Literature search methods employed:

The Medline database was searched for publications on clinical use of mifepristone. Multiple search strategies were employed to ensure identification of all available publications. Search strategies and the results of each are described below. Considerable duplication was found between the searches, therefore one comprehensive list was constructed across all searches. This list consisted of a total of 132 unique papers. Removal from the list of those papers related to (1) single-dose clinical applications such as termination of pregnancy, (2) in vitro studies, (3) preclinical in vivo studies, and (4) generalized review articles resulted in 17 remaining publications. In addition, 11 others were either identified as citations in the articles retrieved or were obtained from personal files. It is these 28 publications that are described in the accompanying review.

Medline search results:

SEARCH STRATEGY (query terms)	**TOTAL NUMBER OF RECORDS RETRIEVED**	**NUMBER OF UNIQUE RECORDS (excludes generalized review articles)**
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND English (Language) AND clinical (all fields)	209	35
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND English (Language) AND clinical trial (all fields) AND 50 (text word) OR 600 (text word) OR 1200 (text word)	76	60
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND randomized clinical trials (MeSH terms)	10	4
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND controlled trial (MeSH terms)	14	11
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND English (Language) AND clinical trial (all fields)	67	17
Mifepristone (substance name) OR RU486 (substance name) OR "RU 486" AND English (Language) AND meningioma (text word) OR Cushing (text word) OR Cushing's (text word) OR cancer (text word) AND clinical (all fields)	42	5
TOTALS	418	132

Action Navigate Edit Help
(F4=exit with no selection)

CDER Medical Library Document Request (MED. LIB.)

Requestor:First Name Int Last Name

Mail Code:HFD-580 Bldg:PKLN Rm Phone

Req #76104 Request Date:10-DEC-1999 Prnt:Y
Received:13-DEC-1999 Status:COMPLETED/ML/S Date:21-DEC-1999

Needed by:24-DEC-1999 Pickup/Mail:P
Title of Article, Book Chapter or Conference Paper
NEW ANALOGS OF MIFEPRISTONE WITH MORE DISSOCIATED ANTIPROGESTERONE ACTI
Author(s) of above
PHILIBERT, D.; HARDY, M.; GAILLARD-MOGUILEWSKY,M.; NIQUE,F.; TOURNEMINE

Enter: Next Field ^H: Prev. Field F3: Save ^E: Query
ESC M: Go to the Menu F2: Quick Lookup F4: Exit/No Save

Enter your first name or just a return to get your info from your last entry.
Count: *1 <OSC><DBG> <Replace>

Action Navigate Edit Help
(F4=exit with no selection)

PHILIBERT, D.; HARDY, M.; GAILLARD-MOGUILEWSKY,M.; NIQUE,F.; TOURNEMINE
Journal Name, Book Title or Conference Name and Date
J. STEROID BIOCHEMISTRY
Editor(s) or Author(s) of Book or Conference Proceedings

Pub Date(MM/DD/YY): / /1989 Vol:34 Issue #1-6 Pages:413-417
Edition: MDLine ID:

Publisher and Place

Source of Above Reference

Comments

Enter: Next Field ^H: Prev. Field F3: Save ^E: Query
ESC M: Go to the Menu F2: Quick Lookup F4: Exit/No Save

Count: *1 <OSC><DBG> <Replace>

Literature Search Request Form (http://cdsmlweb1/dml/Forms/litsearch.htm)

LITERATURE SEARCH REQUEST

PLEASE PRINT ALL INFORMATION

Parklawn Building, Room 11B-40, HFD-230
Phone 301-827-5703, Fax 301-443-6385

1. DATE: 12/8/99

2. NAME: _____ TITLE: _____

3. MAIL CODE & Bldg: HFD-580 & PKLN PHONE _____

4. STATEMENT OF INFORMATION NEEDED (Please use sentences to describe subject. Be specific; include synonyms, keywords, definitions. Also state any points not to be included in the search.):
   1) Search for synthesis and structure characterization information on mifepristone. See structure on disk. CAS # 84371-65-3
   2) Search for synthesis and structure characterization information on estra-4,9-diene-3,17-dione. No CAS #. See disk for structure. 5173-46-6

5. PURPOSE OF SEARCH (IND #, NDA #, Compliance, etc.): NDA # 20-687

6. LIST ANY CURRENT RELEVANT PAPERS (author, title, journal, date):

7. PREFERRED NUMBER OF REFERENCES:

   (X) A few relevant ( ) More general ( ) Comprehensive

8. YEARS TO BE COVERED: _____ 8a. ( ) HUMAN ( ) ANIMAL

9. LANGUAGE: ( ) ENGLISH (X) ALL ( ) OTHER (specify) _____

10. UPDATE SEARCH ON MONTHLY BASIS? (X) No ( ) Yes, for _____ months

11. DO YOU WISH TO BE PRESENT WHEN SEARCH IS RUN? ( ) Yes (X) No

12. SEARCH RETRIEVAL FORMAT DESIRED: ( ) Paper ( ) Diskette (X) Email

13. DATE NEEDED BY: ASAP

Literature Search Request Form (http://cdsmlweb1/dml/Forms/litsearch.htm)
TO BE COMPLETED BY SEARCHER ONLY

Request Received by _____

Date Received _____

DATE	VENDOR/FILE	TIME/Dial Units	COST	HITS	DOWNLOAD NAME
12/8	STN/Reg, CAPlus		102.95		
12/9	" "		64.82		
			167.77		

Strategy:

Tox 5173-46-6

**********For Library Use Only**********

Searcher's Name: _____ Date Completed: 12/9/99 H/S/F 1/3/2

6/15/1998

LITERATURE SEARCH REQUEST

PLEASE PRINT ALL INFORMATION

FDA Medical Library
Parklawn Building, Room 11B-40, HFD-230
Phone 301-827-5703, Fax 301-443-6385

1. DATE: 7/12/99

2. NAME: _____ TITLE: OTC Am

3. MAIL CODE & Bldg: HFD-200 PHONE: _____

4. STATEMENT OF INFORMATION NEEDED (Please use sentences to describe subject. Be specific; include synonyms, keywords, definitions. Also state any points not to be included in the search.): New York Times article this weekend 7/10 - 7/11 on RU 486

