IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

Planned Parenthood Arizona, Inc.; Eric Reuss, M.D., M.P.H.; Paul A. Isaacson, M.D., Desert Star Family Planning, LLC; DeShawn Taylor, M.D.,

Plaintiffs,

v.

Mark Brnovich, Arizona Attorney General, in his official capacity; Cara M. Christ, Director of the Arizona Department of Health Services, in her official capacity; Patricia E. McSorley, Executive Director of the Arizona Medical Board, in her official capacity; Richard T. Perry, M.D. Medical Board Chair, in his official capacity; James Gillard M.D., Medical Board Vice Chair, in his official capacity; Jodi A. Bain, Medical Board Member, in her official capacity; Marc D. Berg, M.D., Medical Board Member, in his official capacity; Donna Brister, Medical Board Member, in her official capacity; R. Screven Farmer, M.D., Medical Board Member, in his official capacity; Gary R. Figge, M.D. Medical Board Member, in his official capacity; Robert E. Fromm, M.D., Medical Board Member, in his official capacity; Paul S. Gerding, Medical Board Member, in his official capacity; Lois

Case No.: 2:15-CV-01022-SPL

LODGED: PROPOSED BRIEF OF *AMICI CURIAE* AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS, PHYSICIANS FOR LIFE, NATIONAL ASSOCIATION OF PRO-LIFE NURSES, AND NATIONAL ASSOCIATION OF CATHOLIC NURSES-U.S.A. IN SUPPORT OF DEFENDANTS AND DENIAL OF PRELIMINARY INJUNCTION

Krahn, M.D. Medical Board Member, in her official capacity; Edward G. Paul, M.D. Medical Board Member, in his official capacity; Wanda J. Salter, Medical Board Member, in her official capacity; Jenna Jones, Executive Director of the Arizona Board of Osteopathic Examiners in Medicine and Surgery, in her official capacity; Scott Steingard, D.O., Board of Osteopathic Examiners in Medicine and Surgery President, in his official capacity; Douglas Cunningham, D.O., Board of Osteopathic Examiners in Medicine and Surgery Vice President, in his official capacity; Gary Erbstoesser, D.O., Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Jerry G. Landau, Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Martin B. Reiss, D.O. Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Lew Riggs, Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Vas Sabeeh, D.O., Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity,

Defendants.

Mailee R. Smith*
AMERICANS UNITED FOR LIFE
655 15th St. NW, Suite 410
Washington, D.C. 20005
Mailee.Smith@AUL.org
(202) 289-1478
State Bar No. 6280167 (Illinois)

Attorney for Amici Curiae American Association of Pro-Life Obstetricians & Gynecologists, Physicians for Life, National Association of Pro-Life Nurses, and National Association of Catholic Nurses-U.S.A.

*Admitted pro hac vice

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

Planned Parenthood Arizona, Inc.; Eric Reuss, M.D., M.P.H.; Paul A. Isaacson, M.D., Desert Star Family Planning, LLC; DeShawn Taylor, M.D.,

Plaintiffs,

v.

Mark Brnovich, Arizona Attorney General, in his official capacity; Cara M. Christ, Director of the Arizona Department of Health Services, in her official capacity; Patricia E. McSorley, Executive Director of the Arizona Medical Board, in her official capacity; Richard T. Perry, M.D. Medical Board Chair, in his official capacity; James Gillard M.D., Medical Board Vice Chair, in his official capacity; Jodi A. Bain, Medical Board Member, in her official capacity; Marc D. Berg, M.D., Medical Board Member, in his official capacity; Donna Brister, Medical Board Member, in her official capacity; R.

Case No.: 2:15-CV-01022-SPL

BRIEF OF *AMICI CURIAE* AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS, PHYSICIANS FOR LIFE, NATIONAL ASSOCIATION OF PRO-LIFE NURSES, AND NATIONAL ASSOCIATION OF CATHOLIC NURSES-U.S.A. IN SUPPORT OF DEFENDANTS AND DENIAL OF PRELIMINARY INJUNCTION

Screven Farmer, M.D., Medical Board Member, in his official capacity; Gary R. Figge, M.D. Medical Board Member, in his official capacity; Robert E. Fromm, M.D., Medical Board Member, in his official capacity; Paul S. Gerding, Medical Board Member, in his official capacity; Lois Krahn, M.D. Medical Board Member, in her official capacity; Edward G. Paul, M.D. Medical Board Member, in his official capacity; Wanda J. Salter, Medical Board Member, in her official capacity; Jenna Jones, Executive Director of the Arizona Board of Osteopathic Examiners in Medicine and Surgery, in her official capacity; Scott Steingard, D.O., Board of Osteopathic Examiners in Medicine and Surgery President, in his official capacity; Douglas Cunningham, D.O., Board of Osteopathic Examiners in Medicine and Surgery Vice President, in his official capacity; Gary Erbstoesser, D.O., Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Jerry G. Landau, Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Martin B. Reiss, D.O. Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Lew Riggs, Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity; Vas Sabeeh, D.O., Board of Osteopathic Examiners in Medicine and Surgery Member, in his official capacity,

Defendants.

