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Does ulipristal acetate emergency contraception (ella®) interfere with implantation? ☆,☆☆

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ABSTRACT

Background: Ulipristal acetate (UPA) 30 mg (ella®, HRA-Pharma, Paris, France) acts as an emergency contraceptive (EC) by delaying ovulation. Because it is a selective progesterone receptor modulator, an additional effect on interfering with implantation has been suggested.
Objective: This review discusses the evidence for, and against, an anti-implantation effect of UPA-EC.
Sources of evidence: Primary research on the effect of UPA, at a relevant dose, on endometrium, implantation, efficacy and pregnancy outcome.
Results: UPA-EC does not appear to have a direct effect on the embryo. Changes in endometrial histology are small and not consistent, varying among studies. While UPA-EC affects the profile of gene expression in human endometrium, the findings vary between studies, and it is not clear that these changes affect endometrial receptivity or prevent implantation. UPA at pharmacological concentrations does not appear to have any inhibitory effect on embryo attachment in in vitro systems of human endometrium. UPA-EC is not more effective at preventing pregnancy than chance alone if used after ovulation and does not increase miscarriage rates.
Conclusions: An anti-implantation effect of UPA is highly unlikely at the dose used for EC. Maintaining the warning on the FDA-approved label that "it may also work by preventing implantation to the uterus" might deter some women from using EC, leaving them no option to prevent unwanted pregnancy after unprotected sexual intercourse.

1. Introduction

Ulipristal acetate (UPA) 30 mg was developed for emergency contraception (EC) and approved for marketing in 2009 in Europe (as ellaOne®, HRA Pharma, Paris, France) and in 2010 in the USA (as ella®). There is robust evidence to demonstrate that the main mode of action of the EC product is to block the luteinizing hormone (LH) surge, thereby inhibiting or delaying ovulation [1–3]. However, UPA is a selective progesterone receptor modulator with mixed agonistic and antagonistic activities [4]. Since progesterone is essential for the establishment and maintenance of pregnancy, it has been assumed that UPA-EC would act also by interfering with, or inhibiting, implantation. Implantation of the human embryo involves a complex interaction between the endometrium and the embryo (blastocyst) within a relatively brief time frame, known as the implantation window. Implantation occurs around 6 to 7 days after fertilization, involving three distinct complex steps: apposition, attachment and invasion [5].Abnormal function in either the developing embryo or the endometrium may prevent implantation or result in early pregnancy loss.

This paper discusses the evidence of an effect of UPA-EC directly on the preimplantation embryo; on endometrial histology and morphology and on endometrial bleeding; on markers of endome-

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trial receptivity; and on in vitro models of human embryo-endometrial attachment. We also review relevant clinical evidence on differences in UPA-EC effectiveness before and after ovulation, and on miscarriage rates.

1.1. Methodology

We searched MEDLINE, EMBASE, PubMed, Web of Science and Cochrane register for all publications containing the words *ulipristal acetate OR CDB-2914* (an earlier name for the compound) in any language up to the beginning of March 2019. We extracted and reviewed publications reporting primary research which included the key words and MeSH headings mechanism of action; endometrium; embryo; receptivity; attachment: implantation; efficacy; miscarriage OR pharmacovigilance. We excluded studies in which UPA was administered chronically (e.g., for fibroid treatment) and those in which histological and morphological assessment concerned progesterone receptor modulators-associated endometrial changes.

1.1.1. Effect of UPA on the preimplantation embryo

Evidence from animal studies shows no effect of UPA on early embryo development. Gómez-Elías and coworkers (2016) injected UPA (40 mg/kg), or vehicle only, into superovulated female mice caged with proven fertile male mice just before or after mating [6].The percentage of fertilized eggs recovered from the oviductal ampulla was not significantly different between UPA-treated animals and controls [6]. In the same study, zygotes were recovered from the mated female mice and cultured in vitro for 4 days in the presence or absence of UPA (1000 ng/mL). No difference was observed in the percentage of cleaving embryos or the cleavage speed [6]. While there are no such studies on human embryos, data from both clinical trials and postmarketing surveillance of UPA-EC [7] show no increased risk of early pregnancy loss (miscarriage) or teratogenesis in women who conceive following exposure to UPA-EC. Thus, an effect of UPA 30 mg on embryo viability seems unlikely.

