Progesterone Use to Reverse the Effects of Mifepristone

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OBJECTIVE: To present a series of cases demonstrating successful reversal of mifepristone effects in women who chose to reverse the medical abortion process.

CASE REPORTS: Four of 6 women who took mifepristone were able to carry their pregnancies to term after receiving intramuscular progesterone 200 mg.

DISCUSSION: Mifepristone has been available in the US since 2000. By 2008, approximately 25% of abortions prior to 9 weeks were accomplished with mifepristone. Some women who take mifepristone wish to reverse the medical abortion process. Progesterone competes with mifepristone for the progesterone receptor and may reverse the effects of mifepristone. A PubMed literature search from 1996 to May 2012 did not reveal any trials or case studies evaluating the efficacy of progesterone use to reverse the effects of mifepristone.

CONCLUSIONS: Health care professionals should be aware of the possible use of progesterone to reverse mifepristone in women who have begun the medical abortion process by taking mifepristone and then change their minds.

KEY WORDS: medical abortion, mifepristone, progesterone.

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Mifepristone has been available in the US as an oral tablet since 2000. It is indicated by the Food and Drug Administration (FDA) for termination of pregnancy up to 49 days after the first day of the last menstrual period. Mifepristone is followed 2 days later by misoprostol to complete the abortion.[1]

The drug's development was hailed as a breakthrough in abortion technology and as an advance for women in facilitating control of their bodies and privacy. By 2008, medical abortion replaced surgical abortion in one-fourth of approximately 800,000 abortions performed annually prior to 9 weeks.[2]

We present a series of patients who took mifepristone to terminate their pregnancies and then sought assistance to block the mifepristone effects. The 2-day gap between the ingestion of mifepristone and misoprostol in the typical abortion regimen potentially affords an opportunity to intervene and reverse the effects of the mifepristone. Six physicians in the US trained in NaProTECHNOLOGY protocols at the Pope Paul VI Institute have given progesterone as an antidote to mifepristone, treating 7 patients. The rationale of the proposed treatment was that higher bioavailable levels of progesterone could competitively inhibit the mifepristone to prevent the induced abortion.

Pharmacology of Mifepristone and Progesterone

Mifepristone was first tested to take advantage of its anti-glucocorticoid properties. It binds with high affinity to glucocorticoid receptors, about 4 times as avidly as dexamethasone.[3] When its antiprogesterone properties were discovered it was considered useful for fertility control because of its potential to counteract the actions of progesterone, which is critical for sustaining pregnancy.[4] Additionally, it has been studied for the treatment of endometriosis, uterine fibroids, and Cushing syndrome.[5-7] Mifepristone's most significant application has been in induced abortion because, by binding to the progesterone receptor, placental failure ensues and the developing embryo loses its nutrition and oxygen supply.

Mifepristone is an orally active compound with a nearly 70% absorption rate, but its bioavailability is reduced to approximately 40% because of the first-pass effect.[8] It binds to the progesterone receptor twice as well as progesterone, in addition to binding to the serum transport protein α_1-acid glycoprotein.[9] Demethylation and hydroxylation are catalyzed by CYP3A4; 3 metabolites retain biologic activity. The half-life of mifepristone is approximately 18-25 hours. Mifepris-

Author information provided at end of text.

tone and its metabolites can be measured up to 72 hours after an ingested dose.[10] The half-life of progesterone is longer, approximately 25-55.13 hours.[11-13]

Current Regimens of Medical Abortion

The original FDA-approved regimen of mifepristone and misoprostol paralleled the European protocol that had been used in the 1990s. It consisted of mifepristone 600 mg followed 2 days later by oral misoprostol 400 µg.[14] Later trials evaluated mifepristone 200 mg.[15-18] The FDA and the drug's distributor recommend the 600-mg dose; however, others state that the 200-mg dose has been used in most of 1 million abortions.[19] The success rate of medical abortion decreases with gestational age. In the FDA clinical trials the rate of incomplete abortion was 5% before 49 days and 7-8% at 50-63 days; the rate of an ongoing living embryo ranged from less than 1% before 49 days to 9% at 57-63 days.[14]

Results of Progesterone Therapy

We report on 6 women who were treated with progesterone in an attempt to reverse pregnancy termination after mifepristone ingestion. Four of these women eventually delivered healthy term newborns. A seventh patient was lost to follow-up. Of the 2 abortions, 1 occurred soon after an intramuscular injection of progesterone was administered (patient 6). Data on this patient are incomplete. The other patient (patient 5) received progesterone micronized 200 mg vaginally 7 hours after ingesting mifepristone and receiving progesterone 200 mg intramuscularly 18 hours after mifepristone. However, a live embryo was not documented at the abortion clinic or in the physician's office for this patient.

