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AAPLOG American Association of Pro-life Obstetricians & Gynecologists

AAPLOG Statement on Ohio House Bill 378
Abortion Pill Reversal Information Act
SUPPORT
Presented to the House Health Committee

March 7, 2022
Written Testimony, Donna J. Harrison M.D. Chief Executive Officer

Thank you, Chairman Lipps, Vice-Chair Holmes, and Ranking Member Liston for allowing the American Association of Pro-Life Obstetricians and Gynecologists to present this letter of support for House Bill 378. I am Dr. Donna Harrison, a Board-Certified Obstetrician and Gynecologist and Chief Executive Officer of the American Association of Pro-Life Obstetricians and Gynecologists. As CEO of AAPLOG I speak on behalf of our over 6000 reproductive health professionals, supporting the Abortion Pill Reversal Act.

There is scientific support for effective progesterone administration after mifepristone, which is otherwise known as abortion reversal.

Mifepristone (a/k/a RU-486 or RU-38486) is a drug that blocks the action of a natural pregnancy hormone called progesterone by binding with a woman's progesterone receptors on the nuclear membranes of cells in the uterus, ovary, brain, breast, and immune system. With mifepristone blocking the connection of progesterone with progesterone receptors in the uterus of a pregnant woman, the mother's cells in the placenta stop functioning, which in turn eventually leads to the death of the embryo through, in essence, starvation.[1] Embryonic death is not inevitable, however.

Mifepristone reversal efforts are patterned after a known biological phenomenon which is a basic principle in biochemistry. It is understood, generally, 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."[2] This basic medical principle is used routinely in medicine. When the drug methotrexate is given to kill cancer cells, for example, it can also kill non-cancer cells. In order to "rescue" those non-cancer cells, the drug leucovorin (also known as the vitamin "folinic acid") is given to out-compete the inhibitor, which is methotrexate.[3]

Dr. Harvey Kliman, the director of the reproductive and placental research unit at the Yale School of Medicine who is admittedly pro abortion, told the *New York Times* that mifepristone reversal "makes

[1] Baulieu EE, Segal SJ. The Antiprogestin Steroid RU486 and Human Fertility Control. Proceedings of a Conference on the Antiprogestational Compound RU486. Oct 23-25. Bellagio Italy. Published in the series Reproductive Biology 1984 Sheldon Segal Series Editor 1985 Plenum PresS.
[2] Pelley, John W. in Elsevier's Integrated Review Biochemistry (Second Edition), 2012 p 33-34
[3] *Drug Info: Folinic Acid*, Chemocare.Com, available at: http://chemocare.com/chemotherapy/drug-info/folinic-acid.aspx. [4] Ruth Graham, *A New Front in the War Over Reproductive Rights*: *'Abortion-Pill Reversal*,' The New York Times Magazine (July 18, 2017).

biological sense" and is "totally feasible."[4] Indeed, Dr. Kliman went so far as to say that "if one of his daughters came to him and said she had somehow accidentally taken mifepristone during

pregnancy … he would tell her to take 200 milligrams of progesterone three times a day for several days, just long enough for the mifepristone to leave her system: 'I bet you it would work.'"[5]

It is known that mifepristone not only blocks progesterone receptors but also blocks natural stress hormones (glucocorticoids) by binding with glucocorticoid receptors. Both the manufacturer studies[4] as well as National Institutes of Health (NIH) studies demonstrated that mifepristone blockage of glucocorticoid receptors "can be reversed" by the administration of additional glucocorticoids.[5][6]

This reversibility is also true of the progesterone receptor binding by mifepristone. The developer of the drug, Baulieu (at Figure 3 p 91[8]) documented the rate at which RU486 could be removed from the progesterone receptor, in the presence of high concentrations of progesterone. This pharmacokinetic study clearly shows 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.