1.1.2. Effect on endometrial histology, endometrial thickness and menstrual bleeding

A number of studies have investigated the effects of UPA, given to women at various times in the cycle, on endometrial histology and thickness. In contrast to all the clinical studies and to those on markers of endometrial receptivity, models of embryo attachment and the effect on the preimplantation embryo, all the studies investigating effects on the histology of the endometrium used nonmicronized preparations of UPA, while the marketed UPA-EC product is micronized. Micronization of the drug allowed reduction of the dose from 50 mg to 30 mg when used in tablet form; however, an indirect pharmacokinetic comparison confirmed the similarity of the two formulations. [8] Stratton and coworkers (2000) compared the effect of midfollicular phase administration of unmicronized UPA (10, 50 and 100 mg) versus placebo on endometrial histology [9]. UPA caused a significant dose-dependent decrease in endometrial thickness and a delay in maturation with all three doses. The delay in maturation was assessed by morphology based on Noyes criteria [10]. In this study [9], the lag in endometrial development following exposure to UPA in the follicular phase likely reflects the delay in ovulation described by Brache et al. (2010) [1]: if ovulation is delayed by 5 days, one would expect endometrial maturation to be similarly delayed.

Passaro et al. (2003) evaluated the impact of unmicronized UPA at doses of 1–200 mg given to 36 women during the midluteal phase (LH+6 to +8) on luteal phase length and occurrence of bleeding [11]. While all subjects treated with unmicronized UPA 200 mg (several multiples of the dose used for EC) experienced early onset of vaginal bleeding indicating endometrial breakdown, lower doses did not alter cycle length; for all doses except 200 mg, the length of the luteal phase was not different from that of women treated with placebo. A decline in serum progesterone concentration suggested early luteolysis in 4 of 30 women (just 13.3%) treated with up to 100 mg UPA.

In a third study, Stratton et al. (2010) evaluated the effects on the endometrium of unmicronized UPA (10, 50 and 100 mg) administered during the early luteal phase (LH+1 or +2) in 55 healthy women [12]. This timing of administration is arguably most appropriate for investigating any theoretical effect of UPA on implantation. In contrast to their previous study in which UPA was given during the follicular phase [9], Stratton et al. (2010) reported that administration of unmicronized UPA in the early luteal phase did not delay endometrial maturation compared to placebo. This supports the view that the delayed endometrial development shown in their previous study was most likely secondary to postponement of ovulation. Endometrial thickness was measured by ultrasound on the day of treatment and again on the day of the biopsy (4–6 days following UPA administration). Although there was a statistically significant change ($p<.007$) in endometrial thickness, the mean change was small in magnitude in both placebo-treated women (+1.3±2.3 mm) and UPA-treated women (−0.6±2.2 mm). Compared with placebo, increased progesterone receptor staining in glandular tissue was reported only among women treated with the higher doses of UPA (100 mg). At the 50-mg and 100-mg doses, decreased L-selectin ligand expression, thought to reflect endometrial receptivity [13], was detected. Stratton et al. (2010) suggested that the changes noted in the higher doses "may be the earliest features of the anti-progestational effect... in the luteal phase, heralding other endometrial changes." The effects of the lower doses of UPA were minimal.

While these data suggest that UPA does, expectedly, result in some dose-dependent effects on the endometrium particularly at doses higher than that used for EC, they shed no light on the clinical implications of such effects or on the receptivity of the endometrium to implantation of the human embryo in the EC context. Moreover, the usefulness of histology in determining endometrial "normality" has been called into question as histological delay in endometrial maturation fails to distinguish between fertile and infertile couples and is not accurate in distinguishing cycle days [14–17]. Indeed, a recent study of the endometrial receptivity "meta-signature" stated that "traditional endometrial dating criteria, like tissue histology, are obsolete since their accuracy, reproducibility and functional relevance have been questioned in various randomized studies" [18].

