

PRACTICE BULLETIN 6

EVIDENCE DIRECTING PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS

Number 6 November 16, 2019

The Reversal of the Effects of Mifepristone by Progesterone

Some women who take mifepristone, a progesterone receptor antagonist, in order to terminate their pregnancies, change their minds and desire to stop the medical abortion process before taking the second component, misoprostol. The purpose of this document is to summarize the medical literature regarding the use of progesterone for competitive reversal of the effects of mifepristone at the level of the progesterone receptor, and the application of this basic principle of toxicology in women who change their mind about abortion after taking mifepristone.

Background

Mifepristone abortion background

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.¹ The 2016 FDA protocol for the mifepristone abortion regimen 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.² 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.³

By blocking progesterone receptors, mifepristone leads to the separation of the decidua basalis from the trophoblast. This separation is the primary embryocidal and fetocidal effect of mifepristone.^{4,5,6} Additionally, mifepristone causes softening and dilatation of the cervix.⁷ It also leads to myometrial contractions, increased myometrial sensitivity to prostaglandins^{8,9} and the disinhibition of prostaglandin synthesis by the myometrium.¹⁰ Progesterone has an autoregulatory effect on progesterone synthesis by the corpus luteum. Mifepristone blockade of progesterone receptors within the corpus luteum itself decreases progesterone secretion by the corpus luteum.¹¹ Mifepristone blockade of progesterone receptors is a reversible competitive inhibition.¹² Some women who take mifepristone, a progesterone receptor antagonist, in order to terminate their pregnancies, change their minds and desire to stop

the medical abortion process before taking the second component, misoprostol.¹³

Evidence for Efficacy of Progesterone Reversal of Mifepristone Receptor Blockade

There is pharmacological, animal and human data supporting the effects of mifepristone blockade of progesterone receptors in women who wish to provide an increased chance of embryo survival after ingestion of mifepristone.

1) Biological Feasibility.

It is a fundamental principle of biochemistry that competitive inhibitors (like mifepristone) that replace and block out substrates (like natural progesterone) may be thwarted if there is enough substrate around. “The inhibitor creates a competing equilibrium to that of the substrate (S), removing a fraction of the enzyme to an inactive form. Adding more substrate will yield more of the active enzyme substrate (ES) form.”¹⁴ This basic medical principle is also the foundation of leucovorin “rescue” after treatment of cancer with methotrexate. In the case of leucovorin “rescue” leucovorin (also known as the vitamin “folinic acid”) out-competes the inhibitor, which is methotrexate.¹⁵

Mifepristone was studied and developed as an abortifacient precisely because it antagonizes progesterone, 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.

2) Mifepristone 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.¹⁶ 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.¹⁷ 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.^{18,19} Progesterone’s half-life is approximately 25-55 hours.^{20,21}

The reversibility of mifepristone blockade of glucocorticoid nuclear receptors (GR) was clearly demonstrated by National Institutes of Health (NIH) researchers investigating mifepristone reversible binding of the glucocorticoid receptor. Sternberg reviewed multiple studies showing that the blockade of mifepristone at the glucocorticoid receptor is reversible by administration of additional glucocorticoids.^{22,23}

The reversibility of mifepristone binding to progesterone receptors (PR) is supported by the basic pharmacological research conducted by the manufacturer.²⁴ It shows the rate at which RU486 could be removed from the progesterone receptor, clearly demonstrating that mifepristone’s blockade of progesterone receptors is reversible—not permanent—and that high concentrations of progesterone will reverse the binding of mifepristone at the progesterone receptor.

3) Mifepristone abortion reversibility in animal models

Investigation of progesterone reversal of mifepristone abortion in a pregnant animal model demonstrated clearly that mifepristone blockade of

progesterone receptors can be overcome by the administration of additional natural progesterone.²⁵ In that study, Yamabe separated pregnant rats into three groups. The first group received no drugs, the second group was given mifepristone, and the third group was given mifepristone followed by natural progesterone. 100% of the no-drug group delivered live offspring. Only 33.3% of the mifepristone-only group delivered live offspring. In the mifepristone and then progesterone group, 100% delivered live offspring.

Furthermore, the mifepristone group had characteristic mifepristone induced changes in the myometrium and ovaries; the group that received the mifepristone plus progesterone had no such changes.

Yamabe also examined the clearance rate of mifepristone. In the rats given mifepristone alone, the level of progesterone in the blood began to decrease at 48 hours and continued to decrease at 72 hours. In contrast, where mifepristone was followed by progesterone the progesterone levels were the same at 72 hours as the control group which received no mifepristone.

4) Human data on embryo survival after mifepristone alone.

A systematic review of documented embryo survival by ultrasound after mifepristone alone was performed by analyzing published research during the time before prostaglandins were added to the mifepristone regimen. Davenport conducted a systematic review of published studies that met inclusion criteria of a documented living embryo after mifepristone ingestion without subsequent misoprostol or other prostaglandin. The analysis concluded that a documented living embryo or fetus after mifepristone alone was at most 23%.²⁶

Grossman 2015 reviewed survival rate after mifepristone alone and claimed a survival rate after mifepristone alone at 40%.²⁷ However, this review included studies which did not actually document embryo survival, but used instead numbers of “incomplete abortions” (i.e. retained products of conception). Inclusion of studies which did not document a living fetus results **in falsely elevating the survival rate after mifepristone alone.** Thus the Grossman study cannot be relied upon to give an estimate of actual living embryo survival, but rather **provides a rate of “mifepristone failures”**, some of which include embryo survival, and others which include simply retained products of conception.

