AAPLOG
PRACTICE GUIDELINE

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Reversal of the Effects of Mifepristone by Progesterone

An increasing body of evidence supports the use of progesterone to competitively reverse the effects of mifepristone prior to the administration of misoprostol in early pregnancy. This action has been documented in the drug development literature for mifepristone with in vitro experiments. Animal models have confirmed the ability of progesterone, administered simultaneously or subsequently, to reverse the abortifacient effects of mifepristone, i.e., the blockade of the progesterone receptors. In humans, at least three retrospective cohort studies, a prospective cohort study, and a randomized controlled trial demonstrate that the abortifacient effects of mifepristone in early pregnancy can be stopped and reversed in humans by timely administration of progesterone. This Practice Guideline provides a review of the available literature and guidance for progesterone administration as a treatment for women who have taken mifepristone to initiate medication abortion but have changed their minds about aborting prior to taking the second drug in the regimen, misoprostol. This review explores the existing studies supporting the administration of progesterone (colloquially termed "abortion pill reversal") to overcome the reversible mifepristone blockade of progesterone receptors in early human pregnancies. This Practice Guideline also makes recommendations for progesterone dosing and administration based on what is currently found in the medical literature and expert opinion by physicians involved in administering progesterone to overcome mifepristone blockade.

Background

Pharmacology[1]

The abortifacient actions of mifepristone are not immediate upon ingestion. Mifepristone acts by binding in a reversible and competitive fashion to the progesterone receptor (PR), primarily in cells of the endometrium, myometrium, and decidua. It is a basic principle of biochemistry that a competitive reversible inhibitor of a receptor can be overcome by the addition of more substrate. In this case, the inhibitor is mifepristone, and the substrate is natural progesterone.

Pharmacokinetics

Compared with progesterone, mifepristone binds twice as avidly to progesterone receptors.[2] Mifepristone has a nearly 70% absorption rate, with a bioavailability of about 40%.[3] The half-life of mifepristone is

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

approximately 18-25 hours. The half-life of progesterone is longer, approximately 25-55 hours.[4] Mifepristone and its biologically active metabolites can be measured 72 hours after an ingested dose.[5] By 11 days after a 600mg dose, 83% of the dose has been eliminated in feces and 9% in urine. Mifepristone is undetectable in the serum by 11 days.[6]

The pharmacokinetics of micronized progesterone are available in the FDA printed label[7] and noted as follows: Maximum serum concentrations were achieved within 3 hours. Serum progesterone concentrations are linear and dose proportional in postmenopausal women over the range of 100mg/day to 300mg/day, and similar in men over the range of 100mg/day to 400mg/day. The absolute bioavailability of micronized progesterone is not known.

Mifepristone uses in induced abortion

The use of mifepristone "for the medical termination of intrauterine pregnancy" was approved in the United States in 2000. In 2023, an estimated 63% of U.S. abortions were intentional embryocide/feticide by that chemical agent, most of them utilizing the regimen of mifepristone followed by misoprostol.[8] The current FDA-approved protocol[9] uses mifepristone 200mg orally as a single dose, which disrupts the placental attachment to the endometrium, leading to embryonic or fetal demise. It is followed 24-28 hours later by misoprostol 800mcg buccally, also as a single dose, which causes myometrial contractions that expel the embryo or fetus and placental structures to complete the abortion. The mifepristone-misoprostol protocol is currently approved for pregnancy termination up to 70 days after the first day of the last menstrual period. Misoprostol was added to the mifepristone protocol during pre-approval studies due to a 20-40% incomplete abortion rate with mifepristone alone. Note that this "incomplete abortion rate" was defined as incomplete expulsion of the embryo or fetus and placental structures,[10] and not defined as the presence of one or more continuing living embryos. The abortifacient efficacy of the mifepristone plus misoprostol regimen depends on gestational age, with increasing gestational age leading to increasing numbers of continuing living embryos or fetuses (e.g., Chen[11] cites continued living embryo rate of 0.8% < 9 weeks increasing to 2.9% at 9-10 weeks) and increasing numbers of women with incomplete expulsion of the embryo or fetus and placental tissues.