TABLE OF CONTENTS

TABLE OF AUTHORITIES iv

STATEMENT OF INTEREST OF *AMICI CURIAE* 1

ARGUMENT 2

I. The mechanism of action of mifepristone is undisputed—it blocks progesterone—and it is reversible 3

II. Using progesterone in an attempt to reverse the effects of mifepristone is safe and fulfills FDA guidelines 7

III. Supported by medical data, the Arizona requirement ensures that women are provided all relevant data before making an abortion decision and it comports with clear Supreme Court precedent 10

CONCLUSION 17

TABLE OF AUTHORITIES

CASES

Gonzales v. Carhart, 550 U.S. 124 (2007). 11, 13, 16, 17

Planned Parenthood v. Casey, 505 U.S. 833 (1992). 10, 11, 12, 13, 15, 17

Roe v. Wade, 410 U.S. 113 (1973). 10

FEDERAL STATUTORY AUTHORITY

21 C.F.R. § 50.24. 9

21 C.F.R. § 314.520. 10

STATE STATUTORY AUTHORITY

ARIZ. REV. STAT. § 36-2153(1). 17

ARIZ. REV. STAT. § 36-2153(2). 17

ARIZ. REV. STAT. § 36-2153(2)(f). 17

MEDICAL RESOURCES

Alderson et al., *Luteal Phase Dysfunction* (updated June 14, 2013), available at http://emedicine.medscape.com/article/254934-overview. 8

Baulieu & Segal, *The AntiProgestin Steroid RU 486 and Human Fertility Control*, Conference on the Antiprogestational Compound RU 486 (Bellagio, Italy 1984), reprinted in REPROD. BIO. 4

Chen et al., *Baicalin can attenuate the inhibitory effects of mifepristone on Wnt pathway during peri-implantation period in mice*, J. STEROID BIOCHEM. MOL. BIOL. 149:11 (May 2015). 5

Creinin & Danielsson, *Medical abortion in early pregnancy*, in Paul et al., eds., MANAGEMENT OF UNINTENDED AND ABNORMAL PREGNANCY: COMPREHENSIVE ABORTION CARE (2009). 3

Csapo et al., *Effects of luteectomy and progesterone replacement therapy in early pregnant patients*, AMER. J. OBSTET. GYNECOL. 115(6):759 (May 1973). 8

Csapo & Erdos, *Prevention of the abortifacient action of antiprogesterone serum by progesterone*, AMER. J. OBSTET. GYNECOL. 128(2):212 (May 15, 1977). 5

Food and Drug Administration, *"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet* (last updated June 25, 2014), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm). 8, 9

Food and Drug Administration, Sept. 2000 Approval Letter, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf. 10

Greb, *Disparate actions of mifepristone (RU 486) on glands and stroma in the primate endometrium*, HUMAN REPROD. 14(1):198 (Jan. 1999). 5

Leucovorin Labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/anda/99/40262_Leucovorin%20Calcium_Prntlbl.pdf. 6

Lobaccaro-Henri, *Effect of the progesterone antagonist RU486 on human myometrial spontaneous contractility and PGI2 release*, PROSTAGLANDINS 44(5):443 (Nov. 1992). 5

Mauro et al., *Effect of Antiprogesterone RU486 on VEGF Expression and Blood Vessel Remodeling on Ovarian Follicles before Ovulation* (Apr. 22, 2014). 3

Mifeprex Labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf. 3

Morrow et al., *Glucocorticoids alter fever and IL-6 responses to psychological stress and to lipopolysaccharide*, AMER. J. PHYSIOL. 264(5 Pt 2):R1010-6 (May 1993). 6

Norwitz et al., *Progesterone Supplementation and the Prevention of Preterm Birth*, REV. OBSTET. GYNECOL. 4(2):60 (2011). 7

Paul et al., eds., MANAGEMENT OF UNINTENDED AND ABNORMAL PREGNANCY: COMPREHENSIVE ABORTION CARE (2009). 3

Rode et al., *Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies*, ACTA. OBSTET. GYNECOL. SCAND. 88(11):1180 (2009). 8

Sofuoglu et al., *Vaginal micronized progesterone capsule versus vaginal progesterone gel for lutheal support in normoresponder IVF/ICSI-ET cycles*, PAK. J. MED. SCI. 31(2):314 (Mar.-Apr. 2015). 3, 6

Szekeres-Bartho et al., *A progesterone-induced blocking factor corrects high resorption rates in mice treated with antiprogesterone*, AMER. J. OBSTET. GYNECOL. 163(4 Pt 1):1320 (Oct. 1990). 5

van der Linden et al., *Luteal phase support for assisted reproduction cycles*, COCHRANE DATABASE SYST. REV. (10):CD009154 (Oct. 5, 2011). 8

World Health Organization, *Prenatal administration of progesterone for preventing preterm birth in women considered at risk of preterm birth* (2009), available at http://apps.who.int/rhl/pregnancy_childbirth/complications/preterm_birth/cd004947_gonzalezr_com/en/. 7

STATEMENT OF INTEREST OF *AMICI CURIAE*

Amici American Association of Pro-Life Obstetricians & Gynecologists (AAPLOG), Physicians for Life, National Association of Pro-Life Nurses, and National Association of Catholic Nurses-U.S.A. are national medical associations that support Arizona's newly enacted provision in SB 1318, amending the State's informed consent statute to include information on the potential to reverse a "medical abortion" through safe treatment with progesterone [hereinafter "Arizona regulation"].

