

UPA and LNG in emergency contraception: the information by EMA and the scientific evidences indicate a prevalent anti-implantation effect

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ABSTRACT

Rationale and objectives: Emergency contraceptives pills (ECPs) are described as drugs that work by either inhibiting or delaying ovulation without affecting implantation. In our opinion, as we aim at demonstrating, both EMA documents and the experimental papers indicate that they prevalently inhibit embryo-implantation.

LNG-ECPs: literature: LNG-ECPs never prevent ovulation when are taken in the most fertile days (EMA-EPAR on ellaOne[®] p. 9, first table). Conversely, they prevent the formation of an adequate corpus luteum. When they are taken pre-ovulatory ovulations occur regularly, but pregnancies do not appear. Taken after ovulation, they seem ineffective in preventing pregnancies.

UPA-ECPs: literature: EllaOne[®] prevents ovulation only when is taken in the first fertile day. Thereafter, its anti-ovulatory effect drops sharply and becomes insignificant (8%) 36 h before ovulation, in the most fertile days (Brache); its decreasing anti-ovulatory effect cannot explain a consistently high effectiveness in preventing pregnancies ($\geq 80\%$) that does not decrease depending on which of the 5 d it is taken after unprotected intercourse. Besides, ovulation occurs regularly in 91.7% of women taking ellaOne[®] weekly, for eight consecutive weeks (EMA-CHMP-Assessment Report 'EMA/73099/2015': study HRA2914-554, p. 7). Lastly, Lira-Albarrán administered ellaOne[®] to women in the most fertile pre-ovulatory days: they had normal ovulation, but their endometrium, evaluated through samples obtained in the implantation window, became inhospitable: the expression of 1183 genes was exactly the opposite of that observed in the receptive pro-gestational endometrium. This agrees with information by EMA-CHMP-Assessment Report 'EMA/261787/2009' (p. 8): after UPA administration 'the proteins necessary to begin and maintain pregnancy are not synthesized'.

Conclusions: Emergency Contraceptives work prevalently by preventing embryo-implantation. People shall receive correct information.

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Introduction

Emergency contraception (EC) is defined as the use of any drug, or the intrauterine insertion of devices, with the aim of preventing the appearance of pregnancy after unprotected sex intercourse (UPSI) occurring in the fertile period of the cycle, that is in the 5 d preceding ovulation and in the ovulation-day itself. UPSI in the pre-ovulatory day has the highest probability of conception, followed by that in the ovulation day and in the second day preceding ovulation [1–5]. In these 3 d the frequency of both protected and unprotected intercourse peaks [2,6].

UPSI in fertile days entails two facts that (1) the sperms have already entered the tubes and no day-after drug can reverse their ascent; (2) the ovulation is imminent.

At that time, emergency contraceptive pills (ECPs) can avoid pregnancy in two main ways: by preventing ovulation *in extremis*, thereby preventing fertilisation, or by making the uterus non-receptive to the embryo.

Correct information on ECPs' mechanism of action (MOA) is essential for the woman to express a free and informed consensus to use [7–9].

Our aim is evaluating the primary literature reporting the effects of ECPs in women to understand at the best

through what MOA(s) they can prevent the appearance of pregnancies. As well, we will evaluate the EMA Assessment Reports and official documents by International Health and Scientific Societies and discuss either the information offered to women in the package leaflets, and the information regarding any possible effect of ECPs on already diagnosed ongoing pregnancies.

Mechanism of action of emergency contraceptives

The drugs currently used are Levonorgestrel (LNG), a potent synthetic progestogen, and Ulipristal Acetate (UPA), a potent anti-progestagen with a molecular structure quite similar to that of Mifepristone (RU486).

Their package leaflets affirm, with large support [10–15], that ECPs either inhibit or delay ovulation and therefore prevent fertilisation without affecting implantation.

Theoretically, pregnancy could also be avoided by either affecting the muscular contractions and cilia activity in the human fallopian tubes, which are involved in the transportation of zygote, or inhibiting sperm fertilising capacity [10]. To date, however, nothing about these eventual MOAs has either been demonstrated, or is taken into account in the package leaflets [11–15].

