

Immunopharmacology of ulipristal as an emergency contraceptive

Ralph P Miech

Department of Molecular Pharmacology, Physiology and Biotechnology, Warren Alpert School of Medicine, Brown University, Providence, RI, USA

Abstract: A new progesterone antagonist, ulipristal has been made available as an emergency contraceptive. Ulipristal's major mechanism of action as an emergency contraceptive has been ascribed to its ability to delay ovulation beyond the life span of the sperm. This paper analyzes the potential action of ulipristal (1) when unprotected intercourse and administration of ulipristal occur outside the fertility window and (2) when unprotected intercourse and administration of ulipristal occur at or within 24 hours of ovulation. When unprotected intercourse and the use of a single low dose of ulipristal occur outside of the fertility window, ulipristal behaves like a placebo. When unprotected intercourse and the use of a single low dose of ulipristal occur within the fertility window but before ovulation, ulipristal behaves like an emergency contraceptive by delaying ovulation and thereby preventing fertilization. When unprotected intercourse and the administration of ulipristal occur at or within 24 hours of ovulation, then ulipristal has an abortifacient action. It is proposed that the abortifacient mechanism of a low dose of ulipristal taken after fertilization but before implantation is due to the ability of ulipristal to block the maternal innate immune system to become immunotolerant to the paternal allogenic embryo. Progesterone's critical immunotolerant actions involving early pregnancy factor, progesterone-induced blocking factor, and uterine natural killer cells are compromised by ulipristal.

Keywords: innate immune system, early pregnancy factor, progesterone-induced blocking factor, uterine natural killer cells, selective progesterone receptor modulator

Introduction

Ulipristal is a progesterone antagonist that is being used as an emergency contraceptive (EC) to delay ovulation beyond the life span of the sperm and thus prevent fertilization. This paper describes an additional hypothesis that suggests that ulipristal in certain circumstances blocks the immunotolerance effects of progesterone on the maternal innate immune system (mIIS), resulting in the immunorejection of an embryo attempting to implant.

Progesterone in pregnancy

Progesterone exerts its hormonal effects by binding to specific genomic and nongenomic receptors.^{1,2} Progesterone regulates the inflammatory processes in the human endometrium during both menstruation and implantation of the embryo.^{3,4} Inadequate progesterone synthesis results in spontaneous abortions.⁵ Progesterone has immunomodulating effects on dendritic cells from female mice that result in inhibition of pro-inflammatory cytokine secretion, downregulation of major histocompatibility

Correspondence: Ralph P Miech
50 Woodcrest Drive, Riverside,
Providence, RI 02915, USA
Tel +1 401 433 0431
Fax +1 401 863 1595
Email ralph_miech@brown.edu

Class II expression and decreased T-cell proliferation.⁶ These effects can be reversed by mifepristone, a progesterone antagonist.⁷ Induction of postimplantation pregnancy termination by the use of high dose mifepristone is related to placental effects of mifepristone rather than on unknown effects of mifepristone on the embryo, ie, preimplantation pregnancy termination. Low dose mifepristone has been shown not to affect ovulation but to alter the *in vitro* maturation of dendritic cells, which favors the immunorejection of an embryo attempting to implant.⁸

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) are progesterone receptor ligands that exert a multitude of unique *in vivo* effects that are tissue-selective.^{9–12} SPRMs function as either agonists, antagonists, or mixed agonist/antagonists, depending upon the progesterone sensitive tissue affected by the SPRM.^{13,14} Ulipristal, a chemical and pharmacological analog of mifepristone, is a SPRM that is marketed as a second generation EC under the trade name, ella[®] (Laboratoire HRA Pharma, Paris, France).^{15–20} The pharmacology, pharmacokinetics, efficacy, and safety of ulipristal as an EC have been recently reviewed.²¹ Classifying ulipristal as a contraceptive versus classifying ulipristal as a contragestive have been analyzed.²² “This report will use the classical definitions of both abortion and contraceptive. Abortion is defined as the loss of the embryo occurring either at the preimplantation stage or at the post-implantation stage and contraception is defined as the prevention of fertilization.”

