Embryo Survival after Mifepristone: A Systematic Review of the Literature

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ABSTRACT:

Rationale: Mifepristone was approved in 2000 by the FDA as an alternative to surgical abortion. In the predominant two drug abortion regimen, mifepristone is followed by misoprostol after one to two days. Little has been published on the survival of living embryos after exposure to mifepristone alone. This review of the literature is undertaken to summarize available studies that define embryo survival after mifepristone. This review defines baseline continuing pregnancy rates after mifepristone, to aid in determining the therapeutic value of supplemental progesterone for women desiring to continue their pregnancy.

Methods: PubMed and the Cochrane Database were searched through March, 2016 for articles that depicted embryo survival after ingestion of mifepristone as a single agent. Further studies were found in the reference lists of relevant articles and review articles. The relevant studies that verified embryo survival utilized ultrasound as a criterion for continuing pregnancy.

Results: Of 1855 studies found, 30 studies using mifepristone as a single agent were selected for review. 18 met criteria describing embryo survival. Mifepristone was lethal over a wide range of doses and gestational ages; surviving embryos were present over a similar range. Survival rates using total doses of 200-300 mg ranged from 10-23.3%. In the one study using

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the current prevailing 200 mg single dose regimen, embryo survival was 23.3%. Regimens with total doses ≥400 mg had embryo survivals ranging from 0-18.1% when followed ≥14 days post mifepristone, and 0-50% when followed for 6-8 days after mifepristone. Embryo survival in studies including gestations up to 70 days was ≤25% in three of four studies.
Conclusion: **This literature review shows that mifepristone is an effective embryocidal agent at doses ranging from 200 mg to 600 mg.**

Mifepristone was developed in the 1980's as an anti-progesterone steroid for first trimester abortion and an alternative to surgical abortion. A second drug, a prostaglandin, was added to abortion regimens because mifepristone alone did not produce a sufficiently high rate of complete abortions for clinical use. Since the introduction of this two drug abortion regimen in Europe and China, and FDA approval of mifepristone in the U.S. in 2000, the use of medical abortion has increased world-wide. In the U.S., medical abortion accounted for 31% of all outpatient abortions and 45% of abortions before nine weeks gestation in 2014.[1] The earliest studies on mifepristone showed that the drug was effective as an abortifacient in most instances, even when it failed to evacuate the uterus completely. Clinical mifepristone trials after 1986 added a prostaglandin agent for efficacy. Most of these early trials showed that a proportion of embryos survived mifepristone.

Some women regret their abortion decision soon after ingesting mifepristone but before taking misoprostol, and make a personal decision to interrupt the two drug protocol.[2] A therapy using progesterone for reversing the effects of mifepristone was developed for these women (abortion pill reversal or APR), to promote embryo survival.[3] This review is undertaken to characterize the baseline rate of surviving pregnancies after mifepristone from the original literature. This will aid in assessing the therapeutic value of supplemental progesterone for women desiring to continue their pregnancy.

Development of Mifepristone for Medical Abortion

Methods of medical abortion for first trimester pregnancy were sought since the 1950's. Early efforts involved folic acid antagonists and prostaglandin analogues.[4] Subsequent research in fertility control focused on the role of progesterone, as its name suggests (pro-gestation), in supporting pregnancy. Csapo demonstrated in 1973 that

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[1] Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2014. *Perspectives on Sexual and Reproductive Health,* 2017, 49(1).

[2] Bernard N, Elefant E, Carlier P et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG*.; 2013;120(5):568-74.

[3] Delgado G, Davenport ML. Progesterone use to reverse the effects of mifepristone. *Ann Pharmacother.* 2012; 46(12):46.

[4] Creinin M, Danielsson G. Medical abortion in early pregnancy. *In* Paul M, Lichtenberg ES, Borgatta L et al.,eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care.* Blackwell Publishing Ltd 2009;111-112.

removal of the corpus luteum and resultant withdrawal of progesterone caused expulsion of the embryo; replacement of progesterone resulted in embryo survival.[5] Csapo also sought reversible fertility control, and developed anti-progesterone antibodies for this purpose. Rats were given an anti-progesterone serum to cause abortion; if progesterone was given three hours after the abortifacient preparation, although not as late as six hours, abortion was prevented.[6,7]

The discovery that steroids exerted their actions principally through hormone receptors led to an explosion of research in the 1960's and 1970's.[8] The definitive description of the progesterone receptor in 1970 was an important milestone, leading eventually to the search for compounds that could antagonize progesterone's role in ovulation, nidation, and support of pregnancy.[9] Roussel-Uclaf laboratories in Paris initiated a major program of chemical and biological research to develop a broad range of new steroid molecules with hormonal and anti-hormonal actions. As part of this agenda, Teutsch synthesized mifepristone (RU-486) as a glucocorticoid receptor binder in 1980. When it was discovered that this compound was also a progesterone receptor antagonist, mifepristone was rapidly investigated for abortifacient potential. As an effective abortifacient, mifepristone was recognized as a major breakthrough with potential for a significant impact on human fertility control.[10,11]

After the discovery of mifepristone, research proceeded at a rapid pace. The potential of mifepristone as a reversible agent of fertility control as a menstrual regulator and post-coital menses inducer was explored, in addition to its use as an agent for early abortion. Its toxicology, pharmacokinetics, potential in mapping steroid receptors, myometrial and endometrial effects, and effect on other endocrine conditions such as Cushing's disease were analyzed. Roussel-Uclaf supplied mifepristone to researchers in Europe, China, Japan, and North and South America for rodent, primate and human experiments.

