AAPLOG
PRACTICE GUIDELINE

Number 6, November 2022

The Reversal of the Effects of Mifepristone by Progesterone

Administering medications that slow or arrest the effects of other medications has a long history in medicine. The action of mifepristone, a progesterone receptor antagonist, can be slowed or arrested with progesterone based on biological plausibility and limited cohort data.

Background

Some women who take mifepristone for medication abortion change their minds and desire to stop the medical abortion process before taking misoprostol.[1] Medical induced abortion utilizing mifepristone and misoprostol has been available in the United States since 2000. In 2014, 31% of non-hospital induced abortions were medical induced abortions.[2] The FDA protocol involves the administration of mifepristone 200 mg orally as a single dose, which leads to embryonic or fetal demise, followed 24-48 hours later by misoprostol 800 mcg buccally as a single dose, which stimulates myometrial contractions. The protocol is approved up to 70 days after the first day of the last menstrual period.[3] Misoprostol is part of the protocol because mifepristone alone has an incomplete abortion rate of 20-40%, defined as incomplete expulsion of the uterine contents.[4] By blocking progesterone receptors, mifepristone leads to the separation of the decidua basalis from the trophoblast. This separation is the primary embryocidal and feticidal effect of mifepristone.[4-6] Additionally, mifepristone causes softening and dilatation of the cervix.[4] It also leads to myometrial contractions, increased myometrial sensitivity to prostaglandins[4,7] and the disinhibition of prostaglandin synthesis by the myometrium.[8] Progesterone has an autoregulatory effect on progesterone synthesis by the corpus luteum. Blocking progesterone receptors with mifepristone decreases progesterone secretion by the corpus luteum.[9]

Evidence

There are three types of evidence supporting the use of progesterone to reverse the effects of mifepristone, in women who wish to stop their medical abortions. The first is biologic logic. Mifepristone was studied and developed as an abortifacient precisely because it antagonizes progesterone,

AAPLOG Practice Guideline. This document was developed by authors on the Research Committee. Practice Guidelines are evidence-based documents informing pro-life providers with high-quality, peer-reviewed literature.

competing for the progesterone receptor. It is well known that, in a biological system, increasing the concentration of a ligand will result in that molecule preferentially binding to the receptor compared to other molecules with similar receptor affinity.

Animal experimental data demonstrate that progesterone prevents mifepristone effects. One group of pregnant rats was given mifepristone while a second was given mifepristone and progesterone. In the group that only received mifepristone, 33% of the pups survived. In the group that received mifepristone and progesterone, 100% of the pups survived. Furthermore, the first group had characteristic changes in the myometrium and ovaries; the group that received the combination had no such changes.[10]

Finally, a large case study reviewed 261 births after successful reversal of mifepristone abortions. With the best protocols, the reversal rates were 64-68%.[11]

Pharmacology

Mifepristone is a reversible, competitive antagonist of progesterone at the progesterone receptor (PR). It binds to the PR about twice as avidly as progesterone.[12] 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.[13] It is absorbed better with food than on an empty stomach. After metabolism by the CYP3A4 enzyme, three metabolites retain biologic activity. The half-life of mifepristone is about 18-25 hours. Mifepristone and its metabolites can be measured up to 72 hours after an ingested dose.[12] Progesterone's half-life is approximately 25-55 hours.[13,14]

Mifepristone Efficacy

There has been some confusion and misinterpretation of data surrounding the embryo or fetus survival after exposure to mifepristone but not misoprostol, if no progesterone treatment is offered. Some authors have mistakenly claimed that embryo or fetal survival will be up to 40% if no treatment is administered.[15] Unfortunately, they confuse the incomplete abortion rate (which is defined as incomplete emptying of the uterine contents[16]) with actual embryonic or fetal survival. A paper published in 2016 carefully analyzed the data of early mifepristone studies that were conducted before the two-drug protocol was devised. The analysis concluded that embryo or fetal survival was up to 23%. Thus, 25% survival is used as the historic control when evaluating progesterone therapies.[17]

Indications

Mifepristone reversal with progesterone is indicated in a woman who has an intrauterine pregnancy, has taken mifepristone but not misoprostol and desires to halt the medical abortion process.

Contraindications

Mifepristone reversal with progesterone is contraindicated in a woman with ectopic pregnancy, nonviable embryo or fetus, septic abortion, hemodynamic compromise or allergy to progesterone. Oral micronized progesterone in peanut oil is contraindicated in women with peanut allergy, unless cleared by an allergist.