5. PURPOSE OF SEARCH (IND #, NDA #, Compliance, etc.): _____

6. LIST ANY CURRENT RELEVANT PAPERS (author, title, journal, date):

7. PREFERRED NUMBER OF REFERENCES:

   ( ) A few relevant ( ) More general ( ) Comprehensive

8. YEARS TO BE COVERED: _____ 8a. ( ) HUMAN ( ) ANIMAL

9. LANGUAGE: ( ) ENGLISH ( ) ALL ( ) OTHER (specify) _____

10. UPDATE SEARCH ON MONTHLY BASIS? ( ) No ( ) Yes, for _____ months

11. DO YOU WISH TO BE PRESENT WHEN SEARCH IS RUN? ( ) Yes ( ) No

12. SEARCH RETRIEVAL FORMAT DESIRED: ( ) Paper ( ) Diskette ( ) Email

13. DATE NEEDED BY: Today

TO BE COMPLETED BY SEARCHER ONLY

Request Received by: _____

Date Received 7/12/99

DATE	VENDOR/FILE	TIME/Dial Units	COST	HITS	DOWNLOAD NAME
7/12/99	Lexis - Nexis Majpap, NFT			3	

Strategy: R4486 or R4-486

**********For Library Use Only**********

Searcher's Name _____ Date Completed: 7/12/99

H/S/ 1/4 hr.
1 search

6/15/1998

MIF 000332

MAIL-IT REQUESTED: JULY 12, 1999 100CS2

CLIENT: HFD-200
LIBRARY: NEWS
FILE: MAJPAP,NYT

YOUR SEARCH REQUEST AT THE TIME THIS MAIL-IT WAS REQUESTED:
(RU486 OR RU-486) AND (DATE AFT 7/8/99)

NUMBER OF STORIES FOUND WITH YOUR REQUEST THROUGH:
LEVEL 1... 3

LEVEL 1 PRINTED

THE SELECTED STORY NUMBERS:
1-3

DISPLAY FORMAT: FULL

SEND TO:
FDA/CDER/OTCOM/MEDICAL LIBRARY
5600 FISHERS LN RM 113-7
ROCKVILLE MARYLAND 20857-0001

**********00010**********

(?) not specifically on RU486, but on induced abortions

LITERATURE SEARCH REQUEST

PLEASE PRINT ALL INFORMATION

FDA Medical Library
Parklawn Building, Room 11B-40, HFD-230
Phone 301-827-5703, Fax 301-443-6385

1. DATE: July 7, 1998
2. NAME: _____ TITLE: Medical Officer
3. MAIL CODE & Bldg: HFD-580 PHONE: _____
4. STATEMENT OF INFORMATION NEEDED (Please use sentences to describe subject. Be specific; include synonyms, keywords, definitions. Also state any points not to be included in the search.):

(1) - Information on total number of induced abortions performed in 1991, 1992, 1993 - 1995 in England

(2) - If possible, information for France also

5. PURPOSE OF SEARCH (IND #, NDA #, Compliance, etc.): _____
6. LIST ANY CURRENT RELEVANT PAPERS (author, title, journal, date):
7. PREFERRED NUMBER OF REFERENCES:

( ) A few relevant ( ) More general ( ) Comprehensive

8. YEARS TO BE COVERED: _____ 8a. ( ) HUMAN ( ) ANIMAL
9. LANGUAGE: ( ) ENGLISH ( ) ALL ( ) OTHER (specify) _____
10. UPDATE SEARCH ON MONTHLY BASIS? ( ) No ( ) Yes, for _____ months
11. DO YOU WISH TO BE PRESENT WHEN SEARCH IS RUN? ( ) Yes ( ) No
12. SEARCH RETRIEVAL FORMAT DESIRED: ( ) Paper ( ) Diskette ( ) Email
13. DATE NEEDED BY: Today

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 09-Jul-1998 06:09pm
From: [redacted]

Dept: HFD-230 PKLN 11B40
Tel No: [redacted]

TO: [redacted]
TO [redacted]

Subject: England / France abortions

1) [redacted] called from NLM to see if the fax was coming through; she had tried two machines. I told her that a couple of the pages came through with blank bottoms. She volunteered to bring them by tomorrow morning since she lives off [redacted] ad. I thanked her.

2) [redacted] left a voice mail suggesting we call the Population Council in NY as they and the Allen Guttmacher Center had done "Induced Abortion Worl Reviews." She did not have a recent enough edition to help us. [redacted] said the Population Council's number is 212-339-0500.

3) The articles ACOG sent also came through with some partially blank pages. Please look through them. If you think they contain anything useful and unique, could you ask them to resend to the machine in Tech Opps?

4) Since we received spotily blank faxes from three different locations this afternoon, we should probably put in a repair call for the Doc Del fax machine.

5) After you look at what we have if you think [redacted] and [redacted] need more information, could you the Population Council and International Planned Parenthood?

6) We need to send [redacted] a thank you note (and [redacted].

Thanks.

MIFEPRISTONE MEDICAL ABORTION STUDY

The following pamphlet is a complete description of the Mifepristone Study. We are glad to answer any questions you have or that may arise. This pamphlet includes:

1. A description of the process and the medications
2. A comparison of mifepristone (RU 486)/misoprostol with methotrexate/misoprostol and surgical abortion.
3. Instructions how to use misoprostol
4. A copy of the Consent Form
5. An appointment schedule
6. Copies of a Symptom Log and Satisfaction Questionnaire

Co-Investigators:
Eric Schaff, MD*
Steven Eisinger, MD*
Peter Franks, MD*
Lisa Stadalius, MS, RNC (Nurse Practitioner)

Staff:
November 4, 1996
Office Phone (716) 473-7510 * Hours 8:15-4 pm Weekdays
Pager (716) **264-7123 (24 hours)**

* **Department of Family Medicine, University of Rochester**

MIFEPRISTONE STUDY

OPTIONS COUNSELING

This study is an alternative to surgical abortion. The oth[redacted] options for a pregnant woman include continuing the pregnancy and adoption. We are glad to discuss any of these options.

GOALS OF STUDY

The goals of this research study are to determine (1) whether a low dose of mifepristone (RU 486, the French Abortion pill) is as safe and effective to induce abortion as a higher dose, and (2) whether the second medication, misoprostol, is safe and effective when self-administered vaginally and at home.