1.1.3. Effect on markers of endometrial receptivity

The lack of clinical relevance of studies related to endometrial histology raises the possibility that examination of the biochemical and/or molecular profiles of the endometrium could be more meaningful. Acknowledging the challenges and complexity of obtaining and analyzing "normal" human samples, it has been suggested that such approaches may identify abnormalities in the endometrium which may predispose to abnormal implantation [18].High-density microarray screening has been used to investigate changes in endometrial gene expression following exposure to UPA 30 mg. Fourteen healthy women with regular menstrual cycles were studied during 14 control cycles and 12 cycles treated with a single dose of 30 mg UPA when follicle diameter had reached 20 mm (at which time UPA would not be expected to delay ovulation) [19]. Ovulation in both treated and control cycles was confirmed by serum LH, progesterone and vaginal ultrasound. An endometrial biopsy was taken at day LH+7 in each cycle to isolate RNA for microarray and qPCR analysis, or for histology and

immunohistochemistry. Analysis of the endometrial gene expression profile from UPA-treated and control cycles showed differential expression of PAEP and LIF, genes that are potentially linked to receptivity [20].While PAEP, a progesterone-regulated gene thought to be important for attachment of the trophoblast to the endometrium [21], was markedly down-regulated, down-regulation of LIF in the endometrial glands was modest in the UPA-treated group [19]. Further analysis of the same samples by the same group revealed down-regulation of PRL and STAT3 following UPA exposure [22]. Since these factors are involved in endometrial decidualization, the authors concluded that UPA 30 mg may affect the molecular mechanisms leading to endometrial decidualization.

While UPA affects the profile of gene expression in the endometrium, it is not at all clear that these changes affect endometrial receptivity or prevent implantation. In a review of tools to assess endometrial receptivity, Lessey (2010) concluded that the search for reliable biomarkers for the detection of abnormalities in endometrial receptivity "remains an elusive target" [23]. In a meta-analysis of the results of nine studies involving transcriptomic analysis of human endometrial samples covering the "pre-receptive" and "receptive" phases of the cycle, Altmae and coworkers (2017) stated that while hundreds of up- and down-regulated genes were theoretically involved in endometrial receptivity, the overlap between the studies was relatively small and potential diagnostic biomarkers had not been identified [18]. The limitations of the technology include differences in experimental design, timing and conditions of endometrial sampling, the type of patients/volunteers recruited, transcriptome array/sequencing platforms and genome annotation versions used, data processing and data presentation. In summary, the authors concluded that the role of differentially expressed genes in uterine physiology and pathophysiology remains to be investigated and, importantly, emphasized that none of the molecular markers have yet been successfully applied in clinical therapeutic practice. Whether the changes in endometrial gene expression associated with UPA 30 mg actually translate into any significant impact on endometrial receptivity and pregnancy establishment is uncertain and perhaps unlikely.

1.1.4. Effect on in vitro human embryo-endometrial attachment models

The histological and "omic" studies cited above all suffer from the same weakness, that is, they can only ever investigate human endometrium taken from "normal" volunteers (usually without any proven history of fertility), from women with clinical conditions known to be associated with infertility (such as endometriosis) or from women with a history of failure of implantation often diagnosed after failed assisted conception following transfer of apparently healthy or chromosomally normal embryos. It would be practically impossible to undertake a sufficiently large study involving biopsy of human endometrium in a cycle in which implantation is definitely going to take place (given the rate of successful implantation per cycle, the fact that women wanting to conceive would be extremely unlikely to participate, the fact that it would be considered an unethical study in women who did not want to conceive *and* the fact that it would be impossible to know whether the action of taking the biopsy and removing endometrial samples had affected implantation). Likewise, it is not possible to gain molecular insights from endometrium taken *after* successful implantation on the characteristics of the endometrium *before* implantation occurs (even if such investigations were ethically possible). Thus, while endometrium may look "abnormal" or may have an "abnormal" gene profile, we can never know in vivo whether it will support implantation should it be presented with a healthy fertilized embryo.

