU/L 1 week later. A formal sonogram showed 2 right adnexal masses diagnosed as twin ectopic pregnancies measuring 2.9 cm and 3.0 cm each. She was treated successfully with methotrexate. One woman refused to return for follow-up care. Her outcome was not documented and she was considered "lost-to-follow up."

Complete medical abortions occurred in 25/30 (88%) women and in 25/27 (93%) women excluding the woman who was lost to follow-up and the two women who had ectopic pregnancies. No woman experienced excessive bleeding. Twenty-three women had a decrease in hCG at

first follow-up of >50%. Of the six women who had increases in hCG levels, three had minimal elevations (mean of 33% at first follow-up) that decreased precipitously (<50% of baseline value) by the next visit. Of the other three women with hCG increases at first follow-up (mean of 268% from baseline), two had ongoing pregnancies and 1 had an ectopic pregnancy.

Of the 26 women with a documented bleeding cessation date, the mean length of bleeding was 12.4 days (SD 12). Twenty-one (70%) women reported using an oral narcotic for pain. Twenty-seven women (90%) but 100% of responders to the post treatment questionnaire found the regimen acceptable.

## 4. Discussion

This pilot study used a protocol that differs from the FDA approved regimen in that a lower dose of mifepristone (200 mg) was used, a higher dose of misoprostol (800 mcg) was administered, and misoprostol was used vaginally rather than orally and at home. This regimen has proven to be highly effective in our previous trials.

Women who present for a medical abortion with a very early pregnancy and no gestational sac visible on sonogram are a dilemma for clinicians. Some of these women may undergo an unnecessary medical abortion because they have a failed pregnancy (missed abortion) and would eventually bleed spontaneously, though some of these women will require a non-elective aspiration curettage for excessive bleeding. Other women will have an ectopic pregnancy that requires additional evaluation and treatment. Amenorrhea of more than 35 days, with no sac present, is less consistent with an early intrauterine pregnancy. An hCG greater than the discriminatory level (>2000 IU/L for vaginal probe ultrasound or >3600 IU/L for abdominal probe ultrasound) will help to identify a woman at risk for an ectopic pregnancy [14]. Most of these women, realizing that they have an unintended pregnancy, albeit, early, failed or ectopic, will want some intervention.

Women with no gestational sac on sonogram are at risk for ectopic pregnancy as noted in the two women in this trial. Ectopic pregnancy must also be considered when a sonogram is not used initially and either serial hCG levels are rising or there is no vaginal bleeding after misoprostol. Treatment for early ectopic pregnancy should be commenced as soon as possible to reduce morbidity. Methotrexate is most effective in early ectopic pregnancy [10].

Unexpected were the two women who had ongoing pregnancies. This is considerably higher than the expected 1% of ongoing pregnancies found in other mifepristone studies [5,6] and requires further study. Since the availability of the commercial Mifeprex, we have had another woman who presented with an initial hCG of 150 IU/L and had an ongoing pregnancy after this regimen. In all cases, women with very early pregnancies will require documentation of completion. Methotrexate is an alternative treatment for very early medical abortion and may result in fewer ongoing pregnancies.

Excessive bleeding, the most common cause for surgical intervention in most medical abortion trials, did not occur in this pilot study. The possibility of excessive bleeding requires the availability of 24 h surgical aspiration skills. There is evidence that blood loss is related to gestational age so less excessive bleeding is expected with early intervention [15] i.e., early intervention may be the safest time to offer medical abortion service.

There was one unexpected and serious adverse event in one of the two women who had an ongoing pregnancy. She received methotrexate for an occult pregnancy and then presented with a pelvic infection and a likely methotrexate-induced pneumonitis. She also had a diagnostic laparoscopy and iv fluids that may confuse the clinical course. Infection after medical abortion is very rare because there is no instrumentation of the uterus. Pneumonitis is also rare after methotrexate and has not been previously reported following medical abortion. The woman recovered completely.

## 5. Conclusion

In this pilot study, low-dose mifepristone 200 mg and home administration of vaginal misoprostol 800 μg at 48 h were effective and acceptable to women seeking a very early medical abortion. Ectopic pregnancy must be considered when no gestational sac is present on initial sonogram. There may be a higher rate of ongoing pregnancies when offering mifepristone in very early pregnancy and therefore documentation of a complete abortion is necessary to ensure the pregnancy is neither ongoing nor ectopic.

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**REFERENCE 6**

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# Successful Long-Term Treatment of Refractory Cushing's Disease with High-Dose Mifepristone (RU 486)

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**An extremely ill patient, with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma, experienced complications of end-stage cardiomyopathy, profound psychosis, and multiple metabolic disturbances. Initially treated unsuccessfully by a combination of conventional surgical, medical, and radiotherapeutic approaches, he responded dramatically to high-dose long-term mifepristone therapy (up to 25 mg/kg·d). Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, as well as by the significant reversal of the patient's heart failure, the resolution of his psychotic depression, and the eventual unusual return of his adrenal axis to normal. His 18-month-long mifepristone treatment course was notable for development of severe hypokalemia that was attributed to excessive cortisol activation of the mineralocorticoid receptor, which responded to spironolactone administration. This case illustrates the efficacy of high-dose long-term treatment with mifepristone in refractory Cushing's syndrome. The case also demonstrates the potential need for concomitant mineralocorticoid receptor blockade in mifepristone-treated Cushing's disease, because cortisol levels may rise markedly, reflecting corticotroph disinhibition, to cause manifestations of mineralocorticoid excess. (*J Clin Endocrinol Metab* 86: 3568–3573, 2001)**

CHRONIC EXPOSURE TO excessive corticosteroids in Cushing's syndrome (CS) leads to the development of multiple metabolic abnormalities, including glucose intolerance, dyslipidemia, hypertension, osteoporosis, and weight gain (1). Cushing's disease (CD) accounts for approximately 70% of cases of endogenous CS. The standard initial treatment of CD is transsphenoidal adenomectomy, which achieves cure rates of 70–80% (1). Pituitary macroadenomas (size > 1 cm) are more difficult to cure than microadenomas (size < 1 cm). Patients suffering residual or recurrent disease undergo repeat transsphenoidal hypophysectomy, external beam pituitary irradiation, medical adrenolytic therapy, or surgical adrenalectomy to control the hyperadrenocorticism (1, 2). However, no particular therapy is completely satisfactory. Repeat transsphenoidal surgery results in high relapse rates, therapeutic effects from pituitary radiotherapy are delayed, the steroidogenic enzyme inhibitors for chemical adrenalectomy (metyrapone, mitotane, aminoglutethimide, ketoconazole) are often limited by severe toxicity and inadequate cortisol suppression, and surgical approaches to accomplish total adrenalectomy may not fully extirpate adrenocortical tissue (1, 2). Adrenalectomy also carries the risk of rapid residual pituitary corticotroph growth, *i.e.* Nelson's syndrome.

We describe a patient with refractory CD and multiple medical comorbidities who exhausted conventional therapies but was successfully treated with high-dose mifepristone (RU 486), a glucocorticoid receptor (GR) antagonist (3), as a bridge until the therapeutic effects of delayed radiation therapy became manifest. Not only did the patient's hypothalamic-pituitary-adrenal axis return to normal, but his multiple medical problems all dramatically reversed. During mifepristone therapy, the patient, in addition, required spironolactone, a mineralocorticoid receptor (MR) antagonist, to ameliorate cortisol-induced MR activation, a result of elevated serum cortisol produced by mifepristone-induced corticotroph disinhibition.

## Case Report

The patient was a 51-yr-old African-American retired mechanic who was diagnosed with diabetes mellitus type 2 and hypertension, 6 yr before his evaluation at our institution. One year before admission, he developed recurrent syncope. Transthoracic echocardiography showed severe left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) of 20%. Coronary angiography revealed an isolated 60% occlusion of the left anterior descending artery that underwent percutaneous transluminal angioplasty and stenting. In the 6 months before admission, the patient was treated, at three other hospitals, for recurrent upper and lower extremity abscesses. Several incision and drainage procedures did not yield any microbial etiology. An increased frequency of syncopal episodes, concomitantly with New York Heart Association functional class IV symptoms, led to the patient's referral for evaluation of cardiac transplantation at our facility.

At the time of arrival at our institution, the patient's medications included digoxin, captopril, carvedilol, hydralazine, isosorbide, and insulin. Physical examination showed a wheelchair-bound man, with rounded facies, appearing chronically ill and acutely in distress. His blood pressure was

Abbreviations: 11βHSD, 11β-hydroxysteroid dehydrogenase; BPRS, brief psychiatric rating scale; CD, Cushing's disease; CS, Cushing's syndrome; GR, glucocorticoid receptor; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MR, mineralocorticoid receptor; MRI, magnetic resonance imaging.

130/82, pulse was 92 and regular, height was 1.78 m, and weight was 80 kg. The patient was somnolent and unable to provide any medical history. He was extremely weak and had striking muscular atrophy of the extremities. There were no abdominal striae, but there was palpable hepatomegaly and prominent pedal edema. He had fluctuant, warm, red, tender lesions involving the right upper and left lower extremities. When the patient tried to stand, he developed syncope.

During the subsequent hospitalization, chest radiography showed diffuse cardiomegaly, an electrocardiogram revealed LVH with secondary repolarization abnormality, and a repeat echocardiogram demonstrated LVEF of 22%, concentric LVH, and left ventricular enlargement. The patient's cardiomyopathy was deemed out of proportion to the isolated coronary atherosclerosis. *Cryptococcus neoformans* was cultured from the extremity abscesses, serum *Cryptococcus* antigen titers were positive (1:512), urine and sputum cultures revealed *Candida albicans*, and a left toe skin culture grew *Trichophytum rubrum*. The patient was started on flucytosine and fluconazole to treat the cryptococcosis. His glycemic control was poor, despite using more than 100 U insulin per day. Retinal examination showed diabetic retinopathy, and urine studies revealed proteinuria.

To screen for possible CS, a low-dose (1 mg) dexamethasone overnight suppression test was performed, demonstrating a nonsuppressed serum cortisol (1493 nM). ACTH-dependent CS was diagnosed by finding concomitant elevated ACTH (81 pM) and serum cortisol levels (>828 nM). High-dose (8 mg) dexamethasone did not suppress the cortisol (1294 nM). CRF levels were undetectable. Magnetic resonance imaging (MRI) revealed a cystic 2 × 1-cm pituitary mass (Fig. 1). Formal visual field testing was negative. Computed tomography of the adrenal glands showed bilateral hyperplasia. Despite failure of the high-dose dexamethasone suppression (including a repeat test using 32 mg dexamethasone), the patient was diagnosed with CD (4) but was deemed too ill to undergo confirmatory inferior petrosal sinus sampling. The patient's antifungal regimen was changed to include ketoconazole, because this imidazole derivative can inhibit steroidogenesis (5). However, ketoconazole was incompletely effective, and metyrapone was started, but the latter was abruptly discontinued after coincident development of atrial arrhythmias, requiring cardioversion.

During the patient's transsphenoidal adenomectomy, all visible traces of a soft cystic tumor were removed, but invasion of adjacent structures precluded complete surgical extirpation. A postoperative MRI scan confirmed residual tissue in the sella turcica. Histopathological analysis revealed a necrotic adenoma. A predominant pituitary cell type was unidentifiable by immunohistochemistry, because all immunostaining was inadequate because of the necrotic state of the specimen. Postoperatively, ACTH and cortisol levels declined but remained abnormally elevated (Fig. 2). Ketoconazole was reinstituted at 1200 mg/d to inhibit steroidogenesis. One month later, the patient underwent 3-dimensional conformal external beam radiotherapy, receiving 5040 cGy to the pituitary bed in 28 fractions over 6 wk. On ketoconazole, the patient developed extreme nausea and elevated transaminases (ALT 228 IU/L), necessitating a change to mitotane therapy (2 g/d) for 2 months. His ACTH remained more than 18 pM; and serum cortisol, more than 773 nM. His gonadal axis declined: total testosterone, 1.9 nM (normal, 12.1–24.9); free testosterone, 0.01 nM (normal, 0.04–0.11); and FSH, less than 1 IU/L (normal, 1.55–9.74). He was started on im testosterone therapy.

On psychiatric evaluation, the patient was severely depressed, with a 21-item Hamilton depression rating scale score of 27 (normal, <5). Although he denied symptoms of overt psychosis, his brief psychiatric rating scale (BPRS) was 38 (normal, <18). He showed significant cognitive impairment, as indicated by grossly diminished scores on multiple aspects of the paragraph recall test and the Stroop color-word test.

## Materials and Methods

Serum cortisol was measured using the IMMULITE competitive immunoassay (Diagnostic Products Corp., Los Angeles, CA), whereas ACTH was determined by ARUP Laboratories (Salt Lake City, UT) using a chemiluminescent immunoassay. Other measurements were per-

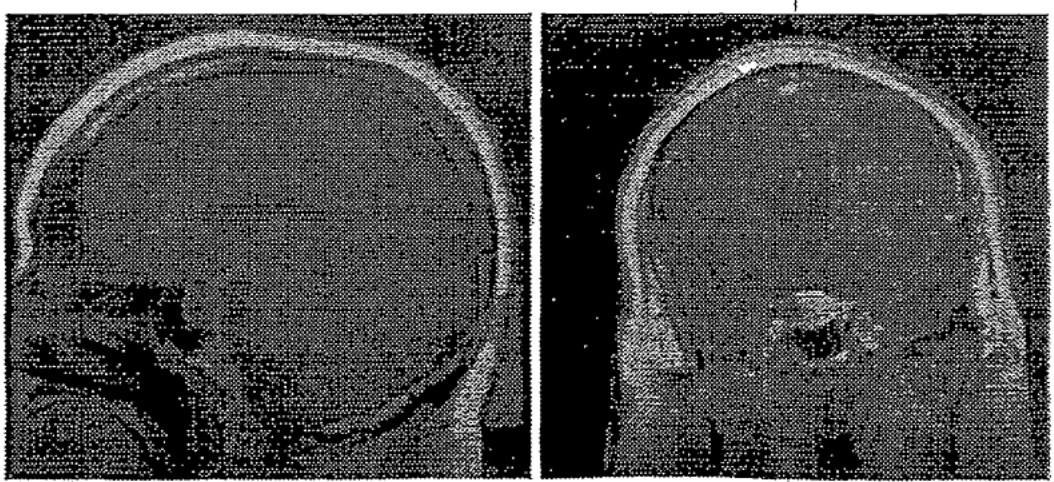

FIG. 1. Brain MRI images of a 51-yr-old man with CD. Sagittal T1-weighted (*left panel*) and coronal T1-weighted postgadolinium (*right panel*) MRIs of the brain demonstrate a cystic pituitary mass measuring approximately 2 × 1 cm.

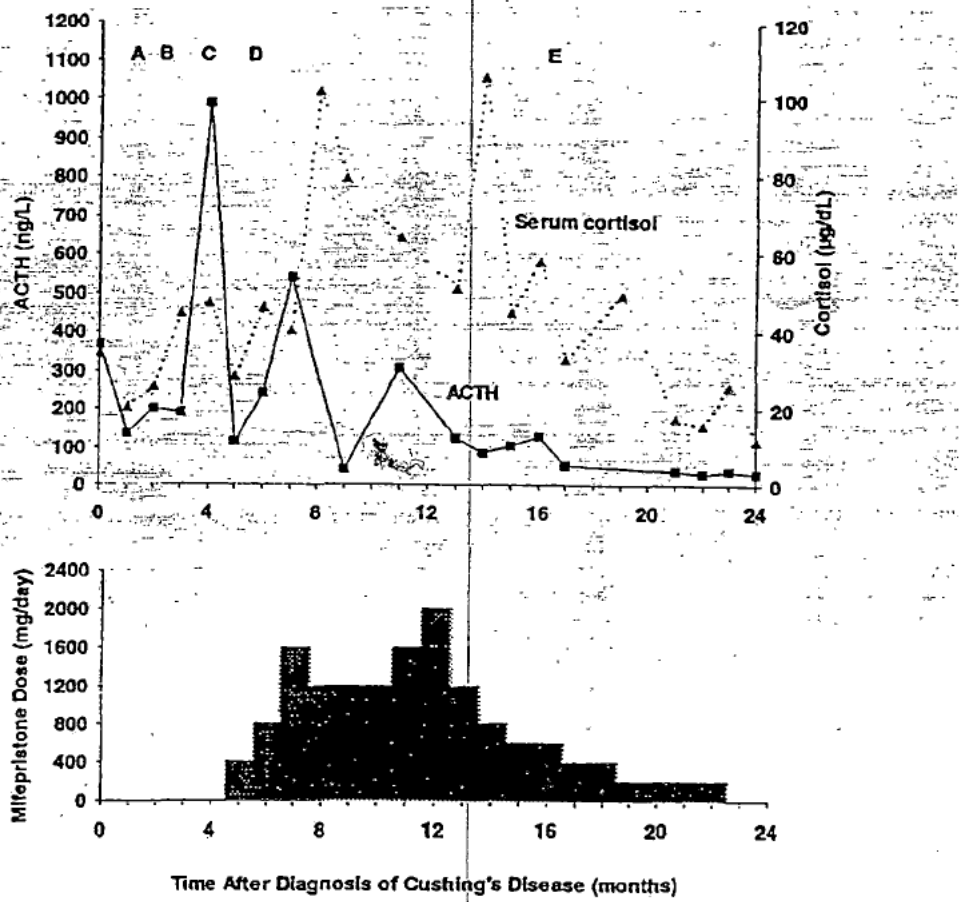


FIG. 2. Adrenal axis function in a man with CD treated with mifepristone. Note that measurements of serum cortisol are expressed in μg/dl (1 μg/dl = 27.59 nM), and those of ACTH are expressed in ng/L (1 ng/liter = 0.22 pM). A, Transsphenoidal resection of pituitary adenoma; B, start of external beam radiotherapy; C, end of external beam radiotherapy; D, medical adrenolytic therapy; E, acute adrenocortical insufficiency.

formed in the Stanford Clinical Laboratory using standard procedures. Bone mineral densitometry was assessed by dual-x-ray absorptiometry employing a Hologic, Inc. (Bedford, MA) QDR 4500 apparatus. Neuropsychiatric testing used the Hamilton depression rating Scale (HAMD-21), brief psychiatric rating scale, Stroop color-word test, and paragraph recall test, as reported previously (6).

