REPRODUCTION
REVIEW

Mechanisms involved in the contraceptive effects of ulipristal acetate

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Abstract

The use of emergency contraception (EC) methods is increasing worldwide as it constitutes an effective way to prevent unplanned pregnancy after unprotected sexual intercourse. During the last decade, ulipristal acetate (UPA), a selective progesterone receptor modulator, has emerged as the most effective EC pill, and it is now recommended as first-line hormonal treatment for EC in several countries. Its principal mechanism of action involves inhibition or delay of follicular rupture, but only when administered during the follicular phase before the luteinizing hormone (LH) peak. However, considering the high efficacy of UPA, it is possible that it also exerts contraceptive effects besides ovulation. In the present review, we summarize and discuss the existing evidence obtained on the effect of UPA on sperm function and post-ovulatory events as potential additional mechanisms to prevent pregnancy. The bulk of evidence collected so far indicates that UPA would not affect gamete function; however, it could impair embryo–uterine interaction. Thus, besides the described effects on ovarian function, UPA contraceptive effectiveness might also be attributed to post-ovulatory effects, depending on the moment of the female cycle in which the drug is administered.

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Introduction

The use of contraceptive methods allows people to fulfill their desired number of children and determine the spacing between pregnancies. The World Health Organization states that ensuring access to preferred contraceptive methods is essential to securing the well-being and autonomy of women, while supporting the health and development of communities. Among the different methods available, emergency contraception (EC) involves the use of drugs or devices as a back-up method to prevent pregnancy after unprotected sexual intercourse or after misuse or failure of another contraceptive method.

The copper intrauterine device (Cu-IUD) has been used as EC for more than 35 years and is the most effective method available that can even be left in place as ongoing contraception afterward. Guidelines for the use of Cu-IUDs for EC recommend inserting the IUD within 5 days of unprotected sexual intercourse or no later than 5 days after ovulation if this event can be reasonably determined, to avoid the possibility of an abortifacient effect (Cleland *et al.* 2012). The mechanisms of action include deleterious effects of the Cu^{2+} ions on sperm function and fertilization. In addition, Cu^{2+} ions prevent endometrial receptivity and implantation in case fertilization has already occurred (Cheng *et al.* 2012). However, its use as EC is limited due to the requirement of trained healthcare professional for the device insertion (Gemzell-Danielsson *et al.* 2014), and the uncertainty that the Cu-IUD is inserted before the implantation of an embryo has taken place (Cleland *et al.* 2012).

Considering the fundamental role of progesterone (P4) during the whole fertilization process ranging from ovulation to sperm function, implantation and pregnancy development (Blackmore *et al.* 1991, Carson *et al.* 2000, Ramathal *et al.* 2010, Lishko *et al.* 2011, Strunker *et al.* 2011), it is not surprising that several synthetic compounds that present pure antagonist or a mixture of agonist/antagonist actions on P4 receptors (PR) (Chabbert-Buffet *et al.* 2005), known as selective PR modulators (SPRM), have been developed with applications in contraception.

Of the existing modulators, mifepristone (RU486) presents anti-P4 activity on PR in humans (Leonhardt & Edwards 2002). Low doses of mifepristone (10–25 mg) are used as EC in a limited number of countries including Armenia, China, Russia, and Vietnam. However, the fact that higher doses are used for medical termination

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of pregnancy is the reason why it is not worldwide distributed as EC method.

The Yuzpe regimen combining two intakes of the oral contraceptives ethinylestradiol (EE, 100 µg) and levonorgestrel (LNG, 0.5 mg) has been widely used for EC (Task Force on Postovulatory Methods of Fertility Regulation 1998, Trussell *et al.* 1998). Today, given the availability of more effective options, this regimen is limited to countries where there is no access to other EC methods. The development of pills containing LNG (1.5 mg) has replaced the Yuzpe regimen. A randomized clinical trial comparing both methods showed that LNG prevents significantly more pregnancies than the Yuzpe regimen, and its effectiveness increases when the drug is administered close to the time of coitus. The mechanism of action of LNG is to delay or inhibit ovulation when given prior to the LH surge (Croxatto *et al.* 2004), without affecting endometrial development or P4 levels (Durand *et al.* 2001). *In vitro* studies did not show any effect of the drug on mouse and human blastocysts development (Munuce *et al.* 2005, Lalitkumar *et al.* 2007). Moreover, the effect of LNG on implantation has been largely ruled out (Lalitkumar *et al.* 2007, Meng *et al.* 2009, Palomino *et al.* 2010).