Methods

A 2018 article published in a peer-review medical journal detailed the successful reversal of mifepristone utilizing progesterone, given within 72 hours of the mifepristone ingestion. Two-hundred fifty-seven births after reversal were studied. An historic control rate of 25% embryo or fetal survival after mifepristone exposure, if no treatment was offered, was used as the comparator. The overall reversal rate was 48% ($p < 0.001$). With the high dose oral protocol, the reversal rate was 68% ($p < 0.001$); the rate with the injection protocols was 64% ($p < 0.001$).[11]

Complications

1. The documented birth defect rate in babies born after mifepristone reversal is 2.7%, compared to the generally quoted rate of 3% in the general population.[11] Mifepristone is embryocidal or feticidal but not teratogenic, according to Practice the American College of Obstetrician Gynecologists.[18]
2. The preterm birth rate is 2.7%, compared to 10% in the general population.[11,19]

Clinical Considerations and Recommendations

Utilizing the data from the 2018 Delgado study, two protocols can be recommended for women who change their minds after taking mifepristone and want to halt the medical abortion process.[11]

1. High Dose Oral Protocol

   Progesterone micronized 200 mg capsule two by mouth as soon as possible and continued at a dose of 200 mg capsule two by mouth twice a day for three days, followed by 200 mg capsule two by mouth at bedtime until the end of the first trimester.[11] Oral progesterone should be taken with food to improve absorption.

2. Intramuscular Protocol

   Progesterone 200 mg intramuscular as soon as possible and continued at a dose of 200 mg intramuscular once a day on days two and three, then every other day for a total of seven injections. Some clinicians may choose to continue intramuscular treatment longer since this recommendation is based on relatively small numbers.[11]

A sonogram should be obtained as soon as possible to confirm intrauterine location, viability and gestational age. If ultrasonography is not immediately available, treatment should not be delayed unless there is suspicion of an ectopic pregnancy, septic abortion or other complication that requires immediate gynecologic attention in a hospital or similar setting.

Summary of Recommendations and Conclusion

The following recommendations are based on limited and inconsistent scientific evidence (Level B):

Some women change their minds after starting the mifepristone abortion process and wish to reverse the effects of mifepristone to stop the medical abortion. The current research suggests that using progesterone to counter the effects of mifepristone and stop the abortion process is both safe and effective. Since there is no alternative treatment for women who change their minds, it is reasonable to offer this life-saving and life-changing treatment to these women.

References

1. Delgado G, Davenport M. Progesterone Use to Reverse the Effects of Mifepristone. Ann Pharmacother 2012;46. Published Online, 27 Nov 2012, theannals.com, DOI: 10.1345/aph.1R252.
2. Jones RK and Jerman J. Abortion incidence and service availability in the United States, 2014. Perspectives on Sexual and Reproductive Health, 2017, 49(1), DOI: 10.1363/psrh.12015.
3. Medication Guide, Mifeprex. www.fda.gov/downloads/drugs/drugsafety ucm088643.pdf (accessed November 19, 2016).
4. Creinin, M, Gemzell Danielsson, K. Chapter 9, Medical abortion in early pregnancy, in Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care. Published Online: 22 May 2009 DOI:10.1002/9781444313031.ch9.
5. Johannisson E, Oberholzer M, Swahn ML, Bygdeman M. Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486. Contraception 1989; 39: 103–107.
6. Schindler AM, Zanon P, Obradovic D, Wyss R, Graff P, Hermann WL. Early ultrastructural changes in RU-486-exposed decidua. Gynecol Obstet Invest 1985; 20: 62–67.
7. 10 Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br J Obstet Gynaecol 1988; 95: 126–134.
8. Herrmann WL, Schindler AM, Wyss R, Bishof P. Effects of the antiprogesterone RU 486 in early pregnancy and during the menstrual cycle. In: Beaulieu EE, Siegel S, eds. The Antiprogestin Steroid RU 486and Human Fertility Control. Plenum, New York, 1985: 259–262.
9. Ottander U, et al. A Putative Stimulatory Role of Progesterone Acting via Progesterone Receptors inthe Steroidogenic Cells of

the Human Corpus Luteum. Biology of Reproduction March 1, 2000 vol. 62 no.3 655-663.

10. Yamabe, S; Katayana, K; Mochuzuki, M Folio endocrine. 65, 497-511, 1989. The Effects of RU486 and Progesterone on Luteal Function During Pregnancy.
11. Delgado G, Condly S, et al. A Case Series Detailing the Successful Reversal of Mifepristone using Progesterone. Issues in Law and Medicine vol .33 no. 1.
12. 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.
13. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. Eur J Obstet Gynaecol Reprod Bio; 2002;101:113-20.
14. Drug Bank Progesterone. http://www.drugbank.ca/drugs/DB00396 (accessed 2011 Oct 8).
15. Grossman D et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: A systematic review, Contraception (2015) September 2015 Volume 92, Issue 3, pp. 206–211, DOI: 10.1016/j.contraception.2015.06.001).
16. Medical Dictionary. medical-dictionary.thefreedictionary.com/incomplete+abortion (accessed November 20, 2016).
17. Davenport M, Delgado G, Khauv V. Embryo survival after mifepristone: review of the literature. Issues in Law and Medicine 2017, 32 (1): 3-18.
18. Medical Management of First Trimester Abortion. ACOG Practice Bulletin 143 March 2014, reaffirmed 2016.
19. Preterm Birth. http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed December 7, 2016).