## Results

The patient remained extremely ill, and it was anticipated that the radiotherapy would not show benefit for at least 1 yr. Chemical adrenalectomy had been unsuccessful, and the patient's cardiac status was considered too tenuous to undergo adrenalectomy, even via a laparoscopic approach. Given the lack of feasible effective therapies, the patient was initiated on mifepristone at 400 mg/d (~6 mg/kg·d). This was done with his informed consent, permission from the human subjects committee, and an Investigational New Drug approval from the Food and Drug Administration. It was hoped that mifepristone, begun 5 months after diagnosis of CD, would control the hypercortisolism until the radiotherapy took effect.

During the initial 8 months of mifepristone treatment, the dose was gradually increased to a maximum of 2000 mg/d (~25 mg/kg·d) in response to continued signs of hypercortisolism (Fig. 2). It was recognized that the fluctuating, but persistently elevated, serum ACTH and cortisol could not accurately reflect therapeutic efficacy, because mifepristone antagonizes the hypercortisolemic effects at the receptor level, not by altering corticosteroid production (7). Severe hypokalemia (potassium < 3 mM) developed, requiring high-dose potassium replacement and initiation of spironolactone therapy. However, clinical findings attributable to CS slowly improved, and the mifepristone dosage was titrated downwards over the following 10 months. The accompanying fall in ACTH and cortisol concentrations likely represented delayed effects of radiotherapy, although spontaneous improvement could not be ruled out (8). In month 10 of mifepristone therapy, at 800 mg/d (~10 mg/kg·d), the patient experienced an episode of suspected adrenocortical insufficiency, manifested by weakness, orthostatic hypotension, and hypoglycemia (serum glucose ~1.1 mM, not on antidiabetic drugs), which necessitated dexamethasone bolus therapy and mifepristone dose reduction, to which he responded.

By month 18 of mifepristone therapy, the patient's overall appearance was markedly improved, and he now walked unassisted. The ACTH had fallen (<8.8 pM), and the serum cortisol was not only suppressible, by low-dose dexamethasone to 30 nM, but was also normally responsive to exog-

enous corticotropin (from 433 to 1112 nM). Presuming an intact hypothalamic-pituitary-adrenal axis, the mifepristone dose was tapered and discontinued.

Of the severe metabolic, cardiovascular, and neuropsychiatric dysfunction (Table 1) associated with CD, the most remarkable improvement in this patient was his transformation from a wheelchair-bound heart-transplant candidate to an active individual walking 1–2 miles a day. The echocardiographic finding of a marked increase in LVEF, to 35–40%, corroborated this observation. The multiple fungal infections did not recur after cessation of antifungal agents. The severe insulin resistance abated, and glycemic control remained in a desirable range without the use of antidiabetic medications. The marked hypertriglyceridemia regressed without therapy. Markers of bone turnover and bone mineral density improved. The hypokalemia resolved, and the blood pressure has been well controlled, with the remaining antihypertensives consisting of carvedilol and furosemide to treat the congestive heart failure. Other medications included levothyroxine [to treat mild hypothyroidism; $FT_4$, 10.2 pM (normal, 9.0–25.7); TSH, 7.22 U/L (normal, 0.4–4.0)], im testosterone, and digoxin.

The patient's neuropsychiatric status improved dramatically. His elevated BPRS score, indicating psychosis, entirely resolved; and his mood normalized. His cognition improved substantially, with dramatic correction in all aspects of the Stroop color-word and paragraph recall tests. After recovery, the patient revealed that he had been far more psychotic than he had admitted at the onset of mifepristone treatment, describing previous visual hallucinations and feelings of being observed by unseen people. He had not initially acknowledged these symptoms because he thought that he would "sound crazy" (which indicates preserved insight).

## Discussion

17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one, also known as RU 38486, RU 486, or mifepristone is a potent antagonist of both glucocorticoid and progestin receptors (3). Its clinical properties yield an effective contraceptive, as well as abortifacient; and it may have potential benefit in treating CS, unresectable meningioma and leiomyoma, refractory endometriosis, metastatic breast cancer, and even psychotic depression (6, 9). We describe a patient with a pituitary macroadenoma, causing refractory CD, associated with multiple severe physiologic derangements that regressed after amelioration of hypercortisolism. Mifepristone was used successfully to antagonize the effects of hypercortisolism while awaiting the delayed remission induced by pituitary irradiation. Our report, describing the highest dose of mifepristone achieved for the longest duration reported in a patient with CS, coincides with the recent approval of mifepristone for usage in the United States, and it supports the utility of this therapy in managing hypercortisolism.

Previous reports have described clinically therapeutic mifepristone usage in more than 14 patients with CS (10, 11). A potential adverse effect experienced by these and other patients treated with high-dose mifepristone for long periods involves episodes of possible adrenal insufficiency that cannot be confirmed biochemically but that resolve after exogenous glucocorticoid administration and mifepristone

**TABLE 1.** Hormonal, metabolic, cardiovascular, and neuropsychiatric indices at diagnosis of Cushing's disease and before, during, and after mifepristone therapy

| Index | At initial diagnosis | At start of mifepristone therapy | During mifepristone therapy | After mifepristone therapy | Normal values |
|---|---|---|---|---|---|
| Hormonal | | | | | |
| ACTH (pM) | 81 | 20 | 28 | 6 | 2.9–11.4 |
| Serum cortisol (nM) | | | | | |
| Fasting | 949 | 1076 | 1402 | 320 | 166–580 |
| After dexamethasone, 1 mg | 1493 | — | — | 30 | <138 |
| Exogenous insulin use (U/d) | 115 | 70 | 40 | 0 | 0 |
| Metabolic | | | | | |
| Serum osteocalcin (nM) | — | 0.80 | 6.43 | 7.66 | 0.99–2.39 |
| Bone mineral density ($g/cm^2$) | | | | | |
| Left total hip | — | — | 0.795 | 0.822 | age-dependent |
| Lumbar spine (1–4) | — | — | 0.977 | 0.989 | age-dependent |
| Hemoglobin A1c (%) | 11.5 | 10.4 | 7.7 | 6.9 | 4–6% |
| Serum cholesterol (mM) | | | | | |
| Total | — | 8.11 | 7.17 | 5.28 | <5.18 |
| HDL | — | 0.91 | 0.54 | 0.85 | >0.91 |
| LDL | — | — | — | 3.52 | <3.37 |
| Fasting triglycerides (mg/dl) | — | 4.83 | 5.48 | 2.00 | <2.26 |
| Potassium (mM) | 4.0 | 4.2 | 3.0 | 4.4 | 3.5–5.0 |
| Cardiovascular function | | | | | |
| New York Heart Association functional class | IV | IV | II–III | I | 0 |
| Estimated left ventricular ejection fraction | 19% | — | 30% | 35–40% | >50% |
| Neuropsychiatric function | | | | | |
| 21-Item Hamilton-D score | — | 27 | 18 | 8 | <5 |
| BPRS score | — | 38 | 20 | 18 | 18 |

HDL, High-density lipoprotein; LDL, low-density lipoprotein; —, not available.

dose reduction (cited within Refs. 3 and 11). The difficult monitoring of therapeutic efficacy stems from the lack of a biomarker of GR activity. Because mifepristone antagonizes the GR of the pituitary corticotrophs, as well as that of peripheral tissues, its administration causes disinhibition of ACTH release, with consequently increased levels of ACTH and serum cortisol (7). Thus, patients undergoing mifepristone treatment may manifest seemingly paradoxical findings of elevated circulating ACTH and cortisol concentrations accompanying symptoms of adrenocortical insufficiency. In our patient's case, the additional inhibition of MR by spironolactone may have further contributed to the symptoms that suggested adrenal insufficiency.

Notable aspects of this patient's case include the pronounced, yet reversible, cardiac failure, as well as the severe hypokalemia. These clinical effects may be attributable to abnormal overactivation of MR. In physiological settings, the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) converts cortisol, an avid GR- and MR-binding glucocorticoid, to its 11-keto analog (cortisone), a non-GR, non-MR-binding glucocorticoid (12). This conversion protects the MR from cortisol, thereby maintaining the *in vivo* specificity of MR activation by aldosterone, which circulates in concentrations 100-1000 times less than that of cortisol. However, in CS, where the capacity of 11βHSD to guard the MR is overwhelmed or impaired, illicit cortisol overstimulation of MR leads to hypokalemic alkalosis and hypertension (13). Because mifepristone inhibits cortisol binding to GR, but not to MR, and causes ACTH disinhibition to further exacerbate endogenous hypercortisolism (which is likely to have provoked hypokalemia in this case), we treated this patient, in addition, with the MR antagonist spironolactone. The combination therapy was intended to prevent deleterious effects of cortisol- mediated receptor activation by achieving dual blockade of GR and MR.

The end-stage heart failure that dramatically improved, after the amelioration of glucocorticoid excess, raises the question of whether the cardiomyopathy was directly caused by hypercortisolism (14, 15). Patients with endogenous CS are commonly affected by severe LVH out of proportion to the degree of concomitant hypertension (14, 15), and this LVH frequently leads to heart failure. Are such adverse cardiovascular findings in CS mediated by cortisol activation at the GR and/or at the MR level? MRs have been reported to occur not only in kidney epithelium but also in myocardium, and increased cardiac fibrosis is seen in endomyocardial biopsies from CS patients (14), reminiscent of the fibrosis and other abnormalities attributed to aldosterone-associated MR activation in congestive heart failure (16). The same processes contributing to the progression of heart failure are effectively attenuated or reversed by antialdosterone therapy (17, 18). Thus, it is possible that the cardiomyopathy of CS may result from cortisol-mediated overstimulation of myocardial MR, just as the features of apparent mineralocorticoid excess in CS may result from cortisol-mediated overactivation of renal epithelial MR, with both abnormal findings being manifested in the setting of overwhelmed or defective 11βHSD activity.

The patient's marked elevation in serum cortisol and ACTH was nonsuppressible after high-dose dexamethasone; this is consistent with other reports of pituitary macroadenomas causing CD and does not necessarily denote an ectopic ACTH syndrome (4). Furthermore, it can be postulated that the hormonally aggressive behavior of the patient's macroadenoma potentiated not only the cardiomyopathy but also the hypokalemia and hypertension, the latter two findings of which are much more commonly observed in CS patients with ectopic ACTH-secreting tumors (13). A striking clinical result of this case is the reappearance of an ostensibly normal hypothalamic-pituitary-adrenal axis, at the patient's most recent evaluation; this result is uncommonly reported, given that the treatment of refractory CD tends to render patients adrenocortical-deficient.

The association between hypercortisolism and neuropsychiatric symptoms has been known for decades, with an estimated prevalence of psychiatric dysfunction of more than 40% in patients with CS (19). Psychosis and cognitive impairment are noted less commonly than depression, but this may stem from the use of inappropriate detection techniques. If suitable tests to reveal psychosis and impaired cognition are used, it is possible that the symptoms of patients with CS would best be classified as psychotic major depression or major depression with cognitive impairment. Our patient's features of depression improved markedly after treatment of CS, although he exhibited residual insomnia and anxiety. However, the psychosis totally abated, and cognition normalized. Interestingly, the recognition of the link between adrenal axis dysfunction and affective disorders has led to successful use of mifepristone in treating psychotic depression, as detailed in a separate report (6).

In conclusion, an improved understanding of the interactions between glucocorticoids, mineralocorticoids, receptors, and end-organ effects, in conjunction with the rational application of receptor antagonists, can lead to directed therapy of the numerous morbidities associated with severe CS. In this report, combination use of mifepristone and spironolactone allowed the dramatic reversal of cardiovascular, metabolic, and neuropsychiatric abnormalities in a patient with refractory CD.

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**Medical management of early fetal demise using a combination of mifepristone and misoprostol.**

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# Medical management of early fetal demise using a combination of mifepristone and misoprostol

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**BACKGROUND: This study aims to assess the efficacy of a combination of mifepristone and misoprostol in the management of missed miscarriage and anembryonic pregnancy. METHODS: Data of 220 consecutive women with miscarriage, undergoing medical evacuation of the uterus were collected prospectively at an early pregnancy assessment unit in a tertiary referral hospital. Each woman received a single oral dose of mifepristone 200 mg and 36–48 h later vaginal misoprostol 800 μg. Three hours following the first dose, two further doses of misoprostol, 400 μg each, were administered vaginally or orally at 3 h intervals. Women who failed to pass products of conception were offered repeat medical regime with misoprostol. Success was defined as complete uterine evacuation within 3 days, without the need for surgical evacuation. RESULTS: The overall success rate of medical management was 84.1%. Mifepristone alone induced natural expulsion of products of conception in 18.1% of women. The median dose of misoprostol required was 1600 μg and the median induction miscarriage interval after first prostaglandin administration was 8.04 h (range: 0.58–50.54 h). Of the 142 women who were symptomatic at presentation the medical regime failed in 30 (21.1%), compared with five (6.4%) failures of the 78 who were asymptomatic ($P = 0.007$). Of the 35 women who had surgical evacuation, eight required an emergency curettage for bleeding. CONCLUSIONS: The combination of oral mifepristone 200 mg with vaginal or oral misoprostol is an alternative to surgical management of early fetal demise, although it is not as effective as surgery.**

*Key words:* anembryonic pregnancy/fetal demise/mifepristone/misoprostol/missed miscarriage

## Introduction

The terms 'delayed miscarriage or early fetal demise' denote missed miscarriage (presence of a non-viable embryo/fetus) and blighted ovum (anembryonic pregnancy with absent embryonic echo) (RCOG Study Group, 1997). The two conditions are felt to represent different aspects of the same clinical process. A blighted ovum results from an early disturbance of normal embryonic development. In missed miscarriage, an intrauterine sac is seen with an embryo without cardiac activity. Apart from the distinction made at the time of vaginal scan, no clinically significant differences are observed between the two conditions. The diagnosis of early fetal demise has become more common since the introduction of transvaginal ultrasound, and accounts for ~21% of all miscarriages seen in our early pregnancy assessment unit (EPAU) in Aberdeen.

The clinical management of miscarriage has changed little over the years and up to 88% of women undergo surgical uterine evacuation (Hemminki, 1998). There are well-documented risks associated with surgical uterine evacuation (Farell *et al.*, 1982; Heisterberg *et al.*, 1986) and potential cost savings (Hughes *et al.*, 1996) can be generated by promoting alternative strategies of management. The success of expectant management of missed miscarriage appears too low to justify its routine use in clinical practice (Jurkovic *et al.*, 1998), although it may be an acceptable approach in individual patients. Various medical regimens with or without the anti-progesterone, mifepristone, and a prostaglandin analogue have been described to treat early fetal demise. Their efficacy vary widely from 25–92%, depending on the type of miscarriage, outcome measures used, the dose, duration and route of prostaglandin administration (El-Refaey *et al.*, 1992; Creinin *et al.*, 1997).

Based on our experience of first trimester abortion (El-Refaey and Templeton, 1994; El-Refaey *et al.*, 1995; Ashok *et al.*, 1998), we developed a regimen comprising mifepristone 200 mg followed by a combination of the vaginal or oral administration of misoprostol (800–1600 μg) for the management of early fetal demise. We now report our experience of this regimen in 220 consecutive cases.

