RU486 and PROSTAGLANDIN ANALOGUES in the CHEMICAL ABORTION

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The beginning

Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu EE.
The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy.
CR Seances Acad Sci III. 1982 May 17;294(18):933-8.

📖RU-486 is a steroid which possesses a great affinity for the progesterone receptor, does not have a progesterone activity, but is indeed a strong antagonist of progesterone effects in animals. Oral administration induces the interruption of the luteal phase of the menstrual cycle and that of early pregnancy in women. Its mode of administration and its properties enable us to envisage a new methodology for menstrual cycle regulation and human birth control.

Abortion methods

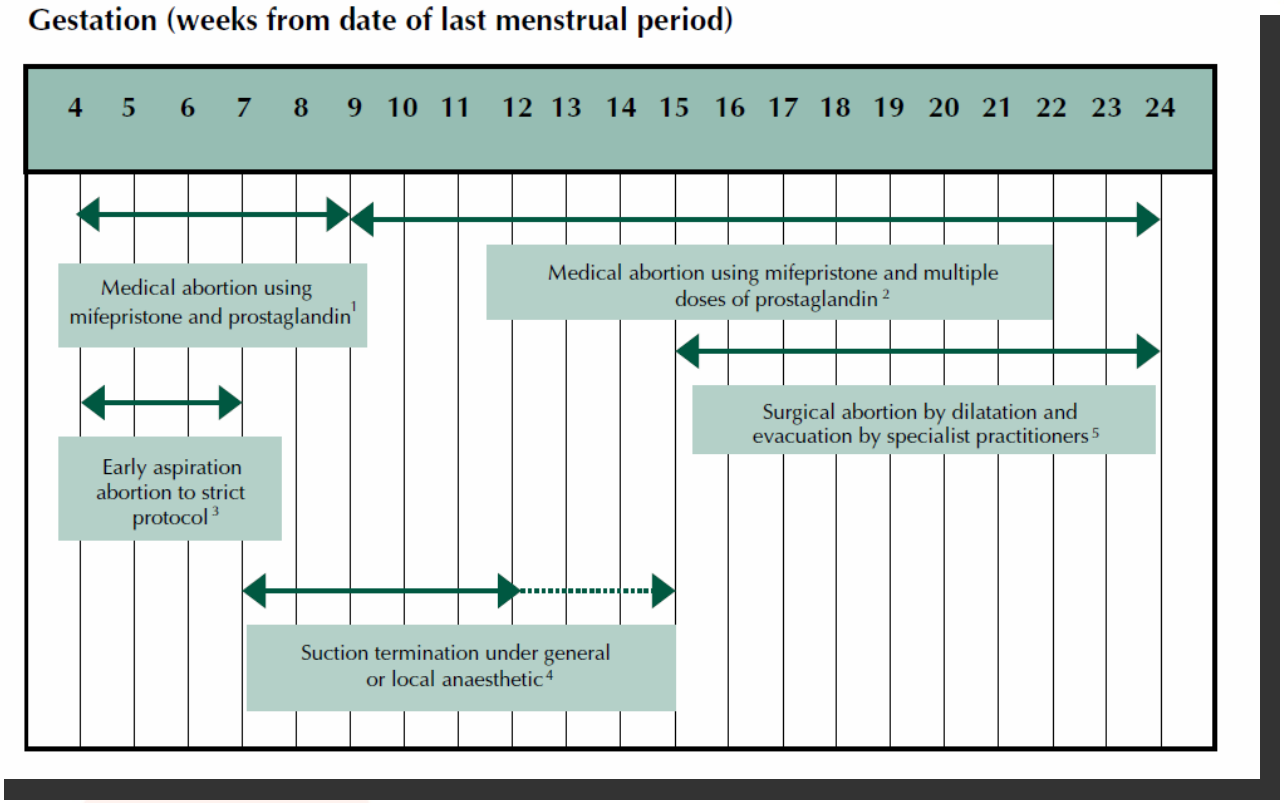
MEDICAL ABORTION DEFINITION

- Early pregnancy termination, generally before 9 weeks' gestation resulting from abortion-inducing medications and without primary surgical intervention.

CURRENTLY AVAILABLE MEDICAL ABORTION REGIMENS

- **Mifepristone** and a **prostaglandin analogue**
  (in the majority of the world, the analogue misoprostol is used)
- **Methotrexate** and **misoprostol**
- **Misoprostol** alone

M.D. Creinin, *Early medical abortion with mifepristone and other agents: overview and guidelines*, National Abortion Federation, 2002



1. Medical abortion using a single oral dose of the anti-progesterone, mifepristone, followed by a single dose (vaginal or oral) of prostaglandin (also known as pharmacological or non-surgical abortion).
2. Medical abortion using a single oral dose of the anti-progesterone, mifepristone, followed by multiple doses (vaginal or oral) of prostaglandin (also known as pharmacological or nonsurgical abortion).
3. Surgical abortion by means of suction aspiration (using electric or manual suction) at gestations below 7 weeks. To increase confidence that the gestation sac has been removed, protocols include safeguards such as magnification of aspirate and follow-up serum hCG estimation.
4. Conventional suction termination using electric or manual suction, under general or local anaesthetic. The uterus is emptied using a suction curette. Sharp curettage with metal instruments is not employed.
5. Surgical abortion at later gestations using a combination of suction (usually electric) curettage and specialised forceps.