In an early experiment Yamabe demonstrated the ability of supplemental progesterone to block mifepristone abortions in rats. After four days 66.7% of rats given mifepristone alone aborted, but 100% of rats given progesterone in addition to mifepristone

[5] Csapo AI, Pulkkinen MO, Wiest WG. Effects of luteectomy and progesterone replacement therapy in early pregnant patients. *Am J Obstet Gynecol.* 1973;115(6):759-65.

[6] Csapo, AI, Erdos T. The critical control of progesterone levels and pregnancy by antiprogesterone. *Am J Obtet Gynecol.* 1976; 126 (2):598-601.

[7] Csapo, AI, Erdos T. Prevention of the abortifacient action of antiprogesterone by progesterone. *Am J Obtet Gynecol*. 1977; 128(2):212-4.

[8] Fannon SA, Vidaver RM, Marts SA. An abridged history of sex steroid hormone receptor action. *J Appl Physiol*. 2001; 91(4): 1854-59.

[9] Milgrom E, Atger M, Baulieu EE. Progesterone in uterus and plasma. IV. Progesterone receptor(s) in guinea pig uterus cytosol. *Steroids*. 1970 ;16(6):741-54.

[10] Teutsch G. Analogues of RU-486 for the mapping of the progestin receptor: synthetic and structural aspects. *In* Beaulieu EE, Siegel S, eds.*The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum;1985: 249-258.

[11] Initially named RU-38486, the 38,486th compound synthesized by Roussel-Uclaf from 1949 to 1980; the name was later shortened to RU-486.

failed to abort.[12] This study demonstrated that mifepristone blockage of progesterone receptors was reversible, and that progesterone rescue could block the abortifacient effect of mifepristone if given soon after mifepristone dosing.

An important early symposium on mifepristone in Bellagio in 1984 published mifepristone research in *The Antiprogestin Steroid RU 486 and Human Fertility Control.*[13] At this symposium it was already becoming apparent that, although mifepristone was an effective abortifacient, it did not result in a sufficient percentage of complete abortions (total evacuation of the uterus) to be clinically useful as a single agent. In the late 1980's, prostaglandins were added to mifepristone regimens to achieve a higher rate of complete abortion and this method of abortion was promoted for gestations up to 49 days. Simpler regimens of single dose mifepristone were used, and in the 1990's studies were performed using two drug mifepristone-prostaglandin regimens in later gestations up to 63 days. The FDA approved a regimen of 600 mg mifepristone and 400 mcg oral misoprostol up to 49 days in 2000; the regimen was revised in 2016 to consist of 200 mg mifepristone and 800 mcg buccal misoprostol for use in gestations up to 70 days.[14] In the United States mifepristone is not available in retail pharmacies, and is always given by abortion providers under direct observation. At the time of mifepristone ingestion, misoprostol is typically dispensed for home use after 1-2 days.

Mechanisms of Action of Mifepristone

Early research demonstrated the ability of mifepristone to abort pregnancies by several mechanisms. The primary mechanism is binding to the endometrial progesterone receptor, causing deterioration of the maternal decidua, and resulting eventually in detachment of the embryo from the endometrium.[15] Mifepristone also softens the cervix, either as a primary effect or possibly due to detachment of the embryo causing prostaglandin release, facilitating abortifacient action.[16] The rise of prostaglandin following administration of mifepristone was measured in initial mifepristone investigations.[17,18] Other early mifepristone studies measured an increase in uterine contractility following

[12] Yamabe, S. Katayama K, Mochizuki M. The effect of RU 486 and progesterone on luteal function during pregnancy. *Nihon Nalbunpi Gakkai Zasshi*. 65:497-511.

[13] Beaulieu EE, Siegel S, eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York: Plenum; 1985

[14] United States Food and Drug Administration. Mifeprex (mifepristone) information. March 30, 2016.

[15] Beaulieu EE. RU-486: An antiprogestin steroid with contragestive effect in women. *In*:Baulieu EE, Siegel S,eds: *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum, 1985:2-6.

[16] Baulieu EE. Contragestion with RU 486: a new approach to postovulatory fertility control. *Acta Obstet Gynecol Scand Suppl*. 1989. 149: 5-8.

[17] Herrmann WL, Schindler AM, Wyss R et al. Effects of the antiprogesterone RU 486 in early pregnancy and during the menstrual cycle. *In* Beaulieu EE, Siegel S,eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum; 1985:179-198.