A well-designed study in an animal model demonstrated directly that mifepristone blockage of progesterone receptors can be overcome by the administration of additional natural progesterone.[7] That study 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. Every member of the no-drug group delivered live offspring. Only 33.3% of the mifepristone-only group delivered live offspring. In the third group, which was given mifepristone and then progesterone, 100% delivered live offspring.[8]

Natural progesterone has routinely been given to women during pregnancy for over 50 years. For instance, progesterone administered by various routes is the standard of care for women who become pregnant by in-vitro fertilization (IVF). As such, the IVF industry has looked carefully to see if there are any indications of an increased risk from natural progesterone and have found none.[9] In addition, in

[4] Baulieu EE, Segal SJ. The Antiprogestin Steroid RU486 and Human Fertility Control. Proceedings of a Conference on the Antiprogestational Compound RU486. Oct 23-25. Bellagio, Italy. Published in the series Reproductive Biology 1984 Sheldon Segal Series Editor 1985 Plenum Press.

[5] Webster JI, Sternberg EM "Review: Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids andglucocorticoid receptors in toxic sequenlae of exposure to bacterial and viral products" Journal of Endocrinology (2004) 181 207-221; Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH), *Emerging Clostridial Disease Workshop*, May 11, 2006 (revised June 22, 2006), at page 23.

[6] Baulieu EE, Segal SJ. The Antiprogestin Steroid RU486 and Human Fertility Control. Proceedings of a Conference on the Antiprogestational Compound RU486. Oct 23-25. Bellagio, Italy. Published in the series Reproductive Biology 1984 Sheldon Segal Series Editor 1985 Plenum Press.

[7] Yamabe S, et al. The effect of RU486 and progesterone on luteal function during pregnancy. Nihon Naibunpi Gakkai Zasshi. 1989 May 20;65(5):497-511. Attached as Exhibit B.

[8] Yamabe S, et al. The effect of RU486 and progesterone on luteal function during pregnancy. Nihon Naibunpi Gakkai Zasshi. 1989 May 20;65(5):497-511.

[9] *Progesterone*: *Risks and Benefits,* Society for Assisted Reproductive Technology, available at: https://www.sart.org/patients/a-patients-guide-to-assisted-reproductive-technology/stimulation/progesterone/.

women who have progesterone deficiencies in early pregnancy for various reasons, it is common to use natural progesterone to supplement the deficiency.[10]

This extensive usage has allowed us to know, for decades now, that using natural progesterone in pregnancy is safe. It is important in this discussion to understand that progestins, (chemicals which are like natural progesterone but which have other effects) have been associated with hypospadias. Critics of APR use this misleading argument, but this effect has not ever been seen with natural progesterones.

[5] Ruth Graham, *A New Front in the War Over Reproductive Rights*: *'Abortion-Pill Reversal,'* The New York Times Magazine (July 18, 2017).

The argument is misleading because progestins are NOT natural progesterone. Rather, they are chemicals which are similar to progesterone in some ways, but contain actions which progesterone does not have.[11] In the end, there is simply no evidence that natural progesterone has ever, after decades of its widespread use in pregnancy, been shown to increase the risk of birth defects.

There are three studies in humans which indicate that natural progesterone supplementation may increase the chances of survival of their baby after taking mifepristone but before taking misoprostol. There was a small peer-reviewed case series out of Australia (Garratt) that was published in 2017 in the *European Journal of Contraceptive and Reproductive Health Care*. Though small, that case series documented similar results to Dr. Delgado, with two out of three women who attempted reversal with progesterone achieving success with live, healthy births.[14]

There are also now two research studies in women in the U.S. who used abortion pill reversal to try to give their babies the best chance to live. The small 2012[12] case series report on a total of six women who had used progesterone after mifepristone. Four of those women went on to complete delivery of live born infants. No malformations were observed in the children.

The 2018.[13] case series was much larger and more substantial. In it, Dr. Delgado and his coauthors analyzed the records of 547 women who took progesterone after mifepristone in an attempt to reverse the mifepristone effects. Of those 547 women, they found an overall embryo survival rate, at 20 weeks gestation of 48%. The authors then analyzed the survival rates based on how and in what doses the progesterone was given, and they found a remarkable 68% survival rate if the progesterone was taken by mouth or by intramuscular injection.