RCOG, *The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline*, 2004; p.45

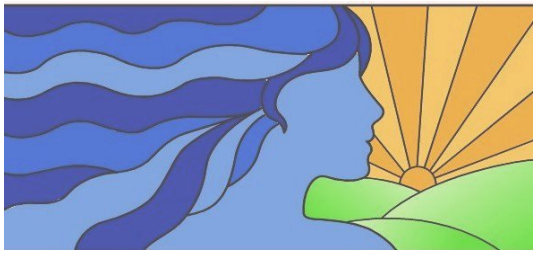
Pharmacology

Mifepristone (RU 486)

- Derivative of norethindrone that binds to the progesterone receptor with an affinity equal to progesterone without activating the receptor, thereby acting as an "antiprogestin".
- Alters the endometrium to cause separation of the trophoblast from the decidua, and increase prostaglandin release. Has no direct effect on the trophoblast. Also softens the cervix to allow expulsion.

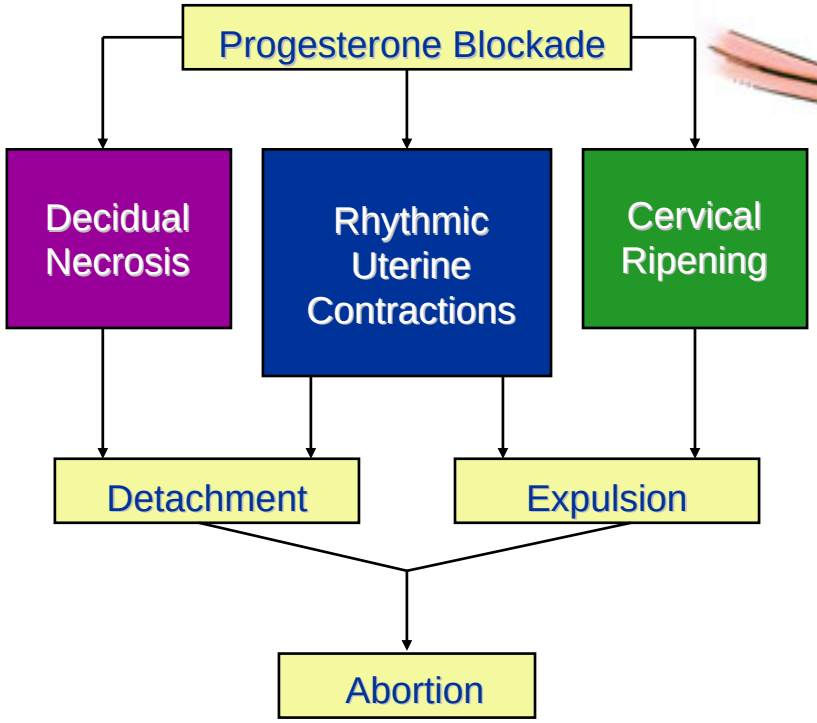
Misoprostol

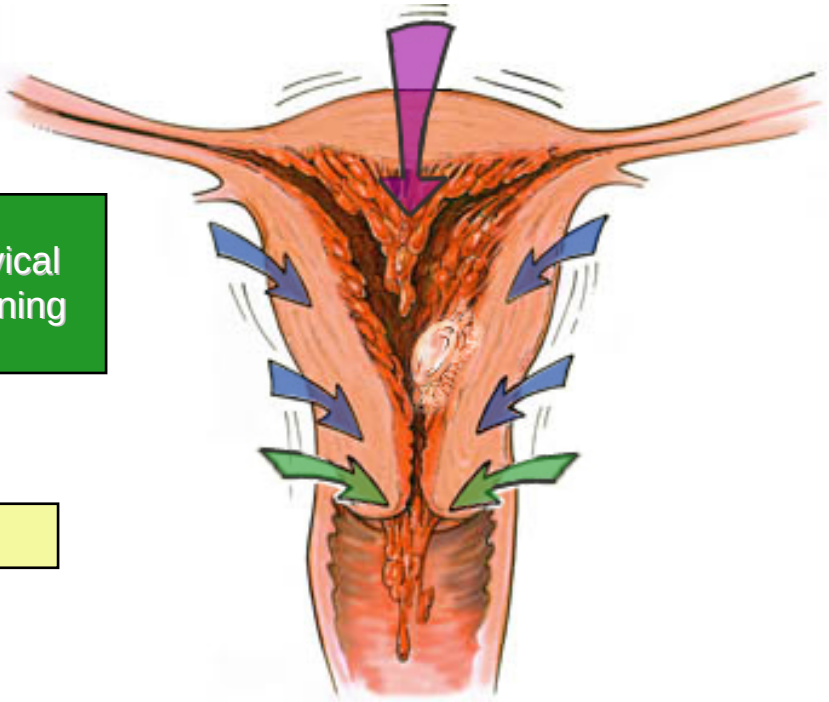
- An inexpensive PGE1 analogue in a tablet form (FDA-approved for oral administration) that is stable at room temperature. Misoprostol is used to prevent gastric ulcers in persons taking anti-inflammatory drugs on a long-term basis, in regimens for abortion, and for labor induction.