[18] Somell C, Olund A. Induction of abortion in early pregnancy with mifepristone. *Gynecol Obstet Invest* 1990;30(4):224-27.

mifepristone ingestion, in aiding expulsion of the pregnancy.[19,20] The Bellagio symposium included papers discussing both the primary mifepristone effect on the endometrium, as well as the secondary mechanisms of abortifacient effect of mifepristone, including effects on cervix, myometrial contractility, prostaglandins, and hypothalamic and pituitary effects in animal and human subjects.[21] Additional early research by Das and Catt found that mifepristone acted on placental tissue in vitro and reduced hormone secretion; this effect was reversed by administration of additional progesterone.[22]

Further animal and human studies in more recent decades have elucidated other important actions of mifepristone. Niinimaki in 2009 demonstrated that ingestion of 200 mg mifepristone caused a shrinkage in ovarian volume two days after administration, in pregnancies up to 63 days.[23] Other researchers have specifically studied the effect of mifepristone on VEGF protein. VEGF protein, involved in angiogenesis and formation of blood vessels, has receptors in the decidua, placental tissue, and ovary, and is critical to the development of vasculature throughout pregnancy. It affects downstream signaling in numerous pathways. Mauro found that mifepristone impaired VEGF production, blood vessel network, and remodeling in the ovarian follicle.[24] Wan showed that mifepristone suppressed VEGF expression in chorionic villi.[25] Additionally, mifepristone VEGF effects may have delayed repercussions for pregnancy. Mice subjected to repeated mifepristone abortions were found to have reduced placental VEGF expression in subsequent pregnancies and a significantly increased incidence of pregnancy loss. A key modulator of VEGF in angiogenesis is TSP-1. Mifepristone has been found to inhibit and progesterone to enhance TSP-1 mRNA in endometrial-derived Ishikawa cells.[26] These examples are not an exhaustive summary, but instead a representative sample of the prolific literature on the actions and molecular biology of mifepristone. It is apparent that mifepristone ingestion can compromise pregnancy integrity by several mechanisms and in multiple target organs, usually involving progesterone receptor blockade.

[19] Bygdeman M, Swahn ML. Progesterone receptor blockage: effect on uterine contractility and early pregnancy. *Contraception*. 1985; 32(1):45-51.

[20] Swahn ML Cekan S, Wang V et al. Pharmacokinetic and clinical studies on RU-486 for fertility regulation. *In* Beaulieu EE, Siegel S,eds.*The Antiprogestin Steroid RU 486 and Human Fertility Control.* New York, Plenum;1985. 249-258.

[21] Beaulieu EE, Siegel S ,eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum, 1985.

[22] Das C, Catt K. Antifertility actions of the progesterone antagonist RU 486 include direct inhibition of placental hormone secretion. *Lancet*. 1987; 330 (8559):599-601.

[23] Niinimaki M, Ruokonen A, Tapaneinen JS et al. Effect of mifepristone on the corpus luteum in early pregnancy. *Ultrasound Obstet Gynecol*. 2009; 34 (4):448-453.

[24] Mauro A, Martelli A, Berardinelli P et al. Effect of antiprogesterone RU486 on VEGF expression and blood vessel remodeling on ovarian follicles before ovulation. *PLOS One*. 2014. Vol 9; 4: 1-13. Doi. org/10.1371/journal.pone.005910.

[25] Wan H, Liu H, Xi N et al. Effect of tamoxifen combined with mifepristone on VEGF and TGF-β_1 expression in early pregnancy chorionic villi. *Reproduction and Contraception*. 2007-03.

[26] Mirken S, Archer DF. Effects of mifepristone on vascular endothelial growth factor and thrombospondin-1 mRNA in Ishikawa cells: implication for the endometrial effects of mifepristone. *Contraception.* 2004;70(4):327-33.

Role of Ultrasound

In determining the success or failure in mifepristone as an abortifacient, ultrasound technology is crucial in ascertaining embryo survival. Clinical use of ultrasound began in the 1960's. The gestational sac and its growth in early pregnancy, using an abdominal probe and full bladder technique, were described by Donald and Abdullah in 1968.[27] In 1973 reliable discernment of fetal heart tones by 45 days gestation was described.[28] In a 1975 study of bleeding in early pregnancy, ultrasound diagnosed spontaneous abortion accurately in 231 of 237 subjects (97.5%).[29] Determination of gestational age by fetal crown-rump length was described in 1976.[30] By the 1980's, at the time of the original mifepristone studies, most of the institutions involved in mifepristone research had the ability to use ultrasound clinically to determine fetal gestational age and viability, usually with transabdominal probes. The first transvaginal probes were introduced in 1985.[31]

Most mifepristone researchers used ultrasound to determine the number of complete uterine evacuations. Some investigators noted continuing living pregnancies.[32] However, because the key objective of many of these studies was to assess mifepristone's effectiveness in producing a complete abortion, embryo survival was not noted or assessed by all examiners even in some cases when ultrasound was used. Thus in this review, we identify those studies which noted continuing survival by documenting continuing living pregnancies.