Significantly, *Amicus* AAPLOG held the title of "special interest group" within the American College of Obstetricians & Gynecologists (ACOG) for 40 years, from 1973 until 2013, until ACOG discontinued the designation of "special interest group." At the time, ACOG recognized AAPLOG as one of its largest special interest groups. AAPLOG has endorsed the safe use of progesterone to potentially reverse the abortifacient effects of mifepristone.

Amici present this brief as a counter to that of Plaintiffs' *amici* [hereinafter "ACOG" or "ACOG Brief," docket entry 48], demonstrating that there is differing opinion in the medical community on the reversibility of "medical abortion." Contrary to the claims in ACOG's brief, *Amici* demonstrate herein that the reversal process is actually based on well-established medical science, is safe for women, and falls within the guidelines of the Food & Drug Administration (FDA). Given the "wide discretion" the Supreme Court requires for States when there is medical disagreement on the effect of an abortion regulation, along with its repeated affirmation of informed consent statutes, it is clear that the claims of Plaintiffs and their *amici* must fail.

Amici urge this Court to deny Plaintiffs' request for preliminary injunction.

ARGUMENT

"Medical abortion" involves the provision of two drugs: mifepristone ("RU-486"), which is administered first and starves the embryo of progesterone, and misoprostol, which is administered up to three days later and works by inducing contractions to expel the fetus and the placenta from the uterus. As physicians know exactly how mifepristone works—by blocking progesterone—some physicians have started utilizing a process by which progesterone is restored after the use of mifepristone but before the use of misoprostol—thereby potentially saving the pregnancy.

In light of the fact that some women come to regret their abortions and could benefit from knowing about this "reversal" process, the Arizona Legislature amended its already-established informed consent statute to require information that "[i]t may be possible to reverse the effects of a medication abortion if the woman changes her mind but that time is of the essence," and the inclusion of additional information on the possibility in the state-prepared materials. The Arizona regulation is entirely informational and makes clear that the reversal process is only a "possibility." It does not require an abortion provider to participate in any reversal attempt.

Contrary to claims by Plaintiffs and their *amici*, the reversal process is based on well-established medical data, *see* Parts I and II, *infra*, and Arizona's regulation comports with Supreme Court precedent affirming the State's interest in ensuring that women receive accurate information about abortion. *See* Part III, *infra*. In fact, because the Court has directed that "wide deference" be given to states where there is medical disagreement on the effect of an abortion regulation, *id.*, the medical evidence presented in this brief necessitates the denial of a preliminary injunction.

I. The mechanism of action of mifepristone is undisputed—it blocks progesterone—and it is reversible

How mifepristone works is undisputed. After an embryo has implanted in a woman's uterus, further development of the embryo is dependent upon progesterone.[1] Without progesterone, the embryo will starve and die.

Mifepristone, however, is a synthetic anti-progesterone steroid that works by blocking progesterone receptors.[2] It competes with natural progesterone (*i.e.*, the progesterone produced by the woman's body) to fill specific receptors in the mother's ovary (which makes the progesterone needed to sustain the pregnancy) and in the womb (which holds the embryo).[3] Both the mifepristone molecule and the progesterone molecule will bind and release at a particular site, but the mifepristone molecule binds more tightly to the receptor, thereby blocking progesterone and causing the embryo to starve and die.

It is this undisputed mechanism of action that is at work when Plaintiffs administer mifepristone to women seeking "medical abortions." Because mifepristone does not result in a complete abortion in some cases, misoprostol is used to induce contractions to expel the "pregnancy" from the uterus.[4]

---

[1] *See, e.g.*, Sofuoglu et al., *Vaginal micronized progesterone capsule versus vaginal progesterone gel for lutheal support in normoresponder IVF/ICSI-ET cycles*, PAK. J. MED. SCI. 31(2):314 (Mar.-Apr. 2015).

[2] *See, e.g.*, Paul et al., eds., MANAGEMENT OF UNINTENDED AND ABNORMAL PREGNANCY: COMPREHENSIVE ABORTION CARE (2009).

[3] *See* Mauro et al., *Effect of Antiprogesterone RU486 on VEGF Expression and Blood Vessel Remodeling on Ovarian Follicles before Ovulation* (Apr. 22, 2014); Creinin & Danielsson, *Medical abortion in early pregnancy*, in Paul et al., eds., *supra*.

[4] *See, e.g.*, Mifeprex Labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf. All sites last visited July 15, 2015. ACOG claims that 8 to 46 percent of women who take mifepristone alone will "continue their pregnancies" without use of progesterone, but it relies on semantic gamesmanship. ACOG brief, at 5-6. Terms such as "continued

Understanding the science behind the mechanism of action of mifepristone allows physicians to design a specific "reversal" for a woman who has ingested mifepristone (but not yet misoprostol). Because physicians know exactly how mifepristone works, physicians know that an increased concentration of progesterone can displace mifepristone from the progesterone receptors. This allows the woman's body to respond to natural progesterone and to effectively fight the effects of the mifepristone blockage. This is a basic principle of reversible competitive binding of drugs to receptor sites and is a foundational concept in drug development.