Mechanism of Action:

Mifepristone + Misoprostol induced abortion





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FDA U.S. Food and Drug Administration Department of Health and Human Services

The approved Mifeprex regimen for a medical abortion through 49 days' pregnancy is:

Day One
Mifeprex Administration
3 tablets of 200 mg of Mifeprex orally at once

Day Three
Misoprostol Administration
2 tablets of 200 mcg of misoprostol orally at once

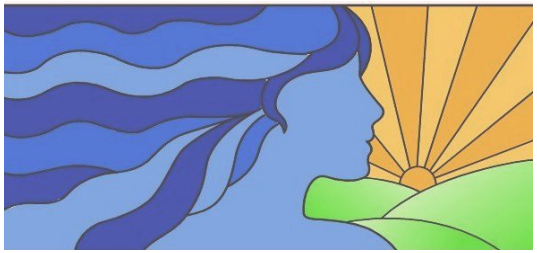
Day 14
Post-Treatment
The patient must return to confirm that a complete termination has occurred.
If not, surgical termination is recommended to manage medical abortion treatment failures.

The safety and effectiveness of other Mifeprex dosing regimens, including use of oral misoprostol tablets intravaginally has not been established by the FDA

INTERRUPTION OF INTRAUTERINE PREGNANCY WITH SEQUENTIAL USE OF PROSTAGLANDIN ANALOGUE, UP TO 63 th DAY OF AMENORRHEA			
GESTATIONAL AGE	RU486	MISOPROSTOL	GEMEPROST
< 49 th day	600 mg per os	400 µg per os	
	600 mg per os		1 mg (vaginal administration)
	200 mg per os		1 mg (vaginal administration)
50° - 63 th day	600 mg per os		1 mg (vaginal administration)
	200 mg per os		1 mg (vaginal administration)
SOFTENING AND DILATATION OF THE CERVIX BEFORE THE SURGICAL TERMINATION OF PREGNANCY DURING THE FIRST TRIMESTER			
	200 mg per os	Surgical termination of pregnancy within 36-48 h.	
PREPARING TO PROSTAGLANDIN ANALOGUES IN THE INTERRUPTION OF PREGNANCY BEYOND THE FIRST TRIMESTER			
	600 mg per os	Prostaglandin analogues (Gemeprost ,vaginal administration)	
INDUCTION OF LABOR FOR FETAL DEATH IN WOMB			
	600 mg per os for 2 consecutive days	Induction of labor by usual methods if it did not start 72 hours after the first administration of mifepristone	

	Committee for Medicinal Products for Human Use (CHMP)		
Gestational Age	≤ 49 days	≤ 49 days	from 50 to 63 days
Mifepristone Dose	600 mg	200 or 600 mg	200 or 600 mg
Prostaglandin Dose	Misoprostol 400 µg (PO)	Gemeprost 1 mg (PV)	Gemeprost 1 mg (PV)
Safety Information	●The risk of fatal infections when 200 mg mifepristone is followed by non-authorised vaginal administration of misoprostol tablets for oral use; ●The interactions of mifepristone with other medicines; ●The use of mifepristone and prostaglandin analogues in patients with haemostatic disorders or severe anaemia.		

European Medicines Agency. *Plenary Meeting Monthly Report*. London, 29th March 2007



Completion of Medical Abortion

- Timing varies somewhat depending on mifepristone regimen
- Onset of bleeding
  - Bleeding after mifepristone can occur
  - 80-92% bleed within 4 hours of misoprostol
  - Average onset 2-4 hours post misoprostol
  - 98% of women bleed within 24 hours of misoprostol
- Expulsion
  - 60-93% abort within 5 hours of misoprostol
  - ~ 90% abort within 24 hours after misoprostol

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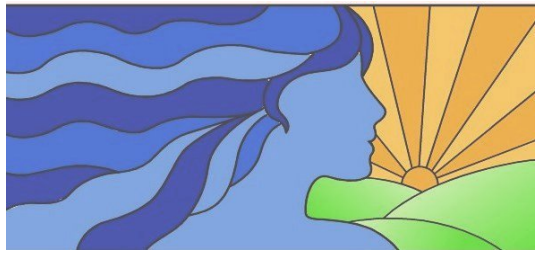
NATIONAL ABORTION FEDERATION

Schaff, et al. *Contraception* 1999
Wiebe, et al. *Obstet Gynecol* 2002
Creinin, et al. *Obstet Gynecol* 2004



Follow-up Care

- Determine if abortion is complete
- Continuity of care preferable
- Provide emotional support and assistance, as needed
- Provide information, ask/answer questions, listen, and observe

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WHO Model List Essential Medicines
15th edition (March 2007)

22. OXYTOCICS AND ANTIOXYTOCICS	
22.1 Oxytocics	
□ ergometrine	injection, 200 micrograms (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule
Complementary List	
misoprostol	*vaginal tablet, 25 micrograms*
mifepristone - misoprostol **	*tablet 200 mg - tablet 200 micrograms* ** requires close medical supervision*

Where permitted under national law and where culturally acceptable.