ECs

ECs are employed after a single episode of either unprotected intercourse or condom failure. Levonorgestrel, a first-generation EC, is effective as an EC if taken within 72 hours after intercourse and if taken in the follicular phase and prior to the rising levels of luteinizing hormone (LH).^{23,24} Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an *in vitro* endometrial culture model.²⁵ Ulipristal's effectiveness as an EC is extended up to 120 hours after intercourse in the follicular phase and is also effective as an EC if taken during rising LH levels prior to ovulation.^{26–29}

The mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception have been described.²⁴ The mechanism of action of low dose of ulipristal (30 mg) as an EC has been attributed exclusively to the mechanism of delaying ovulation for several days until the deposited sperm are no longer capable of fertilizing the ovum.^{27,30,31}

Because ulipristal has a long biological half-life of 32 hours, it is able to delay ovulation past the life span of sperm.²¹ To date, there have been no reports of any immunopharmacologic adverse reactions attributed to the delay of ovulation by ulipristal. Sperm are capable of fertilizing an ovum from a few minutes after intercourse up to 5 days (120 hours) later by those sperm that were stored in the cervical crypts. On the other hand, the ovum is only capable of being fertilized for 24 hours after ovulation.^{32,33} Ulipristal has a placebo effect when both unprotected intercourse and the administration of ulipristal occur more than 24 hours after ovulation. However, there is a unique circumstance and time period in which ulipristal would have a direct abortifacient effect rather than a contraceptive effect. When unprotected intercourse occurs within the fertility window (ie, less than 120 hours (5 days) before ovulation or not more than 24 hours after ovulation) and ulipristal is taken after fertilization, then ulipristal would have an abortifacient effect. An abortifacient effect of ulipristal can occur when ulipristal is taken post-fertilization but prior to implantation, when the progesterone levels are relatively low. The following analysis proposes that ulipristal unleashes an immunological attack on the implanting embryo.

Multiple mechanisms of action of ulipristal

Ulipristal binds to selective progesterone receptors in the uterus and corpus luteum, resulting in three abortifacient mechanisms: (1) failure of the decidua to develop and become receptive to implantation of the blastocyst, (2) failure of secretions of uterine glands in the decidua to maintain an implanted embryo, and (3) the return of spontaneous uterine contractions.^{34–36} There is potentially a fourth mechanism involving the immunological rejection of the blastocyst's trophoblast cells in a host-versus-graft rejection mechanism during the embryo's attempt to implant into the decidua. This fourth mechanism, proposed in this paper, involves the mIIS during the first 5–10 days after fertilization.³⁷

Immunosuppression of the innate immune system in pregnancy

For a pregnancy to be successful, one of the many vital actions of progesterone is its ability to induce selective immune tolerance of the mIIS toward the paternal allogeneic embryo, beginning with fertilization and extending through implantation.^{38–44} During implantation, this induced tolerance of the mIIS is unique in that the mIIS is still able to provide a defense against the bacteria that invade the decidua.^{45,46} Since the protective zona pellucida and the surrounding

granulosa cells are of maternal origin, the mIIS is not triggered by the foreign paternal antigens on the encapsulated embryo. Thus, from fertilization to the shedding of the zona pellucida, the developing embryo is shielded from initiating an immunological attack.⁴⁷ Activation of the innate immune system would result in pregnancy loss.⁴⁸ After shedding of the zona pellucida, implantation of the blastocyst can begin, and several factors are involved in the initiation of the selective immunotolerance of an implanting paternal semi-allogeneic graft.^{49–51} For example, human leukocyte antigen G plays a key role in implantation by modulating cytokine secretion to control trophoblastic cell invasion and to maintain a local immunotolerance.^{52–58} The decidua secretes glycodeclin, a protein with proposed immunomodulatory activity during nidation.⁵⁹ To avoid rejection, the villous trophoblast population of cells that are exposed to maternal blood lacks both major histocompatibility complex class I and class II molecules.⁶⁰ Immunotolerance is further aided by progesterone's ability to stimulate both systemic and uterine regulatory T cells, (CD4⁺CD25⁺ Treg cells) so that anti-inflammatory T helper (Th)-2 cells predominate over the pro-inflammatory Th-1 cells.^{61–66} Th-1 cells produce inflammatory cytokines associated with spontaneous abortion, while Th-2 cells secrete anti-inflammatory cytokines associated with immunotolerance.⁶⁷