## Materials and methods

A consecutive series of 220 women with 'delayed miscarriage' (missed miscarriage and anembryonic pregnancy) between 6 and 13 weeks, during the period 1998–1999, were studied. All women had chosen to undergo medical rather than surgical treatment. The study was performed in the EPAU at Aberdeen Maternity Hospital. The

Table I. Comparison of details of women with missed miscarriage and blighted ovum

| | Missed miscarriage ($n$ = 139) | Anembryonic pregnancy ($n$ = 81) | $P$ value |
|---|---|---|---|
| Age (mean ± SD) | 31.67 ± 6.39 | 31.61 ± 5.61 | NS |
| Multiparity | 97 (69.7%) | 53 (65.4%) | NS |
| Previous miscarriages | 47 (33.8%) | 20 (24.6%) | NS |
| Symptomatic at presentation | 89 (64.0%) | 53 (65.4%) | NS |
| Medical evacuation on mifepristone alone | 30 (21.5%) | 10 (12.3%) | NS |
| Medical evacuation on full regimen | 87/109 (79.8%) | 58/71 (81.6%) | NS |
| Surgical evacuation | 23 (16.5%) | 12 (14.8%) | NS |
| No analgesia | 55 (39.5%) | 23 (28.4%) | NS |
| Parenteral analgesia | 22 (15.8%) | 16 (19.7%) | NS |
| Readmission | 8 (5.7%) | 6 (7.4%) | NS |

NS = not significant.

assessment of gestational age was based on menstrual history and all ultrasound measurements (crown–rump length, gestational sac diameter) were within the first trimester. The diagnosis of missed miscarriage was confirmed on ultrasound by the absence of a fetal heart pulsation when the crown–rump length was >6 mm and of an anembryonic pregnancy by absent fetal pole in a gestational sac >25 mm in diameter. Successful treatment was defined as complete uterine evacuation using medical regimen without the need for surgical intervention.

All women with a miscarriage were counselled appropriately, and were offered a choice of medical or surgical treatment. Women who consented to medical management received a single oral dose of 200 mg of mifepristone in hospital. Unless miscarriage 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 to the EPAU 36–48 h later. On admission, four tablets (a total of 800 μg) of misoprostol were inserted into the posterior vaginal fornix by a nurse. Following administration of the first dose, a further two doses of misoprostol (two tablets each) 400 μg were given vaginally every 3 h. If bleeding was heavy misoprostol was administered orally. If products of conception were passed on the ward, the women were observed for 4 h before being allowed home. Following misoprostol administration pulse, blood pressure, temperature and systemic symptoms were monitored hourly. Oral (paracetamol 500 mg plus dihydrocodeine 10 mg) or parenteral analgesia (morphine 10 mg) was administered every 4–6 h as required. Patients who failed to pass products of conception overnight were offered a choice of either repeat medical regimen (misoprostol 800, 400, 400 μg at 3 h intervals, orally or vaginally) or surgical evacuation. Complete uterine evacuation was confirmed clinically by observing expelled products of conception and speculum examination. In the event of uncertainty ultrasound scan was performed.

All women were offered a follow-up appointment within 2 weeks of treatment, at the hospital or in the community (referring doctor or midwife). Those women who were allowed home without passing products of conception on the ward were given an emergency telephone number for contacting staff if they were concerned at any time. The women were followed up in the hospital with ultrasound assessment undertaken if indicated.

Data were analysed using the SPSS for Windows Statistical Package (Kinnear and Gray, 1994). In presenting the results, continuous variables are presented as means with standard deviations and ranges. Categorical variables are given as numbers (percentage) and associations were tested using the Fisher's exact or $\chi^2$ tests as appropriate. Kaplan–Meier survival analysis was used to compare (by means of the Log Rank test) the cumulative miscarriage rates in relation to parity. Differences were regarded as statistically significant if $P < 0.05$.

## Results

Of the 220 women with early fetal demise, 139 (63.1%) had a missed miscarriage and 81 (36.8%) had an anaembryonic pregnancy. A comparison of patient characteristics, presentation, treatment outcome, induction–miscarriage interval and complications between the two groups is shown in Table I. There were no significant differences.

The mean ± SD age of the 220 women was 31.6 ± 6.1 years (range 16–44). Of the 220 women, 67 (30.4%) were primiparous and 153 (69.5%) had one or more previous pregnancies. The mean gestation, by best estimate at the time of mifepristone administration, was 10.1 ± 1.84 weeks of amenorrhoea (range 6–13). At presentation to the EPAU, 84 (38.2%) had vaginal bleeding, five (2.3%) had pain and 53 (24.1%) had both pain and bleeding. Seventy-seven (35%) women were asymptomatic and the diagnosis was made at the routine first visit scans.

Of the 220 women, 44 complained of heavy bleeding within 48 h of mifepristone administration alone and in 40 complete miscarriage was confirmed on ultrasound scan. Four had emergency curettage for heavy bleeding. The treatment outcome is summarized in Figure 1. Among the 176 women who went on to receive misoprostol, complete miscarriage occurred in 145 (without the need for surgical intervention). Thus, the overall success rate was 185/220 (84.1%). The indications for surgical intervention are shown in Table II. Eight women had emergency curettage for bleeding, four before and four after misoprostol administration. A total of seven women had a blood loss >500 ml but none required a blood transfusion.

Of the 142 women who were symptomatic at presentation (pain/bleeding) the medical regime failed in 30 (21.1%) who required surgical evacuation of the uterus, while five (6.4%) women of the 78 who were asymptomatic (diagnosis of non-viable pregnancy on routine ultrasound) required surgical intervention—a statistically significant difference ($P = 0.007$). Of the 185 patients who had a successful outcome, complete

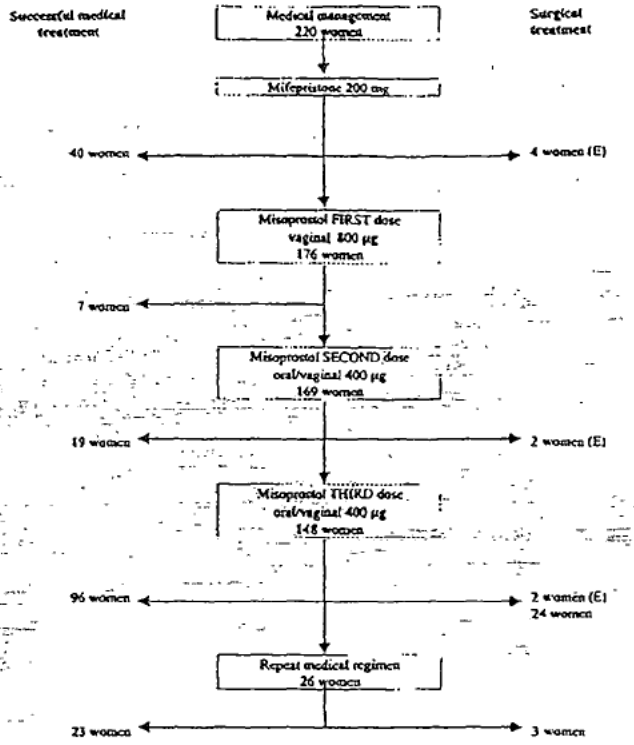


Figure 1. Outcome of medical treatment in 220 consecutive women with early fetal demise. E indicates women who had emergency curettage.

Table II. Indications and time interval for surgical intervention

| Indications | Total number (%) |
|---|---|
| Emergency curettage for bleeding | 8 (22.8) |
| Incomplete miscarriage | 14 (40.0) |
| No products passed | 6 (17.1) |
| Patient choice | 6 (17.1) |
| Molar pregnancy | 1 (2.8) |
| Total | 35 (15.9) |
| Misoprostol to surgical intervention interval | |
| Before misoprostol | 4 |
| Up to 3 days | 22 |
| 4–14 days | 5 |
| ≥15 days | 0 |

uterine evacuation was confirmed clinically in 130 (70.3%) and ultrasonically in 51 (27.6%).

The median number of misoprostol doses required was three (800 + 400 + 400 µg). Of the 54 women who did not miscarry following overnight stay (three doses of misoprostol), 28 (51.9%) opted for surgical evacuation. The medical regimen was repeated in the remaining 26 patients, of whom 23 (88.5%) had a complete miscarriage. Of the 176 women who received the full mifepristone/misoprostol regimen, the induction-miscarriage interval could be accurately determined in 148 (84%) and of these, 74 (50.0%) miscarried within 6 h of receiving first dose of misoprostol. The median induction–miscarriage interval was 8.04 h (range among those observed:

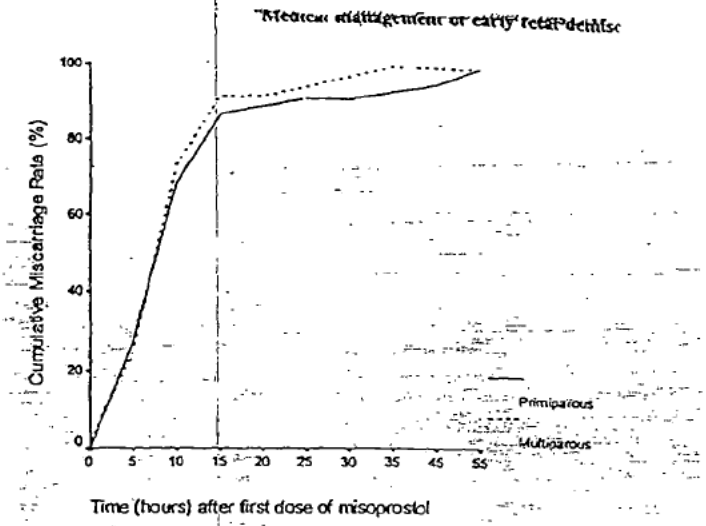


Figure 2. Cumulative percentage of women who miscarried in relation to parity, by 5 h intervals from the time of administration of first dose of misprostol.

0.58–50.54). The median (range) induction–miscarriage interval was 8.16 h (2.0–50.54) and 8.0 h (0.58–30.92) in primigravid and multigravid patients respectively. The two groups were compared by Kaplan–Meier survival analysis and no significant difference was found between the two groups (Log Rank test). The cumulative frequency of induction–miscarriage interval is shown in Figure 2.

Data on analgesic use were recorded in 219 women in the study. Of these, 78 (35.6%) required no analgesia (including 40 women who miscarried following mifepristone alone). 101(46.1%) required oral analgesia only, two received diclofenac suppositories and 38 (17.4%) required parenteral opiate analgesia.

Fourteen (6.3%) women who had had medical treatment for miscarriage required readmission. Of these, four (1.8%) had presumed pelvic infection, five (2.2%) required surgical curettage for prolonged bleeding, four (1.8%) had problems unrelated to the miscarriage and one (0.5%) had a molar pregnancy. One hundred (45.5%) women were given follow-up appointments in hospital, of which 82 (82%) attended. Sixty-three (28.6%) women declined an appointment and the remaining 57 (25.9%) were followed up in the community (referring doctor or midwife).

## Discussion

To our knowledge, this study of 220 women represents the largest reported series of the medical regimen for early pregnancy demise. Although incomplete miscarriage may be managed with misoprostol alone (Henshaw *et al.*, 1993; Chung *et al.*, 1997), in the presence of an intact sac and closed cervix (early fetal demise), priming with the antiprogesterone mifepristone makes the regimen more effective (El-Refaey *et al.*, 1992; Hinshaw, 1997). The overall success rate of our regimen was 84.1%, but the true efficacy—by excluding women who had surgical evacuation by choice—was 86.4%.

Nielsen *et al.* reported a success rate of 52% using a combination of 400 mg of mifepristone and 400 µg of

Table III. Published data on regimens of medical management of miscarriage and their efficacy

| Study | Regimen | Efficacy (%) |
|---|---|---|
| Pandian *et al.*, 2001[a] | Misoprostol 600 µg, 400 µg, 400 µg–2 hourly (PO) | 84.8 |
| Demetroulis *et al.*, 2001[b] | Misoprostol 400 µg (PV) | 82.5 |
| Nielsen *et al.*, 1999[b] | Mifepristone 400 mg<br>Misoprostol 400 µg (PO) | 82.0 |
| Nielsen *et al.*, 1997[c] | Mifepristone 400 mg<br>Misoprostol 400 µg (PO) | 52 |
| Creinin *et al.*, 1997[c] | Misoprostol 400 µg (PO) | 25 |
| | Misoprostol 800 µg (PV) | 88 |
| Herabutya and O-Prasertsawat, 1997[c] | Misoprostol 200 µg (PV) | 83.3 |
| Hughes *et al.*, 1996[c] | Mifepristone 200 mg<br>Misoprostol 400 µg, 600 µg, 400 µg (PO) | 89.1 |
| Chung *et al.*, 1997[b] | Misoprostol 400 µg, 400 µg, 400 µg–over 48 h (PO) | 70.6 |
| Egarter *et al.*, 1995[c] | Gemeprost 1 mg | 76.7 |
| de Jonge *et al.*, 1995[a] | Misoprostol 400 µg (PO) | 13 |
| Chung *et al.*, 1994[b] | Gemeprost 1 mg | 45.4 |
| Henshaw *et al.*, 1993[a] | Sulprostone 0.5 mg (i.m.) or Misoprostol 400 µg (PO) | 96 |
| Lelaidier *et al.*, 1993[c] | Mifepristone 600 mg | 82 |
| El–Rafeay *et al.*, 1992[c] | Mifepristone 600 mg<br>Misoprostol 400 µg, 200 µg 2 h apart (PO) | 96 |

[a]Incomplete miscarriage.
[b]Incomplete miscarriage, missed miscarriage and anembryonic pregnancy.
[c]Missed miscarriage and anembryonic pregnancy.
PO = per oral; PV = per vaginal; i.m. = intramuscular.

misoprostol, both taken orally with 13% of women requiring emergency curettage (Nielsen *et al.*, 1997). In our series, emergency surgical intervention was necessary in only 3.6%. Medical treatment may have been less successful in the Nielsen study because of the smaller dose (400 µg) of misoprostol administered by the oral route rather than the vaginal route. Vaginal administration of misoprostol has been shown to be more effective in comparison with the oral route in the context of medical management of miscarriage and first trimester termination of pregnancy (El-Refaey *et al.*, 1995; Creinin *et al.*, 1997). Plasma concentrations and bio-availability of misoprostol tend to be greater and prolonged when administered vaginally compared with the oral route (Zieman *et al.*, 1997). In our study, split analysis showed that the medical regimen was more effective in women who were asymptomatic at presentation (93.5%) with a non-viable pregnancy being diagnosed on routine scanning as opposed to women who presented with pain and/or bleeding (78.8%). In comparison Nielsen *et al.* only included women who were asymptomatic at presentation and had an efficacy rate of only 52% (Nielsen *et al.*, 1997).

In our study we used clinical parameters for defining success of the method. Once products of conception were passed and bleeding ceased, we did not perform an ultrasound scan to confirm an empty uterus unless indicated. However studies suggesting a lower efficacy with the medical regimen made ultrasound scan assessment of all women following treatment to confirm an empty uterus (Nielsen *et al.*, 1997). Only five of the women in this series required subsequent surgical evacuation following discharge from hospital for prolonged bleeding. Our work confirms no real advantage in scanning all women following treatment. In addition to increasing surgical evacuation rates this would also increase the use of resources.

The natural expulsion of products of conception with 200 mg of mifepristone alone occurred in 18.1% of women, while Lelaidier *et al.* reported 82% expulsion rates using a dose of 600 mg of mifepristone alone (Lelaidier *et al.*, 1993). It has been shown that for termination of early pregnancy a single dose of 200 mg mifepristone is as effective as 600 mg, when used in combination with a prostaglandin analogue (WHO Task Force, 1993). However a higher dose of mifepristone may be required for medical treatment of miscarriage, probably due to a change in progesterone receptor sensitivity, and this is reflected in the higher success rate (96%) from our early study using 600 mg (El-Rafaey *et al.*, 1992). This needs to be confirmed in the context of future studies. Mifepristone is relatively expensive and a reasonable success rate (>80%) can be achieved by using a combination of 200 mg mifepristone with misoprostol. Misoprostol is cheap, effective and does not require special storage facilities, hence is a promising alternative in the developing world. Most published studies using misoprostol alone for medical management of delayed miscarriage have a success rate of 13–83% (de Jonge *et al.*, 1995; Herabutya and O-Prasertsawat, 1997). Should mifepristone be unavailable, regimens using misoprostol alone may have a place in clinical practice. Table III summarizes published data with respect to medical regimens and success rates.

Demetroulis *et al.* showed that a single dose of misoprostol 800 µg administered vaginally was successful in 82.5% of women with early pregnancy failure, which included women with incomplete miscarriage, missed miscarriage and anembryonic pregnancy (Demetroulis *et al.*, 2001). If women with an incomplete miscarriage were excluded the failure rate of misoprostol alone for medical management of missed miscarriage and anembryonic pregnancy would have been 23.1% in the above study. This confirms the results from our

series and previous studies that priming with the anti-progesterone mifepristone makes the regimen more effective (El-Refaey *et al.*, 1992; Hinshaw, 1997). Demetroulis *et al.* (2001) also showed that 82.5% of women who underwent the medical regimen for early pregnancy failure were satisfied with treatment compared with 58% of those who underwent surgical treatment.