Recent studies addressing the attachment of human embryos to endometrial cells using in vitro models may come closest to providing direct evidence of the effects of ECs on endometrial receptivity. Berger and colleagues (2015) used endometrial biopsies from healthy women with proven fertility taken at LH+4 to create a three-dimensional human endometrial cell culture system [24]. Viable human blastocysts were randomly added to the cultures in the presence of UPA 0.4 μM (n=10) or vehicle alone (n=10), and attachment rate of the embryos to the endometrial cells was assessed. Exposure of the endometrial cells to UPA at a dosage equivalent to EC did not affect embryo viability, and importantly, there was no significant difference in the rate of embryo attachment between the UPA-treated and the control groups (p=.650). Using the same in vitro system and study design, the group had also reported no significant effect of levonorgestrel (LNG) 10 μM on human embryo attachment compared to control cultures (43% versus 59%) [25]; this concurred with another two studies which demonstrated that postovulatory administration of LNG did not prevent pregnancy in monkeys [26] nor result in gene expression changes in human endometrium [27] . In contrast, mifepristone at doses of 10 μM or 0.5 μM (a dose lower to that shown to prevent pregnancy) did effectively inhibit embryo attachment in the three-dimensional in vitro co-culture model mentioned above [25,28].

In the Berger et al. study (2015), in addition to blastocyst attachment, the expression of a subset of genes known to be involved in endometrial receptivity was monitored in the in vitro endometrial cell culture system. [24] After removal of the blastocyst, total RNA was extracted from the day 3 cultures and real-time PCR analysis was performed with primers specific to 17 genes thought to be vital for endometrial receptivity and embryo implantation. The analysis revealed that out of these 17 genes, 2 were significantly up-regulated and 4 down-regulated; the majority remained unaltered after UPA exposure [24].The profile of the up- or down-regulated genes after UPA treatment was quite different from that reported by Lira-Albarran et al. [19] whose study was done on human endometrium in normal cycles without exposure to embryo. The overall results from the in vitro model by Berger et al. (2015) suggest that the changes in endometrial gene expression identifiable after UPA exposure do not affect the attachment of the embryo to the endometrial cells.

Consistent with this notion, another study using a different in vitro model reported no effect of UPA on embryo attachment [29]. In this study, Li et al. (2018) co-cultured human endometrial cells with human trophoblastic spheroids (embryo surrogate) in the presence of UPA (0.04, 0.4 and 4 μM) or mifepristone (10 μM). While mifepristone significantly suppressed embryo attachment, UPA did not inhibit embryo attachment under the same condition. Collectively, these results indicate that UPA at pharmacological concentrations does not appear to have any interfering effect on embryo implantation in this in vitro system.

1.1.5. Evidence from clinical data

If UPA 30 mg had an effect on the establishment of pregnancy, it might be expected to increase the rate of miscarriage. However, analysis of all pregnancies reported during development and since the launch of ellaOne® in Europe and published in 2014 showed that 13.64% of the pregnancies with known outcomes ended in spontaneous miscarriage [7], which was not different from the rate of spontaneous miscarriage reported in the general population. In a prospective study conducted on 700 Hong Kong women requesting EC within 120 h of unprotected intercourse, Li et al. (2016) showed UPA to be effective at preventing pregnancy if taken before ovulation had occurred but ineffective if taken after ovulation [30]. The time of the cycle was estimated using three parameters: cycle day (based on the date of the last menstrual period and length of the last three menstrual cycles); serum LH, estradiol and progesterone

concentrations measured on the day of UPA intake; and the presence and size of the leading ovarian follicle measured by ultrasound on the day of UPA intake. The percentage of pregnancies prevented was calculated from the observed number of pregnancies and the number expected in the cohort using the Trussell formula [31]. A significantly lower pregnancy rate ($p<.0001$) was observed among women who received UPA before ovulation compared to the expected rate based on the Trussell formula. However, a significant difference was not similarly observed ($p=.281$) among those receiving UPA after ovulation. These data suggest that UPA is ineffective at preventing pregnancy if taken after ovulation, implying that UPA has negligible effect on postovulatory mechanisms related to establishment of pregnancy.