Teratology

TERATOGENICITY

- **Misoprostol**

The use of misoprostol in the first trimester has been associated with two specific types of anomalies.

- Five cases of a frontal and/or temporal defect in the skull without other anomalies were described in women who had taken misoprostol 400 µg to 600 µg orally and/or vaginally.

- Gonzalez et al. reported on seven cases of limb abnormalities, four of whom also had a diagnosis of Möbius sequence (mask-like facies with bilateral sixth and seventh nerve palsy and frequently coincident micrognathia). The mothers all had taken misoprostol 200 µg to 1800 µg orally or vaginally between 4 to 12 weeks amenorrhea to attempt abortion. There were three other children born with similar anomalies after maternal misoprostol ingestion. Two children had limb deficiencies (one with Möbius sequence) and one child had Möbius sequence.

M.D. Creinin, *Early medical abortion with mifepristone and other agents: overview and guidelines*, National Abortion Federation, 2002

Bos-Thompson MA, Hillaire-Buys D, Roux C, et al.
Möbius syndrome in a neonate after mifepristone and misoprostol elective abortion
Ann Pharmacother. 2008 Jun;42(6):888-92.

DISCUSSION: Möbius syndrome is characterized by unilateral or bilateral palsy of the abducens (VI) and facial (VII) cranial nerves. [...]. The critical period for the development of Möbius syndrome following teratogen exposure appears to be 5-8 weeks of gestation. To date, mifepristone alone does not appear to have induced Möbius syndrome. In contrast, oral or vaginal misoprostol administration can lead to a significant increase in Doppler-measured uterine artery resistance and may induce uterine contractions. If these occur during the critical embryonic period, they may cause flexion in the areas of the sixth and seventh cranial nerves and decreased blood flow.

CONCLUSIONS: Ineffective use of mifepristone and misoprostol in the first trimester of pregnancy may be associated with a risk of Möbius syndrome, primarily due to misoprostol activity. Women with ongoing pregnancy after failed abortion with misoprostol administration should be informed of this risk.

Miller MT, Ventura L, Strömland K.

Thalidomide and misoprostol: ophthalmologic manifestations and associations both expected and unexpected.

Birth Defects Res A Clin Mol Teratol. 2009 Jul 28. [Epub ahead of print]

CONCLUSIONS: Ocular malformations and dysfunction are frequent findings from early exposure in pregnancy of two teratogens, thalidomide and misoprostol. The most common eye manifestations are unusual ocular motility disorders and tearing aberrations. [...] Mothers of more than 50% of the patients with Möbius sequence in the Brazilian studies gave a history of attempted but failed abortions using misoprostol. [...] To a lesser extent, it also supports the idea that the most common time of exposure is in the 4th to 6th week after fertilization.

Side effects

DEFINITIONS

- **Side Effect**: effect of treatment, other than the intended outcome, that might include physiological or psychological consequences.

- **Complication**: effect resulting from treatment that has potentially serious clinical consequences and requires medical intervention.

In addition to the expected effects of vaginal bleeding and cramping, the most common side effects reported after use of the mifepristone and misoprostol regimen are:

SIDE EFFECTS	from (%)	to (%)
Nausea	36	67
Diarrhea	8	23
Headache	13	32
Dizziness	12	37
Vomiting	13	34
Fever or chills	4	37

Stewart FH, Wells ES, Flinn SK, Weitz TA. *Early Medical Abortion: Issues for Practice.* UCSF Center for Reproductive Health Research & Policy: San Francisco, California, 2001.

WARNING SIGNS AFTER EARLY ABORTION [1]

- Soaking 2 or more maxipads per hour for 2 consecutive hours.
- Sustained fever (100.4°F; 38°C) or onset of fever beginning more than 6 to 8 hours after misoprostol.
- No bleeding within 24 hours after using misoprostol (may indicate ectopic pregnancy or lack of response to treatment).

MANAGEMENT OF COMMON SIDE EFFECTS: BLEEDING [2]

- Usually exceeds typical menstrual bleeding
  - If patient saturates 2 maxipads/hour for 2 consecutive hours, contact provider
  - Surgical intervention to control bleeding: 0.4% to 2.6%
  - Transfusion required: 0.2%
- Longer duration than with vacuum aspiration
- No significant difference in total blood loss between medical abortion & vacuum aspiration

[1]National Abortion Federation, *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations.* Washington, D.C.: National Abortion Federation, 2001.
[2]National Abortion Federation, *Overview of Medical Abortion: Clinical and Practice Issues,* 2005.

Severe Adverse Events

Gary MM, Harrison DJ.
Analysis of Severe Adverse Events related to the use of mifepristone as an abortifacient.
Ann Pharmacother 2006;40:191-197.

With mifepristone abortions, the rate of failure to cause complete termination of pregnancy increases dramatically, along with hemorrhagic events, as the gestational age and the size of the placenta increases.
The US clinical trial demonstrated a failure rate of 8% at 49 days or less from the last menstrual period (LMP), increasing to 17% at 50–56 days from the LMP, and further increasing to a 23% failure at 57–63 days from the LMP, [...].