Medical termination of pregnancy up to 9 weeks, using a combination of mifepristone and misoprostol, had an efficacy of 97.5% (El-Refaey *et al.*, 1994). More recently the feasibility of medical abortion has been shown at gestations between 9 and 13 weeks to have an efficacy of 95% (Ashok *et al.*, 1998). However medical management of early non-viable pregnancy has a much lower efficacy, probably attributable to low progesterone concentrations following fetal demise. The lower failure rate of the medical regime in asymptomatic women compared with symptomatic may also be explained by the same hypothesis. The side effects of misoprostol have not been assessed in this study. However it is well known in the context of medical abortion that the commonest side effects experienced by women are gastro-intestinal (El-Refaey *et al.*, 1995).

Patient acceptability has been shown to be similar between surgical and medical evacuation for incomplete miscarriage and early fetal demise (RCOG, 2000). Acceptability tends to decrease with increasing symptoms and gestation. The uptake of the medical regimen for early fetal demise at our EPAU was 45%. It may be possible to introduce medical management without admission to the EPAU, particularly at early gestations. Out of 54 who did not miscarry following overnight stay, 26 women (48.1%) opted for repeat regimen; 23 (88.5%) were successful. This emphasises the value of offering repeat medical treatment if the standard regimen fails.

Eighteen women did not attend hospital follow-up and 28.6% of women declined an appointment. The Grampian Region is unusual in terms of its catchment population, and there is only one main hospital within a radius of 50 miles. While acknowledging that an unknown number of women may have consulted their General Practitioner with symptoms and minor complications, it can be assumed that any women with a significant complication would have been referred to hospital for further treatment.

In conclusion, medical treatment with 200 mg of oral mifepristone in combination with 800, 400 and 400 μg of vaginal misoprostol given sequentially at 3 h intervals is an effective and safe alternative to surgical and expectant management of early fetal demise. Therefore extending the availability of medical management of early fetal demise at EPAU would reduce the need for surgery and associated complications. Finally, medical management increases women's choice of methods.

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**Feasibility of administering mifepristone as a once a month contraceptive pill.**

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# Feasibility of administering mifepristone as a once a month contraceptive pill

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**Many women find the idea of a once-a-month contraceptive pill an attractive concept. Mifepristone has been shown to be effective as a contraceptive if administered in the early luteal phase. We tested the contraceptive efficacy of 200 mg of mifepristone on day luteinizing hormone (LH) + 2 in a group of 32 women who used a fertility monitor to identify the LH surge. We also recruited a control group, comprising 20 women who were trying to conceive. In this group, 12 women conceived during a total of 50 control cycles (probability of pregnancy 0.25–0.32). Women in the treatment group contributed to a total of 178 cycles and there were two pregnancies (probability of pregnancy 0.01). An LH surge was not detected in 34 cycles (19.1%). In 20 cycles (11.2%) this was due to imperfect use while 14 were monitor method failures (7.9%). Treatment with mifepristone in the early luteal phase did not disrupt the cycle length but women reported slight vaginal bleeding in 15% of the cycles. The combination of a home-use fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an acceptable contraceptive option with minimal side effects. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which required less compliance, could be devised.**

*Key words:* contraceptive/home use fertility monitor/LH surge/Mifepristone/once-a-month pill

## Introduction

Hormonal contraception is used by almost 100 million women world-wide. However, many women are deterred from using it because of perceived risks to health such as breast cancer or side effects such as weight gain. Most of the risks and the side effects are the results of prolonged exposure to steroids and many women, in a variety of cultural settings, find the idea of a pill which they need take only once each month, an attractive concept (Rimmer *et al.*, 1992; Glasier *et al.*, 1999).

Progesterone is essential for the establishment and maintenance of human pregnancy. The anti-progesterone mifepristone is a synthetic 19-norsteroid, which acts by blocking the action of progesterone at the receptor level (Spitz and Bardin, 1993), and thus, has multiple potential anti-fertility actions. When administered in the early luteal phase mifepristone retards endometrial development, without disturbing the timing of menses (Swahn *et al.*, 1988; Berthois *et al.*, 1991; Maentausta *et al.*, 1993). It also alters uterine contractility to a pattern more usually seen in the late luteal phase (Gemzell-Danielsson *et al.*, 1990). In 1993 Gemzell-Danielsson and colleagues conducted a pilot study in which a single dose of 200 mg of mifepristone was given in the early luteal phase [2 days following the surge of the lutenizing hormone (LH) in urine]. Out of 124 cycles in which coitus took place during the fertile period, only one pregnancy was observed (Gemzell-Danielsson *et al.*, 1993). There was no disruption of the timing of the subsequent menstrual bleed, although in 35% of the cycles slight vaginal bleeding was reported 2–3 days after treatment.

The main problem in developing a once-a-month contraceptive is finding a means that, both reliably and easily, identifies the start of the LH surge. Gemzell-Danielsson tried to solve this problem by using the LH sticks for home urine testing (Ovu-quick; Organon). In their study 12 out of 169 cycles were deemed to be anovulatory. However, it is not possible to determine if the LH surge truly was absent, or if the method failed to detect a surge. The woman may have read the test result wrongly or even failed to perform a test on the appropriate day.

Unipath (Bedford, UK) have developed a technology that can be used in the home to monitor changes in urinary hormones. This system comprises disposable test sticks and a hand held monitor, which together are used to detect changes in the levels of oestrone-3-glucuronide (E3G), a urinary metabolite of oestradiol, and LH, to indicate the potentially fertile days leading up to ovulation. The time from the first significant rise of LH in the urine to ovulation is reported to be around 24–48 h (Collins, 1996). The monitor thus should provide a convenient method of identifying the early luteal phase. Summary data for up to six consecutive cycles can be stored in the monitor memory and these data can be retrieved.

We investigated the contraceptive efficacy of 200 mg of mifepristone on day LH + 2 in a group of women who used this monitor to identify the LH surge.

## Materials and methods

This was a single centre study in healthy female volunteers, approved by the Lothian Research Ethics Committee. All subjects gave written informed consent to participation. Fifty-two sexually active women, with regular (25–32 day) menstrual cycles were recruited from a large Family Planning Clinic in Edinburgh. If the women had a significant medical condition or if they or their partners had a history of fertility problems, they were excluded from the study.

### *Treatment group*

Thirty-two women were recruited to the treatment group. None had been taking hormonal preparations within the 2 months prior to the start of the study and all had had at least two spontaneous menstrual periods since stopping hormonal contraception. All women underwent screening at the time of recruitment including a routine physical and gynaecological examination. A venous blood sample was taken for full blood count, serum biochemistry and liver function. The study started on day 1 of the menstrual period following screening, and lasted for up to seven consecutive menstrual cycles in which subjects took 200 mg mifepristone once per month.

### *Control group*

The control group consisted of 20 healthy women with regular menstrual cycles who were trying to become pregnant (for less than 6 months prior to the enrolment in to the study) and hence, were not using contraception. They were provided with a monitor, which they used according to the manufacturer's instructions. Women were advised that their chance of conception would be higher if they were to have sexual intercourse during the fertile period, identified by the monitor. The controls took part in the study until pregnancy occurred or for a maximum of six cycles if they did not conceive.

### *Procedure*

All subjects and controls were provided with a home use hormone monitoring system (Unipath, Bedford, UK). The system comprises a hand-held monitor and disposable dual-assay urine test sticks, and is used to simultaneously detect LH and E3G levels in early morning urine. The monitor optically measures the intensity of the lines that form on the test sticks after sampling, and the system will delineate three levels of fertility (Low, High and Peak Fertility) according to the optical signal changes detected. Low fertility will be displayed from day 1 of the cycle, until the hormone levels rise above the baseline levels. A change from low to high fertility is triggered by detection of elevated E3G levels, to concentrations typically between 20 and 30 ng/ml. The change from high to peak fertility is triggered by the detection of an LH surge, typically with a concentration >30 IU/l.

Peak fertility is displayed on the day of the LH surge and on the following day. Subsequently high fertility is displayed for 1 day prior to a return to low fertility. At the start of each menses, the subjects pressed the 'm' button on their monitor to initiate that cycle of use, at a time suitable for testing the first urine of the day. For the rest of the month, the subjects were required to consult the monitor display each morning (3 h either side of the time when 'm' button was set) to determine whether they needed to perform a test that day. Beyond this 6 h time window the monitor would not accept a test. The system requests one test every day for up to a total of 10 or 20 tests, depending on the length of the woman's cycle, and the timing of her LH surge. Embedded software within the monitor collects and analyses data from each cycle to identify and display fertility status to the user, and stores data for several months.

Mifepristone (Laboratories Exelgyn, Paris, France) was taken 2 days after the day of the first day of peak fertility (LH surge). With each cycle, subjects followed the same protocol, and were reviewed by the investigator monthly, on day LH + 2. Just before taking the 200 mg tablet of mifepristone, a venous blood sample was taken, and later assayed for progesterone. At the beginning of the study, if the LH surge was not identified by day 21 of the cycle, the subject was instructed to continue testing, but mifepristone was not given in that cycle. The subject was also advised to use barrier contraception from day 21 until the onset of the next menses. After the second pregnancy (which occurred due to a failure in detecting an LH surge), we changed this practice. We calculated the estimated day of LH surge for each month based on information from the previous cycles. If the women did not detect an LH surge either within 3 days after the anticipated day of LH surge or by day 19, a blood sample was taken for rapid serum progesterone assay. If the progesterone level was >5nmol/l and if the woman was at risk of pregnancy, mifepristone was administered.

All subjects and controls kept a menstrual record card, recording all vaginal bleeding experienced during the study and the days on which they had sexual intercourse. Subjects also marked the first day of the peak fertility as identified by the monitor and the day of taking the study medication.

If menstruation was overdue by more than one week the investigator performed a pregnancy test. Provided this was negative, the subject continued in the study and the next cycle was deemed to start with the onset of menses. Since the effect of mifepristone taken in very early pregnancy is unknown, and teratogenic effects could not be ruled out, women who would not consider terminating any pregnancy were not recruited to the treatment group.

At the end of the study, the subjects attended for a final visit, when a routine physical and gynaecological examination was performed. Full blood count, serum biochemistry and liver function were reassessed.

The following definitions were created for the purpose of the study.

**Imperfect use:** was defined as failure to detect an LH surge through performing the test incorrectly (e.g. dipping a test stick in urine 30 or more min before it being read by the monitor), or failing to perform tests as requested by the monitor.

**Monitor method failures:** were defined as failure to detect an LH surge despite performing all tests as requested.

**High fertile days:** days preceding the urinary LH surge as indicated by the monitor to be potentially fertile.

**Peak fertile days:** The first day of a significant rise in urinary LH detected by the monitor, and the following day.

**The fertile period:** of the cycle was defined as 3 days before until 2 days after the urinary LH surge (LH–3 to LH+2).

**Exposure cycles:** were cycles in which women reported having sexual intercourse at least once during the fertile period.

### *Statistical analysis*

Cycle lengths and serum progesterone concentrations were compared by two-sample *t*-tests. Confidence limits for efficacy were derived from confidence limits for relative risk calculated by the Greenland and Robins method (Greenland and Robins, 1985).

## Results

Table I shows the demographic characteristics of the women who took part in the study.

Table I. Demographic data.

| | Treatment group ($n$ = 32) | Control group ($n$ = 20) |
|---|---|---|
| Age | | |
| Range | 18–39 | 26–40 |
| Mean (± SD) | 30 (± 5.4) | 32.9 (± 4.5) |
| BMI | | |
| Range | 19–38 | 21–29 |
| Mean (± SD) | 23.6 (± 4.3) | 23.8 (± 2.7) |
| Smokers (%) | 7 (21.9) | 1 (5) |
| Non-smokers (%) | 21 (65.6) | 16 (80) |
| Ex-smokers (%) | 4 (12.5) | 3 (15) |
| Previous pregnancies | | |
| 1+ (%) | 19 (59.4) | 14 (70) |
| Never been pregnant (%) | 13 (40.6) | 6 (30) |
| Ever abortion (%) | 15 (46.9) | 5 (25) |
| Married/Co-habiting (%) | 28 (87.5) | 20 (100) |
| Single (with a regular boy friend) (%) | 4 (12.5) | 0 (0) |

The women in treatment group were slightly younger (mean age 30 years) than those in the control group (mean age 32.9 years). Otherwise there were no differences between subjects and controls.

### *The probability of pregnancy in the control group*

Twenty women were recruited to the control group and three withdrew before completing the study. Two withdrew from the study as they found using the system 'too stressful' and one withdrew because she no longer wished to plan a pregnancy. Data were collected from 50 control cycles during which 12 pregnancies occurred. Average frequency of intercourse was 1.7 episodes per week in the 39 control cycles in which the women kept a record of their sexual activity. In 37 cycles women had intercourse at least once during the fertile period (FP). In two cycles intercourse did not occur during the FP, while in 11 cycles the exposure status was unknown, as women failed to keep a record of sexual activity. Eight pregnancies occurred in the first exposure cycle.

If we assume that all 11 cycles from which information on sexual activity was lacking were exposure cycles, the probability of pregnancy was 0.25. However if those cycles were all non-exposure cycles, the probability of conception would be 0.32. Therefore among the control group the overall probability of pregnancy if sexual intercourse took place at least once during the fertile period lies between 0.25–0.32.

### *Contraceptive efficacy of the method*

Thirty-two volunteers were treated with a single dose of 200 mg of mifepristone administered in the luteal phase of the cycle as their sole method of contraception between one and seven cycles. They contributed a total of 178 cycles, and in 167 cycles mifepristone was administered. Eight women withdrew from the study before completion; two women moved out of the area, three ended their relationship, two conceived during the study and one lost confidence in the method.

Two clinical pregnancies occurred in the 178 cycles studied. The first pregnancy was a true treatment failure, which occurred in a woman (para 1) who took mifepristone on day 14 (LH + 2) of her first treatment cycle. She opted for a surgical termination of pregnancy, which was performed at 8 weeks of gestation (confirmed by ultrasound scanning). In the second woman (para 3), an LH surge was not identified in her third study cycle hence she did not receive treatment with mifepristone, menses did not occur and on day 37 after her last menstrual period an ectopic pregnancy was diagnosed and treated surgically. In a third woman a biochemical pregnancy was diagnosed (serum βHCG only rising to 34 IU/l), which was spontaneously and completely aborted by day 34 of the third study cycle after taking mifepristone on day 14 (LH + 2). This woman continued in the study and completed six treatment cycles.

The mean frequency of sexual intercourse was 1.8 episodes per week in 167 treatment cycles in which sexual activity was recorded. If we assume the probability of pregnancy in the treatment group is similar to the control group (0.25–0.32), the expected number of clinical pregnancies during the 178 cycles (in which 140 were exposure cycles) studied should be between 35–48.3. The observed number was two. Therefore, the efficacy of the method is 94.3% (95% confidence interval 75.4–98.7) – 95.9% (95% CI 82.5–99.0).

When calculating the efficacy of the method, we excluded the 29 cycles during which women were not exposed to a risk of pregnancy, and the three cycles in which mifepristone was taken in the follicular phase.

### *Contraceptive efficacy of luteal phase administration of mifepristone*

In 145 cycles in which mifepristone was taken in the early luteal phase (within 2 days of the urinary LH surge) 117 were exposure cycles (Table II). Exposure status was unknown in eight cycles and in 20 cycles women were not at risk of pregnancy. In the 117 exposure cycles, there was only one clinical pregnancy.

In 19 (10.7%) cycles, no LH surge was declared by the monitor but mifepristone was given as coitus had taken place during the fertile period of the cycle (calculated according to the usual cycle length and usual day of LH surge). Occurrence of ovulation was confirmed by serum progesterone of >5 nmol/l in all 19 cycles and treatment was administered prior to day 21 of the cycle in each case [between day 13–21 of the cycle, mean 16.9 (SD ± 2.1) days]. There were no pregnancies in these cycles.

If the probability of pregnancy in all exposure cycles in the study is 0.25–0.32 (the same as that of the control group), between 34–46 clinical pregnancies would be expected in the 136 ovulatory cycles in which mifepristone was taken in the luteal phase. The observed number was one. Hence, the contraceptive efficacy of luteal phase mifepristone is between 97.1% (95% CI 78.00–99.6) – 97.8% (95% CI 83.9–99.7).