WHO-pioneered trials led to the development of ulipristal acetate (UPA, 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl-19-norpregna-4,9-diene-3,20-dione)), a second-generation SPRM derivative of 19-norprogesterone previously known as CDB-2914. In addition, the National Institute of Child Health and Human Development (NICHD) supported both preclinical and Phase I-II studies. In the last 10 years, UPA has been introduced as an EC pill (30 mg) in more than 50 countries, and it is currently recommended as a first-line hormonal treatment for EC due to its higher effectiveness and similar rate of side effects compared to LNG (Gemzell-Danielsson *et al.* 2014). In several countries, however, the use of UPA as EC has not been approved yet, although lower doses (5 mg) are authorized for the treatment of uterine fibroids (Levens *et al.* 2008). A temporal comparison between the aforementioned EC methods is shown in Table 1.

P4 exerts its action on the normal reproductive functions of women through its interaction with two isoforms of intracellular receptors with transcriptional activity, PR-A and PR-B (Mote *et al.* 1999, Patel *et al.* 2015). UPA binds with high affinity to both isoforms of PR, exhibiting agonist and antagonist properties (Blithe *et al.* 2003, Chabbert-Buffet *et al.* 2005, Gemzell-Danielsson & Meng 2010). On the other hand, UPA has a lower binding affinity to the glucocorticoid or androgen receptor than mifepristone (Gemzell-Danielsson & Meng 2010). UPA is rapidly absorbed after ingestion of a 30 mg pill, reaching maximum concentrations of 176 ± 89 ng/mL in the first 2 h, with a half-life of 32.4 ± 6.3 h (Snow *et al.* 2011). This drug is distributed bound to plasma proteins, such as albumin, whereas neither sex hormone-binding globulin (SHBG) nor corticosteroid-binding globulin (CBG) appears to serve as serum carriers for UPA in monkeys or humans (Larner *et al.* 2000). Its metabolization would be mainly through cytochrome P450 and its mono-demethylated metabolite is pharmacologically active (Snow *et al.* 2011).

During the past years, efforts have been made to elucidate the mechanisms underlying UPA activity as EC with the idea that a better understanding of its mode of action is crucial to give women the possibility to choose in an informed manner among the different available methods. The present review summarizes the available data on the mechanisms through which UPA may act when used for preventing pregnancy after unprotected sexual intercourse.

Effectiveness of UPA

The effectiveness of UPA as EC has been evaluated through various clinical trials. A Phase III trial including 2221 women showed that UPA was more effective

Table 1 Temporal evolution of hormonal methods and devices used in EC.

Method	Chemical structure	Date of introduction	Worldwide acceptance
Cu-IUD	Chemical device	1970s	Very effective method to prevent pregnancy. It requires technical and medical expertise and facilities. Uncomfortable insertion of the device.
Yuzpe	Steroidal EE + Norgestrel (later replaced by LNG)	1970s	Effective and well tolerated method available without prescription in many countries. Discontinued due to the risk of venous thromboembolism and unpleasant side effects of EE.
Mifepristone	Steroidal, SPRM, P4-antagonist	1980s	Limited use due to moral and religious reasons as the drug induces pregnancy termination.
LNG	Steroidal	1980s	Twice as effective as the Yuzpe, it is the "gold standard" of oral EC available without prescription over the world. Effective up to 72 h post-unprotected sexual intercourse.
UPA	Steroidal, SPRM, P4 agonist/antagonist	2009	Available under prescription in several countries. Effective up to 120 h post-unprotected sexual intercourse. In several countries, its use is limited for uterine fibroids treatment.

For additional information see Goldstuck (2014) and ESHRE CapriWorkshop Group *et al.* (2015).
EC, emergency contraception; EE, ethinyl estradiol; IUD, Intrauterine device; LNG, levonorgestrel; P4, progesterone; SPRM, selective progesterone receptor modulator; UPA, ulipristal acetate.

than LNG, even up to 120 h after unprotected sexual intercourse (Glasier *et al.* 2010), regardless of the day of the menstrual cycle the participant took the pill. Another study that specifically evaluated its effectiveness between 48 and 120 h after intercourse showed that the pregnancy rate after UPA intake was only 2.1%, whereas the expected pregnancy rate without protection was 5.5% (Fine *et al.* 2010). Moreover, when the pill intake took place between 96 and 120 h, only 1.3% of women became pregnant (Fine *et al.* 2010), confirming that the window in which UPA was effective could be extended up to 5 days compared to the 3 days recommended for LNG.

Effects of UPA on ovulation

A large body of evidence has shown that UPA has an inhibitory effect on ovulation when administered during the follicular phase. In particular, during the mid-follicular phase, with follicles between 14 and 16 mm in diameter, a single dose between 10 and 100 mg produced a delay in follicular rupture and suppression of plasma levels of estradiol (Stratton *et al.* 2000). On the other hand, when women with follicles larger than 18 mm in diameter took the pill, a delay in follicular rupture occurred between 5 and 6 days in 59% of the cases (Brache *et al.* 2010). The blockage or delay in ovulation was observed in 100% of women who at the moment of the pill intake presented low levels of LH, and in 79% of those who had increased levels of this hormone (Brache *et al.* 2013). In these cases, the intake of UPA suppressed the increase in LH and the appearance of the peak. However, once LH levels had reached maximum values at the time of UPA administration, women ovulated normally. Moreover, a pharmacodynamic study based on repeated use of UPA (every 7 or 5-day pill-intake during 8 weeks) showed that the drug delays follicular rupture but ovulation eventually occurs with time in most subjects (Jesam *et al.* 2016).