Gary MM, Harrison DJ.
Analysis of Severe Adverse Events related to the use of mifepristone as an abortifacient.
Ann Pharmacother 2006;40:191-197.

RESULTS: The most frequent AERs were hemorrhage (n = 237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious cases; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life threatening) and 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.

CONCLUSIONS: Hemorrhage and infection are the leading causes of mifepristone related morbidity and mortality. AERs relied upon by the FDA to monitor mifepristone's postmarketing safety are grossly deficient due to extremely poor quality.

Gary MM, Harrison DJ.

Analysis of Severe Adverse Events related to the use of mifepristone as an abortifacient.

Ann Pharmacother 2006;40:191-197.

The 607 AERs included 5 deaths: 2 Californians, from sepsis; a Tennessee woman with a ruptured ectopic pregnancy; a Swedish teen, from massive hemorrhage; and a British female, from "unknown etiology." This last patient presented to the emergency department in shock and was found on autopsy to have 1 liter of blood in her stomach and 2 gastric ulcers. Sepsis is a known risk factor for stress-related gastrointestinal bleeding; thus, sepsis is a plausible etiology for shock in this patient. Three deaths were not documented in these AERs: a participant in Canadian trials, from sepsis; an Asian Californian, from sepsis (December 2003); and a white Californian, from sepsis (June 2005). The FDA recently announced findings from the Centers for Disease Control and Prevention that all 5 of the sepsis deaths (4 Americans, 1 Canadian) have been linked to *Clostridium sordellii*. Thus, there has been a total of 8 known deaths to date, [...].

Miech RP.

Pathopharmacology of excessive hemorrhage in mifepristone abortions.

Ann Pharmacother. 2007;41: 2002-2007.

OBJECTIVE: To explain a pathopharmacologic mechanism that initiates an increase in hemorrhage following medical abortions with mifepristone. [...]

DATA SYNTHESIS: Inescapable bacterial contamination of the decidua accompanies spontaneous, surgical, and mifepristone abortions and is routinely overcome by activation of the innate immune system. The combination of the induction of NO (*nitric oxide*) synthase (NOS) and local production of NO is one of the key features of the activation of the innate immune system's phagocytes. NO is a potent vasodilator and is associated with menstrual menorrhagia. Glucocorticoids prevent the overproduction of NOS and NO and thereby contribute to the control of hemorrhage in the postabortion phase.

CONCLUSIONS: Blockade of the glucocorticoid receptors by mifepristone can result in an excess of NO that is theorized to be the cause of excessive hemorrhage seen in mifepristone abortions.

Jillian T. et al.
Safety of mifepristone abortions in clinical use.
Contraception 2005;72:175-178.

Table 3
Mifepristone complication proportions for 2001–2004 ($N = 95,163$)

		95% CI (Poisson)
Failed attempted abortion	3.5/1000	3.1–3.9
Any complication	2.2/1000	1.9–2.5
Bleeding[a]		
Heavy bleeding	1.3/1000	1.0–1.5
Heavy bleeding and transfusion	0.5/1000	0.4–0.7
Infection		
Endometritis/endomyometritis	0.2/1000	0.1–0.3
Sepsis	2.1/100,000	0.3–7.6
Septic shock, death	1.1/100,000	0.3–5.9
Other[b]	0.2/1000	0.1–0.3

[a] Women experiencing both bleeding and infection are listed in the infection category.
[b] This category includes other complications that resulted in hospital treatment, including allergic reactions, pain, nausea and other medical conditions not directly related to the mifepristone abortion.

What is *Clostridium sordelli* and why is it included in the WARNINGS section of the Mifeprex label?

- *Clostridium sordellii* is a bacteria that is anaerobic (it can live without oxygen)
- *Clostridium sordellii* can produce toxins that are rapidly fatal.
- Rare infections with *Clostridium sordellii* can occur following childbirth (vaginal delivery and caesarian section)
- Infections can also occur rarely with pelvic, abdominal or bone (orthopedic) surgery, and deep skin infections.
- The bacteria may also be present in women's intestinal and rectal areas and cause no symptoms whatsoever, not producing any toxins. This is called "colonization" and is not known to be a health problem.

It is unclear exactly what factors cause the bacteria to produce the toxins in women.

McGregor JA, Equiles O.
Risks of mifepristone abortion in context.
Contraception 2005;72(5):393. (Letters to the editor)

We suggest that mifepristone use impairs hosts responses and may predispose to lethal infection caused by toxigenic C. sordellii and other pathogens. Mifepristone (RU-486) is a potent competitive inhibitor of both progesterone and glucocorticoid receptors. Mifepristone powerfully interferes with glucocorticoid receptormediated stress responses. Mifepristone's anti-glucocorticoid effects have been evaluated at genomic, cellular and organism levels. In animal models of sepsis, mifepristone blocks endocrine stress responses and increases lethality. Clostridium sordellii exists in low numbers in the reproductive tracts of many women. Toxigenic strains of C. sordellii produce multiple exotoxins: the two principal agents are aptly named "lethal" and "hemorrhagic" toxins. These two molecules account for the dramatic lethality of C. sordellii infection.