### *Performance of the home use hormone monitor*

In 140 treatment cycles an LH surge was identified by the monitor, which equates to 90.9% LH surge detection when calculated for perfect use cycles; and 80.5% when imperfect use cycles are also included in the total. In 127 cycles this

Table II. Treatment cycle details.

| | Total no. cycles | Exposure cycles | Unknown exposure | No Exposure |
|---|---|---|---|---|
| Mifepristone administered | 167 | 136 | 8 | 23 |
| In follicular phase | 3 | 0 | 0 | 3 |
| In luteal phase | 164 | 136 | 8 | 20 |
| Early luteal phase | 145 | 117 | 8 | 20 |
| LH + 2 | 127 | 100 | 7 | 20 |
| LH + 1 | 17 | 16 | 1 | 0 |
| LH + 0 | 1 | 1 | 0 | 0 |
| In luteal phase (unknown LH status) | 19 | 19 | 0 | 0 |
| Mifepristone not given | 11 | 5[a] | 0 | 6[b] |
| Total | 178 | 140 | 8 | 29 |

[a]LH surge missed, at risk of pregnancy but after day 21.
[b]Anovulatory cycle $n = 1$, LH surge missed and no risk of pregnancy $n = 5$).

was confirmed by a subsequent rise in serum progesterone of >5 nmol/l in the early luteal phase. This information was not available from nine cycles (blood samples lost or not collected). In the remaining four cycles serum progesterone was between 2–5 nmol/l, 1 or 2 days following the urinary LH surge as detected by the monitor. This may have been due to an early detection of the first significant rise in urinary LH. None of these five cycles were prolonged after taking mifepristone, hence it is unlikely that they were anovulatory.

There was a total of 38 (21.3%) cycles in which an LH surge was not detected. Among them, one (0.6%) was an anovulatory cycle, defined by serum progesterone not rising above 5 nmol/l in the mid-luteal phase. In three (1.7%) other cycles we administered mifepristone on day 19, before the monitor had identified an LH surge. Serum levels of progesterone (taken on the day of administering mifepristone) confirmed that in these cycles mifepristone was administered in the follicular phase. All three cycles were prolonged (43–52 days).

In the remaining 34 cycles an LH surge probably occurred (as suggested by a rise in serum progesterone of >5 nmol/l) but was not identified by the monitor. Fourteen were missed due to monitor method failure (7.9%) and 20 were a consequence of imperfect use of the system (11.2%).

### *Cycle length*

Mifepristone when given in early luteal phase did not significantly affect the cycle length ($P = 0.35$). The mean of the usual cycle length was 28.3 days (SD ± 1.3) and during the treatment cycles it was 28.0 days (SD ± 1.9).

### *Side effects*

Women kept a record of vaginal bleeding in 139 out of the total 144 cycles where mifepristone was taken on LH + 2. Mifepristone induced vaginal bleeding within 72 h in 21 cycles (15%). In a further 19 cycles, our volunteers took mifepristone in the luteal phase but the LH status was not known. In 17 of those cycles (>89%), mifepristone induced a vaginal bleed.

Serum progesterone values in blood samples taken just prior to mifepristone administration were available for 136 cycles. The mean serum progesterone value was significantly ($P < 0.0001$) higher in those cycles where mifepristone induced bleeding when compared to the mean value for the cycles without bleeding [21.72 (SD ± 9.04) nmol/l versus 13.33 (SD ± 6.23) nmol/l].

Two women spontaneously reported improvement of their pre-menstrual symptoms during cycles in which mifepristone was administered, while one reported worsening. In one woman hepatic alanine aminotransferase (ALT) was elevated at 103 IU/l (normal range 10–40 IU/l) at the end of the study but returned to normal within 2 months. One woman complained of diarrhoea 12 h post mifepristone in one cycle, three reported menstrual cramping within 72 h of taking mifepristone; two women reported a reduction in menstrual blood loss.

## Discussion

A single dose of 200 mg of mifepristone administered once a month is an effective contraceptive method with an overall efficacy of 95% increasing to 97% if administered at the correct time (i.e. the early luteal phase). Thus our results are in agreement with the findings of a previous study (Gemzell-Danielsson *et al.*, 1993).

One criticism of previous work in this field has been the lack of a suitable control group for the subjects studied. Unlike the Gemzell-Danielsson study, we were able to compare the results with a contemporaneous control group using the same methodology in the same cultural setting. In this control group, if sexual intercourse took place on a fertile day the probability of a pregnancy was 0.25–0.32. The calculated probability of pregnancy in a cohort of couples monitored during a study of natural family planning (WHO, 1983) was 0.486 if intercourse took place 3 days prior to and a day after the peak day of mucus discharge. The difference in the probability of pregnancy between our study and a variety of other published series (Table III) may be explained by the fact that we have extended our definition of the fertile period to 6 days (3 days prior to the urinary LH surge until 2 days after). Other authors (Wilcox *et al.*, 1995) have calculated that the likelihood of conceiving during an ovulatory cycle to be 0.37 (95% confidence interval 0.31–0.48) if daily sexual intercourse took place during a 6 day fertile period (four days before and a day after ovulation). The lower frequency of intercourse in

Table III. Probability of clinical pregnancy.

| | No. of exposure cycles | No. of pregnancies | Probability of pregnancy |
|---|---|---|---|
| Wilcox *et al.*, 1995[b] | 129 | 34 | 0.26 |
| Our control group[b] | 37–48 | 12 | 0.25–0.32 |
| Our treatment group[b] (monitor + mifepristone) | 140–151 | 2 | 0.01 |
| Our treatment group[b] (mifepristone in luteal phase) | 136–143 | 1 | 0.007 |
| Gemzell-Danielsson *et al.*, 1990[a] | 124 | 1 | 0.008 |
| WHO study[a] | 72 | 35 | 0.48 |

[a]The length of the fertile period defined as 4 days.
[b]The length of the fertile period defined as 6 days.

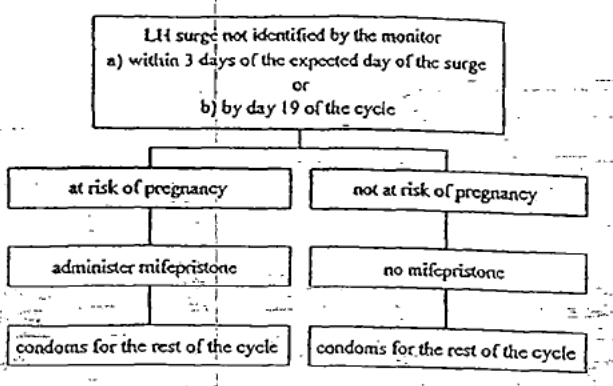


Figure 1. Algorithm for administering mifepristone when the LH surge is not identified

our group (untimed intercourse averaging 1.7 per week) may also explain the lower probability of pregnancy.

The limiting factor in this once-a-month approach to administering anti-progesterone is the accurate detection of the LH surge. Clearly, the failure to detect accurately the LH surge has a big impact on the overall effectiveness of the method. Using laboratory assay of LH in blood or urine to identify ovulation is neither practical nor convenient for long term use in the general population. The monitor provided us with an opportunity to overcome these problems. Gemzell-Danielsson *et al.* (1993) reported 49% accuracy using home LH detection sticks (Gemzell-Danielsson *et al.*, 1993). Although the monitor performed better (over 80.5% accuracy), both of these methods remain below the required standard. We studied 32 women over a total of 178 cycles. Imperfect use of the system accounted for failure to identify an LH surge in 11.8% cycles while 7.9% were due to monitor method failure. Compliance difficulties are associated with all contraceptives and non-compliance in ~12% of cycles is probably no worse than with any other method which demands action from the user, for example, compliance rates reported from oral contraceptive pill users range from 3.4–100% (Wheble *et al.*, 1981; Molloy *et al.*, 1985; Hamilton and Hoogland, 1989). Although our study population consisted of women who were motivated and committed and some of them already had experience in using natural family planning methods, they found the short, inflexible testing window set on day 1 of the cycle to be particularly demanding. This is inconsistent with couples using the monitor in order to get pregnant (Bonnar *et al.*, 1999). The prevalence of imperfect use is likely to rise in the general population compared with that typical of a research study.

During the course of the study we developed an algorithm (Figure 1) for the administration of mifepristone if an LH surge was not identified. In 19 exposure cycles (out of 28 cycles in which an LH surge was not identified) mifepristone was administered using this algorithm and there were no pregnancies. Given that the methods available to be used in real life to time the administration of mifepristone cannot be 100% accurate, such an algorithm will be essential to deal with a missed LH surge.

In our study, mis-timed administration of mifepristone led to predictable effects. When administered during the proliferative phase of the menstrual cycle, mifepristone inhibited follicular development, and delayed the mid cycle LH surge, leading to a delay in ovulation and subsequent prolongation of the menstrual cycle (Liu *et al.*, 1987; Luukkainen *et al.*, 1988; Swahn *et al.*, 1988). Ovulation may occur later in that cycle, leaving women at risk of conception. In our study, when administered in the late follicular phase (in error) in three cycles, mifepristone prolonged the cycle length (43–52 days). The women were advised to use condoms for the remainder of that cycle and none of the three cycles resulted in pregnancy.

Administration of mifepristone in the mid or late luteal phase induces a bleed within a few days of treatment, which may or may not be followed by a second bleed at the time of expected menstruation (Shoupe *et al.*, 1987; Swahn *et al.*, 1988). In our study, in 17 out of the 19 cycles where mifepristone was taken after ovulation (the LH status unavailable and probably later than on LH + 2), inter-menstrual vaginal bleeding occurred (89.5%). Moreover, there was an increased risk of bleeding seen in those women who may have taken mifepristone slightly later in the LH + 2 window. The mean serum progesterone concentration was significantly higher in those women who had bleeding after taking mifepristone within LH + 2, when compared with those who did not. The higher serum progesterone value in some on LH + 2, could be due to a delayed identification of the first significant rise in urinary LH, or because of a more rapid increase in serum progesterone due to early ovulation. Nevertheless, in our group of women, in all cycles where mifepristone induced a vaginal bleed, a second bleed occurred at the time of the expected menses. Therefore, while the bleeding may have been inconvenient, it did not jeopardise efficacy or continued use of the method. There was less inter-menstrual bleeding (15% of the cycles) reported in our study when mifepristone was taken within LH + 2, less than half of that reported by Gemzell-Danielsson *et al.* (32%) (Gemzell-Danielsson *et al.*, 1993). This is possibly due to the fact that the majority of women in our study received mifepristone at the correct time. In their study, in 51% of the cycles, mifepristone was taken between 3 and 5 days after the LH surge.

In conclusion, the use of the combination of home use

fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an attractive contraceptive option with minimal side effects. However, to be an effective contraceptive method, the women have to be committed to using a device, which identifies the LH surge, in order that the pill can be taken at the correct time in the cycle. Whilst this regimen may be acceptable to motivated women, it may be regarded as too complicated for others to adopt on a routine basis. There was evidence of such non-compliance in this study, with 11.2% of LH surges being missed as a consequence of imperfect use of the monitor. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which obligated less compliance, could be devised.

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# Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial

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**Objective** To examine the clinical efficacy of mifepristone 600 mg followed on the same day or two days later by misoprostol 400μg orally in women undergoing medical termination of pregnancy whose pregnancies have a gestational age up to 49 days.

**Design** Prospective, randomised trial.

**Setting** Clinical research office.

**Participants** Eighty-six women, requesting elective termination of a pregnancy which has a gestational age of ≤ 49 days.

**Methods** After administration of mifepristone 600 mg, participants were randomised to take misoprostol six to eight hours later (Group 1) or 48 hours later (Group 2). Women returned for a follow up evaluation 24 ± 1 hours after taking the misoprostol. Participants in Group 1 who had not aborted received a second dose of misoprostol to take 48 hours after the mifepristone. All women returned approximately two weeks after receiving mifepristone. If termination of pregnancy had still not occurred and the pregnancy was non-viable, the woman returned again in three weeks.

**Main outcome measures** Rate of complete abortion 24 hours after administration of misoprostol.

**Results** At 24 hours after receiving misoprostol, 21/42 (50%, 95% CI 35%, 65%) women in Group 1 and 40/44 (91%, 95% CI 82%, 99%) women in Group 2 had complete abortions. By follow up two weeks later after the administration of mifepristone, 40/42 (95%, 95% CI 89%, 100%) women in Group 1 and 43/44 (98%, 95% CI 93%, 99%) women in Group 2 were known to have complete abortions. Nausea, vomiting or diarrhoea in women using the standard regimen (Group 2) occurred in 68%, 36%, and 20%, respectively.

**Conclusions** After treatment with mifepristone 600 mg, administration of misoprostol 400 μg orally on the same day is not as effective at causing abortion within the first 24 hours compared with the standard time interval of 48 hours between medications.

## INTRODUCTION

In Europe and China more than three million women have received mifepristone, an antiprogestin, in a treatment regimen for medical termination of pregnancy. Complete abortion at gestations up to 49 days occurs in 64% to 85% of women when mifepristone is used alone in doses of 140mg to 1600mg administered over one to 10 days[1]. However, when mifepristone is followed two days later by a prostaglandin analogue, the efficacy rate for complete abortion increases to 87% to 97%[2].

Misoprostol is an inexpensive, orally active prostaglandin analogue that is used for the prevention of gastric ulcers induced by non-steroidal anti-inflammatory drugs; the dose is 200μg four times daily. Its effects on uterine tone are similar to those of other prostaglandin analogues[3]. When misoprostol 400μg orally is administered 48 hours after mifepristone 600mg, abortion occurs in 92% to 97% of women whose pregnancies have a gestational age of ≤ 49 days[4,5]. Side effects are similar to those reported with other prostaglandin analogues. Currently, misoprostol is the prostaglandin analogue most commonly used with mifepristone for early abortion.

The largest clinical evaluation of the mifepristone–misoprostol combination was an American multicentre trial involving 17 sites, including free-standing clinics, Planned Parenthood clinics and university hospitals[5]. The protocol was similar to that used in common practice in France. Woman received mifepristone 600mg orally, and returned two days later to receive misoprostol 400μg orally. Approximately 25% of participants had bleeding that was equivalent to or heavier than their menses during the interval between the medications; only 11% of those women (3% of the total study population) had aborted. A total of 2015 women with a gestation of up to 63 days were included in the final analysis. The complete abortion rate up to 49 days' gestation was 92%; however, the rate declined to 83% from 50 to 56 days amenorrhoea and

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77% from 57 to 63 days amenorrhoea. The time of expulsion was known for 1468 women, of whom 84% aborted within 24 hours after the administration of misoprostol[5].

Based on these, and many other published trials, the standard time to administer the prostaglandin analogue after mifepristone is 36 to 48 hours. The endometrium of a non-pregnant uterus begins to thin between 18 and 32 hour after the administration of antiprogestin[6]. Studies have demonstrated that the myometrium has more reactive contractility to low dose prostaglandin after treatment with mifepristone[7]. However, there are no studies that identify the time interval at which the increased reactivity to prostaglandin analogues occurs in a pregnant uterus.

It is therefore worthwhile to investigate the efficacy of administration of a low-dose prostaglandin analogue sooner than 48 hours after the administration of mifepristone. Regimens with a shorter interval between mifepristone and misoprostol, if effective, would lessen the time necessary for a medical abortion to occur and, potentially, increase acceptability. In addition, since approximately 55% of women bleed during the 48 hours between mifepristone and misoprostol with the standard regimen[5], administration of the drugs on the same day would decrease such an undesirable side effect.

This study was performed as a preliminary evaluation of the efficacy of mifepristone and misoprostol given on the same day for medical termination of a pregnancy with a gestational age of up to 49 days. Due to funding restrictions, we tested the hypothesis that the standard regimen would have resulted in expulsion within 24 hours of misoprostol in 90% of women treated with the standard regimen (i.e. the 48 hour interval between mifepristone and misoprostol) and 65% in women treated on the same day. If the regimens did appear similarly effective, then a larger study would be performed to test equivalence.

## METHODS

Healthy women at least 18 years of age were enrolled in a prospective, randomised trial approved by the Institutional Review Board of Magee-Womens Hospital of the University of Pittsburgh Health System. Entry criteria included: 1. a singleton intrauterine pregnancy not exceeding a gestation age of 49 days as documented by vaginal ultrasound; 2. requesting an elective abortion; 3. willing to comply with the schedule of visits; 4. willing to have a surgical abortion if indicated; 5. adequate venous access for multiple phlebotomies; and 6. access to a telephone.

Exclusion criteria included: 1. contraindications to mifepristone including chronic systemic corticosteroid administration or adrenal disease; 2. contraindication to misoprostol including glaucoma, mitral stenosis, sickle cell anaemia, poorly controlled seizures, or known allergy to prostaglandins; 3. haemoglobin less than 10 gm/dL; 4. cardiovascular disease including angina, valvular disease, arrhythmia, or cardiac failure; 5. known coagulopathy or treatment with anticoagulants; 6. pregnancy with an intrauterine device *in utero*; and 7. breastfeeding.

Women who enrolled signed an informed consent form and agreed to suction evacuation of the uterus, should the pregnancy be viable (defined as the presence of cardiac activity on vaginal ultrasound) 14 days after initiating the study. Vaginal ultrasound was performed and gestational age estimated using the following criteria: gestational age (days) = mean sac diameter (mm) + 30[8], or embryonic pole (mm) + 42[9]. Mean sac diameter ([length + width + depth]/3) was used to estimate gestational age only when no embryonic pole is present. Estimated Gestational Age was based on the last menstrual period; however, if the ultrasound estimate differed by four days or more from the gestational age by the last menstrual period, the ultrasound estimate was used.