TO PARTICIPATE

1) be 18 or older and able to give informed consent
2) be in good health / no major illnesses
3) be no more than 8 weeks pregnant by ultrasound
4) be willing to come to the Day 4-8 visit and, if needed, Days 15 and 36. Be willing to call when bleeding stops.
5) be willing to have blood drawn and a vaginal ultrasound
6) have access to a phone and emergency transportation
7) agree to a surgical abortion, if needed
8) live within 2 hours of study site
9) not eat one hour before and after taking mifepristone

OVERVIEW

The initial screen occurs by phone. The first visit lasts approximately 60 minutes and consists of a gynecologic exam, an ultrasound, a urine pregnancy test, blood tests for Rh type and hemoglobin for anemia, and reviewing and signing the consent form. Mifepristone is then taken by mouth. The woman has the choice to either return to the office in 2 days for misoprostol insertion or take home the misoprostol to use in 2 days.
FOLLOW UP IS CRITICAL TO ENSURE THE ABORTION IS COMPLETE.

FEES

At the first visit, the full fee is due (some insurances now cover [redacted]ur study.) This fee includes all visits, ultrasounds, lab tests, and a surgical abortion, if needed. The mifepristone and misoprostol is provided without charge.

BLOOD TYPE -> RH NEGATIVE

If your blood type is Rh negative (examples, O negative or A negative), you will be given a routine additional injection called Rhogam to prevent antibodies from being made that could harm future pregnancies.

MIFEPRISTONE vs SURGICAL ABORTION

A first trimester surgical (or aspiration) abortion usually occurs from as early as 6-7 weeks to 12-13 weeks. Bleeding is usually minimal after the procedure. Complications of bleeding, infection, and perforation of the uterus are rare. The procedure is usually covered by insurance. Medical abortion occurs as early as 4 weeks and as late as 8 weeks and is most effective the earlier the pregnancy.

MEDICAL ABORTION IS NOT FOR EVERYONE

Medical abortion involves using medications that have side effects. Uterine cramping can be painful. Rarely, bleeding can be excessive. Witnessing the abortion may be emotionally difficult. And, waiting 2 to 15 (uncommon) days is trying. Some women may not want to be part of a study.

Despite the above, almost 90% of women from most medical abortion studies have said they would still prefer a medical abortion.

STUDY MEDICATIONS

MIFEPRISTONE

Mifepristone (RU-486, the French "abortion pill") is a medication that blocks the action of progesterone, a hormone needed to maintain pregnancy. It causes an early pregnancy to detach from the uterine wall. Although there are no significant side effects from the medication, mild nausea, vomiting, diarrhea can occur. Mifepristone has been used by 250,000 women in Europe and China and found to 95% effective at safely inducing an early abortion.

Several studies indicate that smaller doses of mifepristone are equally effective as larger doses.

Mifepristone is waiting for US Food and Drug Administration (FDA) approval and is not available other than in studies like this one.

MISOPROSTOL

A second required medication, misoprostol (Cytoctec) is approved in the US when taken by mouth to prevent stomach ulcers. If used with 36-48 hours after mifepristone, it is very effective at causing the uterus to contract (cramp) and a pregnancy to be expelled. It is not FDA approved for abortion. Smokers should abstain for four hours after using medication.

The side effects from misoprostol may include nausea, vomiting, diarrhea, and abdominal cramping. Studies have shown there are fewer side effects when misoprostol is placed in the vagina than when taken by mouth. Side effects are common but typically mild and last only a few days except for vaginal "spotting" which can last a few weeks.

INSTRUCTIONS HOW TO USE MISOPROSTOL

Two days (Study Day 3) after taking mifepristone, you will have the option to **(1)** return to the office to have 4 tablets of misoprostol placed in the vagina and then wait in the office up to four hours when cramping , bleeding and the abortion should occur, or, **(2)** you can take home four misoprostol tablets and place them in the vagina with your finger.

For office use: Bring a good book and a friend if you want to wait.

For home use:

1. first empty your bladder
2. use your finger to push the 4 tablets deep into the vagina and rest on your back for thirty minutes
3. expect cramping and bleeding for the next 1-10 hours
4. drink several large glasses of fluids and get up from a lying position slowly to avoid feeling dizzy
5. eat lightly because of the possibility of vomiting
6. use Tylenol or Tylenol #3 at the beginning of cramps
7. contact us for excessive bleeding, or problems at (716) 264-7123
8. please keep your follow up appointment on study Day 4-8

Plan to take the misoprostol at a time when you can lie down afterwards. For example, take it before going to bed or on a morning when you can rest. For support, have your partner or a friend around when you use the misoprostol.

Bleeding: What to Expect

Over 50% of women experience some bleeding before using misoprostol. If heavy bleeding occurs prior to using misoprostol, please contact us. You may not need misoprostol.

For most women, heavy bleeding will occur within hours of using the second medication, misoprostol. Expect heavy bleeding and cramping for the first 1-2 days. Pregnancy tissue may appear like clots, thicker than clots or a small sac. The bleeding can persist for a couple of weeks. Some women have experienced a second episode of heavy bleeding a few days after the initial bleeding if they had not completed the abortion.

Use a sanitary pad until the bleeding lightens, then a tampon is fine if desired.

No Bleeding: Don't Panic

If there is no bleeding, we will insert 4 more tablets of misoprostol in the vagina at the first follow up visit (study day 4 to 8). You will be asked to return on study day 15 (2 weeks from your first visit). If the pregnancy is growing at the Day 15 visit, we will recommend a surgical abortion. If the pregnancy has stopped growing we will ask you to come back on study day 36. If the pregnancy tissue has not passed by study day 36, we will recommend a surgical abortion.

Cramping: What You can Do

It is common to have cramping. Severe cramps often means that some pregnancy tissue is passing down the uterus through the cervix and can occur even before bleeding. For comfort, use 1 or 2 tablets of Tyl[redacted] or Tylenol #3 (with codeine) every four hours. Other helpful measures include heating pad, back rub, relaxation techniques.

Emergency Plans

It is rare to have an emergency, but important to be prepared. Abortion is a private matter and some women would prefer no one else know, but it could be dangerous to delay care in the event of an emergency. Each woman should have an emergency plan (mainly for excessive bleeding): how to call us, who might drive with her, and directions how to reach us or the nearest hospital.