The exhaustive initial studies of mifepristone, published by the Rockefeller Foundation, made clear how mifepristone works:

> Competition between hormone [*i.e.*, progesterone] and antihormone [*i.e.*, mifepristone] for the binding site of the receptor is the basic physical mechanism for explaining reversible antihormonal activity of antihormones.[5]

The studies also demonstrated how the effects of mifepristone can be reversed:

> The steroidal derivative RU 486 (17 beta-hydroxy-11 beta-(4-dimethyl-aminophenyl)-17 alpha-(prop-1-ynyl) ester-4, 9-dien-3-one) is the first potent anti-progestin to be used clinically. RU 486 blocks the action of progesterone by a reversible inhibition of the action of progesterone on its own receptors. This reversibility allows endocrine functions to return quickly to normal after discontinuation of treatment.

This "reversibility" happens because natural progesterone eventually displaces mifepristone from the progesterone receptor. Using simple principles of

---

pregnancy" or "treatment failure" include dead fetuses and living but damaged fetuses (which will later "miscarry"), as well as fetuses who could potentially survive to term. Thus, claiming that a woman's pregnancy may "continue" without progesterone does not necessarily mean that the embryo survives.

[5] Baulieu & Segal, *The AntiProgestin Steroid RU 486 and Human Fertility Control*, Conference on the Antiprogestational Compound RU 486 (Bellagio, Italy 1984), reprinted in REPROD. BIO.

pharmacokinetics, a physician can understand that the more progesterone available to displace mifepristone from the receptor, the faster will be the "return to normal" as described in the study. Thus, the initial foundational research studies that paved the way for Plaintiffs' eventual use of mifepristone to terminate pregnancy not only demonstrated the clear mechanism of action, but also that the mechanism of action can be reversed.

Further research in humans demonstrates that progesterone can also reverse the effects of mifepristone on the muscle[6] and the lining of the womb.[7] This reversibility of the "anti-hormone" effects of mifepristone has long been demonstrated in animal models. For example, two studies demonstrated that giving progesterone could block the abortifacient effects of progesterone blockers, if the progesterone was given soon enough after the blocker.[8] In one study, 100 percent of mice given mifepristone aborted, but after mice were given progesterone-treated serum, only 6 percent aborted.[9]

Other drugs have also been proven to reverse other effects of mifepristone in animal models.[10] Further, the anti-glucocorticoid effects of mifepristone can be reversed by adding back enough of the blocked hormone[11]—and while this is not the mechanism of action leading to the termination of pregnancy, this reversal further supports the fact

---

[6] Lobaccaro-Henri, *Effect of the progesterone antagonist RU486 on human myometrial spontaneous contractility and PGI2 release*, PROSTAGLANDINS 44(5):443 (Nov. 1992).
[7] Greb, *Disparate actions of mifepristone (RU 486) on glands and stroma in the primate endometrium*, HUMAN REPROD. 14(1):198 (Jan. 1999).
[8] *See, e.g.*, Csapo & Erdos, *Prevention of the abortifacient action of antiprogesterone serum by progesterone*, AMER. J. OBSTET. GYNECOL. 128(2):212 (May 15, 1977).
[9] *See, e.g.*, Szekeres-Bartho et al., *A progesterone-induced blocking factor corrects high resorption rates in mice treated with antiprogesterone*, AMER. J. OBSTET. GYNECOL. 163(4 Pt 1):1320 (Oct. 1990).
[10] Chen et al., *Baicalin can attenuate the inhibitory effects of mifepristone on Wnt pathway during peri-implantation period in mice*, J. STEROID BIOCHEM. MOL. BIOL. 149:11 (May 2015).

that treatment with blocked hormones can indeed reverse the effects of mifepristone if provided in a timely manner.

Not only has the reversibility of mifepristone been examined throughout scientific literature since the initial published study on the drug's effects, but similar well-established medical techniques provide further support for the provision of progesterone to protect pregnancy. As already explained, mifepristone works by blocking progesterone, inducing a progesterone deficiency which mimics a natural disease process called Luteal Phase Defect. Physicians have been treating Luteal Phase Defect for decades by administering progesterone to women.[12] Thus, the logical scientific application of understanding mifepristone's effect on pregnancy is to give the specific antidote to that effect: progesterone.

This process of reversing the effects of mifepristone is analogous to another well-established medical regimen: methotrexate and "leucovorin rescue."[13] Methotrexate, a chemotherapy drug, poisons certain metabolic processes which are more active in cancer cells. It works specifically by blocking the action of folic acid. But because methotrexate cannot precisely target cancerous cells while bypassing normal cells, the metabolic processes in the normal cells are affected as well. Typically, physicians allow the methotrexate to work for a day or two, and then give the patient a high dose of folic acid (a drug called leucovorin) to compensate for what has been lost. This flooding of

---

[11] *See, e.g.*, Morrow et al., *Glucocorticoids alter fever and IL-6 responses to psychological stress and to lipopolysaccharide*, AMER. J. PHYSIOL. 264(5 Pt 2):R1010-6 (May 1993).