Progesterone use to outcompete mifepristone and reverse mifepristone abortifacient effects

It is not rare for women who have started the medical abortion process to change their minds.[12] Some women decide, under the guidance of a medical professional, to exercise their autonomy by utilizing progesterone to attempt to counteract the effects of mifepristone and thus maintain

their pregnancies after taking mifepristone but before taking misoprostol.[13] In 2021, Aultman et al. examined 19 years of mifepristone adverse event reports (AER) data and reported that 102 of 452 patients (22.6%) with ongoing pregnancy after taking mifepristone regimens changed their minds after learning of the continuing living embryo/fetus and chose to continue their pregnancies.[14] Additionally, a U.K. study found that 10% of women whose pregnancy had continued despite taking both mifepristone and misoprostol opted to continue their pregnancies.[15]

Some women immediately regret initiation of a mifepristone abortion and seek help, hoping to maximize the chances of survival for their embryo/fetus. Since mifepristone's action at the progesterone receptor is known to be reversed in pharmacokinetic studies as well as animal models, and since progesterone has been commonly and safely used in pregnancy for more than seven decades in other progesterone-deficient setting such as IVF and threatened or recurrent pregnancy loss, administration of progesterone to counter a mifepristone-induced progesterone deficiency has biologic plausibility and is clinically reasonable.

Defining the optimal dose of progesterone

For the purpose of determining the efficacy of progesterone to reverse the abortifacient effects of mifepristone, it is necessary to define a control group of women who have taken mifepristone alone but subsequently have a living embryo.

Defining the historic control: the survival rate of embryos with mifepristone alone

Davenport et al. published a systematic review of early mifepristone monotherapy studies in order to calculate a historic control rate of survival of embryos up to 70 days of gestation after ingestion of mifepristone alone without subsequent misoprostol or another prostaglandin.[16] The review found that 18 of the 30 articles investigating mifepristone monotherapy had adequate criteria to determine embryo survival. However, six of these 18 studies were actually duplicates, i.e., identical study arms in different journal articles or early versions of later studies. Thus, twelve unduplicated studies were reviewed, which utilized ultrasound to distinguish between incomplete or missed abortion and embryo survival at the end of the respective study period. The mean of embryo survival rates was 12.6%. Five of the studies of pregnancies up to 49 days in 493 subjects utilized a single 600mg dose and had survival rates of 9.4-17.1%. Three studies with a total of 58 women with pregnancies less than 49 days utilized the current predominant U.S. dose of 200-300mg and documented embryo survival rates of 10-23.3%. There were four studies of 83 women with pregnancies up to 70 days and daily doses of 100-200mg, and with total doses 400-800mg; in three of those four studies, embryo survival was <25%. In the remaining study (Elia, 1985

N=18 patients) the survival rate was 50%; however, in that study, the researchers performed vacuum aspiration only two days after completion of mifepristone, in some of the cases.[17] Therefore, subsequent studies have utilized 25% as the historic expectant management survival rate.[18-20]

This information is summarized in Table 1 below:

TABLE 1: Summary of literature re: surviving embryos after use of mifepristone alone 1985-2024

Mifepristone efficacy study	Cited in scoping or systematic review	Mifepristone dose/day (mg)	Duration (days)	Total dose (mg)	Gestational age limit (days)	Follow up (days)	N	Surviving embryos	Continuing pregnancy	Method used to determine continuing pregnancy
Kovacs 1984, 1985	B, C, D, G	100 x 2/day	4	800	≤ 42	14	8	0	0.0%	Ultrasound
Vervest-Haspels 1985	B, C, D	100-200	4	400-800	35-55	14	35	0	0.0%	Ultrasound
Vervest-Haspels 1985	B, C, D	200	4	800	56-70	14	9	0	0.0%	Ultrasound
Maria (Eur J) 1988	B, C, D, G	600	1	600	≤ 42	7	149	14	9.4%	Ultrasound
Grimes 1988	B, G	600	1	600	≤ 49	14	50	5	10.0%	No explicit method used to determine continuing pregnancy. Complete abortion defined as "vaginal bleeding and declining beta-human chorionic gonadotropin (β-hCG) titer."