Early pregnancy factor (EPF), progesterone-induced blocking factor (PIBF), and phenotypically altered decidua natural killer cells (DANK) are intimately involved in allowing the mIIS to set up a selective tolerance of the implanting embryo.⁶⁸ Since both mifepristone and ulipristal alter the natural functioning of progesterone receptors involved in EPF, PIBF, and DANK, progesterone is prevented from inducing the necessary selective tolerance state of the mIIS cells in the decidua, the uterine stoma, and the corpus luteum. This allows mIIS cells to reject the implanting or newly implanted embryo.

EPF

Within microseconds after fertilization, the ion channels in the zygote's cell membrane open resulting in a permanent negative charge that sweeps across the surface of the zygote's cell membrane preventing additional sperm from gaining access to the interior of the fertilized ovum. Then, within minutes after fertilization, the zygote secretes an enzyme that changes the zona pellucida from a sol to a gel, which forms an additional barrier that sperm are not able to penetrate and protects the embryo from both physical damage and cellular immunological attack as the embryo

begins its 5–7 day journey through the fallopian tube into the interior of the uterus. Within hours after fertilization, the developing embryo begins secretion of ovum factor, which stimulates progesterone-primed maternal ovaries to secrete EPF. EPF has immunomodulatory properties, and it is an extra cellular form of protein chaperonin 10.^{69–71} EPF is the first of three mechanisms that suppresses the mIIS to prevent immunological rejection of the embryonic trophoblast cells. The invading trophoblast cells of the blastocyst constitute a semi-allograft that would be rejected without the suppression of the mIIS by progesterone. Developing trophoblasts of the embryo take over from the ovaries and maintain the secretion of EPF. EPF binds to a specific lymphocyte population that releases soluble suppressor factors.³⁹ Figure 1 depicts the proposed mechanism by which EPF suppresses the mIIS.

A variety of cellular and signaling mechanisms use nuclear factor (NF)- κ B to generate pro-inflammatory cytokines, inflammatory mediators, and cytotoxic cells as agents to protect humans from infections, tumors, and carcinogens.^{72,73} NF- κ B is a ubiquitous transcription factor. Since NF- κ B functions as the master switch in immune system's protective mechanisms, NF- κ B may operate in the rejection of semi-allogenic cells.^{50,74,75} Thus EPF could achieve immunosuppression of uterine immune cells by activating I- κ B, the naturally occurring inhibitor of NF- κ B.⁷⁶

PIBF

In pregnant mice, due to endocrine stimulation by progesterone, splenic lymphocytes synthesize and secrete

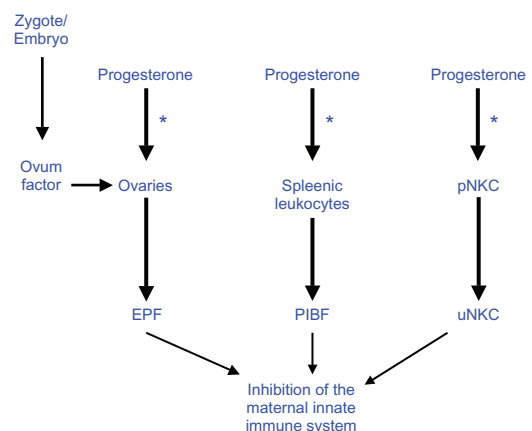


Figure 1 Immunosuppression of the innate immune system in pregnancy. Normal suppression of the maternal innate immune system begins with fertilization and is a result of EPF and progesterone-dependent secretion of T helper-2 cytokines, the inhibitor of nuclear factor kappa beta, interleukin-10, and tumor growth factor beta.

Note: *When blocked or modulated by ulipristal, the maternal immune innate system is free to immunologically attack the trophoblast cells of the implanting embryo in a host-versus-graft reaction.