[12] *See, e.g.,* Sofuoglu et al., *supra*.

[13] *See, e.g.*, Leucovorin Labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/anda/99/40262_Leucovorin%20Calcium_Prntlbl.pdf.

the patient's body with folic acid is called a "leucovorin rescue," and it in essence counteracts the action of methotrexate.

It is upon this well-established medical procedure that the reversal of mifepristone builds. Because physicians know exactly how mifepristone works (*i.e.*, blocking progesterone), physicians know that treating a woman with progesterone can displace mifepristone from the progesterone receptors. This allows the woman's body to respond to natural progesterone and to effectively fight the effects of the mifepristone blockage.

Contrary to the claims of Plaintiffs and their *amici*, the medical theory supporting the mifepristone reversal process is based on the application of decades of reliable science and is bolstered by credible medical evidence and practice, making it an evidence-based procedure. Its use is not "radically new," but has been utilized in analogous pregnancy conditions for over four decades.[14]

II. Using progesterone in an attempt to reverse the effects of mifepristone is safe and fulfills FDA guidelines

Natural progesterone is a hormone that a woman's ovary produces to sustain a developing embryo and fetus. The pharmacological use of progesterone in pregnancy is not new, and its safety has been determined by numerous epidemiologic studies and clinical trials.[15] In fact, the safety of progesterone is repeated in a statement by the World Health Organization (WHO), approving progesterone for use in pregnancy.[16]

Not only is progesterone undisputedly safe in pregnancy, but it is routinely used to protect pregnancies or treat related complications. For example, progesterone has been

---

[14] *See* Part II, *infra*.

[15] *See, e.g.*, Norwitz et al., *Progesterone Supplementation and the Prevention of Preterm Birth*, REV. OBSTET. GYNECOL. 4(2):60 (2011).

[16] WHO, *Prenatal administration of progesterone for preventing preterm birth in women considered at risk of preterm birth* (2009), available at

used for over four decades to help prevent preterm birth.[17] Similarly, with the advent of *in vitro* fertilization, progesterone has been used for two decades for women with low estrogen production after transfer of an embryo.[18] In addition, for the last four decades, when an ovary has to be removed early in pregnancy (such as when a woman suffers from ovarian torsion), physicians sustain that pregnancy by providing progesterone.[19] As already discussed, physicians routinely administer progesterone to women with recurrent low progesterone in the first trimester (Luteal Phase Deficiency).[20]

According to the FDA guidelines on "off-label" uses of drugs, there is no need for an investigational study on the use of natural progesterone in the support of pregnancies threatened by progesterone deficiency induced by mifepristone:

> Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. ***Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission*** of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB).[21]

---

http://apps.who.int/rhl/pregnancy_childbirth/complications/preterm_birth/cd004947_gonzalezr_com/en/.

[17] *See*, *e.g.*, Rode et al., *Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies*, ACTA. OBSTET. GYNECOL. SCAND. 88(11):1180 (2009).

[18] *See*, *e.g.*, van der Linden et al., *Luteal phase support for assisted reproduction cycles*, COCHRANE DATABASE SYST. REV. (10):CD009154 (Oct. 5, 2011).

[19] *See*, *e.g.*, Csapo et al., *Effects of luteectomy and progesterone replacement therapy in early pregnant patients*, AMER. J. OBSTET. GYNECOL. 115(6):759 (May 1973).

[20] *See* Alderson et al., *Luteal Phase Dysfunction* (updated June 14, 2013), available at http://emedicine.medscape.com/article/254934-overview; *see also* Part I, *supra*.

[21] FDA, *"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet* (last updated June 25, 2014), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm) (emphasis in the original and added).

Using progesterone to reverse the effects of mifepristone is not an "investigational use," which, as the FDA describes, suggests the use of an approved product in the context of a clinical study protocol.[22] Specifically, an "off-label" use of a drug does not require submission of an Investigative New Drug Application (IND) if all six of the following conditions are met:

1) It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

2) It is not intended to support a significant change in the advertising for the product;

3) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

4) It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

6) It does not intend to invoke 21 CFR 50.24.[23]

Significantly, the use of progesterone to reverse the effects of mifepristone in pregnancy meets all of the above criteria. Therefore, according to FDA guidance, there is no need for an Institutional Review Board (IRB) review or an IND or accompanying clinical trial, and progesterone can be used to attempt to reverse the effects of mifepristone.[24]

---

[22] *Id*.

[23] *Id*. (bracketed information in the original). 21 C.F.R. § 50.24 involves exceptions from informed consent requirements, and is not invoked by the mifepristone reversal process.

[24] There is a sharp contrast between the off-label use of progesterone for reversal of mifepristone, and the off-label use of mifepristone (and accompanying misoprostol) for the termination of pregnancy. Progesterone was approved by the FDA through its normal approval process, which thereafter provides physicians leeway in prescribed uses. Conversely, mifepristone (brand name Mifeprex) was approved under the rubric of

III. Supported by medical data, the Arizona requirement ensures that women are provided all relevant data before making an abortion decision and it comports with clear Supreme Court precedent

Informed consent is foundational for good medical care. In the last 23 years, the Supreme Court has explicitly affirmed informed consent requirements in the context of abortion. In no other area of abortion jurisprudence has the Court been so clear. Informed consent laws have been repeatedly upheld as constitutional, withstanding multiple legal challenges.