It should be noted that the murine model has become a tool to investigate the molecular mechanisms by which UPA could block the follicular rupture. In mice, the intraperitoneal administration of UPA together with hCG (mimicking the LH peak) prevents ovulation (Palanisamy *et al.* 2006, Gomez-Elias *et al.* 2016), constituting a good pre-clinical model for these studies. In this regard, later studies in this animal model demonstrated that the observed anti-ovulatory effect was the consequence of a repression of PR-regulated genes critical for ovulation (Nallasamy *et al.* 2013). When the drug was administered 8 h after hCG or later, UPA effectiveness to inhibit ovulation significantly declined (Nallasamy *et al.* 2013, Gomez-Elias *et al.* 2016), indicating that female mice respond to UPA in a similar way than humans, and supporting the use of this animal model to further evaluate the mechanisms of action of UPA as EC.

As previously shown, unlike LNG whose anti-ovulatory effects are restricted to the follicular phase prior to the increase in LH levels, UPA inhibits follicular rupture even if it is administered during the LH surge (Brache *et al.* 2013). This difference has been the justification for the greater effectiveness of UPA compared to LNG. However, given that the LH peak may occur within the 120-h window women have to take the UPA pill, the anti-ovulatory effect would not seem to be sufficient to justify the high effectiveness described for UPA. In this regard, a Hong Kong-based clinical trial including 700 women who required EC showed that administration of a 30 mg UPA pill is able to prevent pregnancy even after ovulation has occurred (percentage of pregnancies prevented calculated for 650 included patients: post-ovulation: 51.5%, pre-ovulation: 81.1%). Although statistical significance was not reached, the authors attribute it to the modest sample size analyzed in their study (Li *et al.* 2016). These clinical results emphasize the idea that although today UPA is the most effective oral option as EC, more studies are still required to fully clarify its mechanism of action. In view of this, the higher effectiveness of the drug can be attributed to additional interference on sperm function and/or to post-ovulatory events discussed in the following sections.

Effects of UPA on sperm function

In their transit through the female reproductive tract, spermatozoa are exposed to increasing levels of P4 secreted by the cumulus cells and the corpus luteum. It has been shown that P4 facilitates the interaction of gametes in the female genital tract in various animal species (Libersky & Boatman 1995, Holt & Fazeli 2010) through the regulation of processes associated with sperm capacitation. This hormone induces extracellular Ca^{2+} influx into the sperm (Blackmore *et al.* 1991, Lishko *et al.* 2011, Strunker *et al.* 2011), protein tyrosine phosphorylation (TyrP) (Chung *et al.* 2014) and other signaling cascades that end in the occurrence of chemotaxis, hyperactivation and acrosome reaction (Teves *et al.* 2006, Baldi *et al.* 2009, Sagare-Patil *et al.* 2012). Considering that sperm are transcriptionally inactive cells, these effects would be mediated by non-genomic P4 membrane receptors. Although the identity of the protein or protein complex that leads to the occurrence of P4-induced phenomena in sperm has not been elucidated so far, UPA could exert agonist or antagonist action on them, affecting sperm function. In this regard, spermatozoa may be stored up to 5 days within the female genital tract before fertilization, the reason why fertile days of the menstrual cycle are the 5 days preceding ovulation and the day after LH peak (Wilcox *et al.* 1995). This period of time would be an opportunity for UPA to interfere with sperm function regardless of the timing of the pill intake and the LH peak in the pill-user.

Initial studies in rats evaluated the effect of UPA on the male reproductive tract (Wang *et al.* 1995). No effect on epididymal maturation, post-meiotic sperm development, spermatogenesis, and fertility were observed. *In vitro* studies showed that exposure of human sperm to a wide range of UPA concentrations (1–10,000 ng/mL), including those present in the female serum after EC intake, did not affect sperm survival, signaling events associated with TyrP or spontaneous and human follicular fluid induced-acrosome reaction (Munuce *et al.* 2012). Nonetheless, UPA prevented DNA damage of human spermatozoa *in vitro*, probably due to a detoxification activity of the drug of the reactive oxygen species (ROS) produced by sperm metabolism in culture (Munuce *et al.* 2013). Altogether, these results indicated that sperm capacitation and P4-induced acrosome reaction take place in the presence of UPA with no agonist/antagonist activity of the drug. On the other hand, other authors have described several mild effects of UPA on P4-induced acrosome reaction, hyperactivation and $[Ca^{2+}]_i$ increase (Ko *et al.* 2014). In addition, in the presence of a P4 gradient, UPA induced a chemo-repellent behavior in sperm (Guidobaldi *et al.* 2017). Although this direct effect was observed at lower concentrations than those in pill-users sera, these results opened the possibility that sperm fertilizing ability could be compromised in the presence of UPA.