Danger Signs: When to Contact Us

* **Excessive bleeding (soaking 4 pads over 2 hours)**
* Severe abdominal pain, nausea or vomiting

Surgical Abortion May Be Needed If

The pregnancy is continuing at the 2 week visit (1-2%?)
There is excessive vaginal bleeding (1%?)
Non-viable pregnancy tissue remains after 5 weeks (1-2%?)

Contraception

You should avoid sexual activity until the abortion is complete. We want to help with future contraception and have free samples of birth control pills. We have the three month injection, Depo-provera, for a charge ($55). Educational materials are also available on the above plus the five year Norplant capsules. Women without primary health care will be given choices where to obtain routine gynecologic health care in the future.

THE SYMPTOM LOG

We want to determine the side effects of the medicines. Please use the SYMPTOM LOG on the following page daily and bring it to all visits.

SATISFACTION QUESTIONNAIRE

We have included a copy of the Satisfaction Questionnaire. It must be completed when the abortion is over.

METHOTREXATE ABORTION

Methotrexate is another alternative for a non-surgical medical abortion. It was first approved by the FDA in 1954. It is now used for some cancers, arthritis and psoriasis. It ends a pregnancy by blocking a vitamin (folic acid) from rapidly growing cells (such as fetal cells) so they can not divide.

It has been used for over 10 years to treat early ectopic pregnancy (a dangerous situation in which a pregnancy grows in the fallopian tube). It is over 90% effective, side effects are mild and brief, and future pregnancies have NOT been affected. Methotrexate abortion takes longer than Mifepristone ranging from 6 to 21 days.

Side effects of low dose methotrexate are uncommon but may include mild sores in the mouth, nausea, vomiting, diarrhea, and, very infrequently, a decrease in your blood cells. Past studies have shown that most women have minimal or no side effects. There are some diet restrictions

SATURDAY MORNING PROTESTS

We have some peaceful anti-abortion protesters every Saturday morning at the front driveway. It is best to ignore them.

THE DAILY SYMPTOM LOG

Please record the times bleeding and cramping started, & misoprostol and any other medication used.

DAYS

Week Day															
Calendar															
Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Misoprostol			X												
Nausea "N"=Yes															
Vomiting "V"=Yes															
Diarrhea "D"=Yes															
Bleeding "H"=Heavy "M"=Mod. "L"=Light															
Cramping "C"=Yes															
Other "Y"=Describe															
Medications "T"=Tyl.#3 "A"=Advi "O"=Other															

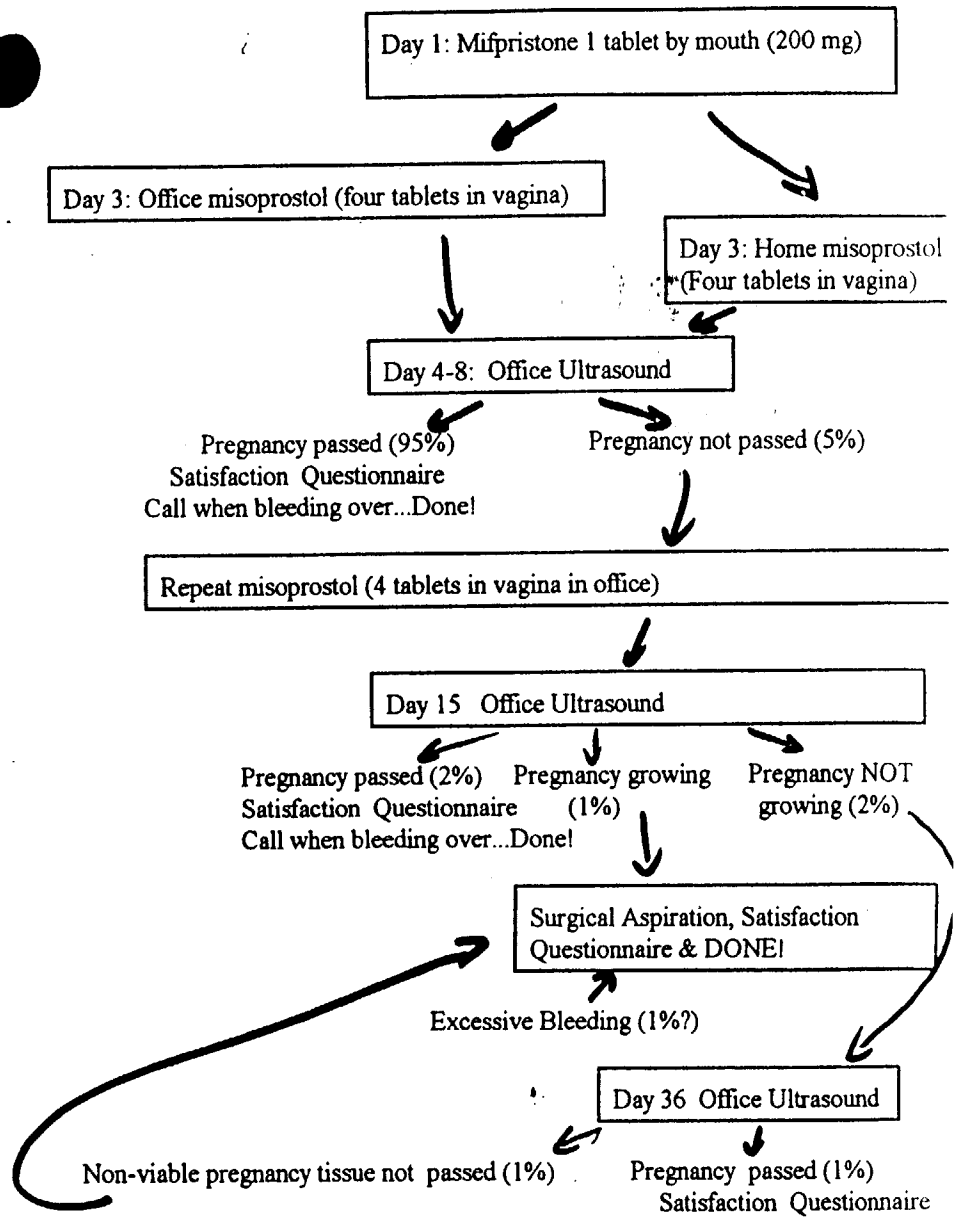
Time Misoprostol Tablets were inserted:_____AM or PM

Time Cramping was first noticed:_____AM or PM

Time Bleeding was first noticed :_____ AM or PM

Please list any Medications taken/date/time:

FLOW CHART



SATISFACTION QUESTIONNAIRE

THIS IS THE QUESTIONNAIRE YOU WILL BE ASKED TO COMPLETE AT YOU[redacted] FINAL VISIT.