1.2. Limitations

There are limitations to the research discussed. It is difficult to draw clinical conclusions from small changes in endometrial histology or morphology. Animal models of implantation can shed light on the molecular and mechanical events involved in the discrete stages of implantation, but different animal models show wide mechanistic variation [32], and none can replicate the complete process of human implantation. While microarrays can identify genes that appear to be involved in the process of implantation and can demonstrate changes in the patterns of gene expression when tissue is exposed to UPA, they cannot prove which of the many genes involved are critical. It is a challenge to ascribe functions to genomic features, and although tempting, "guilt by association" should not be inferred [33].

In vitro models are limited by the fact that they do not reflect the native architecture that constitutes the receptive endometrium in vivo. We know of no data on tissue levels of UPA after a single dose in the human. Thus, it is difficult to confirm that the experimental dosage of UPA is truly equivalent to the tissue concentration after UPA-EC intake; 0.4 μM is the peak serum concentration of UPA after an oral dose of 30 mg, and it is reasonable to believe that the experimental dose used in these models was relevant to the EC context.

An understanding of the endometrial response to embryonic attachment in primate species may apparently provide some insights into human implantation. However, there are significant differences between species. Further refinement of the in vitro human implantation model used by Berger et al. [24] and repeating those experiments with larger numbers of human embryos would at least provide confirmation of the comparison between the effect of UPA, LNG and mifepristone on human implantation models.

2. Conclusions and clinical relevance

While it is not possible to conclude that UPA-EC never has an effect on implantation, the evidence suggests that at the dose used for EC, interference with implantation does not seem a likely mechanism of action.

Does it really matter? The label for UPA-EC in the USA states that "The likely primary mechanism of action of ulipristal acetate for emergency contraception is therefore inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy" [34]. Religious and moral views sometimes influence contraceptive method of choice [35,36], and the possibility that a contraceptive may work by inhibiting implantation deters some women from using the method. The label for LNG (Plan B, Barr Pharmaceuticals), the only other oral EC available in the United States, similarly advises potential users that "it may inhibit implantation (by altering the endometrium)" [37], and the copper intrauterine device certainly inhibits or interrupts implantation if inserted at the critical stage of the cycle [38]. Women who are deterred from using a contraceptive because they are told that it interferes with implantation would have no options for preventing unwanted pregnancy if they have unprotected sex or make a mistake with their usual contraceptive method. Ironically, without the choice to use EC, they may ultimately have to choose between continuing an unwanted pregnancy and having an induced abortion.

Despite the statement in the US label for ella® on the possibility that it may interfere with implantation, most authorities, based on reviews of the recent evidence, have concluded either that UPA-EC does not, or is unlikely to, interfere with implantation (Box 1). Clinical guidelines are developed for healthcare providers, however, and women considering using EC do not read them. Most women who use EC do not take it at a time in the cycle when any theoretical effect on implantation would be relevant. It is surely time to review the wording of the FDA-approved label for ella® and give women what they deserve, i.e., information which accurately reflects the level of evidence that exists stating that UPA-EC does not work by interfering with implantation.

Box 1.

Joint statement by the German Society for Gynaecologic Endocrinology and Reproductive Medicine and the Professional Association of Gynaecologists: "Both LNG 1.5mg and UPA 30 mg do not act to prevent implantation in the employed doses and with a single dose." [39]

The International Society of Gynecological Endocrinology: "There is no evidence to suggest that an effect on the endometrium accounts for the efficacy of UPA in preventing pregnancy at a dose of 30 mg, nor that UPA 30 mg is abortifacient." [40]

The American College of Obstetricians and Gynecologists: "Review of the evidence suggests that EC is unlikely to prevent implantation of a fertilized egg." [41]

The European Consortium for Emergency Contraception: "There is no evidence that, at the doses of LNG or UPA used for EC, these methods would prevent implantation or cause an abortion.EC pills should not be confused with drug regimen used for legal termination of pregnancy." [42]

The UK Faculty of Sexual and Reproductive Health: "UPA-EC has not been demonstrated to be effective as EC when administered after ovulation." [43]

The International Consortium for Emergency Contraception: "The primary mechanism is disruption of ovulation. Other mechanisms have been postulated but are not well supported by data. No evidence supports the theory that EC pills interfere with the implantation of a fertilized egg. EC pills do not cause abortion of an existing pregnancy." [44]

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