Competitive assays with fluorescent-labeled P4 showed that a concentration of UPA higher than expected in the plasma of UPA-users (10,000 ng/mL vs 100–1000 ng/mL) is required to specifically displace labeled P4 from P4-binding sites on human sperm head (Zumoffen *et al.* 2017), supporting that UPA does not modulate sperm function through the sperm head P4-binding sites. Ca^{2+} channel CatSper, localized in the sperm flagellum and involved in the rapid Ca^{2+} influx produced by P4, has been proposed as the sperm P4 receptor (Lishko *et al.* 2011, Strunker *et al.* 2011). Despite playing a vital role in the regulation of sperm hyperactivation, it is strongly suspected that P4-induced activation of this channel can also mediate an indirect elevation of $[Ca^{2+}]_i$ in the head (Singh & Rajender 2015, Brukman *et al.* 2019). A possible interaction and/or effect of UPA on this channel requires further investigation.

Effects of UPA on gamete interaction and early embryo development

As stated before, P4 secreted by the cumulus cells facilitates gamete interaction in several species (Libersky & Boatman 1995, Holt & Fazeli 2010). Therefore, gamete interaction was a possible target for UPA actions on events occurring after ovulation and before implantation. Considering the ethical reasons involved in the use of human oocytes for gamete interaction research, an experimental approach through heterologous gametes assays as mouse cumulus penetration and hamster oocyte penetration test (HOPT) allowed the indirect evaluation of UPA effects on human sperm-fertilizing ability. At concentrations comparable to those found in pill-users serum, UPA did not impair the human sperm ability to either penetrate the cumulus or to fuse to and penetrate the egg, supporting the idea that the drug does not interfere with, at least, these stages of the sperm–egg interaction process (Zumoffen *et al.* 2017).

The use of the mouse model allowed the evaluation of the effect of UPA on the complete homologous *in vitro* fertilization (IVF) process as well as in early embryo development (Gomez-Elias *et al.* 2016). When cumulus–egg complexes were used, the presence of the drug did not affect IVF, suggesting that hyperactivation and acrosome reaction, the two critical P4-dependent processes required for fertilization, occurred normally in UPA-incubated mouse spermatozoa.

IVF was also performed with cumulus-free mouse eggs, a condition that not only evidences subtle deficiencies in sperm-fertilizing ability (Nishimura *et al.* 2004, Da Ros *et al.* 2008), but in which P4 is not present during sperm capacitation or gamete interaction. In this case, the presence of UPA did not alter the fertilization rate, supporting that the drug does not interfere with sperm-egg interaction (Gomez-Elias *et al.* 2016).

In vitro and *in vivo* experiments in mouse showed the lack of effect of UPA on embryo early development, measured not only by the percentage of blastocysts obtained in the presence of the drug but also by the kinetics of *in vitro* development to the blastocyst stage (Gomez-Elias *et al.* 2016, Gómez-Elías *et al.* 2019). These results are similar to those obtained with LNG (Munuce *et al.* 2005) but differ from those showing that mifepristone impairs mouse embryo development both *in vivo* and *in vitro* (Roblero *et al.* 1987, Yang & Wu 1990), supporting that the mechanism of action of UPA and LNG might be different from that of mifepristone.

Effects of UPA on oviductal function

The oviduct plays a fundamental role in the reproductive process being the site where both interaction of gametes as well as development and transport of the resulting embryo take place (Li & Winuthayanon 2017). Most of these actions are mediated by muscular contractions and ciliary activity in the oviduct (Lyons *et al.* 2006), regulated by P4 (Mahmood *et al.* 1998, Wanggren *et al.* 2008). In accordance with this, the expression of PR in ciliated epithelial cells of adult mice and human oviducts has been demonstrated (Teilmann *et al.* 2006). Different studies have reported that the pharmacologically relevant dose of UPA inhibits both ciliary beat and muscle contraction of fallopian tube strips *in vitro* (Li *et al.* 2014). In this way, the effect of this drug on oviductal physiology could constitute an additional post-ovulatory mechanism of pregnancy

prevention by interfering with gametes and embryo transport and/or storage.