On a scale from "Strongly Disagree" to "Strongly Agree", please answer the following questions:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. Overall, the procedure went well.					
2. The cramping pain was acceptable.					
3. The bleeding was acceptable					
4. The side effects of medications were acceptable					
5. The time waiting till the abortion was over was acceptable.					
6. I would recommend using misoprostol at home.					
7. I would recommend this over a surgical abortion to other women seeking an abortion.					
8. If I needed another abortion, I would choose this procedure over a surgical abortion.					

Please answer the following questions (you can use extra paper if needed):

9. What would have made the procedure easier?

***10. What additional remarks would you tell another woman considering this procedures?

A STUDY OF MIFEPRISTONE AND MISOPROSTOL FOR EARLY INDUCED ABORTION: COPY OF CONSENT FORM

Investigators:
Eric Schaff, M.D., Steven Eisinger, M.D.,
Peter Franks, M.D., Lisa Stadalius, MS, RNC [24-Hour Phone (716) 264-7123]

Research Study and Purpose

The purposes of this study are (1) to determine the safety, effectiveness and acceptability of using two medications - mifepristone (RU 486) and misoprostol - to end an early pregnancy up to 8 weeks gestation and (2) determine whether a lower dose of mifepristone is as effective as the standard dose. Locally, 150 subjects will be enrolled and, nationally, a total of 300 subjects

Mifepristone (RU-486) is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. Misoprostol is a prostaglandin-type medication that causes the uterus to contract (cramp) and a pregnancy to be expelled. Misoprostol is an approved drug in the United States when taken by mouth to prevent irritation or ulcers in the stomach of people using aspirin-like pain medicine. Lower doses of mifepristone have been as effective as the standard dose when studied with another prostaglandin but not with misoprostol.

More than 250,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of abortion. In Europe, misoprostol used after mifepristone has been shown to be safe and effective to end pregnancy. Mifepristone in combination with a prostaglandin has also been approved for use in France, China, Britain and Sweden from 7-9 weeks pregnant. This study is being done in an effort to get mifepristone and misoprostol registered with the U.S. Food and Drug Administration (FDA) so that these drugs can be used in the United States to induce medical abortions.

The usual procedure to end a pregnancy is a suction abortion which is known to be over 99% effective.

Description of Procedures

This study lasts until the abortion has occurred and all questionnaires are complete. Before and after abortion counseling is available to you at your request.

To participate in this study, you must:

1) be equal to or greater than 18 years old and able to give informed consent.
2) be in good health and live or work within 2 hours.
3) have an early pregnancy less than or equal to 56 days (8 weeks) by vaginal ultrasound. The ultrasound is performed by placing the probe (similar in size to a metal speculum) gently into the vagina. The probe is first disinfected and covered with a condom.

4) accept blood testing for anemia and blood type on Day 1. If your blood type is Rh negative, you will receive an additional medication called Rhogam to prevent a blood disease in fut[redacted] pregnancies.

5) have access to a telephone for follow up.

6) not eat any food for 1 hour before or after taking mifepristone, not smoke cigarettes for 4 hours after taking mifepristone as well as after taking the misoprostol, use only sanitary pads until the bleeding lightens, and not have intercourse (sex) until after the abortion is confirmed.

7) not have a known allergy to misoprostol.

8) be willing to return in 2 days to have misoprostol inserted in your vagina to induce cramping and expulsion of the pregnancy or you may elect to do this at home. If you choose to return to the office, you may choose to stay for 4 hours. If you choose to use misoprostol at home, you will place 4 tablets with your finger high up in the vagina 2 days later (Study Day 3). You will need to rest for the next several hours when cramping, vaginal bleeding and the abortion is likely to occur. You may use over-the-counter "Tylenol" pain medications or the Tylenol #3 prescribed for you for cramping. If bleeding becomes excessive (soaking more than 4 pads over 2 hours) you will contact us for prompt medical attention.

9) be willing to come back in 3 to 7 days (Study Day 4-8) for a repeat (vaginal) ultrasound.

1. If the abortion is over by ultrasound, you will complete the final questionnaire. If the bleeding has not stopped, you will notify us by phone when your bleeding has stopped. Your participation in the study is complete.
2. If the abortion has not happened, the provider will place 4 tablets of misoprostol in the vagina and you can wait up to 4 hours in the office. You will return on Day 15.
3. On Day 15, if the abortion is over by ultrasound, you will complete the final questionnaire. If the bleeding has not stopped, you will notify us by phone when your bleeding has stopped. Your participation in the study is complete.
   a. If the pregnancy is growing, you will be scheduled for a surgical abortion and asked to complete the final questionnaire.
   b. If the abortion has not happened but the pregnancy is not growing, you can choose to be scheduled for a surgical abortion or you can return in three weeks (study day 36) or sooner for reassurance.
4. On Day 36, if the abortion has not occurred, a surgical abortion will be performed.

10) be aware that a surgical abortion procedure is strongly recommended if the mifepristone/misoprostol fails (1 in 20 patients) because misoprostol can cause severe birth defects in this pregnancy.

11) keep a daily record of any medications used and any symptoms and side effects you experience. There will be a final questionnaire to complete. You can refuse to answer any questions that make you uncomfortable.

12) consider a method of birth control to use after the abortion is complete because a repeat pregnancy can occur in the next menstrual cycle.

Risks and Discomforts

Venipuncture: Blood tests are uncomfortable and may leave a bruise.

Vaginal Ultrasound: This procedure is similar to a pelvic examination and may be uncomfortable.