										Otherwise, the patient was classified as "failed to abort" and underwent suction curettage.
Kovacs 1984, 1985	B, C, D, G	50 x 2/day	4	400	≤ 42	14	10	1	10.0%	Ultrasound
Sitruk-Ware 1985	B, D	400, 300, 200, 100	4	1000	≤ 49	14	10	1	10.0%	Ultrasound
Swahn 1985	B, D	50	4, 6	200-300	≤ 49	14	10	1	10.0%	Ultrasound
Ylikorkala 1989	B, C, D, G	600	1	600	≤ 43	14	47	5	10.6%	Ultrasound
Kovacs 1984, 1985	B, C, D, G	25 x 2/day	4	200	≤ 42	14	18	2	11.1%	Ultrasound
Maria (J Gyn) 1988	B, C, D, G	600	1	600	≤ 49	7	174	20	11.5%	Ultrasound
Carol 1989	B, C, D, G	600	1	600	33-43	NR	50	6	12.0%	Ultrasound
Swahn 1985	B, D	100	4	400	≤ 49	14	6	1	16.7%	Ultrasound
Somell 1990	B, D, G	600	1	600	≤ 42	7	70	12	17.1%	Ultrasound
Hermann 1982, 1985	B, D	200	4	800	42-56	7	11	2	18.2%	Ultrasound
Maria (J Gyn) 1988	B, C, D, G, S	200	1	200	≤ 49	7	30	7	23.3%	Ultrasound

Cameron 1986	B, C, D, G	150	4	600	≤ 56	14	20	5	25.0%	Ultrasound
Birgerson 1988	B, G	10, 25, 50 x 2/day	7	140, 350, 700	≤ 49	7, 14	153	41	26.8%	No explicit method used to determine continuing pregnancy. If hCG level was <10% of initial value then patient classified as having a complete abortion.
Zheng 1989	B, G	600	1	600	≤ 42	7	204	64	31.4%	Authors defined "persisting pregnancy" as "no expulsion of the conceptus" and "gradual" increase of serum or urine hCG. Authors did not define "gradual."
Swahn 1989	B, G	50 x 2/day	4	400	≤ 49	14	14	5	35.7%	No explicit method used to determine continuing pregnancy. Author classified women with "intact amniotic

										sac" as a "treatment failure" but did not verify the existence of a living embryo.
Zheng 1989	B, G	600	1	600	≤ 49	7	95	44	46.3%	Authors defined "persisting pregnancy" as "no expulsion of the conceptus" and "gradual" increase of serum or urine hCG. Authors did not define "gradual."
Elia 1985	B, D	200	4	800	35-63	6	18	9	50.0%	Ultrasound
APRScience.org										
9 Jan 2024	B=DeBeasi 2023									
	C=Creinin 2019									
	D=Davenport 2017									
	G=Grossman 2015									
	S=Stifani 2023									

Table 1 used with permission from APRScience.org

Defining the efficacy of progesterone to reverse the abortifacient effects of mifepristone

This Practice Guideline will utilize 25% as the historical control for the survival rate of embryos exposed to mifepristone alone, and summarize our review of the published literature when progesterone is given after ingestion of mifepristone. A search of PubMed using the terms "RU38486 and progesterone," "RU486 and progesterone," mifepristone and progesterone," and "abortion pill reversal" yielded 526 articles.

Nine studies met the following criteria for analysis in this practice guideline:

- For in vitro studies, the inclusion criteria were mifepristone administration to cultured trophoblasts followed by progesterone administration and measurement of mifepristone binding activity.
- For animal studies, the inclusion criteria were mifepristone administration to pregnant animals followed by progesterone administration (Yamabe-coadministration of progesterone) and subsequent measurement of live offspring.
- For human studies, the inclusion criteria were mifepristone administration followed by progesterone administration and subsequent measurement of continued living embryo/s at least two weeks following mifepristone administration for women who were not pregnant, or subsequent measurement of progesterone-related biological activity for women who were not pregnant.

There was one in vitro study (1987 Das) that met the inclusion criteria.

There were two animal studies (1989 Yamabe and 2023 Camilleri) that met the inclusion criteria in addition to animal study results cited by the FDA Pharmacology Review.