Case Reports

CASE 1

A 19-year-old woman, gravida (G) 1 para (P) 0, elected to have the mifepristone effects reversed at gestation age 8 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 30-40 hours following mifepristone ingestion. The progesterone regimen was given 2 consecutive days and then 2 doses every other day, and then twice a week until 9 weeks 5 days.

Progesterone 200 mg in oil intramuscularly was restarted at 11 weeks 2 days and given twice weekly; the dose was then decreased to 100 mg twice a week and stopped at 29 weeks 5 days.

A viable male was delivered at 37 weeks. No untoward effects of progesterone noted and no birth defects were noted. Neonatal complications included neonatal physiologic jaundice and circumcision wound infection.

CASE 2

A 25-year-old woman, G8 P7007, elected to have the mifepristone effects reversed at gestation age 11 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 72 hours following mifepristone ingestion.

Further progesterone treatment included an intramuscular injection of 200 mg in oil for 2 weeks, then progesterone micronized orally for 5 months. No untoward effects of progesterone were noted.

A viable infant was delivered, with no neonatal complications or birth defects noted.

CASE 3

A 19-year-old woman, G3 P1011, elected to have the mifepristone effects reversed at gestation age 7 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 36-48 hours following mifepristone ingestion.

Further progesterone treatment included an intramuscular injection of 200 mg in oil 2 more times the first week, then weekly for 5-6 weeks, then 200 mg in oil twice weekly for 2 weeks, then micronized progesterone orally for 5 months. No untoward effects of progesterone were noted.

A viable infant was delivered at 39 weeks 3 days, with no neonatal complications or birth defects noted.

CASE 4

A 20-year-old woman, G1 P0, elected to have the mifepristone effects reversed at gestational age 7 weeks 4 days. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 46 hours following mifepristone ingestion. Further progesterone treatment included an intramuscular injection of 200 mg in oil twice weekly for 19 weeks. No untoward effects of progesterone were noted.

A viable female infant was delivered at 40 weeks 1 day, with no neonatal complications or birth defects noted.

CASE 5

A 21-year-old woman elected to have the mifepristone effects reversed; gestational age was unknown. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil (time following mifepristone ingestion unknown). The abortion was completed soon after the progesterone injection.

CASE 6

A 19-year-old woman, G1 P0, elected to have the mifepristone effects reversed at gestational age 7 weeks. Misoprostol had not been ingested. The initial micronized

progesterone oral capsule dose was 200 mg administered intravaginally 7 hours following mifepristone ingestion. Further progesterone treatment included an intramuscular injection of 200 mg 18 hours after ingestion, which was repeated 2 days later. No untoward effects of progesterone were noted.

The abortion was completed 3 days after mifepristone ingestion.

Discussion

The experience of these patients suggests that medical abortion can be arrested by progesterone injection after mifepristone ingestion prior to misoprostol due to the competitive action of progesterone versus mifepristone. Possible confounding factors are the lack of embryocidal and feticidal efficacy of mifepristone with increasing gestational age and the absence of documentation of viable pregnancy before ingestion of mifepristone in some patients. We welcome further clinical trials utilizing this protocol or others, in order to have an evidence basis for the best protocol. We believe that if further trials confirm the success without complications of this or similar protocols, it should become the standard of care for obstetrician-gynecologists, family physicians, and emergency department physicians to attempt mifepristone reversal on patient request.

SUGGESTED PROTOCOL

A rational protocol for treating women who have ingested mifepristone and then wish to continue the pregnancy can be considered. We drew on our experience of successfully treating pregnant women with threatened spontaneous abortion or low serum progesterone levels with intramuscular progesterone using the protocol of Hilgers.[19,20] Progesterone has been studied extensively and appears to be safe during all trimesters of pregnancy.