Abbreviations: EPF, early pregnancy factor; PIBF, progesterone-induced blocking factor; pNKC, peripheral natural killer cell; uNKC, uterine natural killer cell.

a factor that immunosuppresses the maternal immune system.^{77,78} This factor, PIBF, inhibits natural killer cell (NKC) cytotoxicity, stimulates production of asymmetrical antibodies, and increases interleukin (IL)-4 production.^{79,80} The net result of PIBF is to inhibit Th-1 cytokine responses and increase Th-2 responses.^{81–85} PIBF has been shown to have an anti-abortive effect in mice. NKC activity has been shown to be significantly lower in pregnant women when compared with nonpregnant women. Spontaneous abortions in women have been associated with increased NKC activity, and NKCs are recruited into the decidua during early pregnancy in both mice and humans. Splenic cells from mice on day 8.5 of pregnancy treated with anti-PIBF immunoglobulin G had a fourfold increase in natural killer activity when sacrificed on day 10.5. Mice injected with mifepristone on day 8.5 of pregnancy and sacrificed on day 10.5 had an increased abortion rate and a decrease in PIBF-producing cells in the spleen.^{86,87} Early termination of pregnancy induced with mifepristone is associated with a disturbance of progesterone-mediated immunosuppression.⁸⁸ It is reasonable to assume that ulipristal, a derivative of mifepristone, would exert the same effect as mifepristone on lymphocytes that synthesize and secrete PIBF during pregnancy.

Phenotypic conversion of peripheral NKCs (pNKCs) to uterine NKCs (uNKCs)

NKCs provide the first line of defense of the mIIS against transplanted semi-allogenic cells, tumor cells, and cells infected with bacteria or viruses.^{89–95} Cytotoxic materials are delivered from NKCs to adverse target cells via a cellular structure known as an immune synapse that is composed of microscopic nanotubes.^{96–98} Chemokines and cytokines are secreted by the implanting embryo, resulting in the recruitment of maternal pNKCs (CD56^{dim}CD16⁺).⁹⁹ These pNKCs under the direct influence of progesterone undergo a phenotypical conversion to uNKCs (CD56^{bright}CD16⁻) and regulate embryo development.^{100–102} This conversion appears to be controlled by the trophoblast secretion of tumor growth factor-beta into the local environment of the decidua.^{94,103} Furthermore, chorionic gonadotrophin (hCG), secreted by the preimplantation developing embryo within the fallopian tube, contributes to maternal immunotolerance by regulating the Fas-Fas ligand system.¹⁰⁴ Also, hCG is a stimulator of uNKC proliferation.^{103,105} The phenotypical uNKCs are crucial for the secretion of angiogenic factors, such as vascular endothelial growth factor for the remodeling of the vasculature

of the spiral arteries in formation of the placenta.^{106–108} Low-dose mifepristone has been shown to act as an anti-implantation drug by causing a dysregulation of uNKCs during implantation.³ Progesterone suppression of tumor necrosis factor α , IL-1 β , and IL-12 is prevented by mifepristone.^{3,109} It is postulated that ulipristal also acts in a similar manner to mifepristone in causing a dysregulation of uNKCs, resulting in the destruction of the embryo by NKCs.

Summary

The mechanism of action of a low-dose ulipristal (30 mg) as an EC has been attributed exclusively to the delaying of ovulation by 5 days. This particular mechanism of action occurs when both unprotected intercourse and the administration of ulipristal occur within the fertile window. However, a single low dose of ulipristal has a placebo effect when both unprotected intercourse and the administration of ulipristal occurs more than 24 hours after ovulation. Furthermore, when unprotected intercourse occurs during the fertile window and the administration of ulipristal occurs after ovulation, then ulipristal exerts an abortifacient action. It is proposed that the mIIS is responsible for the destruction of the implanting embryo via a host-versus-graft reaction involving ulipristal interference with EPF, PIBF, and decidual NKCs within the mIIS.

Datasources

MEDLINE, PubMed, and Google Scholar databases were searched (1980–June 2011). Key search terms were: progesterone, ulipristal, mifepristone, emergency contraceptives, early pregnancy factor, progesterone induced blocking factor, uterine natural killer cells, and pregnancy immunosuppression. Search of the literature was limited to the English language.

Disclosures

This paper was presented at the 2011 meeting of the American Association of the Pro-Life Obstetricians and Gynecologists. The author reports no conflicts of interest in this work.

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