There were five pregnant human studies (2012 Delgado, 2017 Garrett, 2018 Delgado, 2023 Turner, and 2020 Creinin) which met the inclusion criteria, and an additional human study (2025 Tapia-Pizzaro) on nonpregnant females exploring the effects of progesterone administered after mifepristone. Each of these will be briefly discussed below. In addition, one randomized controlled trial using medoxyprogesterone acetate (Depo-Provera) coadministered at the time of mifepristone ingestion will be discussed.[21]

<u>In vitro cell culture study</u>

1987 Das

In cultured human syncytiotrophoblasts, mifepristone exposure decreased production of human chorionic gonadotropin (hCG), progesterone, and human placental lactogen (hPL). The addition of progesterone to the cultures prevented the mifepristone inhibitory effects on the production of hCG and hPL, signifying antagonization of the mifepristone actions.[22]

Animal studies

FDA Pharmacology Review

In FDA's review of mifepristone pharmacology, the FDA noted the following data:

> **Combination of RU 38 486 and progesterone outcome of gestation in rabbits**
>
> *"This was a combination of two studies in HY* [Hyla breed] *rabbits. Groups of 10 females were given 4* [low dose] *or 8* [high dose=HD] *mg/kg RU486 on day 6 or 7 to day 15 of gestation. Other groups received 100 mg/kg progesterone alone or RU486 + progesterone. RU486 treatment alone resulted in 66% - 100% fetal loss. There was one abnormality (celosomia) in a HD* [high dose] *fetus. In combination with progesterone, RU 486 had no effect on gestation other than a slight reduction in fetal weight in the 4 + 100 mg/kg dose group. Thus the abortifacient activity of RU486 is antagonized by progesterone allowing for normal pregnancy and delivery."*[23]

Thus, the FDA noted in embryotoxicity experiments in rabbit models that progesterone given with mifepristone is protective against the abortifacient activity of mifepristone. It is noteworthy that in the section quoted above, the FDA states clearly: *"Thus, the abortifacient activity of RU486 is antagonized by progesterone allowing for normal pregnancy and delivery."* Those rabbits who received progesterone with mifepristone had no abortions in contrast to those rabbits who received mifepristone alone.

1989 Yamabe

A Japanese rat study early in the development of mifepristone provides basic science evidence of the ability of progesterone to negate the effects of mifepristone. In 1989, Yamabe et al. gave mifepristone alone to a control group of approximately 20 pregnant rats, while the experimental group of approximately 20 pregnant rats was given mifepristone and progesterone concurrently. The rats were then divided into subgroups and sacrificed at 24, 48, 72, and 96 hours. Although the detail of survival by hours is not recorded in the study, the study does report that "in the control group that only received mifepristone, only 33% of the embryos survived. In the experimental group that received mifepristone and progesterone, 100% of the embryos survived. Furthermore, the control group that received mifepristone alone had characteristic changes in the myometrium and ovaries; the experimental group that received both mifepristone and progesterone had no such changes."[24]

2023 Camilleri and Sammut

In 2023, Camilleri and Sammut created a rat model mimicking the human APR experience with progesterone administered subsequently to mifepristone, instead of concurrently[25] as in the Yamabe paper. In addition, the Camilleri paper followed the rats to the end of gestation, in contrast to the short-term follow-up of 24-96 hours in the Yamabe paper. None of the rats

receiving mifepristone alone had continuing pregnancies, while 81% of the group that received mifepristone followed by progesterone had ongoing pregnancies with live fetuses to the end of gestation. In the group of rats receiving mifepristone followed by progesterone, there was evidence that the abortion process had been initiated, since the mifepristone plus progesterone group had initial weight loss similar to the group of rats that received mifepristone only, and uterine bleeding was not statistically different from the rats that received mifepristone only. However, in the mifepristone plus progesterone group, after administration of progesterone, the rats had a recovery of weight gain parallel to the control group of pregnant rats who received neither mifepristone nor progesterone. This study demonstrated that the effects of mifepristone administration occur shortly after administration but can be reversed by subsequent administration of progesterone.