Sperm can be retrieved from the fallopian tubes within 5 min to 2 h after insemination in the vagina (Kunz *et al.* 1996) and the isthmic region of the tube forms a reservoir that enables sperm to stay vital and maintain their fertilizing capacity for several days up to ovulation (Suarez & Pacey 2006). Therefore, the effect of UPA on the oviduct could alter sperm interaction with the oviductal epithelium. However, the lack of effect of UPA on the ability of human spermatozoa to interact *in vitro* with human tubal explants (Zumoffen *et al.* 2017), supports the idea that sperm binding to the oviduct would not depend on the ciliary beating and/or contractility. Therefore, impairment of sperm-oviduct interaction and the subsequent sperm distribution would not be a mechanism of UPA-mediated EC.

As stated before, evidence does not support a significant direct effect of UPA on human sperm function nor on sperm-oviductal epithelium interaction. However, these results did not evaluate the possible effect of UPA on *in vivo* sperm transport through the female genital tract, a parameter that is not feasible or ethical to analyze in humans. It is important to point out that UPA would not alter the cervical mucus viscosity precluding a possible effect on sperm transit to the uterine cavity (Jesam *et al.* 2016). The development of a mouse model in which UPA was administered just after mating and when ovulation has already occurred showed no effect of the drug on the percentage of fertilized eggs (Gomez-Elias *et al.* 2016), constituting the first *in vivo* evidence showing that the administration of UPA does not affect sperm transport or gamete interaction. In addition, the finding that injection of UPA just before mating did not affect *in vivo* fertilization (Gomez-Elias *et al.* 2016) indicates that the rapid transport of sperm is also unaffected by UPA.

Transport of the embryo through the oviduct to the site of implantation in the uterus could also be modulated by oviductal mobility and, therefore, it could constitute another possible point of action of UPA. As a consequence, an alteration in embryo transport could result in a desynchronization between the resulting blastocyst and the endometrium for its correct implantation. Although the effect of UPA on human embryo transport has not been studied because of ethical and technical limitations, the results obtained when using animal models have shed light on this possibility. Embryo transport to the uterus was studied in mouse females treated with a single post-ovulatory dose of UPA and no differences were obtained in either the number of collected embryos or the percentage of embryos recovered from the uterus compared to controls (Gómez-Elías *et al.* 2019), ruling out a potential effect of UPA on this event. This could also be the case in humans considering the fact that the risk of ectopic pregnancies in UPA users did not differ from that observed in the general population (Levy *et al.* 2014).

In summary, although the *in vitro* inhibitory effects of UPA on ciliary beating and muscle contraction of the fallopian tubes have been described, studies performed so far indicate that, if any *in vivo* effects exist, they would not have a strong impact on the transport or interaction of gametes and embryos.

Effects of UPA on uterine physiology and implantation

P4 plays a fundamental role in implantation by acting on the acquisition of endometrial receptivity, embryo adhesion and decidualization (Ramathal *et al.* 2010). P4 genomic receptors PR-A and PR-B are expressed in both the epithelium and the uterine stroma (Mote *et al.* 1999, Patel *et al.* 2015). In the proliferative phase, both isoforms are present in both compartments, although PR-A is found in greater proportion. After ovulation, the levels of the two isoforms decrease in the glandular epithelium, but persist in the stroma (Mangal *et al.* 1997, Mote *et al.* 1999). In particular, the use of mutant mice showed the fundamental role of PR-A in endometrial function: its lack produces a completely altered implantation and decidualization in addition to the inability of the females to ovulate normally (Mulac-Jericevic *et al.* 2000). In view of this, it is possible that UPA intake after ovulation could modulate the uterine physiology/receptivity. However, the effect of a single dose of UPA on uterine function has been poorly studied in women. In particular, the ingestion of an unmicronized 50 mg pill of UPA during the mid-follicular phase produced a delay in endometrial maturation (Stratton *et al.* 2000) while when ingested in the early luteal phase resulted in a dose-dependent decrease in the thickness of the endometrium (Stratton *et al.* 2010). Although some authors affirm that doses with endometrial effects would not be relevant for EC (Gemzell-Danielsson *et al.* 2014), others indicate that, in fact, the 30 mg micronized formulation of UPA (currently on the market) would be pharmacokinetically equivalent to the one used by Stratton and collaborators (Mozzanega *et al.* 2013). On the other hand, the prolonged use of low doses of UPA (5 mg/day for 9–13 weeks) for the treatment of uterine leiomyomas has led to numerous studies on the effects of UPA on uterine physiology (Williams *et al.* 2012, Whitaker *et al.* 2017). These treatments would produce endometrial histological alterations called PR modulators-associated endometrial changes (PAEC). In particular, the administration of UPA has been associated with low levels of glandular and stromal proliferation. However, it has not yet been clarified if the effects reported on uterine physiology could contribute to the contraceptive action of UPA. In this regard, it has been recently shown that the mid-cycle (when dominant

follicle diameter reached 20 mm) administration of a single dose of UPA modifies the global gene expression of endometrial biopsies taken during the receptive phase, showing changes compatible with a non-receptive endometrial phenotype (Lira-Albarrán *et al.* 2017) and changes in genes involved in the process of endometrial decidualization (Lira-Albarrán *et al.* 2018), a prerequisite for successful implantation.