On the day of consent, a history and physical examination, baseline haemoglobin, and blood graph were performed. At least 24 hours after obtaining consent (as required by the Pennsylvania Abortion Control Act), the women ingested mifepristone 600mg in front of a member of the research staff, if all of the entry criteria were met. The day of this visit was considered study day one. If the woman's blood graph was Rh-negative, she also received Rh-immune globulin 50 μg intramuscularly.

The women were given two tablets of misoprostol 200 μg to take home. They were randomised to take the misoprostol six to eight hours (Group 1) or 48 hours (Group 2) after taking the mifepristone. Randomisation was performed using a random number table to create 100 women in each of the two groups; the group was assigned by opening the next sequentially numbered sealed opaque envelope. The randomisation sequence and preparation of the envelopes were performed by a person unrelated to the study. The researchers and medical staff were not blinded to group assignment.

All participants were given written instructions with a 24-hour phone number for emergencies. The directions stated to call the Research Office if vaginal bleeding exceeded two soaked sanitary towels in one hour for two consecutive hours. All women received a prescription for 20 tablets of codeine phosphate 30 mg. The women were instructed to use ibuprofen or acetaminophen initially and to use the prescribed narcotic only if necessary.

All women returned 24 ± 1 hours after taking the misoprostol, at which time they were questioned about side effects that occurred during the interval between mifepristone and misoprostol and after the misoprostol, as well as the time of administration of the misoprostol. When questioned about severity of bleeding, the women

were instructed that "bleeding" was defined as flow equal to or heavier than menses, and "spotting" was flow lighter than menses. A vaginal ultrasound scan was performed. If the woman was in Group 1 and the gestational sac was still present, she was given an additional 400 μg (two tablets) of misoprostol to take orally 48 hours after she received the mifepristone.

All women returned for a follow up visit between days 14 and 20. A history of events since the prior visit was obtained. A vaginal ultrasound scan was performed if the examination at the last visit had not demonstrated absence of the gestational sac. If the gestational sac and embryonic cardiac activity were present, a surgical termination of pregnancy was performed. If the gestational sac was still present without cardiac activity, the women returned in three weeks (day 36) at which time her history was taken and another ultrasound scan performed. If the vaginal ultrasound scan on day 36 showed the gestational sac to be still present, the woman was offered a surgical termination of pregnancy. If she declined intervention at this time then she was followed at one or two weekly intervals until she either aborted or requested a surgical abortion. All women were permitted at any time to request a surgical procedure rather than continuing to wait for expulsion.

### Statistical analysis

The sample size was estimated based on complete abortion rates 24 hours after the misoprostol, of 90% with the standard regimen (48-hour interval) and 65% with administration of the misoprostol six to eight hours after the mifepristone. A sample of 86 women was calculated to have an 80% power to detect this difference using the $z$-statistic at a two-tailed significance level of 0.05[10]. Statistical analyses were performed using Fisher's exact test, Wilcoxon non-parametric rank tests, and $\chi^2$ analysis with Yates' correction where appropriate. The procedure was considered successful if complete abortion occurred without requiring a suction evacuation of the uterus. Body surface area was calculated using a body surface area table[11].

## RESULTS

The characteristics of the women are presented in Table 1. One (2.3%) of the women in Group 2 aborted during the interval between mifepristone and misoprostol. She called the office with heavy bleeding beginning 27 hours after the mifepristone; ultrasound evaluation in the office confirmed expulsion of the pregnancy, so she was instructed not to use the misoprostol. Of the remaining 43 women in Group 2, forty-two (97.6%) used the misoprostol 48 hours ± 0.5 hours after the mifepristone. The other woman used the misoprostol two hours after the 48-hour mark. All of the women in Group 1 used the misoprostol at the correct time.

At 24 hours after receiving misoprostol, 21/42 women in Group 1 (50%, 95% CI 35%, 65%) and 40/44 women in Group 2 (91%, 95% CI 82%, 99%) had complete abortions (RR = 0.55 [95% CI 0.42, 0.73]). By follow up two weeks after the mifepristone, 40/42 women in Group 1 (95%, 95% CI 89, 100%) and 43/44 women in Group 2 (98%, 95% CI 93%, 100%) were known to have complete abortions (RR = 0.97 [95% CI 0.90, 1.06]). One woman in Group 1 was lost to follow up after she received the mifepristone; as her final outcome could not be verified, her treatment was considered to have failed. One woman in Group 1 was thought to have aborted after a single dose of misoprostol but was seen on day 51 with an incomplete abortion requiring surgical evacuation of the uterus. One woman in Group 2 had a collapsed gestational sac 24 hours after receiving misoprostol. This sac remained at the two-week and five-week follow up visits. She continued to experience intermittent bleeding and requested surgical evacuation. The pathology report for both of the women who had surgical evacuation of the uterus showed chorionic villi.

Information on cramping and bleeding after the first dose of misoprostol is presented in Table 2. Information on the duration of vaginal bleeding and spotting was available for 37 (88%) and 38 (86%) women in Groups 1 and 2, respectively. Total vaginal bleeding lasted 17 (SD9) days and 17 (SD10) days, respectively. Only one woman had vaginal bleeding that soaked two sanitary towels in one hour for two consecutive hours; this occurred in the woman who aborted after the mifepris-

Table 1. Characteristics of the women. Values are given as $n$ (%) or mean [SD].

| | Group 1 ($n = 42$) | Group 2 ($n = 44$) |
|---|---|---|
| Age (years) | 26 [6] | 25 [7] |
| Gravidity | | |
| 1 | 7 (17) | 11 (25) |
| 2 | 11 (26) | 13 (30) |
| 3 | 10 (24) | 7 (16) |
| 4 | 8 (19) | 2 (5) |
| >5 | 6 (14) | 11 (25) |
| Mean (SD) | 3 [1] | 3 [3] |
| Parity | | |
| 1 | 17 (40) | 18 (41) |
| 2 | 12 (29) | 11 (25) |
| 3 | 8 (19) | 8 (18) |
| >4 | 5 (12) | 7 (16) |
| Mean (SD) | 1 [1] | 1 [1] |
| Marital status | | |
| Single | 33 (79) | 33 (75) |
| Married | 7 (17) | 5 (11) |
| Divorced or separated | 2 (5) | 6 (14) |
| Prior termination of pregnancy | 20 (48) | 22 (50) |
| Body surface area ($m^2$) | 1.80 [0.2] | 1.80 [0.2] |
| Gestational age (days) | 44 [4] | 43 [5] |

Table 2. Cramping and bleeding after misoprostol. Values are given as mean (SD). Women in Group 1 received a second dose of misoprostol 400 μg orally if the abortion had not occurred within 24 hours of the initial dose. Data for bleeding and cramping for Group 1 are only for the first dose of misoprostol. Women in Group 2 received only a single dose of misoprostol.

| | Group 1 ($n = 42$) | Group 2 ($n = 44$) |
|---|---|---|
| Onset of bleeding (h) | 3.8 (3.0) | 2.7 (2.5) |
| Onset of cramping (h) | 2.9 (2.8) | 1.4 (1.4) |
| Total days of bleeding | 16.9 (9.2) | 17.0 (10.2) |

tone without using misoprostol. Her bleeding subsided during the third hour and no intervention other than telephone contact was required. No women required a blood transfusion.

Side effects are presented in Table 3. The incidence of vomiting, bleeding and spotting in women who received misoprostol on the same day was significantly less compared with women who received misoprostol 48 hours after the mifepristone. Otherwise, there was no difference between the groups in their side effects. There was no statistical difference in side effects after misoprostol between the groups, including after the repeat dose of misoprostol when needed for the women in Group 1. The overall rate of nausea, vomiting or diarrhoea during the medical abortion process (after either or both medications) for women using the standard regimen was 68%, 36%, and 20%, respectively. One significant complication was a tubo-ovarian abscess occurring nine days after the administration of misoprostol and a successful abortion. The woman responded well to treatment with seven days of intravenous antibiotics followed by seven days more of oral antibiotic therapy.

Analgesia was not required at any time by 8 of 42 (19%) and 11 of 44 (25%) women in Groups 1 and 2, respectively ($P = 0.7$); all of these women aborted successfully. All o. the remaining women used only oral medication; 24% and 28% ($P = 0.9$) of women in Groups 1 and 2, respectively used narcotics for pain relief.

## DISCUSSION

This is the first published trial to evaluate the use of mifepristone and a prostaglandin analogue on the same day for medical termination of pregnancy. Clearly, after treatment with mifepristone 600 mg, the administration of misoprostol 400 μg orally on the same day is not as effective at causing abortion within the first 24 hours compared with the standard time interval of 48 hours between medications.

Only 5% of women had any bleeding within six to eight hour after mifepristone, and that was only spotting. In the standard treatment group, 52% of women experienced bleeding during the 48 hours between the drugs. This rate is consistent with the 55% rate reported by Spitz *et al.*[5] after 600 mg mifepristone and the 48% rate reported by Schaff *et al.*[12] in 933 women after mifepristone 200 mg. Thus, bleeding during the 48-hour standard interval appears to occur in approximately half of the women after using mifepristone and usually begins more than eight hours after the mifepristone.

In the French study of Peyron *et al.*[4], mifepristone 600 mg followed in 36 to 48 hours by misoprostol 400 μg orally in women up to 49 days gestation, resulted in nausea, vomiting and diarrhoea being reported by 43%, 17% and 14%, of the women, respectively. In contrast, the women in our study reported these side effects in 68%, 36%, and 20%, respectively; these rates are nearly

Table 3. Side effects after treatment with mifepristone 600 mg and misoprostol 400 μg orally for early abortion. Values are given as *n* (%) or RR with (95% CI).

| | Mifepristone | | | Misoprostol[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | RR[b] | Group 1 | | RR[b] | Group 2 | RR[c] |
| | $n = 42$ | $n = 44$ | | 1st dose $n = 42$ | 2nd dose $n = 18$ | | $n = 43$ | |
| Nausea | 18 (43) | 21 (48) | 0.90 (0.56, 1.43) | 23 (55) | 3 (17) | 2.90 (1.00, 8.41) | 18 (42) | 1.31 (0.84, 2.05) |
| Vomiting | 2 (5) | 12 (27) | 0.17 (0.04, 0.73) | 5 (12) | 2 (11) | 1.07 (0.23, 5.02) | 6 (14) | 0.85 (0.28, 2.58) |
| Diarrhea | 0 | 1 (2) | 0.98 (0.93, 1.02) | 15 (36) | 4 (22) | 1.57 (0.60, 4.08) | 8 (19) | 1.92 (0.91, 4.04) |
| Cramping | 13 (31) | 20 (45) | 0.68 (0.39, 1.19) | 39 (93) | 16 (89) | 1.04 (0.87, 1.26) | 35 (81) | 1.14 (0.97, 1.35) |
| Dizziness | 7 (17) | 11 (25) | 0.67 (0.29, 1.56) | 12 (29) | 3 (17) | 1.71 (0.55, 5.35) | 8 (19) | 1.54 (0.70, 3.37) |
| Spotting | 2 (5) | 23 (52) | 0.09 (0.02, 0.36) | – | – | – | – | – |
| Bleeding | 10 (24) | 18 (41) | 0.59 (0.46, 0.76) | 32 (90) | 18 (100) | 0.90 (0.82,1.00) | 43 (100) | 0.90 (0.82, 1.00) |
| Headache | 6 (14) | 9 (20) | 0.70 (0.27, 1.79) | 5 (12) | 3 (17) | 0.71 (0.19, 2.68) | 8 (19) | 0.64 (0.23, 1.80) |
| Warmth/chills | 10 (24) | 10 (23) | 1.05 (0.49, 2.26) | 12 (29) | 5 (28) | 1.03 (0.42, 2.49) | 13 (30) | 0.95 (0.49, 1.83) |

[a] One woman in Group 2 aborted after mifepristone and did not receive misoprostol. Data was missing for one of the 19 women in Group 1 who received a second dose of misoprostol.

[b] Relative risk and 95% confidence intervals; 1st dose versus 2nd dose.

[c] Relative risk and 95% confidence intervals of 1st dose of misoprostol in Group 1 compared to Group 2.

identical to those reported in the American study by Spitz *et al.*[5] (61%, 26%, and 20%, respectively). Thus, either French women have a lower rate of side effects from medical termination of pregnancy or do not report side effects when they occur.

Similarly, use of narcotic drugs in the French studies is different to that reported in the United States. Peyron *et al.*[4] reported that 81% of women experienced cramping and only 16% requested any pain relief, which consisted of a non-opiate analgesic. In the American trial reported by Spitz *et al.*[5], 29% of women received a narcotic analgesic. Women in both of these trials were required to remain in the office for four hours after misoprostol for observation. In contrast, the women in our study used the misoprostol at home, a practice that has been well-documented in the medical literature to be safe and effective[12–14]. Still, the use of narcotics was approximately the same as that reported in American women who remain under observation[5]. Overall, the use of narcotic analgesics is more prevalent in the United States compared with France.

Studies using mifepristone 200 mg followed in 48 hours by misoprostol 800 μg vaginally appear to result in higher rates of complete abortion and more rapid expulsion compared with oral misoprostol[12,15]. Thus, it is possible that a regimen with vaginal misoprostol may hold promise for same day treatment. Since a same-day regimen is desirable from the woman's point of view and has fewer side effects (especially bleeding), vaginal misoprostol given on the same day as mifepristone deserves investigation.

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# Medical abortion as an alternative to vacuum aspiration: first experiences with the 'abortion pill' in The Netherlands

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ABSTRACT

**Objective** To establish to what extent medical abortion is desired as a supplement to existing care provision in The Netherlands and to establish the (dis)advantages of medical abortion versus surgical vacuum aspiration.

**Methods** The research project began in November 1999 and ended in September 2000. In two abortion clinics, the clients were asked to answer some questions about their expectations (before treatment) and their experiences with the treatment (at the post-treatment check-up). At the post-treatment check-up, the clients were also asked to fill out the Hopkin's Symptom Checklist (HSCL) which is an objective measure for the psychological and physical well-being of the clients during the previous week.

**Results** One hundred and thirty-one clients who chose medical abortion and 131 clients who chose surgical vacuum aspiration participated in the study. The failure rate was 3.3% for medical abortion and 1.5% for surgical vacuum aspiration. Of the medical abortion clients, 80.2% reported they were satisfied with this treatment and 68.1% said they would choose the same treatment procedure in the future. For vacuum aspiration, these figures were 92.9% and 83.2%, respectively.

The most reported advantage of medical abortion was the fact that it was a pill, and no surgical procedures were necessary. The most reported disadvantages of medical abortion were the amount of blood loss and insecurity concerning the time of abortion.

**Conclusions** Medical abortion seems to be a good supplement to the existing care provision in The Netherlands and should be offered in other clinics.

KEY WORDS Medical abortion, Comparative study

## INTRODUCTION

Mifepristone (Mifegyne®), also known as the 'abortion pill', was developed by the French professor, Emil-Etienne Baulieu, and was introduced onto the French market in 1989 by the pharmaceutical company, Roussel Uclaf, under the name of RU 486. Within the same year, the Medicines Evaluation Board

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in The Netherlands proposed a registration request for RU 486. Several months later, Roussel decided not to continue with further distribution of mifepristone, due to pressure from the pro-life movement in several countries. Registration procedures in The Netherlands were also halted. In the years following, RU 486 was eventually introduced in a few countries: Great Britain in 1991 and Sweden in 1992[1]. At the end of 1998, a request for mifepristone was proposed to the European Community, and, since the end of 1999, mifepristone has been available on the Dutch market.

Mifepristone is an antiprogestin, which can cause spontaneous abortion within the first weeks of pregnancy. In France, the use of mifepristone is limited to the period up to 49 days after the first day of the last menstrual period (in other words, until 3 weeks late) and, in Great Britain and Sweden, up to 63 days (5 weeks late). Mifepristone acts as a competitive blockade against progesterone (a hormone necessary for sustaining pregnancy) which, in turn, causes the uterine lining to shed. Simultaneously, mifepristone heightens the sensitivity of the myometrium, which is necessary for the contraction effects of prostaglandin during pregnancy. The substance itself does not work as a prostaglandin; it is combined with a small dose of a prostaglandin[2], for example, misoprostol. This is a synthetic form of prostaglandin $E_1$ analog which is stable at room temperature. It can be administered orally (buccally or sublingually) and vaginally, and has a half-life of approximately 90 min. Misoprostol stimulates uterine contractions and has a softening effect on the cervix. Dangerous side-effects have not been reported and the gastrointestinal side-effects are relatively mild[3]. Therefore, in addition to the fact that it is less expensive than other prostaglandins, such as gemeprost, misoprostol is becoming more popular in gynecological procedures.