Human Studies

2025 Tapia-Pizarro

Researchers in Chile using RNA sequence technology looked at endometrial samples taken from non-pregnant women who had received luteal phase mifepristone vs. women who received luteal phase mifepristone plus vaginal progesterone. The study determined that 83% of mifepristone-mediated RNA transcription changes in the secretory endometrium of non-pregnant women of normal fertility were reversed when vaginal progesterone was administered. Additionally, the mifepristone effect of delayed maturation of the endometrium was decreased by the progesterone supplementation.[26]

Progesterone administration after mifepristone in human pregnancies

There are five other human studies that point to the effectiveness and safety of progesterone to reverse the abortifacient effects of mifepristone: three are case series or retrospective cohort studies; one is a single-arm prospective study; and one[27] is a prospective, randomized placebo-controlled, trial.[28] These studies are summarized in the table below.[29] Note that the Delgado 2018 study is a single study but is listed in the table as Delgado 2018 a-h, since these eight arms used different progesterone doses and routes of administration.

TABLE 2: Research supporting APR in human pregnancies

Study	Mifepristone dose (mg)	Delivery regimen. Progesterone dose (mg)	N	Surviving embryos	Surviving pregnancy rate (%)	Type of study
Delgado 2018a	NR	Vaginal suppository. Dose not reported.	34	11	32%	Observational case series

Delgado 2018b	NR	Vaginal oral capsules. Variety of doses, not reported.	156	61	39%	Observational case series
Delgado 2018c	NR	IM: 200mg x 1 injection.	50	24	48%	Observational case series
Delgado 2018d	NR	IM 200mg x 2-5 injections.	36	21	58%	Observational case series
B, c, Delgado 2012	NR	IM and/or oral: 200mg (1 or 2 per day), duration 9 weeks to 5 months.	6	4	67%	Observational case series.
Garratt 2017	NR	Vaginal: 400mg (2 per day) for 3 days, 400mg at night for 6 days, 200mg at night for 6 days.	3	2	67%	Observational case series
Delgado 2018e	NR	Oral: 2 x 200mg capsules (2 per day) for 3 days, 2 x 200mg capsules daily until end 1st trimester.	31	21	68%	Observational case series
Creinin 2020	Oral: 200mg	Oral: 2 x 200mg capsules (2 per day) for 3 days, 2 x 200mg capsules daily until study exit visit	5	4	80%	Randomized controlled trial
Turner 2023	NR	Oral: 4 x 100mg capsules (2 x day) for 3 days, 4 x 100mg capsules at night for 16 days.	6	5	83%	Single-arm clinical trial
Delgado 2018f	NR	IM: 200mg x 11+ injections	19	17	89%	Observational case series
Delgado 2018g	NR	IM 200mg x 9-10 injections	10	9	90%	Observational case series
Delgado 2018h	NR	IM: 200mg x 6-8 injections	9	9	100%	Observational case series
APRScience.org						
10 Jan 2024						
NR = Not reported IM = Intramuscular						

Table 2 used with permission from APRScience.org

Each of the studies in the table is briefly reviewed below:

1. The 2012 Delgado and Davenport study[30] was a case series of seven women who attempted to reverse their mifepristone abortions using progesterone. Of the initial seven, one was lost to follow-up. Of the remaining six, four of the women delivered healthy, term babies. Two completed their abortions, despite taking progesterone.
2. The 2017 case series by Turner and Garratt[31] detailed three women at 6-7 weeks of gestation who attempted reversal of their mifepristone abortions. Two of the three delivered healthy babies at term
3. The 2018 study by Delgado et al.[32] was the largest retrospective review to date. Of the 754 screened who called the APR Hotline and were screened, 207 (27%) were excluded. Of the 207 excluded, 38 were excluded because they initiated progesterone more than 72 hours after the ingestion of mifepristone, 57 were excluded because they chose to complete their abortions surgically or by taking mifepristone again or by taking misoprostol, and 112 (15% of the 754 screened) were lost to follow-up before 20 weeks. Of note, more recent studies have used embryo or fetus survival at two weeks after initiation of progesterone therapy as the primary endpoint since mifepristone is unlikely to have an effect two weeks after ingestion.