Nelson R.
Mifepristone linked to lethal toxic shock syndrome.
The Lancet Infectious Diseases 2006;6:11.

"In addition to binding to and blocking progesterone receptors, mifepristone also binds to and blocks glucocorticoid receptors", says Ralph Miech (Brown University, Providence, RI, USA). "Mifepristone has a high affinity for both of these receptors, and blockage of glucocorticoid receptors leads to a malfunctioning of both the innate immune system and the hypothalamic-pituitary-adrenal axis [HPA axis]."
The blockage of progesterone receptors leads to necrotic embryo, placenta, and deciduas, and the presence of necrotic tissue within the uterus provides an ideal anaerobic medium for the growth and multiplication of *C. sordellii*, [...]

Aronoff DM, Hao Y, Chung J, et al.

Misoprostol impairs female reproductive tract innate immunity against *Clostridium sordellii*.

The Journal of Immunology 2008;180:8222-8230.

Fatal cases of acute shock complicating *Clostridium sordellii* endometritis following medical abortion with mifepristone (also known as RU-486) used with misoprostol were reported. The pathogenesis of this unexpected complication remains enigmatic. Misoprostol is a pharmacomimetic of PGE2, an endogenous suppressor of innate immunity. [...] The intrauterine but not the intragastric delivery of misoprostol significantly worsened mortality from C. sordellii uterine infection, and impaired bacterial clearance in vivo. Misoprostol also reduced TNF-alpha production within the uterus during infection. [...] In vitro, misoprostol suppressed macrophage TNF-alpha and chemokine generation following C. sordellii or peptidoglycan challenge, impaired leukocyte phagocytosis of C. sordellii, and inhibited uterine epithelial cell human-defensin expression. [...] Our data provide a novel explanation for postabortion sepsis leading to death and also suggest that PGE2, in which production is exaggerated within the reproductive tract during pregnancy, might be an important causal determinant in the pathogenesis of more common infections of the gravid uterus.

Fjerstad M, et al.

Rates of serious infection after changes in regimens for medical abortion.

N Engl J Med. 2009;361:145-151.

CONCLUSIONS: The rate of serious infection after medical abortion declined by 93% after a change from vaginal to buccal administration of misoprostol combined with routine administration of antibiotics.

DISCUSSION: [...] Potential limitations of our study should be noted. We do not have data available on the rates of follow-up of women after medical abortion, and it is possible that the reporting of serious infections is incomplete.

Patient agreement
(Mifeprex Label, 2005)

PATIENT AGREEMENT

1.I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2.I discussed the information with my health care provider (provider).
3.My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4.I believe I am no more than 49 days (7 weeks) pregnant.
5.I understand that I will take Mifeprex in my provider's office (Day 1).
6.I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7.My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8.Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about day 14) after i take Mifeprex to be sure that my pregnancy has ended and I am well.
9.I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.

PATIENT AGREEMENT

10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.

PATIENT AGREEMENT

14.I will do the following:

✓contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
✓contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
✓contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
✓return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
✓return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature:
Patient Name (print):
Provider's Signature:
Name of Provider (print):
Date:

Clarka WH, Goldb M, Grossmanc D, Winikoff B.
Can mifepristone medical abortion be simplified? A review of the evidence and questions for future research.
Contraception 2007;75:245-250.

CONCLUSIONS: "Simplifying the medical abortion regimen by reducing the number of visits required and by avoiding the routine use of ultrasound imaging has the potential to increase the availability, affordability and acceptability of the treatment and to help it meet its promise as a real alternative to surgical abortion in the first trimester".

1. Simplifying the first medical abortion visit
2. Eliminating the second medical abortion visit
3. Simplifying the third, or follow-up, medical abortion visit

Gomperts RJ, Jelinska K, Davies S, et al.

Using telemedicine for termination of pregnancy with mifepristone and misoprostol in settings where there is no access to safe.

BJOG. 2008;115(9):1171-1175.

Women on Web is a service that uses telemedicine to help women access mifepristone and misoprostol in countries with no safe care for termination of pregnancy (TOP). This study reviews the telemedicine service. After an online consultation, women with an unwanted pregnancy of up to 9 weeks are referred to a doctor. If there are no contraindications, a medical TOP is conducted by mail. After maximising the follow up from 54.8 to 77.6%, 12.6% decided not to do the TOP and 6.8% of the women who did the medical TOP at home needed a vacuum aspiration. Telemedicine can provide an alternative to unsafe TOP. Outcomes of care are in the same range as TOP provided in outpatient settings.

From Chemical Abortion To Contraception

Broekhuizen FF.

Emergency contraception, efficacy and public health impact.

Curr Opin Obstet Gynecol. 2009 Aug;21(4):309-12.

RECENT FINDINGS: Mifepristone (not available in the USA) is the agent of choice. Emergency contraception has not reduced the number of unintended pregnancies. Acceptance by healthcare providers and the public has not been optimal, and multiple financial and healthcare system barriers to use emergency contraception continue to exist. The public health impact of emergency contraception has been disappointing.