In *Planned Parenthood v. Casey*, 505 U.S. 833 (1992), the Court upheld Pennsylvania's extensive informed consent requirement. The Court first reexamined its holding in *Roe v. Wade* and provided guidance to lower courts in determining the constitutionality of abortion regulations. It began by reaffirming *Roe*'s "essential" holding that a woman has a "right" to "choose to have an abortion" (before viability) without "undue interference from the State," and that the state has a legitimate interest from the outset of pregnancy in protecting the health of the woman and the life of the unborn child. *Id*. at 846.

The Court noted, however, that *Roe*'s affirmation of the state's "important and legitimate interest" in the life of the unborn child had been given "too little acknowledgement and implementation" in subsequent decisions, some of which utilized a

---

"Subpart H," a special provision in the Code of Federal Regulations for drugs that "can be safely used ***only if distribution or use is restricted***." 21 C.F.R. § 314.520 (emphasis added). Under Subpart H, the FDA "will require such postmarketing restrictions as are needed to assure safe use" of the drug approved. *Id*. Per Subpart H, the FDA approved mifepristone with physician restrictions, such as a required signed Patient agreement in which the physician attests that the pregnancy is not more than 49 days. Thus, off-label use of mifepristone—such as providing it to women over 49 days—would violate the clear FDA restrictions on its use. No such restrictions pertain to the use of progesterone. *See*, *e.g.*, FDA, Sept. 2000 Approval Letter, available at

strict scrutiny analysis. *Id*. at 871. This use of strict scrutiny led to "the striking down of some abortion regulations *which in no real sense deprived women of the ultimate decision*" and "went too far." *Id*. at 875 (emphasis added). The Court concluded that treating all governmental attempts to influence a woman's decision as unwarranted is "incompatible with the recognition that there is a substantial state interest" in the life of the unborn child (as well as in maternal health) throughout pregnancy. *Id*. at 876.

After explicitly rejecting strict scrutiny, the plurality in *Casey* articulated the "undue burden" standard: only where state regulation imposes an undue burden on a woman's ability to choose abortion does the state overreach. *Id*. at 874. The Court elaborated:

> A finding of an undue burden is a shorthand for the conclusion that a state regulation has the purpose or effect of placing a substantial obstacle in the path of a woman seeking an abortion of a nonviable fetus.

Id. at 877.[25]

The plurality in *Casey* also provided some "guiding principles" to help direct the federal courts as to what constitutes a "substantial obstacle":

> a) What is at stake is the woman's right to make the ultimate decision, not a right to be insulated from all others in doing so.

---

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf (highlighting a required Patient Agreement).

[25] Like the plaintiffs here, the plaintiffs in *Casey* asserted a First Amendment claim. *Casey*, 505 U.S. at 884. Having determined that "a requirement that a doctor give a woman certain information as part of obtaining her consent to an abortion is, for constitutional purposes, no different from a requirement that a doctor give certain specific information about any medical procedure," *id*., the Court disposed of the plaintiffs' First Amendment claims in three sentences, stating that the claim is "subject to" reasonable licensing and regulation by the State, and thereby demonstrating that the proper analysis for such First Amendment claims in the abortion context is the undue burden test. *Id*. As the Court said in *Gonzales v. Carhart*, the "law need not give abortion doctors unfettered choice in the course of their medical practice, nor should it elevate their status above other physicians in the medical community." *Gonzales*, 550 U.S. 124, 163 (2007).

b) Regulations which do no more than create a structural mechanism by which the State … may express profound respect for the life of the unborn are permitted, if they are not a substantial obstacle to the woman's exercise of the right to choose.

c) Unless it has that effect on her right of choice, a state measure designed to persuade her to choose childbirth over abortion will be upheld if reasonably related to that goal.

d) Regulations designed to foster the health of a woman seeking an abortion are valid if they do not constitute an undue burden.

Id. at 877-78.

The Court was clear: strict scrutiny was rejected; the undue burden standard is appropriate for the review of abortion regulations; and regulations that do not place a substantial obstacle in the way of a woman's decision are constitutional.

With this standard in mind, the Court concluded that Pennsylvania's informed consent statute "cannot be considered a substantial obstacle to obtaining an abortion, and, it follows, there is no undue burden." *Id*. at 882, 883. In upholding the law, the Court held that a state may take steps to ensure that a woman's choice is thoughtful and informed:

> Even in the earliest stages of pregnancy, the State may enact rules and regulations designed to encourage her to know that there are philosophic and social arguments of great weight that can be brought to bear in favor of continuing the pregnancy to full term and that there are procedures and institutions to allow adoption of unwanted children *as well as a certain degree of state assistance if the mother chooses to raise the child herself*.

Id. at 872 (emphasis added). The Court continued:

> In attempting to ensure that a woman apprehend *the full consequences* of her decision, the State furthers the legitimate purpose of *reducing the risk that a woman may elect abortion, only to discover later, with devastating psychological consequences, that her decision was not fully informed*.