   "After exclusions, there were 547 patients with analyzable outcomes who underwent progesterone therapy. There were 257 births (47%) Another four were pregnant with viable fetuses but were lost to follow-up after 20 weeks gestation (0.7%). The overall rate of reversal of mifepristone was 48%." Thus 48% (N=261) had survival of the fetus to at least 20 weeks. This was statistically significant more than the 25% historic control ($p<0.001$) as derived from the upper limits of embryo survival in the Davenport meta-analysis.

   Of note, a subgroup of 31 women received a high-dose oral protocol consisting of progesterone 400mg twice a day for three days, followed by 400mg at night until the end of the first trimester. That subgroup had a reversal rate of 68% (21/31). Another subgroup that received at least one 200mg dose of intramuscular progesterone had a reversal rate of 64% (80/125).

   The preterm birth rate in the entire cohort that was followed to delivery was 2.7% (7/257), which compares favorably with the U.S. preterm birth rate of 10%.[33] The birth defect rate was 2.7% (7/257), compared to the U.S. rate of about 4% [38].

4. In 2023, Turner and Garratt published a small, prospective, single-arm study conducted in Australia.[34] Six patients with gestational age 40-70 days were

enrolled over a one-year period. The study utilized the high-dose oral protocol from the Delgado 2018 study. Five of the six reached the primary endpoint of fetal survival two weeks post initiation of progesterone therapy. The other had a completed abortion.

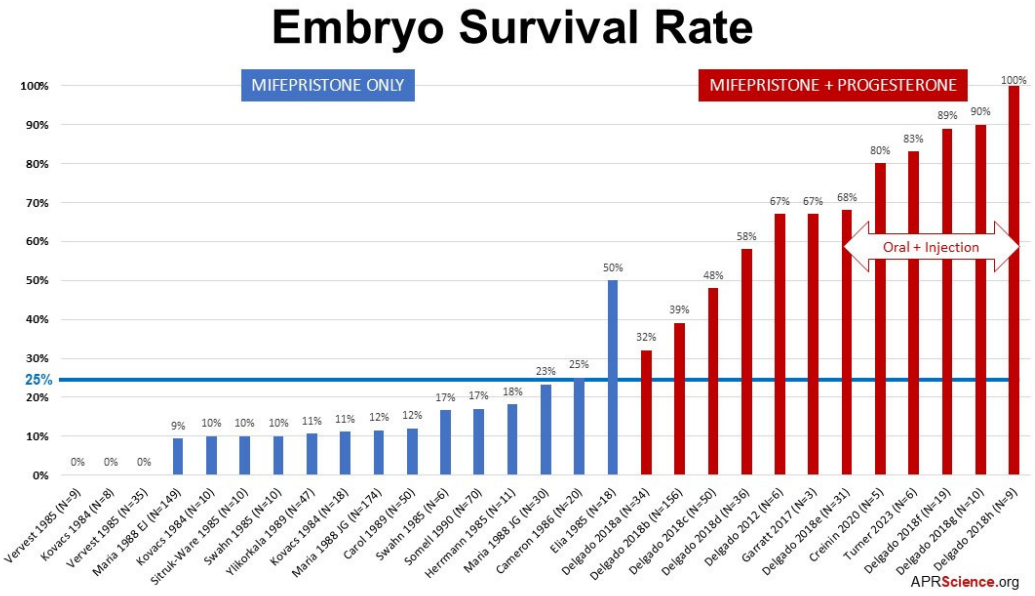
5. Creinin et al. conducted the only prospective, randomized, placebo-controlled trial that was designed to evaluate the high-dose oral protocol found in the 2018 Delgado et al. study compared to placebo.[35] A pretrial power analysis, utilizing Davenport's historic control rate of 25% survival with expectant management and the 68% reversal rate from the high-dose oral protocol in the 2018 Delgado et al. study, predicted that a total of 40 patients would be needed, 20 in each arm. The study was terminated after 12 patients were enrolled, and two withdrew, leaving ten patients to be evaluated: five patients in the mifepristone plus placebo group (control) and five patients in the mifepristone plus progesterone group (treatment). The study was terminated for safety reasons before statistical significance was reached; three women were labeled as having a hemorrhage, one in the mifepristone plus progesterone group and two in the mifepristone plus placebo group. The two hemorrhages in the mifepristone plus placebo group necessitated emergency room treatment, including emergent surgical completions, and one was transfused one unit of packed red blood cells. The one hemorrhage in the mifepristone plus progesterone group was self-limiting. She went to the emergency room but was found to have completed her abortion and did not require any intervention. So, this was not an actual safety concern.