Although endometrial alterations after UPA intake have been reported, its *in vivo* impact on implantation has not been evaluated in humans due to ethical reasons. Through an *in vitro* approach, the effect of the drug on the interaction of human embryos (Berger *et al.* 2015) or trophoblastic spheroids made from JAr cells (Li *et al.* 2017) with endometrial constructs or cultures was evaluated. There were no changes in the adhesion of the embryos or spheroids to the endometrial cells with respect to the controls, nor in the levels of genes associated with the implantation process, suggesting that UPA would not affect implantation. However, the endometrial cells used in these studies were not obtained from UPA-treated women. Altogether, these *in vitro* approaches do not fully-emulate the *in vivo* implantation process. Once again, the use of animal models allowed further evaluation of the effects of the drug in implantation.

Previous reports in rats and rabbits showed that the administration of a high single dose of UPA at the post- or peri-implantation period is effective in blocking pregnancy (Reel *et al.* 1998, Hild *et al.* 2000). However, these experimental designs did not mimic the human situation in which UPA must be taken up to 5 days after sexual relation, meaning during the pre-receptive period. More recent experiments in mice, in which the drug was administered during the pre-receptive period, better resembling the situation in pill-user women, shed light on the possible *in vivo* effects of UPA on implantation (Gómez-Elías *et al.* 2019). In this case, UPA-treated females presented a decrease in the number of conceptuses compared to controls. This decrease was consistent with a lower number of early implantation sites detected in treated females (Fig. 1). It is interesting to note that when UPA was injected closer to the moment of mating, its effect on pregnancy was more variable among treated females (Gómez-Elías *et al.* 2019). This variability is in agreement with the lower effectiveness of post-ovulatory intake of the drug observed in the clinical trial previously mentioned (Li *et al.* 2016).

The histological and functional analysis of mouse uteri showed that the administration of UPA produced glandular and stromal alterations at the receptive period as well as a completely impaired ability to respond to an artificial decidualization stimulus (Fig. 1). In particular, the histological studies showed a desynchronized combination of glandular and stromal elements in the uteri of the females treated

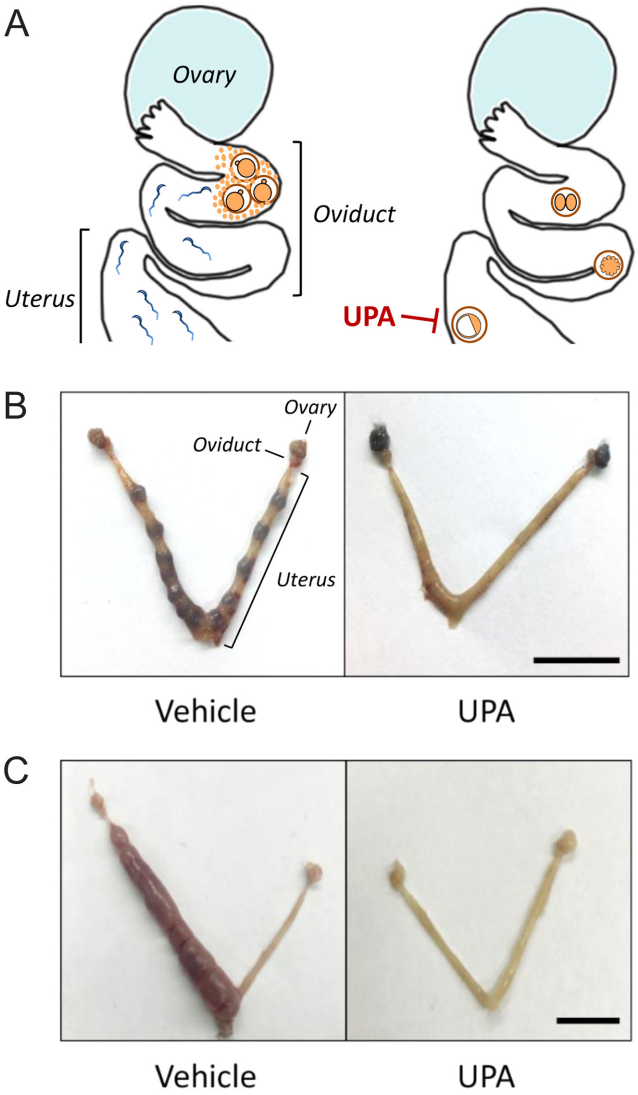

Figure 1 *In vivo* effects of the post-ovulatory administration of UPA in mouse. (A) Diagram representing the evaluated processes occurring in the female tract after ovulation took place. While no detrimental effects were observed in gamete transport and interaction, and embryo transport and development, UPA interfered with embryo-uterine interaction. (B) The administration of UPA to females after mating produced a dramatic reduction in the number of early implantation sites (stained with Evans blue dye) compared to controls injected with vehicle. (C) UPA administration abolished the decidualization response when one uterine horn (left horn) received an artificial decidualization stimulus.