5) Human data on embryo survival after mifepristone followed by natural progesterone

2012 Delgado

Delgado 2012²⁸ reported a small case series of six women who changed their minds about abortion after taking mifepristone, and sought help to enhance the chances that their embryo would survive the attempted abortion with mifepristone. Of the six women given natural progesterone, four of those women went on to complete delivery of live born infants. No malformations were observed in the children.

2016 Garrett

In a small case series from Australia, Garrett reported the results of three women who attempted to increase their chances of embryo survival after ingesting mifepristone by using natural progesterone. Two out of these three women who attempted reversal with progesterone delivered live, healthy neonates.²⁹

2018 Delgado

In a much larger 2018 retrospective chart review, Delgado reviewed the records of 754 patients who decided to attempt to reverse the medical abortion process after taking mifepristone but before taking misoprostol, by administration of natural progesterone within 72 hours of the mifepristone ingestion. Two-hundred fifty-seven births after reversal were found. 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% ($p < 0.001$).³⁰

As a historical comparator, Delgado used a 25% survival rate with mifepristone alone, which was actually higher than the maximum survival rate determined by the historical review by Davenport. Despite comparing with a higher survival rate, Delgado demonstrated a statistically significant survival over mifepristone alone.

Dr. Delgado and his co-authors also analyzed their results by gestational age at the time of reversal attempt and found that the success rate increased with increasing gestational age.

In addition, Dr. Delgado and his co-authors analyzed the interval of time between mifepristone injection and progesterone administration and found that success rates were the same as long so the progesterone was given within 72 hours of the use of mifepristone. This is consistent with what we know about mifepristone, which is that it takes several days to act and thus does not kill the embryo immediately. This finding is also consistent with the Yamabe

study, which found that in the rats given mifepristone alone, the level of progesterone in the blood began to decrease at 48 hours and continued to decrease at 72 hours. In contrast, where mifepristone was followed by progesterone the progesterone levels were the same at 72 hours as the group which had not received anything.

Safety analysis revealed no increase of birth defects when compared to the general population which is consistent with other studies which have found no increase in malformation rate over the general population in infants who are born after exposure to mifepristone in utero.^{31,32} In addition, Dr. Delgado found that the preterm delivery rate was 2.7%, as compared to the 10% of preterm births in the general population.

2019 Creinin

A recent study by Creinin,³³ which was halted for safety considerations, found a similar survival rate after mifepristone plus progesterone as the original small case series of Delgado in 2012.

In the control arm of the study, six women were given mifepristone plus placebo. The results were compared to six women who received mifepristone plus progesterone in the regimen recommended by Delgado. One woman in each arm withdrew. Of the remaining five women in each arm, four of the five women who received progesterone (80%) had living fetuses at the 2 week follow up as documented by ultrasound prior to their surgical abortion. 1 of the 5 (20%) women who received progesterone self-referred to the ER for heavy bleeding but was found to have completely passed the fetus and thus she did not require a D&C as the bleeding had stopped after passage of tissue. No further treatment was required.

In contrast, **in the placebo group which received only mifepristone**, 2 of the 5 women (40%) in the mifepristone alone group had severe hemorrhage requiring emergency D&C and one of those women also required a blood transfusion. It was **due to the severe hemorrhage in the mifepristone alone group, not the progesterone group, that the study was halted**. Of note, 2 of the 5 women (40%) in the mifepristone alone arm had ongoing pregnancies at follow up.

Evidence for the safety of natural progesterone treatment in pregnancy.

Natural progesterone has routinely been given to women during pregnancy for over 50 years and is in fact standard of care after in-vitro fertilization (IVF). The IVF industry has concluded that there is no increased risk from natural progesterone supplementation in early pregnancy.^{34,35} Natural progesterone is commonly used to supplement hormonal deficiency in at-risk early pregnancies.³⁶

Reported association of artificial progesterone like compounds (progestins) with hypospadias occurring in the male infants born to women who used progestins during pregnancy do not apply to natural progesterone, which has a long and demonstrated safety record in pregnancy. There is no evidence after decades of use for luteal support in IVF that natural progesterone has ever been shown to increase the risk of birth defects.

Further reassurance is derived from the large retrospective review of Delgado which showed no increased risk of birth defects in 257 births after abortion pill reversal,³⁷ and in the two studies demonstrating no increase in malformation rate in live births after mifepristone without progesterone.^{38,39}

In summary, using natural progesterone to counter the effects of ingested mifepristone is logical, and founded on basic principles of biochemistry, animal studies, and analysis of human experience. Given the long history of progesterone use in pregnancy, the established safety of progesterone use in early pregnancy for both the mother and her fetus in IVF pregnancies, the known ability of progesterone to counteract the abortive effects of mifepristone in animal models, and the actual evidence in humans of the efficacy and safety of abortion pill reversal, it is reasonable to offer this treatment to women who desire to give their fetus increased chances for survival after ingestion of mifepristone.

Clinical Considerations and Recommendations

Q *Who is a candidate for Abortion Pill Reversal attempt?*

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.

Q *Who is not a candidate for Abortion Pill Reversal attempt?*

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.

Summary of Recommendations and Conclusion

The following recommendations are based on good and consistent scientific evidence (Level A):

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 women who desire to increase the chances of pregnancy survival.

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.

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The MEDLINE database, bibliographies of relevant guidelines, and AAPLOG's internal sources were used to compile this document with citations from 1985 to the publication date. Preference was given to work in English, to original research, and to systematic reviews. When high-quality evidence was unavailable, opinions from members of AAPLOG were sought.

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