   In the mifepristone plus placebo group, two of five women had ongoing pregnancies, whereas in the mifepristone plus progesterone group, four of five women had ongoing pregnancies. Although this study did not reach statistical significance, the 80% success rate for women treated with progesterone suggests increased survival when progesterone is administered after mifepristone, and there were no actual safety concerns in the group treated with progesterone. The safety concerns about mifepristone reversal with progesterone that have been raised by the authors are unsupported by their findings, since the only actual complications were in the placebo group who did not receive progesterone. Although one women in the progesterone group presented to the ED by ambulance and was evaluated in an emergency room, she needed "no intervention."

   The first author of the Creinin study led the ACOG committee which made recommendations regarding APR, ignoring his own findings of suggested efficacy of progesterone. His own

research as well as the growing body of literature regarding progesterone administration after mifepristone should have led ACOG to conclude at least that further studies are needed.

FIGURE 1: Embryo survival rate display of Table 2



Raymond et al.[36]

In addition to human studies utilizing progesterone after mifepristone but before misoprostol ingestion, there is an additional randomized controlled trial by Raymond et al. comparing efficacy of Depo-Provera administration at the time of mifepristone ingestion (Quickstart) vs. later (Afterstart). The authors state: *"Ongoing pregnancy after initial abortion treatment was significantly more common in the Quickstart group (8/220 [3.6%]) than in the Afterstart group (2/226 [0.9%]); the difference was 2.7% (90% confidence interval 0.4-5.6%)."* This study gives additional strong evidence that even a weaker progesterone analog can decrease the ability of mifepristone to effect fetal demise when administered simultaneously with mifepristone.

Summary

The current medical literature supports the safety and effectiveness of progesterone used to reverse the effects of mifepristone by women who choose to exercise their autonomy and attempt to reverse the abortifacient effects of mifepristone after taking mifepristone but before taking misoprostol. Rates of maintenance of pregnancy range from 48 to 83%. Serious adverse reactions appear to be low in women who take progesterone after ingesting mifepristone.

Safety of progesterone in pregnancy

The literature suggests that mifepristone is not teratogenic. Two large retrospective studies reported birth defect rates lower than the U.S. national average of 4%.[37] The American College of Obstetricians and Gynecologists' Practice Bulletin 225 (2020) reports that mifepristone is not associated with teratogenicity.[38]

Progesterone has a seven-decade safety record for use in pregnancy.[39] The Society of Assisted Reproductive Technology states that no long-term risks have been identified when progesterone is used in pregnancy.[40] The FDA has granted progesterone a Category B rating in pregnancy (generally considered safe to use, e.g. prenatal vitamins).[41] Previous studies utilizing progesterone therapy for the analogous condition of threatened spontaneous abortion have not discovered any short-term safety concerns.[42]

Future research

Randomized controlled trials are needed to further explore the effectiveness and safety of progesterone to reverse the effects of mifepristone. The future trials should include the following:

1. Active comparator trials, comparing different routes of administration and dosing of progesterone
2. Trials exploring the efficacy of different timing of administration of progesterone within the 72 hour window after administration of mifepristone.
3. Trials stratifying efficacy results by gestational age at the time of mifepristone administration, including the criteria used to evaluate gestational age prior to mifepristone ingestion.
4. Longitudinal studies examining rates of obstetrical complications of pregnancies exposed to mifepristone and progesterone, including preeclampsia, preterm birth, placental abruption, fetal growth restriction, etc.
5. Studies examining women's experience with and attitude toward the abortion pill reversal process.

Utilizing a placebo or expectant management group would be unethical, since embryo survival rates were low in the expectant management groups in the early mifepristone monotherapy trials, and subsequent research indicates the efficacy of progesterone in increasing the embryo survival rate. It is unethical to randomize women wanting to maximize their chances that their embryo will survive to an expectant management or placebo group, because treatment with progesterone is benign, and studies show increased embryo survival in women treated with progesterone.