Table 1. Progesterone Dosing and Ultrasound Time Table[a]

Day	Progesterone 200 mg Intramuscularly	Ultrasound to Confirm Viability
1	X	X
2	X	
3	X	
5	X	
7	X	X
9	X	
11	X	
13	X	X
16[a]	X	

[a]Continue twice per week until the end of the first trimester. At end of the first trimester, the dose should be tapered according to the protocol of Hilgers.[19,20]

Protocol

1. Progesterone 200 mg intramuscularly as soon as possible after ingestion of mifepristone.
2. Transvaginal or transabdominal ultrasound as soon as possible to confirm embryonic or fetal viability (Table 1). If less than 6.5 weeks after last menstrual period, monitor serial human chorionic gonadotropin (HCG) levels. However, HCG levels may not increase at the same rate as those of healthy controls.
3. Repeat progesterone 200 mg intramuscularly daily for 2 more days, then every other day until day 13 after the ingestion of mifepristone.
4. Treat with progesterone 200 mg intramuscularly twice weekly until the end of the first trimester and according to the protocol of Hilgers.[19,20] However, do not decrease the dose until the end of the first trimester.

A primary care physician or emergency medicine physician may not want to continue the protocol once it is initiated. Such physicians may want to be ready to refer the patient to a physician comfortable with progesterone supplementation during pregnancy.

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References

1. Mifepristone (Mifeprex) product information. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm (accessed 2011 Sept 28).
2. Guttmacher Institute. Fact sheet August 2011. http://www.guttmacher.org/pubs/fb_induced_abortion.html (accessed 2011 Sept 28).
3. Ghoumari AM, Dusart I, El-Etr M, et al. Proceedings of the National Academy of Sciences. http://www.pnas.org/content/100/13/7953.abstract?ijkey=510caf20e11b12b02a957423f8f97d2dce9e6012&keytype2=tf_ipsecsha (accessed 2011 Sept 28).
4. Potts M Termination of pregnancy in the privacy of one's home. N C Med J 1989;50:531-6.
5. Mei L, Bao J, Tang L, et al. A novel mifepristone-loaded implant for long-term treatment of endometriosis: in vitro and in vivo studies. Eur J Pharm Sci 2010;39:421-7.
6. Spitz IM. Progesterone antagonist and progesterone receptor modulators. Expert Opin Investig Drugs 2003;12:1693-707.
7. Johansen S, Allolio B. Mifepristone (RU-486) in Cushing's syndrome. Eur J Endocrinol 2007;157:561-9.
8. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. Eur J Obstet Gynaecol Reprod Biol 2002;101:113-20.
9. Heikinheimo O, Kekkonen R, Lahteenmaki P. The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestins action. Contraception 2003;68:421-6.

10. Drug Bank. Progesterone. http://www.drugbank.ca/drugs/DB00396 (accessed 2011 Oct 8).
11. United States Department of Labor Occupational Safety & Health Administration. http://www.osha.gov/dts/sltc/methods/partial/pv2001/2001.html (accessed 2011 Nov 2).
12. United States Department of Labor Occupational Safety & Health Administration. http://www.osha.gov/dts/sltc/methods/partial/pv2001/2001.html (accessed 2011 Nov 2).
13. Spitz IM, Bardin W, Benton L, Robbins A, et al. Early pregnancy termination with mifepristone and misoprostol. N Engl J Med 1998;338:1241-7.
14. Schaff EA, Stadalius LS, Eisinger, SH, Franks P. Vaginal misoprostol administered at home after mifepristone for medical abortion. J Fam Pract 1997;44:353-60.
15. Schaff EA, Eisinger SH, Stadalius LS, et al. Low mifepristone and vaginal misoprostol for abortion. Contraception 1999;59:1-6.
16. Schaff EA, Fielding SL, Eisinger SH, Stadalius LS, Fuller L. Low dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days. Contraception 2000;61:41-6.
17. Schaff EA, Fielding SL. A comparison of ARM and Population Council trials. J Am Med Womens Assoc 2000;55(3 suppl):137-40.
18. Swica Y, Winikoff B . High failure rates of medical termination of pregnancy after introduction to a large teaching hospital. Fertil Steril 2008. https://fertstert.wordpress.com/2008/10/30/high-failure-rates-of-medical-termination-of-pregnancy-after-introduction-to-a-large-teaching-hospital/ (accessed 2012 July 5).
19. Hilgers TM. Using progesterone support during pregnancy in the medical and surgical practice of NaProTECHNOLOGY. 1st ed. Omaha, NE: The Pope Paul VI Institute for the Study of Human Reproduction Press, 2006:725-46.
20. NaProTECHNOLOGY. Unleashing the power in a woman's cycle: progesterone support in pregnancy. http://www.naprotechnology.com/progesterone. htm (accessed 2012 Jul 5).