Methodology

All relevant articles in the medical literature on mifepristone as a single agent for abortion were sought in order to define embryo survival in medical abortion. 1553 studies were retrieved from the PubMed data base using the terms mifepristone and RU-486 abortion; 300 were found in the Cochrane data base. Of these 340 were found to be pertinent to efficacy of mifepristone as an abortifacient; these articles were reviewed for study arms using mifepristone as a single agent. Additional studies were found from the references in these articles, as well as reference lists from review articles on medical abortion. This included articles in French, German, and Japanese in addition to English language articles. The initial earliest mifepristone series, some comparing different doses, were retrieved, as well as later studies comparing the efficacy of mifepristone alone with both mifepristone plus prostaglandins and surgical abortion. Thirty studies were found with

[27] Donald I. Ultrasunics in diagnosis (sonar). *Proc Roy Soc Med*. 1969; 62:442-443.

[28] Robinson H, Shaw-Dunn J. Fetal heart rates as determined by sonar in early pregnancy. *BJOG*, 1973;80(9):805-809.

[29] Drumm J, Clinch J. Ultrasound in management of clinically diagnosed threatened abortion. *BMJ*;1975. 2(5968):424.

[30] Drumm JE, Clinch J, Mackenzie G. The ultrasonic measurement of fetal crown-rump length as a method of assessing gestational age. *BJOG*; 83(6):417-421.

[31] Campbell S. A short history of sonography in obstetrics and gynecology. *FVV in ObGyn*; 2013, 5 (3):213-229.

[32] HCG and progesterone were assessed in most studies; estradiol, cortisol, 17 hydroxyprogesterone, aldosterone, ACTH and prostaglandins were measured in others.

at least one arm using mifepristone as a single agent. Articles were reviewed for inclusion cirteria by two reviewers (MD and MH). Twelve had faulty criteria for embryo survival, did not distinguish embryo survival from incomplete abortion, or did not indicate the abortifacient drug(s) used for surviving embryos. Eighteen articles adequately described embryonic survival. Six of these eighteen papers were found to be duplicates, identical study arms in different journal articles, or early versions of later studies. Altogether twelve studies were found to meet inclusion criteria. The most comprehensive paper of the duplicate studies will be cited in the text of this article. Using data from each of the twelve studies, the number of both subjects enrolled and continuing living pregnancies after mifepristone were recorded. The percentage of embryos surviving after mifepristone and 95% Wilson Score confidence intervals (CI) were then calculated for each study.

Studies Included

After mifepristone ingestion, there are three possible outcomes: 1) embryonic demise with complete evacuation of the uterus; 2) embryonic demise with incomplete uterine evacuation or without uterine evacuation (missed abortion); or 3) continuing living pregnancy. Of the 30 studies retrieved, 18 papers and 12 studies in this analysis used ultrasound at the end of the study period. Ultrasound was used either for all subjects or for those subjects without obvious passage of products of conception, with the capability of determining if there were continuing living pregnancies.

All of the twelve included studies clearly distinguished continuing pregnancies from incomplete uterine evacuations. Additionally, two studies differentiated missed abortions from incomplete abortions.[33,34] In the studies included in this analysis, the presence of fetal heart tones is clearly noted in two studies.[35,36] Surviving embryos are described with terminology such as "ongoing pregnancies"[37,38,39] [growing] "conceptus,"[40] "normal, intact, intrauterine pregnancy,"[41] "unaffected" pregnancy,"[42] "uninterrupted

[33] Maria B, Chaneac M, Stampf F, Ulmann A. Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. *J Gynecol Obstet Biol Reprod* (Paris) 1988;17:1089-94.

[34] Maria B, Stampf F, Goepp A, Ulmann A. Termination of early pregnancy by a single dose of mifepristone (RU 486), a progesterone antagonist. *Eur J Obstet Gynecol Reprod Biol* 1988;28:249- 55.

[35] Ylikorkala O, Alfthan H, Kääriäinen M et al.. Outpatient therapeutic abortion with mifepristone. *Obstet Gynecol* 1989;74 (4):653-57.

[36] Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU486 alone or in combination with prostaglandin analogue (gemeprost). *Contraception*. 1986;34 (5):459-68.

[37] Ylikorkala, *supra* note 36.

[38] Maria (Eur J), *supra* note 34.

[39] Cameron, *supra* note 37.

[40] Sitruk-Ware R, Billaud L, Mowszowica I et al. The use of RU 486 as an abortifacient in early pregnancy. *In* Beaulieu EE, Siegel S eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York: Plenum, 1985;243-248.

[41] Herrmann, *supra* note 17.

[42] Vervest HA, Haspels AA, Preliminary results with antiprogesterone RU-486 .(mifepristone) for interruption of early pregnancy. *FertilSteril*. 1985;44 (5): 627-32.

pregnancy,"[43,44,45] "no indication of pregnancy interruption,"[46] "continuing pregnancy,"[47,48,49] or "intact pregnancy."[50,51] These twelve studies provide a basis for determining the percentage of surviving embryos after mifepristone as a single agent.

Studies Excluded

The early mifepristone trials were focused on proving the safety of mifepristone and the drug's performance in producing complete abortions. The description of failures did not always include designating if a living pregnancy was present. Of the 30 studies retrieved that studied mifepristone as a monotherapy for abortion, twelve were excluded for failure to distinguish between incomplete evacuation of the uterus and embryo survival among the abortion failures, for faulty criteria in determining ongoing embryo survival, or for failure to characterize the abortifacient agent(s) of the surviving embryos. It is important to review these studies in some detail because others have erroneously cited them as evidence for continuing pregnancy after mifepristone, ignoring the fact that incomplete evacuation of uterus does not denote a surviving embryo.