Clinical Questions and Answers

Q *When should women who are seeking to stop the effects of mifepristone start progesterone?*

Women seeking to stop the effects of mifepristone and continue their pregnancies should be started on progesterone as soon as possible (within 72 hours) and should not take misoprostol. The available evidence suggests that high-dose oral protocols and intramuscular progesterone have the highest efficacy rates. Ongoing emotional and clinical support by the prescribing practitioner, a social worker, and other counselors is recommended.

Q *What are the current dosage regimens suggested?*

Based on the currently available literature, as well as the experience of researchers and clinicians worldwide utilizing micronized progesterone administration after mifepristone, the optimal dosing appears to by 600mg PO twice a day for two days, followed by 400mg PO twice a day for two days, followed by 400mg PO at night for two weeks or until the end of the first trimester (whichever is longer), given with food. After that, taper progesterone over two weeks. Suggested IM dosing regimen is based on small numbers from the 2019 Delgado study: progesterone 200mg intramuscular as soon as possible and continued at a dose of 200mg intramuscular once a day on days two and three, then every other day for a total of seven injections. Some clinicians may consider continuing intramuscular treatment longer since this recommendation is based on relatively small numbers.[43]

Q *Does dosage vary with gestational age?*

Later gestational ages are associated with better embryo or fetal survival.[43] There is no current evidence that a change in progesterone dosage is needed based on gestational age.

Q *How long should progesterone administration be continued?*

Since mifepristone blockade of the progesterone receptors in the corpus luteum decreases progesterone production by the corpus luteum, and mifepristone half-life is up to 25 hours, and since the metabolites of mifepristone are also biologically active with a long half-life, then it is reasonable to expect that there will be some delay in corpus luteal progesterone production to maintain the pregnancy naturally, and supplemental progesterone support will be necessary. Similarly, mifepristone blocks progesterone production in the placenta. Thus, progesterone support throughout the first trimester is prudent, and expert opinion is that progesterone supplementation should be continued for two weeks or until the end of the first trimester, whichever is longer. After that, taper progesterone over two weeks.

Q *When should an ultrasound be obtained in the course of treatment with progesterone after mifepristone?*

Ultrasonography should be performed as soon as possible to confirm intrauterine location as well as viability. Progesterone treatment should not be delayed if an ultrasound cannot be obtained immediately prior to initiation of treatment. A delay in obtaining an ultrasound should not lead to a delay in the initiation of progesterone therapy, as long as there is no clinical suspicion of ectopic pregnancy or other complication that would require the patient to seek emergency department evaluation. Close follow-up with serial ultrasounds, as medically indicated, is important to confirm the viability of the ongoing pregnancy.

Q *What happens if a woman begins to bleed during the course of treatment with progesterone?*

According to the clinical experience of physicians providing progesterone treatment after mifepristone ingestion, some bleeding is common and, in and of itself, should not lead to cessation of progesterone therapy. Ultrasound confirmation of a continuing living embryo should be obtained as soon as clinically feasible, just as is done in situations of threatened spontaneous abortion, in order to determine continued fetal viability for continuation of progesterone therapy.

Summary of Recommendations and Conclusion

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

1. Administration of progesterone is safe in pregnancy.

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

1. Administration of progesterone is safe and effective for minimizing and possibly eliminating the abortifacient effects of mifepristone.
2. Progesterone therapy should be initiated as soon as possible, within 72 hours after mifepristone use and without taking misoprostol, in women who have a change of intention and want to continue their pregnancy.

The following recommendations are based primarily on consensus and expert opinion (Level C):

1. Progesterone should be given orally: 600mg twice a day for two days, followed by 400mg twice a day for two days, followed by 400mg at night for two weeks or until the end of the first trimester, whichever is longer.
2. After two weeks or the end of the first trimester, whichever is longer, expert consensus suggests tapering progesterone over two weeks.

Conclusion

Based on Level B evidence, the use of progesterone to reverse the abortifacient effects of mifepristone after the ingestion of mifepristone but not misoprostol is safe and effective. Women who seek reversal of their initiated mifepristone abortions should be offered progesterone therapy after an informed consent discussion by clinicians who are treating them.

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