This 2018 study was not "uncontrolled" as some critics would claim. Dr. Delgado and his coauthors used a historical control to determine if the 68% success rate was any different from what would have happened to women if they had not taken progesterone. That historical control was derived from the systematic review by Davenport in 2017.[14] In short, Davenport reviewed all the studies ever published on the outcomes of women who had taken mifepristone alone, but not misoprostol. She found fetus survival rates using total doses of 200-300 mg of mifepristone ranged from 10% to 23.3%. (The current FDA-

[10] American Society for Rep. Medicine. Practice Committee Opinion: Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. Fert. Steril. (2008). 89 (4).

[11] *Progesterone*: *Risks and Benefits,* Society for Assisted Reproductive Technology, available at: https://www.sart.org/patients/a-patients-guide-to-assisted-reproductive-technology/stimulation/progesterone/.

[14]Garratt D, Turner J.V. Progesterone for preventing pregnancy termination after initiation of medical abortion with mifepristone. European Journal of Contraceptive and Reproductive Health Care. 2017 Dec;22(6):472-475.

[12] Delgado G, Davenport M. Progesterone use to reverse the effects of mifepristone. Annals of Pharmacotherapy. 46 2012 Dec;46(12):e36.

[13] Delgado G, et al. A case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone. Issues in Law and Medicine (2018) 33(1): 21- 31.

[14] Davenport ML, et al., Embryo survival after mifepristone: a systematic review of the literature. Issues in Law and Medicine (2017) 32(1):p 3-18.

approved dosage is 200 mg.) In other words, if a woman decides not to take the second pill, and leave it at that, there is a 10 to 23 percent chance the baby will survive, according to the published peer reviewed literature. Delgado and his co-authors chose to use a historical control comparator number (25% survival) which was higher than Davenport's highest number (23.3%). Even with this higher estimate, there was a notable difference between the outcome of women who did not receive progesterone in the historical control (25%) and the outcome of women who received progesterone by the best protocols (68%).

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.

Dr. Delgado and his co-authors also analyzed safety. For example, they looked at the birth defect rate among the 257 women who had successful live births after reversals and followed up after their delivery. They found no increase of birth defects when compared to the general population of births, 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.[15] [16] Similarly, Dr. Delgado found that the preterm delivery rate was 2.7%, a number much lower than the 10% of preterm births in the general population.

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 of progesterone allowing numerous women to save their babies, it is scientifically proper to use this medication in women who are desperate to save their pregnancies after regretting the start of their mifepristone abortion attempt. The use of natural progesterone to counter the effects of ingested mifepristone is logical, medically speaking, and founded on basic principles of biochemistry, animal studies, and analysis of human experience.

Informed consent prior to any procedure requires a disclosure of the procedure, the risks, *and* the alternatives. It is clear from the thousands of calls from women to the abortion pill reversal hotline that some women *do* change their minds about having an abortion after they take mifepristone. And, as demonstrated above, reversal is scientifically plausible and backed by scientific evidence. Thus, since time is of the essence in reversing the effects of mifepristone, it is reasonable to believe that giving women information about the possibility of taking progesterone before and soon after taking mifepristone is necessary so they can be truly assured that they are making a fully informed choice. Women should be informed of this potentially life-saving treatment, especially given the fact that a reversal attempt only involves the administration of a known natural hormone that has been safely used in the infertility industry for over 50 years. Women who are truly sure of their decision to abort will not be harmed by information about what to do if regret arises. And requiring informed consent to include the possibility of reversal will give women who are unsure, or who change their minds, enhanced reproductive options.

[15] Bernard N, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG. 2013 Apr;120(5):568-74. Epub 2013 Jan 24.

[16] Sitruk-Ware A, Davey A. Fetal malformation and failed medical termination of pregnancy. Lancet (1988) 352: p323.

The American Association of Pro-Life Obstetricians and Gynecologists urges you to pass HB 378.

Respectfully submitted,

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Life. It's why we are here.

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