Couzinet found an 85% complete abortion rate overall in 100 subjects and used ultrasound to assess uterine evacuation, but did not note embryo survival.[52]

Dubois and Spitz had large series of 1841 and 1085 subjects, reported 76%-80% complete abortion rates, but did not use ultrasound or denote persisting pregnancy among abortion failures.[53,54]

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[43] Haspels AA Interruption of early pregnancy by the antiprogestational compound RU 486. *In* Beaulieu EE, Siegel S eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum;1985:199-210.

[44] Swahn (Baulieu), *supra* note 20.

[45] Haspels AA.. Interruption of early pregnancy by an anti-progestational compound, RU 486. *Eur J Obstet Gynecol Reprod Biol*. 1985 Sep;20(3):169-75.

[46] Elia D Clinical Study of RU 486 in Early Pregnancy *In* Beaulieu EE, Siegel S eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control.* New York, Plenum; 1985: 211-220.

[47] Carol W, Klinger G. [Experiences with the antigestagen mifepristone (RU 486) in the interruption of early pregnancy]. *Zentralbl Gynakol* 1989;111 (9):1325-8.

[48] Somell C, Olund A. Induction of abortion in early pregnancy with mifepristone. *Gynecol Obstet Invest* 1990;29:13-5. 1990.

[49] Somell C, Olund A., Carlstrom K, Kindahl, H. Induction of abortion in early pregnancy with mifepristone. *Gynecol Obstet Invest* 1990;30:224-27.

[50] Kovacs L, Sas M, Resch BA et al. Termination of very early pregnancy by RU 486–an antiprogestational compound. *Contraception* 1984;29 (4):399-410.

[51] Kovacs L. Termination of Very Early Pregnancy with Different Doses of RU-486: A Phase I Controlled Clinical Trial. *In*: Beaulieu EE, Siegel S eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*.New York: Plenum; 1985:179-198.

[52] Couzinet B, Le Strat N, Ulmann A, et al. Termination of early pregnancy by the progesterone antagonist RU 486 (Mifepristone). *N Engl J Med*. 1986. 315(25):1565-70.

[53] Dubois, C, Silvestre L, Ulmann A [Use of mifepristone in the termination of early pregnancy. The experience in France]. *Presse Med.* 1989. 18(15):757-60.

[54] Spitz IM, Shoupe D, Sitruk-Ware R, et al. Response to the antiprogestagen RU 486 (mifepristone) during early pregnancy and the menstrual cycle in women. *J Reprod Fertil Suppl*. 1989;37:253-60.

Birgerson authored three studies using low daily doses of 20-100 mifepristone given over 7 days; he found rates of complete abortion of 61-71%, but did not use ultrasound for evacuation failures. The subjects were assessed at a seven day follow up exam after the first mifepristone dose, actually during the last day of mifepristone therapy. Vacuum aspiration was performed at 8-10 days following the first mifepristone dose if the patient did not have a history, physical exam, or HCG decline consistent with passage of productions of conception by day 7.[55,56,57] There was no documentation of a living embryo.

Mishell and Shoupe used seven day mifepristone regimens and Grimes used a single 600 mg dose in their mifepristone trials. Although pre-treatment ultrasound was used for dating, these three authors did not use post-treatment ultrasound in treatment failures to ascertain if there were continuing, living pregnancies.[58,59,60]

Swahn in a 1989 study compared abortions with mifepristone alone to abortions with mifepristone and prostaglandin E, but did not clearly delineate how many surviving embryos were in the group using mifepristone as a single agent.[61]

In the study reported by Zheng in China, subjects with gestations less than 49 days were given a single mifepristone dose of 600 mg and assessed after seven days.[62] Outcomes were categorized as complete abortion, incomplete abortion and "persisting pregnancy." Ultrasound was not used at the end of the study to determine "persisting pregnancies." Only clinical and HCG criteria were used, the criteria for "persisting pregnancy" being "absence of expulsion of the conceptus, and *gradual* increase in serum and urine hCG." Zheng does not define "gradual" increase in hCG. Furthermore, urine hCG can be positive as late as one month after complete abortion.[63] Ultrasound was not used to assess those pregnancies in the category of "persisting pregnancy." It is well known

[55] Birgerson L, Odlind V, Johansson E. Clinical effects of RU 486 administered for seven days in early pregnancy. *In*: Beaulieu EE, Siegel S eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control.*New York:Plenum; 1985: 211-220.

[56] Birgerson L, Odlind V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: a comparison of three dose regimens. *Contraception* 1988;38:391-400.

[57] Birgerson L, Odlind V. Early pregnancy termination with antiprogestins: a comparative clinical study of RU 486 given in two dose regimens and Epostane.*Fertil Steril*.1987;48(4):565-70.

[58] Mishell DR Jr, Shoupe D, Brenner PF et al.Termination of early gestation with the anti-progestin steroid RU 486: medium versus low dose. *Contraception*. 1987;35(4):307-21.