Side effects: Uterine cramps and lower abdominal pain are a normal part of the abortion process and are similar or worse than those that may occur with some menstrual periods. The side effects from the medications may include nausea, vomiting, diarrhea, abdominal cramping. Typical side effects have been mild and last only a few days except for vaginal "spotting" which can last a few weeks. Cramping may be helped by pain medications (ibuprofen and Tylenol #3).

Incomplete abortion: It is difficult for a woman to tell whether the study medicines have been totally effective, as some of the pregnancy tissue may still remain in the uterus. Should this occur, an aspiration procedure (like a D & C) may be necessary to complete the abortion. The ultrasound can determine this information.

Heavy vaginal bleeding: Heavy vaginal bleeding may occur at home and require an additional visit. A D&C (suction abortion) may be necessary to stop the bleeding. Although uncommon, large amounts of bleeding may require a blood transfusion.

Continued pregnancy and birth defects: From other studies, approximately 5% of the time, an abortion does not occur. Misoprostol can cause serious birth defects. **Based on current research, neither medicine is known to harm future pregnancies.** Women who fail to abort are strongly advised to have a surgical (suction) abortion. By New York State Law, this abortion must be completed by 20 weeks of gestation.

Inconvenience: If all goes as expected, there will be two office visits (Day 1 and Day 4-8). More visits are required if you choose to have the clinician place the misoprostol tablets in the vagina or the abortion does not happen right away (day 15 and Day 36). Office visits can cause inconvenience.

BENEFITS

The benefits of this study for you are: (1) possibly avoiding a surgical (suction) abortion which includes minor discomforts and rare complications, and (2) possibly terminating the pregnancy 1-2 weeks before a surgical abortion is possible.

ALTERNATIVE TREATMENT

The alternatives to this treatment are: (1) to continue the pregnancy, (2) to have a suction (surgical) abortion, or (3) to participate in another study using methotrexate and misoprostol, if available.

New Findings
Any information developed during the course of this research which may relate to your continuation in this protocol will be provided to you.

Voluntary Participation
Participation in this research project is voluntary and your refusal to participate will not affect your health care or penalize you in any way. You may also discontinue participation at any time without penalty, (but birth defects in this pregnancy are possible if the abortion is not complete.)

Treatment of Research-Related Injury
The physicians performing this study will provide gynecologic care for you in the event of emergencies or physical injury resulting directly form this research project at no cost. Other than that, there is no free treatment nor any monetary compensation for injury resulting from participation in this research project.

Confidentiality
Confidentiality is very important to women seeking abortion services. We want to be able to contact you by phone during the study. We will make every attempt to follow agreed upon instructions as to best times for appointments and telephone calls and what messages to leave to assure your confidentiality.

All information will be kept confidential in your medical record. The information will be analyzed without your name. Representatives from the U.S. Food and Drug Administration may inspect your records pertaining to this study.

Contact Persons
For questions and information regarding health related injury, treatments, participation, withdrawal from the study, and your rights as a patient, please call us at (716) 264-7123 and ask for Dr. Eric Schaff.

Required Signatures

Signature of Subject	Print Name	Date
Signature of Auditor Witness	Print Name	Date
Signature of Investigator (Original copy in chart.)	Print Name	Date

APPOINTMENT SCHEDULE for STUDY

Day	Week Day	Date	Time	Site	Purpose
Day 1				OB-GYN Group	Exam, Ultrasound & Blood Test
Day 3	At home or in the office				4 Misoprostol tablets
Day 4-8					Ultrasound and if done Satisfaction Questionnaire, & Birth Control
Day 15, only if needed					Ultrasound and if done Satisfaction Questionnaire, & Birth Control
Day 36 only if needed				OB-GYN Group	Ultrasound and if done Satisfaction Questionnaire, & Birth Control
PLEASE CALL US WHEN YOUR BLEEDING HAS STOPPED (716-473-7510 OR pager 716 264-7123)					

*** The day before your appointment, please call the office (716) 473-7510 and confirm your appointment or expect a confidential call from us.**

If instructed to return to the Family Medicine Center, it is located one block north of Highland Hospital at 885 South Avenue. Parking is free. Go to the secretary on "Team B" and ask for Dr. Schaff.

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RU486, MIFEPRISTONE: A REVIEW OF A CONTROVERSIAL DRUG.
Author(s) of above
DIPIERRI, D.

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Editor(s) or Author(s) of Book or Conference Proceedings

Pub Date(MM/DD/YY):06/ /1994 Vol:19 Issue #6 Pages:59-61
Edition: MDLine ID:94344489

Publisher and Place

Source of Above Reference
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Comments
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D THERAPEUTIC POTENTIAL.
DRUGS

HFD-120 29-APR-96 29487
RU-486: THE FRENCH EXPERIENCE
HUM-REPROD.

HFD-580 10-DEC-99 76104
NEW ANALOGS OF MIFEPRISTONE WITH MORE DISSOCIATED ANTIPROGESTERONE ACTIVITIES
J. STEROID BIOCHEMISTRY

HFD-870 25-FEB-00 79362
MECHANISM BASED INACTIVATION OF CYTOCHROME P450 3A4 BY MIFEPRISTONE(RU486)
J PHARMACOL EXP THER

OG-000 14-JUN-00 84917
LOW-DOSE MIFEPRISTONE FOLLWED BY VAGINAL...
CONTRACEPTION

HFD-870 17-AUG-00 87099
EVIDENCE FOR HUMAN LIVER MICROSOMAL CYTOCHROME P4503A MEDIATED METABOLISM OF MEF
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Title of Article, Book Chapter or Conference Paper
MIFEPRISTONE, A REVIEW OF ITS PHARMACODYNAMIC AND PHARMACOKINETIC PROPE
Author(s) of above
BROGDEN, RN; GOA, KL; FAULDS, D.

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DRUGS
Editor(s) or Author(s) of Book or Conference Proceedings

Pub Date(MM/DD/YY):03/ /1993 Vol:45 Issue #3 Pages:384-409
Edition: MDLine ID:93238578

Publisher and Place

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Comments
URGENT: NEED FOR REGULATORY DECISION DUE THIS FRIDAY MAY 3!

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RU-486: THE FRENCH EXPERIENCE
Author(s) of above
ULMANN, A; SILVESTRE, L.