The procedure developed in France, and most used, is carried out as follows[4–6]. On the first day of treatment, the woman is administered 600 mg mifepristone (three tablets of 200 mg) in an abortion clinic or hospital. On the third day (48 h after the first administration), the woman returns to the clinic or hospital and is administered 400 µg misoprostol (in the form of pills or vaginal suppositories). Thereafter, she stays 4–6 h in the clinic or hospital for observation. Most clients (approximately 61%) have an abortion within this time-period; others have an abortion at home within the following 24 h. Between days 10 and 12, the woman must return to the clinic or hospital for a follow-up. In the situation where an abortion has not taken place, vacuum aspiration is performed during the follow-up visit.

Some studies report giving a lower dosage of mifepristone[7–9] or giving a second administration of 400 µg misoprostol[5,10–12]. There are also publications which suggest that administration of misoprostol on day 2 or day 4 is equally successful[13].

The reported successful cases using such procedures vary from 95.4% to 98.7% in France[4–6,10,12], 94.8% in the UK[14], 77–92% in the United States[15] and 97.3% in Austria[11]. The success of cases seems to be dependent on the pregnancy duration: the mifepristone–misoprostol combination seems to be most suitable for the termination of pregnancies of a duration of < 49 days of amenorrhea[8,15].

Dutch physicians do not have much experience with medical abortion. The organization of Dutch abortion services, compared to other western countries, is unique. In other countries, specialists in hospitals usually carry out the termination of pregnancies. The procedure is often carried out under general anesthesia with a pregnancy duration usually more than 7 weeks. It is also not unusual that the patient stays for one to several days in the hospital. Treatment in The Netherlands for termination of pregnancy is easily accessible and not unnecessarily medicalized. Almost 90% take place in abortion clinics where the vacuum aspiration procedure is carried out, usually under local anesthesia[16]. After a resting period, the woman is able to return home. The percentage of complications is extremely low (0.3%)[16]. The question to be answered is to what extent is medical abortion, or treatment with the abortion pill, a viable and desired supplement to the Dutch health-care system and what are the advantages and disadvantages of this method of pregnancy termination in comparison to the vacuum aspiration method? The Netherlands Institute for Social Sexological Research (NISSO), in collaboration with two abortion clinics (Stimezo Den Haag and MR'70 in Amsterdam), carried out research looking at the experiences with medical abortion from November 1999 until

December 2000. Within this article, the results from this research will be discussed.

## METHODS

The Medical Ethics Testing Committee approved the research protocol; however, as a consequence of the Medical–Scientific Research with People Act, the review committee put the following restriction into place. Women aged 16–17 years were only allowed to participate if they had written permission signed by both parents.

The research took place from November 1999 until December 2000. Participants were recruited from the two abortion clinics working in collaboration with this project. All the clients who met the research criteria and who qualified for the medical abortion treatment were included (Tables 1 and 2). These clients were then asked to choose between the medical and vacuum aspiration treatment (with or without intravenous sedation). Beforehand, they received neutral information about the different methods. The women who chose to participate in this project were asked prior to the treatment and at the follow-up visit to answer several questions. For example, participants were asked what their expectations were of the chosen method before and after treatment. The Hopkin's Symptom Checklist (HSCL) was also used during the follow-up visit. This questionnaire was used as an objective measurement device for the psychological and physical well-being of the clients during the previous week. The HSCL uses three scales. The first scale measures the complaints concerning the psychoneurological state, the second scale measures physical health and the third scale measures psychological and physical health[17].

The recruitment of participants was difficult. Approximately one-half of all Dutch abortion clients should, when looking at the pregnancy duration (< 49 days of amenorrhea) qualify for a medical abortion: approximately 10 000 women per year. Ultimately, 283 respondents from the two participating clinics were recruited. One hundred and thirty-one women chose medical treatment, 131 women chose vacuum aspiration with local anesthetic and 21 women chose vacuum aspiration with intravenous sedation. This last group is too small to include in further statistical analysis[18].

The data from the questionnaires were calculated with help of an SPSS program. Differences between the groups were tested using Pearson's $\chi^2$ test and the $t$ test for independent samples (significance level at $p < 0.05$).

## RESULTS

### Characteristics of the participants

The average age of the patients opting for the abortion pill was 27.7 years, and 30.4 years for the vacuum aspiration clients. The participants as a whole were highly educated, with 73.9% of the abortion pill clients and 73.3% of the vacuum aspiration clients having a minimum of an intermediate-level secondary school diploma. The high level of education can be explained by a selection bias in the clinics and the fact that the majority of women with lower levels of education (immigrants) cannot speak Dutch fluently. Fluent Dutch was included as part of the criteria to participate in the research (Table 1).

### Failure rate

During treatment with the abortion pill, eight women (6.1%) discontinued treatment. Of the 123 women who completed treatment with the abortion pill, four received additional vacuum aspiration during the follow-up visit. The failure rate of treatment with the abortion pill within this project was 3.3%. Reasons for vacuum aspiration during the follow-up visit were

Table 1 Inclusion criteria for the research

| |
|---|
| Singular pregnancy ≤ 49 days of amenorrhea, diagnosed through an echogram |
| Fluent Dutch |
| Good health |
| AWBZ qualified |
| Aged 16 years or older |
| Prepared to follow visiting schedule |
| Prepared to sign 'informed consent' |
| For clients of 16 or 17 years, permission from parents or legal guardian required |

AWBZ, national health insurance for special medical costs

positive pregnancy tests and continued blood loss (this can be the result of an incomplete abortion). Of the 131 women who completed treatment with vacuum aspiration, two required treatment with an additional vacuum aspiration (1.5%).

### Motivation for chosen treatment and experiences of advantages and disadvantages

Most of the clients agreed that the most important advantage of medical abortion was that no surgical procedure was required. This was mentioned by almost three-quarters of the women who chose the abortion pill. Further, four out of ten women considered it to be a more natural method and approximately one-third considered it to be an advantage that a doctor would not physically handle them. The fact that taking a series of pills does not involve surgery seemed to be the most frequently mentioned advantage following treatment (Table 3). Other significant advantages mentioned following this treatment method were a greater feeling of control ($t = -2.42$, $p = 0.02$), being fully aware of what was happening ($t = -2.95$, $p < 0.01$) and it is a more natural experience ($t = -2.47$, $p = < 0.05$). Also, for some, it was a comforting idea that the abortion could take place at home ($t = -3.76$, $p < 0.001$). The most important disadvantage of medical abortion, mentioned prior to treatment, was that there was a greater chance of failure after treatment. Almost one-half of the women considered this to be a disadvantage. One-third considered it to be a disadvantage that they were required to come to the clinic several times. One-quarter of the clients mentioned the unreliability of the time-frame in which the abortion would take place and the fact that there could be more blood loss (Table 4). Blood loss was mentioned significantly more after treatment ($t = 3.32$, $p = 0.001$). The amount of blood loss is, therefore, disappointing when compared to what was initially expected. The fact that medical treatment had a greater failure rate than vacuum aspiration was actually mentioned less after treatment ($t = 2.65$, $p = 0.01$). This initial perceived disadvantage was mentioned less after a successful treatment.

Women who chose vacuum aspiration mentioned, both prior and following treatment, that the short procedure time and the fact that a direct result was obtained were the most important advantages (Table 5). Pain was mentioned as the most important disadvantage prior to treatment (65.4%) and pain was again mentioned as the most important disadvantage

Table 2 Exclusion criteria

| |
|---|
| Adrenal gland disease or use of corticosteroids |
| With respect to misoprostol: severe bronchial asthma, glaucoma, mitral stenosis, sickle cell anemia, hypertension, prostaglandin allergy |
| History of severe liver, lung or kidney disease |
| Cardiovascular disease |
| Coagulation disorder, use of anticoagulation medicine |
| Intrauterine device insertion |
| Insulin-dependent diabetic |
| Unwilling to stop breastfeeding for 1 week |
| Suspicion of pelvic inflammatory disease |
| Extrauterine gravidity or threatened abortion |
| 35 years or older + smokes more than 20 cigarettes per day + risk factors |
| Unwilling or unable to give up the following medications: salicylic acid, anticoagulants, indomethacin, prostaglandin inhibitors (naproxen, etc.), uterotonica, antipsychotics (haldol trilafon) |

Table 3 Perceived advantages of the abortion pill, prior to and following treatment

| | *Before treatment* | | *After treatment* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Pill, no surgical intervention | 93 | 72.7 | 71 | 80.7 |
| It is a more 'natural' way to terminate a pregnancy | 53 | 41.4 | 46 | 52.3 |
| No doctors touching my body | 39 | 30.5 | 33 | 37.5 |
| Conscious experience | 17 | 13.3 | 20 | 22.7 |
| Self-control | 15 | 11.7 | 21 | 23.9 |
| Chance that abortion will happen at home, in own environment, is high | 14 | 10.9 | 19 | 21.6 |

Table 4 Perceived disadvantages of the abortion pill, prior to and following treatment

| | *Before treatment* | | *After treatment* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Slightly larger chance of failure in treatment | 56 | 45.5 | 25 | 28.1 |
| Necessary to come back to the clinic | 43 | 35.0 | 25 | 28.1 |
| Not sure when abortion will take place | 32 | 26.0 | 27 | 30.3 |
| More blood loss (in comparison to vacuum aspiration) | 30 | 24.4 | 35 | 39.3 |
| No disadvantages/no negative experiences | 17 | 13.8 | 16 | 18.0 |
| Chance that abortion will take place at home is high | 4 | 3.3 | 4 | 4.5 |

Table 5 Perceived advantages of vacuum aspiration (under local anesthetic), prior to and following treatment

| | *Before treatment* | | *After treatment* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Short treatment time | 79 | 62.2 | 96 | 85.0 |
| Direct result | 72 | 56.7 | 72 | 63.7 |
| Smaller chance of failure | 41 | 32.2 | 55 | 48.7 |
| Small chance of or no problems with side-effects such as nausea and diarrhea | 27 | 21.3 | 25 | 22.1 |
| Conscious experience | 17 | 13.4 | 29 | 25.7 |

Table 6 Perceived disadvantages of vacuum aspiration (under local anesthetic), prior to and following treatment

| | *Before treatment* | | *After treatment* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Pain | 85 | 65.4 | 64 | 57.1 |
| Conscious experience | 41 | 31.5 | 23 | 20.5 |
| Position on examination table | 28 | 21.5 | 19 | 17.0 |
| Surgical intervention | 27 | 20.8 | 9 | 8.0 |
| No disadvantages/no negative experiences | 13 | 10.0 | 21 | 18.8 |

following treatment (Table 6). However, pain was mentioned less frequently as a disadvantage following the procedure than prior to it ($t = -1.96$, $p < 0.05$), as was the idea of a surgical procedure ($t = 2.09$, $p < 0.05$) and the fact that it is a conscious experience ($t = 3.59$, $p < 0.001$), following the procedure than prior to the procedure. This means that the actual procedure exceeded prior expectations.

## Information sources

Almost half (46.0%) of the clients who chose medical treatment had chosen the participating abortion clinics especially because such a treatment was available. They had made their choice for this treatment based on information they had received from the media. Family practitioners did not play any role.

Through the research, it became clear that the clients did not always receive the correct information concerning medical treatment, resulting in them coming to the clinic with false expectations. During the explanation of the differences between the two methods at the clinic, it became clear that the medical treatment consisted of taking pills and that they would be required to come back to the clinic several times.

### Physical and psychological effects

The abortion pill clients had higher scores especially on the somatic scale: 55.7% of the women scored higher than average. This high score can probably be explained by the side-effects that were experienced from the medication. Examples on this scale include headaches and lower back pain. The differences between the abortion pill and vacuum aspiration clients are significant on the third scale, the total scale, which measures both the psychological and the physical complaints.

### Satisfaction rate

Of the women who chose the abortion pill, 80.2% were satisfied with the treatment and 68.1% would opt for this method again, if necessary. With vacuum aspiration, the numbers were, respectively, 92.9% and 83.2% (Tables 7 and 8).

## DISCUSSION

Through the research it is evident that the clients regard medical abortion as a positive addition to Dutch public health services. It is clear that the women in both groups were satisfied with the choices they made for treatment. The research encouraged other abortion clinics to start offering medical abortion as well.

Although the abortion pill failure rate (where additional vacuum aspiration was necessary) is higher than with vacuum aspiration, both failure rates (3.3% for medical abortion and 1.5% for vacuum aspiration) are acceptable.

The research does not offer any insight into the use of medical abortion treatment for adolescent girls (under 18 years) and women with lower levels of education, due to the restrictions put in place by the Medical Ethics Testing Committee. Additional insights into the experiences of these groups with the abortion pill could lead to further tightening of criteria used in the selection and screening of clients for the

Table 7 Scale of satisfaction following medical abortion or vacuum aspiration

| | *Medical abortion* | | *Vacuum aspiration* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| 0. Stopped | 8 | 8.3 | — | — |
| 1. Absolutely not satisfied | 4 | 4.2 | 3 | 2.7 |
| 2. Slightly satisfied | 7 | 7.3 | 5 | 4.4 |
| 3. Satisfied | 34 | 35.4 | 70 | 61.9 |
| 4. Very satisfied | 17 | 17.7 | 17 | 15.0 |
| 5. Very much satisfied | 26 | 27.1 | 18 | 15.9 |
| Total | 96 | 100.0 | 113 | 100.0 |

Table 8 Number of patients who would choose the same treatment again

| | *Medical abortion* | | *Vacuum aspiration* | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| 0. Stopped | 8 | 8.5 | — | — |
| 1. No, absolutely not | 5 | 5.3 | 3 | 2.7 |
| 2. No, I don't think so | 5 | 5.3 | 7 | 6.2 |
| 3. I don't know | 12 | 12.8 | 9 | 8.0 |
| 4. Yes, I think so | 18 | 19.1 | 45 | 39.8 |
| 5. Yes, absolutely | 46 | 48.9 | 49 | 43.4 |
| Total | 94 | 100.0 | 113 | 100.0 |

abortion pill, which could lead to formulating standards for responsible qualitative services for these groups.

In relation to the treatment protocol, further research is necessary to look at the possibilities of lower doses of mifepristone and the influences of that on the efficacy of the treatment. At the moment, mifepristone is only registered in The Netherlands as a method for pregnancy termination. In low doses of 10 mg, mifepristone can also be used as a 'late' morning after pill[19–21]. Considering the positive experiences in other countries, it is desirable to research other possibilities for the use of mifepristone in The Netherlands.

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# *APPENDIX 11.6.*

# UPDATED LISTING ON ONGOING PREGNANCIES FROM 1987 TO 2002

| | MIF ALONE | MIF+ MIS | MIF+ SUL | MIF+ UNK | MIF+ PG | MIF+ GEM | TOTAL |
|---|---|---|---|---|---|---|---|
| Normal Babies | 14 | 15 | 2 | 4 | 2 | 5 | 42 |
| Malformation At Term | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| MALF/ TToP | 1 | 1 | 0 | 0 | 0 | 5 | 7 |
| Delayed spont. Abortion | 5 | 1 | 0 | 0 | 0 | 0 | 6 |
| TToP UNK | 4 | 6 | 0 | 0 | 2 | 0 | 12 |
| TToP Normal Foetus | 2 | 14 | 1 | 1 | 1 | 0 | 19 |
| UNK/USNL | 3 | 4 | 0 | 2 | 3 | 0 | 12 |
| UNK | 22 | 16 | 1 | 5 | 1 | 0 | 45 |
| **TOTAL** | 51 | 57 | 4 | 12 | 9 | 13 | 146 |

Update on June 30, 2002

LEGENDS

MIF= mifepristone
MIS= misoprostol
SUL= sulprostone
GEM= gemeprost
PG= prostaglandin (unspecified)
UNK= unknown
TToP= Therapeutic Termination of Pregnancy
USNL= Ultrasound Normal (at second or third trimester)
Delayed Spont. Abortion= Delayed Spontaneous Abortion
MALF/TToP= Malformation with Therapeutic Termination of Pregnancy