[59] Shoupe D, Mishell DR Jr, Brenner PF et al. Pregnancy termination with a high and medium dosage regimen of RU 486. *Contraception*. 1986; 33(5):455-61.

[60] Grimes DA, Mishell DR, Shoupe D et al. Early abortion with a single dose of the antiprogestin RU-486. *Am J Obstet Gynecol*.1988;158 (6 Pt 1):1307-12.

[61] Swahn ML, Ugocsai G, Bygdeman M et al. Effect of oral prostaglandin E2 on uterine contractility and outcome of treatment in women receiving RU 486 (mifepristone) for termination of early pregnancy. *Hum Reprod* 1989;4 (1):21-28.

[62] Zheng SR. RU 486 (mifepristone): clinical trials in China. *Acta Obstet Gynecol Scand Suppl* 1989;149:19-23.

[63] Marie Stopes, a large international abortion service, advises post-abortive women that urine pregnancy tests may be positive as late as 8 weeks after medical abortion. https://www.mariestopes.org.uk/women/abortion/abortion-aftercare/when-should-i-do-pregnancy-test-after-abortion.

that in early gestations serum HCG typically rises rapidly; the median slope for a rise of hCG after 1 day was 1.50, (or a 50% increase); 2.24 after 2 days (or a 124% rise), and 5.00 after 4 days.[64] Although the high failure rates cited in the Zheng study have been used to suggest that mifepristone has a poor embryocidal capacity, the data published in his study is not reliable for determining the rate of embryo survival.

Elia, after his 1985 study using a multi-dose regimen in 18 women with gestations up to 70 days, headed a multi-site trial of mifepristone in 1986. The 1986 study used a single dose of 600 mg or 450 mg mifepristone with 434 and 146 subjects, respectively, and was limited to ≤49 days gestation. He found the following continuing pregnancy rates with 600 mg mifepristone: <35 days 9%, 35-42 days 16%, 43-49 days 27%.; the overall rate for the entire group was 16.1%. At the 450 mg dose continuing pregnancy rates were <35 days 0%, 35-42 days 16%, 43-49 days 23%; the overall continuing pregnancy rate for the entire group was 19%. Unfortunately, although the 1986 study distinguished complete abortions from continuing pregnancies, there is no mention of criteria for continuing pregnancy, ultrasound, or methodology, so we cannot tell if what were termed "developing pregnancies" (grossesses evolutives) were actual living pregnancies or missed abortions. Although Elia did not publish strict criteria for living pregnancies, we see a general trend of increasing continuing pregnancy rates with each week of gestational age and with decreasing doses of mifepristone.[65,66]

Mention must be also made of the review by Grossman et al. of continuing pregnancy after mifepristone.[67] The Grossman review stated that no conclusions about continuing pregnancy rates could be made to apply to current clinical practice due to varying dose ranges and wide confidence intervals in studies using mifepristone as a single agent. However, this review omitted critical mifepristone studies by Sitruk-Ware, Herrmann, Haspels, Vervest and Elia. Additionally, the Grossman review included studies by Grimes, Birgerson, Swahn and Zheng that did not assess abortion failures with ultrasound to verify if living embryos were present, or had other faulty criteria.

Results

The 12 studies that assessed embryonic survival with ultrasound demonstrate that mifepristone is lethal over a wide range of doses and regimens. (See Table 1). Eight studies investigated early pregnancy ≤49 days (Ylikorkala, both Maria studies, Carol, Somell, Sitruk-Ware, Kovacs, Swahn; four included gestations greater than 49 days and up to 70 days (Herrmann, Elia, Cameron, Vervest). Taking all studies into consideration, with daily doses of 50-600 mg and total doses of 200-1000 mg, the percentage of mifepristone survivors varied from 0-50%. Mifepristone was more successful as an

[64] Barnhart KT et al. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. *Obstet Gynecol.* 2004;104(1):50-55.

[65] Elia D, Ulmann, A. RU-486 (mifepristone): des essais cliniques aux perspectives d'utilisation. *Contraception-fertilite-sexualite*. 1986. 14 (12):1099-1103.

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abortifacient in larger doses and earlier gestations. The mean percentage of surviving embryos of all dose ranges and gestational ages was 12.6%, with most studies using total doses of 600 mg or more.

The earliest pioneering studies of 8-44 subjects used divided doses of mifepristone (two to four times daily), and multiple day regimens, over four to six days (Elia, Sitruk-Ware, Herrmann, Vervest, Kovacs, Cameron, Swahn). The highest dose regimens ranged from 150- 200 mg for four days (Kovacs, Hermann, Elia, Vervest) to 200 mg for five days (Sitruk-Ware). Two high dose multi-day studies of gestations ≤49 days showed survival rates of 0-10% (Sitruk-Ware and Kovacs). Four multi-dose studies of 100-200 mg for four days included later gestations up to 70 days. Of these, Hermann found a survival rate of 18.1% in 11 subjects; Vervest had no surviving embryos out of 44 subjects, Cameron had a 25% survival out of 20 subjects; Elia found 50% surviving embryos in 14 subjects.