Id. at 882 (emphasis added). In addition to regulations detailing philosophic, social, and psychological considerations, the Court also held that the State may enact measures requiring physicians to provide information related to the consequences of the abortion on the unborn child, deeming such information "relevant, if not dispositive" to the decision, even when those consequences have no direct relation to the mother's physical health. *Id*. at 873, 882.

The Supreme Court's support for comprehensive informed consent regulations was re-affirmed in *Gonzales v. Carhart*, with the Court holding that "[t]he State has an interest in ensuring so grave a choice is well informed." 550 U.S. at 159. The State's interest is "advanced by the dialogue that better informs the political and legal systems, the medical profession, expectant mothers, and society as a whole…." *Id*. at 160. The Court found it "*unexceptionable to conclude that some women come to regret their choice to abort the infant life they once created and sustained*." *Id*. at 159.

Moreover, the Court explicitly held that state and federal legislatures are given "*wide discretion* to pass legislation in areas *where there is medical and scientific uncertainty*." *Id*. at 163 (emphasis added). In other words, where there is medical disagreement as to the effect of a regulation, a court must give wide deference to the state. The burden rests on the plaintiffs challenging a regulation to prove that there is no medical disagreement. Plaintiffs cannot meet that burden here, as the medical evidence detailed in this *amicus* brief demonstrates. In fact, ACOG's brief, claiming the uncertainty of the reversal process, works directly *against* the Plaintiffs in this regard.

In its brief, ACOG presented a four-point argument against the Arizona regulation, but a close review reveals that every single one of ACOG's points is based on the same erroneous claim: that the reversal process is not based on credible medical data. ACOG's arguments fail, because they are based on a claim that is demonstrably untrue in light of

established medical data that 1) the exact mechanism of action of mifepristone is to block progesterone; 2) the effects of mifepristone can be reversed; 3) progesterone is safely used in other similar pregnancy conditions; 4) other well-established medical techniques utilize the same type of reversal process; and 5) the use of progesterone in an attempt to reverse the effects of mifepristone meets the FDA's guidelines.

Moreover, ACOG fails to articulate any *actual* harm that women may face after receiving the information on potential mifepristone reversal. It cannot claim that use of progesterone is physically unsafe for women in pregnancy,[26] and it certainly cannot argue that mere information about progesterone creates an undue burden. Instead, ACOG claims that the information is "potentially harmful," "potentially confusing," or "may be harmful." It relies on rank speculation, failing to give any concrete evidence that a woman would be physically harmed or prevented in any way from choosing abortion. ACOG brief, at 3, 5, 9.

In fact, Plaintiffs *cannot* establish that this information requirement rises to the level of an "undue burden." The U.S. Supreme Court has already determined that the mere provision of information that might be relevant[27] to a woman's decision is not an undue burden. Plaintiffs and ACOG fail to demonstrate how the Arizona regulation will,

---

[26] ACOG claims that, in an individual physician's judgment, progesterone can pose problems for some patients. ACOG brief, at 9. Obviously, such a possibility would be taken into consideration by the physician who is contacted to potentially reverse the effects of mifepristone. The regulation does not require any physician to perform the process; it only ensures that women receive information about the process. Medical judgment is left intact, and women's specific needs would be evaluated by the physician contacted to assist in reversal.

[27] Provision of information on the reversal process is relevant even for a woman who may choose surgical abortion, as it provides her with information applicable to evaluating which procedure is best for her personal situation.

in any "real sense," deprive a woman "of making the ultimate decision." *Casey*, 505 U.S. at 875.[28]

In addition, ACOG treats the provision of information as if it were made in a vacuum, as if there will be no discussion or opinions rendered by the abortion provider. ACOG brief at 11, 12. Nothing in the Arizona regulation prevents a frank and fluid discussion between patient and provider, nor does it inhibit the discretion of the provider in tailoring informed consent to the patient. If a provider wants to clarify relevance to a particular woman or add any information, he is free to do so. If the provider does not think mifepristone reversal will work, he is free to say so—just as he is free to disagree with any other informed consent provision already required by Arizona law and unchallenged in this case.[29]

ACOG also disingenuously claims that the Arizona regulation "deprives women of evidence-based medical information." *Id*. at 2, 3, 4. Even if ACOG disagrees that mifepristone reversal is evidence-based (which, again, simply points to the disagreement

---

[28] Nor does the benign statement that "it may be possible to reverse the effects of a medication abortion if the woman changes her mind but that time is of the essence" in any way amount to a provider "steer[ing] patients toward" the procedure. ACOG brief, at 5. Nothing in the required statement endorses the procedure, and nothing prevents the physician from stating his own opinion. In fact, the state-prepared materials, which provide information to women seeking mifepristone reversal, ensure that any further information need not come from the provider himself and will not appear to be endorsed by the provider.

[29] There is an assumption that the provider is actually taking an active role in the informed consent process. If the provider simply goes down a checklist of required information, not making himself available for discussion or the answering of questions, then obviously blanket provision of any random informed consent information might confuse a woman. The problem therein is the provider's ineffective provision of informed consent and lack of availability to the woman—not the legislature's requirement that the information be provided. ACOG's objections are, therefore, only relevant in situations where the provider is not accessible to women, undermining its claims altogether.

in the medical community and the wide discretion that should be provided the state), the regulation in no way *deprives* women of information. No withholding of information is required. To the contrary, it is ACOG that desires to withhold the reversal information from *all* women because it has pre-determined that the information is inapplicable to *some* women.