## ONGOING PREGNANCIES

| 1 | N° | Case Number | Date MIF or week of Am. | PG | TERM | DOSE | CAT | TYPE | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|
| 1 | | PMIF0001.87FR$ | (b) (6) 5 w | NO | | 400 | TTOPM | Sirenomelia,* | |
| 2 | GI | PMIF0002.88FR$ | 6 w | SUL | | 600 | TTOP | ** | NL Foetus |
| 3 | 2 | PMIF0001.89FR | 7w | YES | | 600 | TTOP | ** | NL Foetus, Male |
| 4 | 3 | PMIF0002.89FR | | NO | TERM | 600 | NL | *** | Female |
| 5 | 5 | PMIF0004.90FR | | NO | | 600 | TTOP | *** | NL Foetus |
| 6 | 8 | PMIF0003.89FR$ | End 1989, 6-7 w | NO | TERM | 400 | NL | Published,Pons,*,*** | Male |
| 7 | | PMIF0001.90UK£ | 8 w | NO | TERM | 600 | NL | * | Male |
| 8 | | PMIF0002.90UK£ | 8 w | NO | TERM | 600 | NL | * | Male |
| 9 | | PMIF0003.90UK£ | 9 w | NO | TERM | 600 | NL | * | Female |
| 10 | 7 | PMIF0005.90FR | 1990 | NO | | 600 | TTOP | At 2 months, U | NL Foetus |
| 11 | 9 | PMIF0006.90FR | (b) (6) 6 w | SUL | | 600 | U | *, ***, SA? | |
| 12 | 10 | PMIF0007.91FR | | SUL | TERM | 600 | NL | *, ** | Male |
| 13 | | MIF0029.91FR/OS | U | U | TERM | 600 | NL | U | |
| 14 | | MIF0030.91FR/OS | U | U | | 600 | U | *** | NL 2nd semester |
| 15 | 11 | PMIF0008.91FR | 1991 | NO | TERM | 600 | NL | * | |
| 16 | 12 | PMIF0009.92FR/RA | U | NO | | 600 | U | *** | NL 2nd semester |
| 17 | 13 | PMIF0004.92FR$ | CT;47OA | NO | | 600 | U | *** | |
| 18 | 14 | PMIF0010.92FR | (b) (6) 7 w, Trinordiol | SUL | TERM | 600 | NL | * | Female |
| 19 | | PMIF0002.93UK | 8 w | YES | | 600 | U | *** | NL 2nd semester |
| 20 | 15 | PMIF0011.92FR/RA | (b) (6), 5 w | YES | | 600 | TTOP | *, *** | 7,5 |
| 21 | 16 | PMIF0012.93FR | U | MIS | | 600 | TTOP | *** | NL Foetus |
| 22 | 17 | PMIF0013.93FR/RA | 6/7 w a | MIS | | 600 | U | Lost to FU | NL 2nd semester |
| 23 | 18 | PMIF0014.93FR | U | NO | | 600 | TTOP | *** | |
| 24 | 19 | PMIF0015.93FR | (b) (6) 7 w 2 d | MIS | | 600 | U | *** | |
| 25 | | PMIF0003.93UK | U | GEM | TERM | 600 | ABN | Bilateral talipes, * | |
| 26 | 20 | PMIF0016.93FR/RA | (b) (6) vomits) Twice 3 cp | NO | | 1200 | U | U | |
| 27 | 21 | PMIF0017.93FR | 1993 | MIS | | 600 | U | U | |
| 28 | 22 | PMIF0018.93FR | U | MIS | TERM | 600 | NL | * | |
| 29 | 23 | MIF/PG0024.93FR | (b) (6), 5 w | NO | | 600 | SA | * | Bled since MIF, 5 m |
| 30 | 24 | MIF/PG0026.93FR | (b) (6) at 8 w | MIS | | 600 | SA | * | |
| 31 | 25 | MIF0001.94FR$ | At 7 w of am | MIS | | 600 | U | Unsure at start | |
| 32 | | MIF0001.94UK | U | NO | | 600 | U | U | |
| 33 | 26 | MIF/PG9011.93UK£ | (b) (6) 9 w 2 d | GEM | TERM | 600 | ABN | Finger nail defect(3), ** | Oral Contraceptive |
| 34 | | MIF/PG0001.93SE | 48 d | GEM | TERM | 600 | NL | Premature birth/cesarean | DMPA, Male |
| 35 | 27 | MIF0003.94FR | U | YES | TERM | 600 | NL | ** | Male |
| 36 | 28 | MIF0004.94FR | (b) (6) | YES | | 600 | U | **, US NI, Lost to FU | NL 2nd semester |
| 37 | 29 | MIF0005.94FR | 6,5 w of a | U | | 600 | U | U | NL 2nd semester |
| 38 | | MIF0005.94.UK | U | GEM | TERM | 600 | NL | U | |
| 39 | 30 | MIF/PG0029.93FR | (b) (6) 6 w of am | MIS | TERM | | NL | U | Male |
| 40 | 31 | MIF0009.94FR | | MIS | | 600 | TTOP | *** | NL Foetus, 25 w |
| 41 | 32 | MIF0013.94FR | à 52 d of am. | NO | | 200 | U | * | |

## ONGOING PREGNANCIES

| 1 | N° | Case Number | Date MIF or week of Am. | PG | TERM | DOSE | CAT | TYPE | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|
| 42 | 33 | MIF0017.94FR | 7,5 w of am | MIS | | 600 | TTOP | Unsure | Foetus unassessable |
| 43 | 34 | MIF0021.94FR | 7 w of am | MIS | TERM | 600 | NL | * | Female |
| 44 | 35 | MIF0022.94FR$ | (b) (6) 6 w | MIS | TERM | 600 | NL | At 3 Mths (Hepatitis..) | Other medical, Fem |
| 45 | 36 | MIF0003.95FR | 1995 | NO | | 600 | TTOP | * | |
| 46 | | MIF0003.95UK£ | 8 w of pregnancy | GEM | | 600 | TTOPM | **,Talipes Equinovares | OC |
| 47 | 37 | MIF0011.95FR | U | U | | | U | U | |
| 48 | 38 | MIF0005.95FR | (b) (6) | NO | | 600 | U | * | |
| 49 | 40 | MIF0008.95FR | U | MIS | | 600 | TTOP | *** | NL Foetus, Male |
| 50 | 41 | MIF0009.95FR | (b) (6), 7 w, in fact 11 w | GEM | TERM | 600 | NL | *? | |
| 51 | 42 | MIF0012.95FR/RA | 7 w of am | YES | | | TTOP | * | |
| 52 | 43 | MIF0013.95FR | (b) (6) | MIS | | 600 | TTOP | U | |
| 53 | 44 | MIF0015.95FR | 6 w | MIS | TERM | 600 | NL | U | Male |
| 54 | 45 | MIF0019.95FR/RA | mic (b) (6) | NO | TERM | 600 | NL | *** | |
| 55 | 46 | MIF0021.95FR | Beginning (b) (6) 5 w of a. | MIS | TERM | 600 | NL | * | Female |
| 56 | 47 | MIF0004.96UK | (b) (6) 7 w pregnancy | GEM | | 600 | TTOPM | Acheiria/talipes eq/toes abn/,** | Mandibula hypo |
| 57 | 48 | MIF0005.96FR | Unk, 5.5 w of am | MIS | | 600 | U | *, *** | NL 2nd semester |
| 58 | 49 | MIF0007.96FR/RA | (b) (6) | MIS | | 600 | U | *** | |
| 59 | 50 | MIF0003.96SE | | GEM | | 600 | TTOPM | Anencephaly, talipes eq | |
| 60 | 51 | MIF0001.97FR | | NO | | 600 | NL | *** | Female |
| 61 | | 199500383RU(FR) | 55 d of am. | MIS | | 600 | TOP | U | NL Foetus |
| 62 | 52 | 199710066RDF | 6/7 w of am. | NO | | 600 | TOP | * | |
| 63 | 53 | 199710097RDF | (4w of preg) | YES | | | NL | * | |
| 64 | 54 | 199710379RDF | | NO | | 600 | U | * | |
| 65 | 55 | 199710378RDF | 11 w | U | | 600 | TTOP | * | NL Foetus |
| 66 | 56 | 199710383RDF | U<7 w | U | | 600 | U | U | |
| 67 | 57 | 199710467RDF | 6 w | MIS | | 600 | TTOP | | NL Foetus |
| 68 | 58 | MIF0001.97SE | 8 w 4 d | GEM? | TERM | 600 | ABN | Heart malformation, * | |
| 69 | 59 | S970001UK/MIF1 | 6-7 w | GEM | | 200 | TTOPM | Cerebellum atrophy, * | |
| 70 | 61 | S980002F/MIF1 | 6w | MIS | TERM | | NL | U | |
| 71 | | S980001UK/MIF1 | 9 w | MIS | TERM | 200 | NL | ** | Male NL |
| 72 | | S980004F/MIF1 | 7 w | MIS | | 600 | U | *** | US NL at 18 w |
| 73 | | S980005F/MIF1 | 6-7 w | NO | | 600? | U | *** | |
| 74 | | S980009F/MIF1 | 6 w | MIS | | ? | U | | U |
| 75 | | S980001UK/MIF1 | 7 w | GEM | TERM | 200 | NL | *** | NL Male |
| 76 | | S98001UK/MIF1 | 8 w 1 d | MIS | | 200 | TTOP | ** | At 16 w No anomaly |
| 77 | | S980013F/MIF1 | 14.5 w | ? | ? | ? | NL | ? | NL Male |
| 78 | | S980014F/MIF1 | 8 w | ? | ? | ? | NL | ? | Female NL |
| 79 | | S980015F/MIF1 | 16 w + 2 d | ? | ? | ? | NL | ? | NL |
| 80 | | S980016F/MIF1 | 9 w + 3 d | MIS | | 400 | NL | ? | NL at 31 w |
| 81 | | S980017UK/MIF1 | 8-9 w | GEM | | 200 | TTOPM | ***, Hydroceph, cleft P. | Cyclopia, Talipes |
| | | | | | | | | | |

## ONGOING PREGNANCIES

| 1 | N° | Case Number | Date MIF or week of Am. | PG | TERM | DOSE | CAT | TYPE | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|
| 82 | | S980018FR/MIF1 | 6 w | MIS | TERM | 600 | NL | | Male NL |
| 83 | | S980020UK/MIF1 | 13 w | NO | TERM | 600 | NL | * | NL delivery |
| 84 | | S990004F/MIF1 | 7.5 w | MIS | TERM | 600 | NL | *** | Male NL |
| 85 | | S990005F/MIF1 | 6.5 w | MIS | | 600 | TTOP | ***, US Viable at 14 w | No exam |
| 86 | | S990006UK/MIF1 | 14 w | NO | SA | 200 | SA | * | SA |
| 87 | | S990009UK/MIF1 | 8 w | NO | | 200 | NL | * | Male NL |
| 88 | | S990013UK/MIF1 | | NO | | 200 | | * | |
| 89 | | S990007F/MIF1 | 8 w am. | MIS | | | | * | |
| 90 | | S990008F/MIF1 | 7 w | MIS | | | | | |
| 91 | | S990015F/MIF1 | 6 w of pregnancy | NO | | 600 | | *? US NI at 17 w | |
| 92 | | S990016F/MIF1 | 8 w | NO | | 600 | | **, US NI | |
| 93 | | S990019UK/MIF1 | 8 w am | MIS | | 200 | | *, US, Viable preg | |
| 94 | | S990020UK/MIF1 | 8 w 6 days am. | MIS | | 200 | | *** | NI male baby |
| 95 | | S990021UK/MIF1 | 7 w am. | MIS | | | | * | NI baby |
| 96 | | S990022F/MIF1 | 7 w am. | PG | | | | 15 w US NI | |
| 97 | | S990023UK/MIF1 | | NO | | | TToP | *, Intrauterine death | |
| 98 | | S990024UK/MIF1 | 8 w preg. | NO | | 200 | | **, US dead foetus, delayed SA | |
| 99 | | S990025UK/MIF1 | 8 w Preg | MIS | | 200 | | | |
| 100 | | S990026UK/MIF1 | 21 w preg. | NO | | 200 | | * | |
| 101 | | S990027UK/MIF1 | 8 w am | MIS | | 600 | | | |
| 102 | | S990028UK/MIF1 | 15 w am | NO | | 200 | | * | |
| 103 | | S990029UK/MIF1 | 8 w am. | NO | | 200 | | * | |
| 104 | | S990031UK/MIF1 | 21 w preg | NO | | | TTOP | * | |
| 105 | | S990032UK/MIF1 | Mosaic | NO | | 600 | | * | Left multicystic kidney |
| 106 | | S990035UK/MIF1$ | 13-21 w | NO | | 200 | | * | NL baby |
| 107 | | S990036UK/MIF1$ | 13-21 w | NO | | 200 | | * | NL baby |
| 108 | | S20000001F/MIF1 | 8 w preg. | NO | TERM | 600 | NL | Premature birth | NL Male |
| 109 | | S20000002F/MIF1 | 4-5 w preg; | MIS | | 600 | TTOP | At 14 w, U | U |
| 110 | | S20000005F/MIF1 | U | MIS | | 600 | TOP | At 12 w | NL Foetus |
| 111 | | S20000009UK/MIF1 | 20 w preg. | NO | | 600 | SA | * | SA |
| 112 | | S20000010UK/MIF1 | 17-18 w preg. | ? | | 200 | | * | U |
| 113 | | S20000011F/MIF1 | 6-7 w preg. | MIS | | 600 | TOP | At 11 w | U |
| 114 | | S20000012UK/MIF1 | 9 w preg. | ? | | 200 | | * | U |
| 115 | | S20000016F/MIF1 | 7 w preg | NO | | 600 | TOP | * | U |
| 116 | | S20000018UK/MIF1 | mid-tremester | ? | ? | ? | ? | ? | U |
| 117 | | S20000019UK/MIF1 | 6 w preg | NO | | 200 | SA | At 7 w | SA |
| 118 | | S20000020UK/MIF1 | 15 w preg | ? | | 600 | | * | U |
| 119 | | S20000021UK/MIF1 | 17 w preg | ? | | 200 | | * | U |
| 120 | | S20000022UK/MIF1 | 6-7 w preg | MIS | | 200 | ? | ? | U |
| 121 | | S20000023UK/MIF1 | 12 w preg | NO | | 200 | | * | U |
| 122 | | S20000024S/MIF1 | 8-9 w preg | GEM | | 600 | TERM | * * | NL baby |

## ONGOING PREGNANCIES

| 1 | N° | Case Number | Date MIF or week of Am. | PG | TERM | DOSE | CAT | TYPE | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|
| 123 | | S20000025F/MIF1 | ? | NO | TERM | 600 | NL | * | NL Baby |
| 124 | | S20000026F/MIF1 | 5 w preg | MIS | | 600 | | * | U |
| 125 | | S20000027F/MIF1 | 6 w preg | NO | | 600 | | * | U |
| 126 | | S20000028D/MIF1 | 6 w preg | MIS | | 600 | | * | U |
| 127 | | S20000027F/MIF1 | 6 w preg | MIS | TERM | 600 | NL | * | NL Baby |
| 128 | | S20010003F/MIF1 | Date of am (b) (6) | MIS | TERM | 600 | NL | Delivery by Caesarean section (b) (6) | NL baby boy |
| 129 | | S20010012UK/MIF1 | 15 weeks of gestation | NO | | 200 | | * | |
| 130 | | S20010013UK/MIF1 | 10 weeks gestation | MIS | | 200 | | * | |
| 131 | | S20010014UK/MIF1 | First trimester of pregnancy | PG | | 200 | | * | |
| 132 | | S20010015UK/MIF1 | 8 weeks of gestation | MIS | | 200 | | * | |
| 133 | | S20010016UK/MIF1 | First trimester of pregnancy | NO | | 200 | | * | |
| 134 | | S20010017UK/MIF1 | First trimester of pregnancy | MIS | | 200 | SA | At 22 weeks | NL |
| 135 | | S2001023D/MIF1 | First trimester of pregnancy | MIS | | 600 | TOP | ? | U |
| 136 | | S2001024D/MIF1 | 6 weeks of gestation | MIS | | 600 | TOP | ? | U |
| 137 | | S2001025F/MIF1 | 7 weeks of gestation | MIS | | 600 | TOP | At 9 weeks | U |
| 138 | | S2001026F/MIF1 | First trimester of pregnancy | MIS | | 600 | TOP | ? | U |
| 139 | | S2001027F/MIF1 | 7 weeks of gestation | MIS | | 600 | TOP | At 9 weeks | U |
| 140 | | S2001028F/MIF1 | 6 weeks of gestation | MIS | | 600 | TOP | At 10 weeks | U |
| 141 | | S2001029F/MIF1 | 7 weeks of gestation | MIS | | 600 | TOP | At 9 weeks | U |
| 142 | | S2001031UK/MIF1 | 17 weeks of gestation | NO | | 200 | | | U |
| 143 | | S2001032UK/MIF1 | First trimester of pregnancy | MIS | | 200 | | | U |
| 144 | | S2001033UK/MIF1 | 18 weeks of gestation | NO | | 600 | | | U |
| 145 | | S2001034UK/MIF1 | 9 weeks of gestation | NO | | 200 | | | U |
| 146 | | S2001035UK/MIF1 | 10 weeks of gestation | MIS | | 200 | | | U |

**Summary table of ongoing pregnancies**

Abbreviations: ABN (Abnormality at term), Am or ame (amenorrhea), Cat (Category), GEM (Gemeprost), MIF (Mifepristone), MIS (Misoprostol), NL (Normal), OC (Oral contraceptive). OUT (Outcome), PG (Prostaglandins), SA (Spontaneous abortion), SUL (Sulprotone), TToP (Therapeutic Termination of Pregnancy), TToPM (Therapeutic Termination of Pregnancy with Malformation), U or UNK (Unknown), W (weeks), * (changed her mind), ** (diagnosis error), *** (did not return), TOP (Surgical early termination of pregnancy).