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ULMANN, A; SILVESTRE, L.
Journal Name, Book Title or Conference Name and Date
HUM-REPROD.
Editor(s) or Author(s) of Book or Conference Proceedings

Pub Date(MM/DD/YY):06/ /1994 Vol:9 Issue #supp1 Pages:126-130
Edition: MDLine ID:95051443

Publisher and Place

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Background Information

NDA 20-687

Mifepristone

(RU-486)

NDA 20-687; mifepristone; RU-486
BACKGROUND INFORMATION

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  - Cabezas E. Medical Versus Surgical Abortion. *International Journal of Gynecology & Obstetrics*. 1999; 63:S141-S146. 27
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Abortion Provision in the U.S.

DRUDP

June 14, 2000

Number of abortions

1.37 million abortions were performed in the U.S. in 1996 (50 million worldwide, 20 million legal)

Procedures

- 98% by D&C
- 2,988 medical procedures were reported to CDC in 1997
- 4,200 medical abortions were reported to AGI in 1996, and 4,300 in 1st half of 1997, using mifepristone or off-label methotrexate. (AGI data is believed to be more complete than CDC data)
- According to NAF, for medical abortions, the misoprostol is taken at home.

Cost (1997)

Nonhospital facilities, surgical abortion at 10 wk gestation with local anesthesia, $150-$1535 (Average $316)
Medical abortion costs $100-$1250, average $401.

Demographics

- 2% of women ages 15-44 have abortions each year.
- 43% of women have at least 1 abortion by age 45
- 60% of abortions are provided to white women, BUT blacks are 3 times as likely and hispanics are 2 times as likely to have an abortion.

Gestational ages

- 88% of abortions are performed in 1st 12 weeks gestation
- 55% up to 8 weeks
- 36% up to 7 weeks (49 days)
- 43% of abortion facilities provide abortions only through 12 weeks gestation
- 42% of nonhospital facilities provided abortions under 6 weeks gestation in 1996, compared to 33% in 1992

Facilities

- 90% of abortions are performed in clinics
- 3% of abortions are performed in doctor's offices
- 7% of abortions are performed in hospitals
- 42% of nonhospital facilities provide abortion to women less than 6 weeks gestation
- 24 hour emergency contact must be readily available.
- NAF established guidelines for members

Providers

- Forty four states and the District of Columbia have statutes or regulations that prohibit anyone other than a licensed physician from performing an abortion. Only six states (AZ, KS, NH, OR, VT, WV) do not have laws limiting the performance of abortions to physicians.
- Not all physician-only laws prevent non-physician practitioners from performing medical abortions. In rare instances, physician-only laws may not apply to medical abortion because they employ a relatively narrow definition of abortion. (See attached facsimile from National Abortion Federation, pages A-K).
  - HI defines "abortion" as "an operation to intentionally terminate the pregnancy of a nonviable fetus"; RI forbids non-physicians to perform surgical abortion, but not medical abortions; NY's Dept. of Health ruled that physician assistants (PAs) may perform abortions under NY law; MT struck down statutory provisions prohibiting PAs from performing abortions. (Both NY and MT rulings are applicable to medical abortions.)
- The number of abortion providers in the U.S. decreased by 14% (from 2380 to 2042) from 1992 to 1996
- 86% of U.S. counties had no abortion provider in 1996. These counties are home to 32% of women ages 15-44

NAF Guidelines:

- Must be performed by licensed physicians or licensed/certified/registered midlevel clinicians trained in the provision of abortion care, in accordance with state law.
- All personnel performing abortions must receive training in the performance of abortions and in the prevention, recognition and management of complications.
- When midlevel clinicians perform abortions, medical protocols should be in place that adhere to the midlevel provider scope of practice permitted by state law
- Rh immune globulin is to be administered to all Rh- women
- For early medical abortion, the patient must be informed about the need for follow-p contact to ensure that she is no longer pregnant.
- For early medical abortion, the patient must be informed about the efficacy, side effects, and risks, especially excessive bleeding and teratogenicity associated with the medications to be used.
- The patient's willingness to consent to surgical abortion if medical abortion fails must be documented.
- Guidelines are provided for management of complications, post-operative care, disposal of fetal tissue, and Emergency procedures.

Provision of Medical Abortion

- 12% of nonhospital abortion providers offered medical abortion in 1997 (163 providers)
- 43% of nonhospital facilities would provide medical abortion within the next year if mifepristone were approved
- 29% of nonhospital facilities would provide medical abortion within the next year even in mifepristone were not approved.
- Only 12% of OG/GYN residencies require training in 1st trimester surgical abortion. 69% of residents in a required program had clinical experience in the procedure.
- 29% of Family Medicine programs included 1st trimester abortion training (either optional or routine). Only 15% of chief residents had clinical experience with the procedure.
- 54% of OB/GYNs, 45% of FPs, and 54% of nurse practitioners and physician assistants would likely offer mifepristone if approved. (Only 3% of FPs and 2% of NPs and Pas report ever performing surgical abortion)
- Only 19% of OB/GYNs. 11% of FPs, and 13% of NPs and PAs currently provide medical abortion with methotrexate and misoprostol

Safety of surgical abortion

- <1% major complications (1 in 200 procedures), including serious pelvic infection, hemorrhage requiring a blood transfusion or unintended major surgery.
- deaths 1:530,000 up to 8 wk gestation
  1: 17,000 at 16-20 wk gestation
  1: 6,000 at 21 wk gestation and beyond
- risk of death with childbirth is 10 times higher than with abortion

Safety of medical abortion (from French and US trials)

- 4.5% of 1800 French women and 7.9% of 859 US women participating in clinical trials received surgical intervention. 0.4% of French subjects and 1.6% of US subjects received medically indicated intervention, mostly for excessive bleeding. 2.9% of French subjects and 4.7% of US subjects had incomplete abortions at the end of the study protocol, and 1.3% and 1.0%, respectively, had ongoing pregnancies. In addition, 0.6% of US subjects received surgical interventions at the patient's request.
- The mean duration of bleeding was 9 days in the French trials and 16 days in the US trials. However, 0.5% of French subjects and 8.1% of US subjects had bleeding for more than 30 days. 4.3 % of French subjects received vasoconstrictor drugs and 5.5% had a decrease in hemoglobin of more than 2 g/dL. 2 of the 1800 subjects received blood transfusions. 4.8% of US subjects received uterotonic medications, 1.0% received intravenous fluids, and one subject of the 859 received a blood transfusion.
- No serious pelvic infections were reported.
- No deaths have been reported.