ACOG also ignores the fact that some women do indeed come to regret their abortions, no matter how "certain" they seemed to the provider during the informed consent process. *Id*. at 10. Not only has the Supreme Court legally recognized that some women come to regret their abortions, *Gonzales*, 550 U.S. at 159, but ACOG also ignores the practical, real world example of women who have regretted using mifepristone, have been treated with progesterone, and went on to have healthy pregnancies. Clearly, even women who consider themselves "certain" before their abortions change their minds. If it is "unexceptionable to conclude some women come to regret their choice to abort the infant life they once created and sustained," how much more so when a woman learns that her provider failed to provide information that could have helped her reverse the chemical abortion process and go on to have a healthy child.

In reality, ACOG is arguing against informed consent in general, placing the organization on the wrong side of Supreme Court precedent. For example, ACOG claims that "[l]aws that require physicians to give, or withhold, specific information… are detrimental to the patient-physicians relationship and are ill-advised"—*i.e.*, not just laws that require information to which a physician is opposed, but *all laws* that require *any* information. ACOG brief, at 13-14. This position runs contrary to patient autonomy and the very underpinnings of informed consent.

ACOG also objects to the Arizona regulation's provision directing women to "third party," state-prepared materials. *Id*. at 11. Notably, the Arizona informed consent

statute already required providers to inform women that the Department of Health Services maintains a website that describes the unborn child and lists the agencies that offer alternatives to abortion. ARIZ. REV. STAT. § 36-2153(2)(f). Further, ACOG's objection to a required recitation of specific language is undermined by the fact that Arizona's informed consent statute already requires physicians to recite certain information. ACOG brief, at 11; ARIZ. REV. STAT. § 36-2153(1) and (2). Contrary to ACOG's claims allegedly "supporting" informed consent, these objections reveal that ACOG is, in reality, opposed to all informed consent laws in general, and, as such, its objections must be rejected outright in light of *Casey* and *Gonzales*.

Simply put, there is medical disagreement as to the effect of Arizona's regulation, there is therefore no undue burden, and Plaintiffs' claims must ultimately fail. Plaintiffs should not be allowed to undermine informed consent and obstruct patient autonomy.

CONCLUSION

For the foregoing reasons, this Court should deny Plaintiffs' request for preliminary injunction.

DATED: July 28, 2015.

Respectfully submitted:

s/ Mailee R. Smith*
AMERICANS UNITED FOR LIFE
655 15th St. NW, Suite 410
Washington, D.C. 20005
Mailee.Smith@AUL.org
(202) 289-1478
State Bar No. 6280167 (Illinois)

Counsel for *Amici Curiae American Association of Pro-Life Obstetricians & Gynecologists, Physicians for Life, National Association of Pro-Life Nurses, and National Association of Catholic Nurses*
*Admitted pro hac vice

CERTIFICATE OF SERVICE

I hereby certify that on July 28, 2015, I electronically transmitted the attached document to the Clerk's office using the CM/ECF System for filing and transmittal of a Notice of Electronic Filing to the following CM/ECF registrants:

Brigitte Amiri Andrew D. Beck Susan Talcott Camp ACLU – New York, NY 125 Broad St., 18th Floor New York, NY 10004 bamiri@aclu.org abeck@aclu.org tcamp@aclu.org David Brown Hillary Anne Schneller Center for Reproductive Rights 199 Water Street, 22nd Floor New York, NY 10038 dbrown@reprorights.org hschneller@reprorights.org Alice Clapman Helene Krasnoff Planned Parenthood Fed'n of Amer. 1110 Vermont Ave. NW, Suite 300 Washington, D.C. 20005 alice.clapman@ppfa.org helene.krasnoff@ppfa.org Douglas V. Drury Mueller & Drury PC 8110 E. Cactus Rd., Suite 100 Scottsdale, AZ 85260-5210 dougdrury@muellerdrury.com	Victoria Lopez Daniel Joseph Pochoda ACLU – Phoenix, AZ PO Box 17148 Phoenix, AZ 85011 vlopez@acluaz.org dpochoda@acluaz.org Daniel Benjamin Pasternak Lawrence Jay Rosenfeld Squire Patton Boggs LLP 1 E. Washington St., Suite 2700 Phoenix, AZ 85004 daniel.pasternak@squirepb.com lawrence.rosenfeld@squirepb.com Diana Salgado Planned Parenthood Fed'n of Amer. 434 W. 33rd St. New York, NY 10001 diana.salgado@ppfa.org Aubrey Joy Corcoran Kevin D. Ray John R. Tellier Office of the Attorney General 1275 W. Washington St. Phoenix, AZ 85007 aubreyjoy.corcoran@azag.gov kevin.ray@azag.gov john.tellier@azag.gov

s/ Mailee R. Smith*
Counsel for *Amici Curiae*

American Association of Pro-Life Obstetricians & Gynecologists, Physicians for Life, National Association of Pro-Life Nurses, and National Association of Catholic Nurses
*Admitted pro hac vice