SUMMARY: [...] The use of mifepristone for emergency contraception in the USA must be considered.

Agarwal M, Das V, Agarwal A, et al.
Evaluation of mifepristone as a once a month contraceptive pill.
Am J Obstet Gynecol. 2009;200(5):e27-9.

OBJECTIVE: The purpose of this study was to assess the efficacy and safety of mifepristone as a contraceptive pill.

STUDY DESIGN: A prospective case-control study was conducted in a tertiary care center of North India. The study group (n =86) was given 200 mg mifepristone tablets on the 16th day of the menstrual cycle. [...]

CONCLUSION: Mifepristone can be used as a monthly contraceptive pill effectively.

Zhu HX, Zhang WW, Zhuang YL, Huang LL.

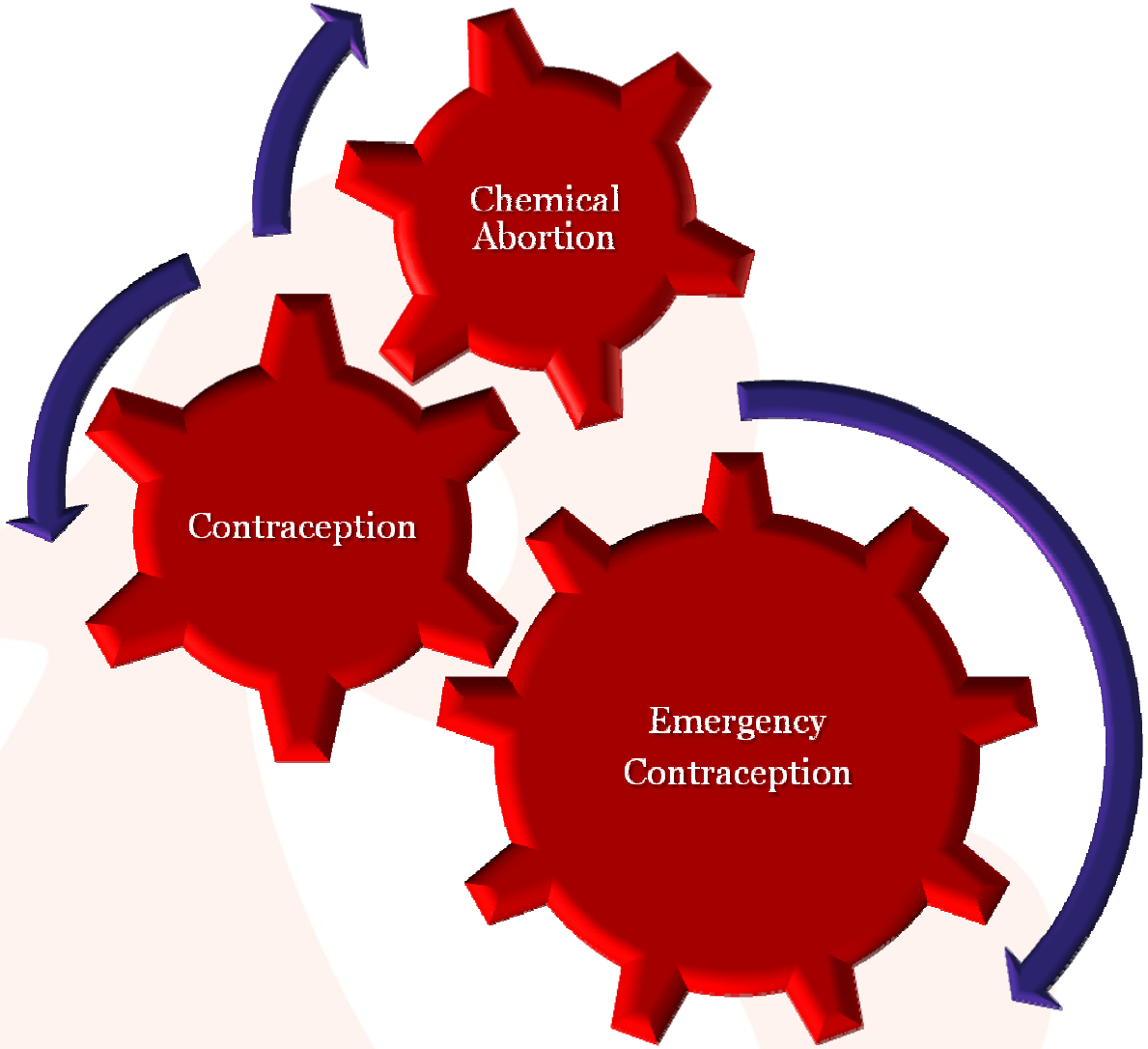
Mifepristone as an anti-implantation contraceptive drug: roles in regulation of uterine natural killer cells during implantation phase.

Am J Reprod Immunol. 2009;61(1):68-74.

PROBLEM: To investigate the immunological mechanism of low-dose mifepristone acting as a contraceptive at the level of the endometrium.