Complications of spontaneous abortions

Although spontaneous abortions are known to be complicated by hemorrhage, infection, and surgical intervention, the available texts do not provide information on the incidence of such complications, and focus instead on the etiologies and management of spontaneous abortion, and recurrent pregnancy loss.

References

The Henry J. Kaiser Family Foundation at http://www.kff.org/
The Alan Guttmacher Institute at http://www.agi-usa.org/pubs/fb_induced_abortion.html

Attachment

NATIONAL ABORTION FEDERATION

June 22, 2000

Food and Drug Administration
HFI-40
Rockville, MD 20857

Dear ____

Yesterday, we were contacted by ____ for information regarding state "physician-only" laws for abortion. Although she had a list of states with physician-only laws, this information alone cannot definitively guide determinations about the role of non-physician practitioners (i.e. advanced practice clinicians such as nurse practitioners, certified nurse midwives, and physician assistants) in providing abortion care. To clarify, we would like to offer you background about physician-only laws and an explanation of other regulations and statutes, specifically those related to the prescriptive authority and scope of practice of advanced practice clinicians, that must be considered in drawing conclusions about which personnel are authorized to provide abortion care.

Physician-only laws first became common with the original movement to criminalize abortion in the late 1800s. The anti-abortion campaign of the nineteenth century is understood as a key component of a larger battle, namely, the attempt of "regular" or "elite" university-trained physicians to attain professional dominance over the wide range of "irregular" medical practitioners - homeopaths, apothecaries, dentists, etc. Thus, the objective of elite physicians was to control the terms under which approved abortions could be performed, restricting their provision to physicians operating in hospitals and for medically indicated reasons.

With the liberalization of abortion laws in the 1970s following the 1973 *Roe v. Wade* decision, many states retained the physician-only provisions in their abortion statutes, reasoning that the deaths, sterility, and other complications associated with illegal abortions could be prevented if such abortions were performed by competent medical personnel in medical facilities. Because many states' physician-only laws predate the laws and regulations governing the scope of practice of advanced practice clinicians, they do not take into account the professional training and abilities of physician assistants and advanced practice nurses, whose professions came into existence in the late 1970s.

In the intervening decades, the nurse practitioner, certified nurse midwife, and physician assistant professions have matured to encompass a multifaceted role in today's health care system. Advanced practice clinicians perform a variety of procedures that are more complex than surgical abortions, and in most states, they are able to prescribe medications, like narcotics, anti-depressants, and hormones. In many states, physician-only laws are in direct conflict with the professional practice acts and corresponding regulations governing advanced practice clinicians, including scope of practice and prescriptive authority.

A

5 Massachusetts Ave. NW Suite 600 Washington, DC 20036 Telephone: 202.667.5881 Fax: 202.667.5890

Because of the regulatory conflicts that exist, some states have taken steps to resolve the ambiguity and determine which regulations take precedence. In fact, the New York State Department of Health issued a declaratory ruling in 1995 indicating that New York's scope of practice regulations for physician assistants supercedes New York State's physician-only law. Further, the Montana Supreme Court ruled in 1999 that a law barring physician assistants from providing abortions was unconstitutional. This year, the Rhode Island Department of Health amended their termination of pregnancy regulations to authorize advanced practice clinicians to provide medical abortion. These are clear examples of the many statutes, regulations, and rulings that together determine the role of advanced practice clinicians on the state level.

To further illuminate the complexity of this issue, we have enclosed relevant portions of two very recent journal articles. The first was published last month in a supplement to the *Journal of the American Medical Women's Association* and includes a discussion of physician-only laws as they pertain to medical abortion. The second is currently in press at the *American Journal of Obstetrics and Gynecology*. We hope that you find these materials helpful. If we can be of any further assistance, please call us at (202) 667-5881.

Sincerely,

Susan Dudley

Susan D. Dudley, PhD
Deputy Director

B

TAB 2

Percentage Rates for Abortion(Abs) Complications
(per 100 patients)

Complications	Medical Abs* (<49 days gestation)	Surgical Abs** (all gestations)	Spontaneous Abs*** (all gestations)
Death	None in Trials	0.001% (1:100,000)	0.0007[1] (0.7:100,000) (0.3:100,000 ≤ 12 wk GA) 59% due to infection 18% due to hemorrhage 13% due to embolism 5% due to anesthesia 5% other causes
Perforations	None in Trials	0.004	
Transfusions	0.1	0.06	
Hemorrhage[2] (>500cc or >2gm/dl)	0.6-2.0	0.05-5.0[3]	
Retained products	3-5	0.5-1.0	
Endometritis/ Salpingitis	None in Trials	1.0-5.0	[4]
Ashermann's (scarring down of uterine cavity)	unknown	0.1-2.3[5]	
Anesthetic	None in Trials	0.2	

*Data from NDA 20-687
**Scott JR, Di Saia PH, Hammond CB, Spellacy WN (eds.) Danforth's obstretics and gynecology, 8th edition. Philadelphia, PA: Lippincott Williams and Wilkins, 1999, p. 577.
***Saraiya Marvelon®, Green C, Berg C, Hopkins F, Koonin L, Atrash H, Obstetrics and Gynecology, Vol. 94; No. 2, August 1999. Pp 172-176.

[1] Databases on spontaneous abortion are incomplete, as there is no required reporting, and not all are managed in hospitals. No references could be found to establish the incidence of hemorrhage, transfusion, retained products, endometritis/salpingitis, Ashermann's syndrome, or anesthetic complications.
[2] A study of measured blood loss with first trimester medical vs surgical abortions by YF Chan, PC Ho, HK Ma, 1993 (*Contraception, Vol 47:pp 85-95, 1993)* revealed >400 cc blood loss in 2.1% of medical Ab vs. 0% of surgical AB, and 300-400 cc blood loss by 5.2% of medical Ab vs. 0% of surgical Ab.
[3] This includes more advanced gestational ages than for medical Ab, and these would be expected to result in larger blood losses
[4] Some spontaneous abortions may be caused by pelvic infection.
[5] This includes more advanced gestational ages than for medical Ab, and these would be expected to result in a higher incidence of Ashermann's Syndrome.