Trials performed from 1986-1990 sought to produce a complete abortion with a single dose of mifepristone, were limited to early gestations, and are the most pertinent relating to current use. A single dose of 600 mg in gestations ≤42-49 days in five studies showed embryo survival ranging from 9.4%-17.1% (Ylikorkala, two Maria studies, Carol, Somell). The largest study of this group by Maria et al. with 174 subjects included gestations up to 49 days, and showed 11.5% continuing pregnancies (CI 7.3-17.4%).

Two early trials limited to gestations ≤42-49 days, studied lower total doses of ≤400 mg, and used multi-dose regimens of 50-100 mg over 4-6 days (Kovacs, Swahn). Embryonic survival rates ranged from 10%-16.7%. Maria studied 30 subjects with gestations ≤49 days using a 200 single dose regimen and found embryo survival of 23.3% (CI 10.6-42.7).

One factor possibly correlated with embryo survival may be the follow up period. Ultrasounds were done at approximately one or two weeks after mifepristone ingestion to assess if the abortion was complete; vacuum aspiration was typically performed in cases of incomplete uterine evacuation. In some studies, the follow up visits were calculated from the first and in others after the last mifepristone dose in multiple day protocols. Of the seven studies with follow up ultrasounds 13-14 days after the last mifepristone dose, average embryo survival was 9.2%, with a range of 0-25% (Ylikorkala, Carol, Sitruk-Ware, Kovacs, Cameron, Vervest, and Swahn). Two of these eight studies had arms with no surviving embryos (Kovacs, Vervest). Five studies with a shorter follow up time of 6-8 days showed an average embryo survival of 14.2% ranging from 9.4-50% (Two Maria studies, Somell, Elia, Herrmann). The decision to perform an early vacuum aspiration was made in some cases only two days after the final mifepristone dose of a multi-day regimen (Elia, 1985). Although no absolute conclusion can be drawn regarding the timing of embryonic demise after mifepristone administration due to the heterogeneity of doses and gestational ages in each group, a trend of a greater embryocidal effect can be seen in the group with the longer follow up period.

EMBRYO SURVIVAL AFTER MIFEPRISTONE							
	Total dose (mg)	Daily Dose (mg)	Gestational Age (days)	Follow up after mifepristone	Subjects	Surviving Embryos	Percent and 95% Confidence Interval
Sitruk-Ware 1985	1000	200	≤49	14days	10	1	10% (0.5-45.9%)
Kovacs (Contraception, Baulieu) 1984, 1985	800	200	≤42	14 days	8	0	0% (0-40.2%)
Herrmann (CR Seances, Baulieu) 1982, 1985	800	200	42-45 46-48 49-52 53-55 Total <56	7 days	2 2 5 2 11	0 0 1 1 2	18.1% (3.2-52.2%)
Elia 1985	800	200	≤35 36-42 43-49 50-56 57-63 Total ≤63	6 days	1 7 5 2 3 18	0 3 3 0 3 9	50% (26.8-73.2%)
Vervest; Haspels (Eur J, Baulieu, FertilSteril) 1985	400-800 800	100-200 200	≤55 56-70 Total ≤70	14 days	35 9 44	0 0 0	0% (0-10%)
Ylikorkala 1989	600	600	≤45	14 days	50	5	10% (3.7-22.6%)
Maria (J Gyn) 1988	600	600	≤49	7 days	174	20	11.5% (7.3-17.4%)
Maria (Eur J) 1988	600	600	≤42	7 days	149	14	9.4% (5.4-15.6%)
Carol 1989	600	600	≤43	14 days	50	6	12% (5.0-0.25.0%)
Somell (Gyn Ob Invest V29, V30) 1990	600	600	≤42	7 days	70	12	17.1% (9.5-28.4%)
Cameron (Contraception, BJOG) 1986,1989	600	150	≤56	14 days	20	5	25% (9.6-49.4%)

Kovacs (Contraception, Baulieu) 1984,1985	400	100	≤42	14 days	10	1	10% (0.5-49%)
Swahn (Baulieu) 1985	400	100	≤49	14 days	6	1	16.7% (0.9-64.5%)
Swahn (Baulieu) 1985	200-300	50	≤49	14 days	10	1	10% (0.5-45.9%)
Maria (J Gyn) 1988	200	200	≤49	7 days	30	7	23.3% (10.6-42.7%)
Kovacs (Contraception, Baulieu) 1984,1985	200	50	≤42	14 days	18	2	11.1% (2-36.1%)
Total among all studies					678	86	12.6%

Discussion

Mifepristone was originally envisioned as a drug for very early abortion to be used shortly after the first missed menses. The early small multi-day trials of larger doses are less pertinent to current practice of single doses of mifepristone. Because of the variety of dose regimens and small numbers in many of these studies, it it not possible to combine them in a meta-analysis of the entire group. When 600 mg mifepristone as a single dose in gestations ≤49 days is used, we find consistent continuing pregnancy rates of under 20% in all studies. The largest study of 174 subjects ≤49 days, a continuing pregnancy rate of 11.5% with narrow confidence intervals (CI 7.3-17.4%) is found. Four other smaller studies of early gestations ≤42-49 days at 600 mg dose confirm similar low continuing pregnancy rates ranging from 9.4-17.1%.