METHOD OF STUDY: Endometrial explants were cultured in vitro with or without mifepristone treatment for 24 hr. Some tissues were fixed and immunostained for CD56, while other tissues were dissociated and cells analysed by three colour flow cytometry for CD3, CD56 and CD16.

RESULTS AND CONCLUSION: [...] It shows that low-dose mifepristone increases the number of CD56(+) NK cells and the percentage of CD3(-) CD56(+) CD16(-) NK subset in receptive endometrium and provides new insights into the immunological mechanism of low dose mifepristone as an anti-implantation contraceptive drug.



Romano L, Di Pietro ML, Faggioni P, Casini M. *RU486: dall'aborto chimico alla contraccezione di emergenza. Riflessioni biomediche, etiche e giuridiche*. Roma: ART, 2008.

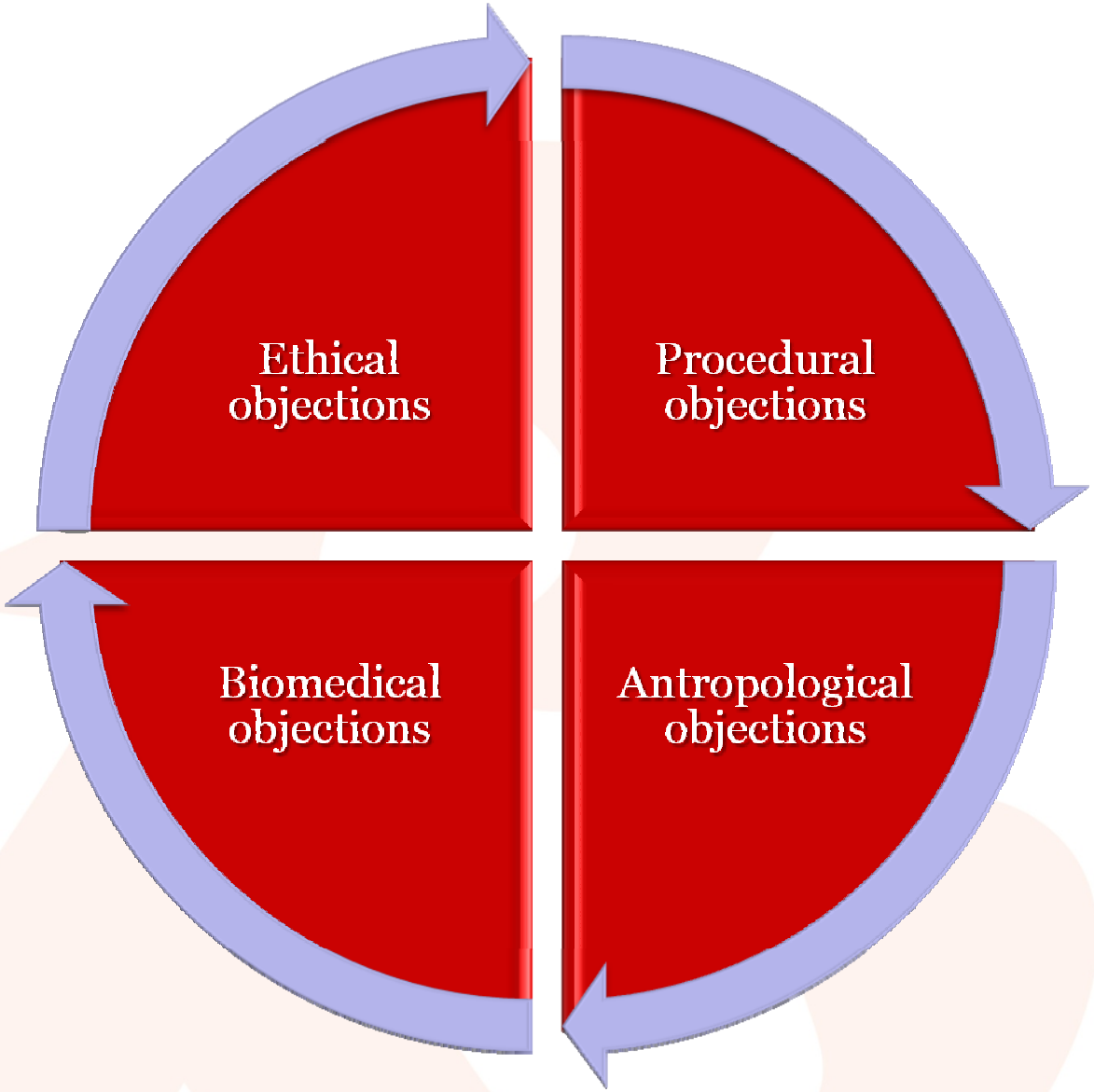
The Chemical Abortion and L.194/78

- As regards the correct application of the procedures according to art. 1, 5, 8, considering both the protocol validated by the FDA that trials, the IVG - although induced at medical facilities - is completed outside.

- The assumption that the introduction in Italy of chemical abortion is consistent with art. 15 L. 194/78 is not scientifically acceptable.

- Objectively impossible to reconcile the chemical abortion with respect to L.194/78 otherwise changed *de facto*.

Objections


Ethical objections
Procedural objections
Biomedical objections
Antropological objections