with UPA, which could be the cause of the defects in the implantation process. It is important to note that hormonal changes of both endometrial compartments are finely regulated throughout the reproductive cycle (Patel *et al.* 2015) and, therefore, the dysregulation of this 'cross-talk' between glands and stroma can alter the synchronicity necessary for a correct functionality of the endometrial tissue. This is consistent with studies describing a direct action of UPA on endometrial thickness (Stratton *et al.* 2010) or on luteal phase length

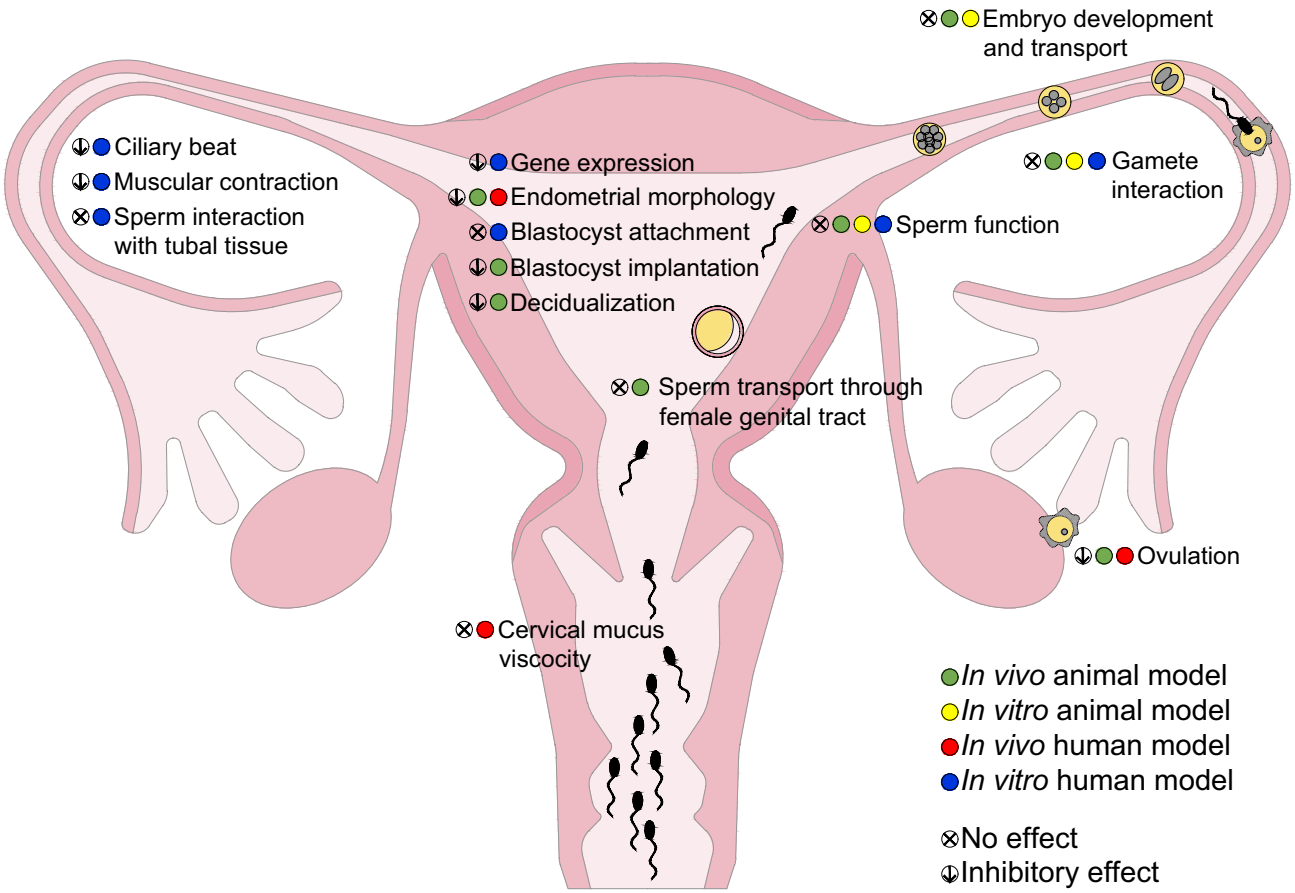

Figure 2 Summary model of UPA effects on the reproductive events from ovulation to implantation. The schematic representation includes the *in vivo* and *in vitro* experimental evidence in human and animal models.