Despite the failure to accurately define criteria for living pregnancies, Elia's large multicenter 1986 trial of gestations ≤49 days gives some indication of trends in actual survival. Continuing pregnancy rates for his entire group of 434 subjects ≤49 days was 16.1% at 600 mg, (CI 12.9-20%) within the confidence limits of Maria's 600 mg trial of 174 subjects. Using the lower 450 mg dose in 146 subjects ≤49 days gestation, the continuing pregnancy rate is 19% (CI 13.3-26.7%). These rates of continuing pregnancies in gestations ≤49 days at 600 mg and 450 mg (16.1% and 19%, respectively) are in line with Maria's single dose 200 mg study of 30 women that showed a continuing pregnancy rate of 23.2%. Although the Maria study is the sole study using a single dose of 200 mg, two small multi-dose studies of ≤42-49 day gestations using 200-300 mg and (50 mg daily for 4-6 days) show continuing pregnancy rates of 10-11.1%. These

rates of continuing pregnancy under 25% confirm the high embryocidal capacity of 200 mg mifepristone for gestations <49 days in current clinical practice.[68,69]

It is more difficult to transpose the embryo survival rates at later gestations from the early literature to contemporary practice using the 200 mg single dose regimen, when mifepristone as a single agent is given. There are only four studies in the early literature enumerating continuing pregnancies that include gestations from 50-70 days.[70,71,72,73] They are all small trials using multi dose regimens with total doses from 400-800 mg, with continuing pregnancy rates of 0-50%. Three of the four studies show continuing pregnancy rates of ≤25%. When misoprostol is added, the continuing pregnancy rates also rise with increasing gestational age.

Of interest for comparison is the original FDA-approved combined regimen of 600 mg mifepristone and 400 mcg oral misoprostol.[74] The U.S. trials of these doses showed an overall continuing pregnancy rate of 3.9% in 2121 subjects with the following breakdown in continuing pregnancies: ≤49 days 1%, 50-56 days 4%, 57-63 days 9%. It should be noted that in a more recent review by Chen and Creinin the continuing pregnancy rate ≤63 days was much lower at 0.8%, and at 64-70 days 2.9%, using 200 mg mifepristone and 400-800 mcg *buccal* misoprostol. In any clinic, the mix of gestational ages will affect the potential continuing pregnancy rate, and will rise with the proportion of later gestations.[75] S. Cameron, head of a large reproductive health service in Scotland, reviewing a study of 105 women with continuing pregnancies ≤63 days gestation after attempted medical abortion, estimated the overall continuing pregnancy rate after mifepristone alone to be 20%.[76,77]

The follow up period after mifepristone ingestion may be a significant factor determining embryonic survival. It is well known that mifepristone binds to endometrial progesterone receptors and releases prostaglandin soon thereafter. However, mifepristone's effects on the corpus luteum, placenta, angiogenesis, ovarian volume, and VEGF protein may act in a delayed fashion, and cause embryonic demise between 7-14 days, affecting continuing pregnancy rates depending on the study protocol. Progesterone secretion shifts from the corpus luteum to the placenta after 49-63 days gestation, when delayed mechanisms of action of mifepristone may play a larger role. Carol found that

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[68] Elia (Cont-fert-sex), *supra* note 66.

[69] Maria (J Gyn), *supra* note 34.

[70] Herrmann, *supra* note 17.

[71] Vervest, *supra* note 43.

[72] Cameron, *supra* note 37.

[73] Elia (Bailieu), *supra* note 47.

[74] Spitz I, Bardin C, Benton L et al. Early pregnancy termination with mifepristone and misoprostol in the United States. *NEJM*. 1998; 338 (18): 1241-47.

[75] Chen MJ, Creinin MD. Mifepristone with buccal misoprostol for medical abortion: a systematic review. *Obstet Gynecol*. 2015;126(1):12-21.

[76] Cameron S. Reviewer's commentary on 'Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study.' *BJOG* 2013;120(5):575.

[77] Bernard, *supra* note 2.

of 50 women who had complete abortions, 7.5% aborted after 7 days.[78] The rodent study by Yamabe showed increasing rates of fetal demise with each additional day after mifepristone injection, although 100% survival occurred with the addition of progesterone.[79] We can speculate that some human embryos surviving after a short follow up period may have undergone a potentially fatal injury from mifepristone, but might survive if given progesterone.

Conclusion

Mifepristone was originally promoted as an effective embryocidal agent in early pregnancy. The early researchers correctly determined that the drug was better at producing embryonic demise than emptying the uterus, and added prostaglandins for effective clinical use. To correctly assess the continuing pregnancy rate after mifepristone as a single agent, ultrasound must be used. This review of studies that accurately verify continuing pregnancy after mifepristone confirms that this agent produces high rates of fetal demise and continuing pregnancy rates of <25% with doses of 200-600 mg at early gestations ≤49 days. There is less data at later gestations, but the majority of available studies using mifepristone doses of 400-800 mg and gestational age limits up to 70 days show continuing pregnancy rates of <25%.

Studies Analyzed (with Duplicates)

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[78] Carol, *supra* note 48.

[79] Yamabe, *supra* note 12.

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