(Passaro *et al.* 2003). Moreover, its prolonged use in low doses for the treatment of uterine leiomyomas resulted in histological alterations with presence of inactive glandular epithelium, altered glandular architecture and aberrant stromal vasculature (Williams *et al.* 2012, Whitaker *et al.* 2017). This mouse model, exhibiting a similar phenotype in terms of alterations in uterine morphology, would support the existence of direct effects of UPA on the physiology of the uterus. In addition to the described morphological alterations, uteri of UPA-treated females presented a clear defect to undergo the decidual reaction (Gómez-Elías *et al.* 2019). It should be noted that the UPA effect observed on the uterine tissue resembles the reproductive phenotype of mice deficient in the PR-A receptor, unable to undergo decidualization (Mulac-Jericevic *et al.* 2000), indicative of a crucial function of this receptor for normal stromal and endometrial epithelium function. In contrast, the lack of PR-B does not affect the ability of the uterus to maintain pregnancy (Mulac-Jericevic *et al.* 2003). Furthermore, studies in human breast cancer cells showed that UPA induces an anti-proliferative effect in the absence of PR-B, suggesting the importance of the PR-A isoform for the action of this drug (Esber *et al.* 2015). All this evidence suggests that, in the mouse uterine tissue the action of UPA would be mainly through PR-A.

Altogether, the results in the mouse model provided strong functional evidence favoring the idea that a single post-ovulatory dose of UPA impairs pregnancy probably due to an effect on embryo–uterine interaction.

Final remarks

The results obtained on the effect of UPA in the different steps of the reproductive process using a variety of *in vitro* and *in vivo* models in different species, and including the well-established action on ovulation, are summarized in Fig. 2 and Table 2. The evidence obtained so far revealed that, although UPA would not significantly affect sperm function, interaction of the gametes or the development of the resulting embryos, post-ovulatory administration of UPA could alter the physiology of the uterus, making it less receptive to the implantation process in the murine model. Considering the genomic evidence with endometrial biopsies and

Table 2 UPA effects on reproductive events in humans and animal models.

Reproductive events	Effects	Studies in humans	Studies in animal models
Ovulation	Prevention or delay of follicular rupture before LH peak	Stratton *et al*. 2000, Brache *et al*. 2010, 2013, Jesam *et al*. 2016	Palanisamy *et al*. 2006, Nallasamy *et al*. 2013, Gómez-Elias *et al*. 2016
Cervical mucus viscosity	No effect	Jesam *et al*. 2016	–
Sperm capacitation/function	No effect	Munuce *et al*. 2012	Gómez-Elias *et al*. 2016
	Inhibition of P4-induced sperm parameters/function	Ko *et al*. 2014, Guidobaldi *et al*. 2017	Guidobaldi *et al*. 2017
Sperm transport	No effect	NDA	Gómez-Elias *et al*. 2016
Oviductal function	Inhibition of ciliary beating and muscle contraction	Li *et al*. 2014	NDA
Sperm-oviduct interaction	No effect	Zumoffen *et al*. 2017	NDA
Gamete interaction	No effect	Zumoffen *et al*. 2017	Gómez-Elias *et al*. 2016
Early embryo development and transport	No effect	NDA	Gómez-Elias *et al*. 2016, 2019
Endometrial morphology and gene expression	Alterations on endometrial physiology	Stratton *et al*. 2000, 2010, Passaro *et al*. 2003	Gómez-Elías *et al*. 2019
	Gene expression compatible with non-receptive endometrium	Lira-Albarrán *et al*. 2017, 2018	
Embryo-uterine interaction	No effect in *in vitro* endometrial constructs	Berger *et al*. 2015, Li *et al*. 2017	
	Inhibition of implantation		Gómez-Elías *et al*. 2019

NDA, no data available.

the clinical trials mentioned above, this post-ovulatory mechanism could be also operating in humans.

The definition of pregnancy is critical to distinguish between a contraceptive that prevents pregnancy and an abortifacient that terminates it. In biological terms, pregnancy is established when a developing embryo has implanted. However, in several countries, the law establishes that pregnancy begins at fertilization, generating a conflict for the definition of methods that act between fertilization and implantation. The effect observed in mice after a post-ovulatory administration of UPA as well as the gene expression profiles obtained in women support the idea that the drug would act as a contraceptive that inhibits embryo-implantation rather than an abortifacient agent that terminates an implanted embryo. Overall, the results included in this review provide novel information on the mechanism of action of UPA as EC with potential clinical implications and are in accordance with the clinical evidence of its high effectiveness until 5 days after the sexual intercourse occurred.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

M J M, M G E, A M C, L B, P S C and D J C participated in the manuscript writing. M J M conceived and designed Table 1 and Fig. 2, M G E designed Fig. 1 and Table 2, and performed the final edition of the manuscript, A M C collected the bibliography and collaborated with Table 2 design, D J C conceived the manuscript and coordinated all the activities.

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