Our opinion, based on primary scientific sources, is that ECPs consistently prevent ovulation only when taken at the beginning of the fertile period. Subsequently, in the days closest to ovulation in which most fertilisations occur [1–3,12] neither LNG nor UPA has any residual anti-ovulatory effect, but transform the endometrium into a non-receptive environment.

We will describe them separately.

Levonorgestrel (LNG; Norlevo[®], Levonelle[®] and Escapelle[®])

A single oral tablet (LNG 1.5 mg) should be taken within 72 h from UPSI in the fertile days [16,17]; its efficacy may persist up to 96 h [17].

Anti-ovulatory effects

The International Federation of Gynecology & Obstetrics (FIGO) and the International Consortium for Emergency Contraception (ICEC) in their 2008, 2011 and 2012 joint Statements [15] state ‘that inhibition or delay of ovulation is LNG ECPs’ principal and possibly only mechanism of action’.

Actually, in the studies quoted in support to the Statements [18–22], ovulation is never inhibited when the women take LNG in the advanced pre-ovulatory, most fertile, days.

The Statements’ authors themselves [23], Brache and Faundes, in their own studies [24–27] conclude that when LNG is taken in the advanced pre-ovulatory phase it ‘resulted in follicle rupture inhibition in 14.6% of the LNG-studied cycles’. They substantially report a very poor anti-ovulatory effect, which is the exact opposite of what they state in the Statements.

At last, EMA itself, in the EPAR on ellaOne[®] updated 31/08/2018 [14], evidences that LNG taken in the fertile days never inhibits ovulation (first table, page 9).

Though unable to prevent ovulation, LNG is effective in avoiding the appearance of pregnancy: in fact, the pre-ovulatory administration of LNG after UPSI in the fertile period makes 70% of expected pregnancies do not appear [28–30]. These data are confirmed by Noé et al. [31]: no clinical pregnancies were observed out of the 13 expected, after pre-ovulatory intake of LNG. In 57 out of 72 *evaluable* patients (79%), however, ovulation occurred regularly. As a consequence, LNG-ECPs certainly avoid the appearance of pregnancies when they are taken in the pre-ovulatory days, but their MOA cannot be ovulation inhibition/delay, as ovulation occurs regularly and fertilisation can ensue.

Endometrial effects

We just evidenced that ovulation occurred regularly in women taking LNG in the pre-ovulatory most fertile period [18–22]. An inadequate corpus luteum was observed in most of them [19–22], which impairs the production of Progesterone, the hormone preparing the endometrium to embryo-implantation. The mid-luteal endometrium from such women was either out-of-phase or quantitatively inadequate [19]. A possible explanation is that pre-ovulatory high-dose LNG (anti-estrogen) might hinder granulosa-luteinisation, a highly estrogen-dependent event: granulosa

cells will be the major component of the corpus luteum, after ovulation, and the lack of an adequate endowment of LH-receptors in them will likely lead to luteal inadequacy.

The hypothesis that other mechanisms can prevent pregnancy in the LNG pre-ovulatory treated women [31] does not hold: 79% of the women ovulate regularly and changes in cervical mucus would (if any) occur only later, ‘the day(s) after’ the sperm ascent into the tube: UPSI occurs in the fertile days and the sperms enter almost immediately. Besides, no modification in sperm function has been either demonstrated after LNG-ECPs or described in the package leaflet.

When, on the contrary, LNG-ECP was taken on the day of, or after, ovulation 100% of expected pregnancies occurred regularly. This is not surprising and is not in contrast with the previous considerations: at ovulation and later, everything is done as to adequacy and functionality of the corpus luteum. Once formed, after ovulation, it will start producing progesterone correctly, differently from what happens when the woman receives LNG pre-ovulatory. Adding some more exogenous LNG at this time will not hamper endometrial secretive development and implantation can occur regularly.

This is further confirmed by the finding that LNG-ECPs may not affect the *in vitro* embryo-attachment to physiological receptive mid-luteal endometrium [32,33]: this tissue is already endowed with all what is needed for attachment. This finding only indicates that LNG-ECPs taken 5 d after fertilisation cannot prevent attachment, as already shown [29,31], but is quite useless in the clinical practice of EC, as luteal UPSI never leads to fertilisation [34–36].

Ulipristal acetate (UPA; ellaOne[®])

A single oral tablet (micronised UPA 30 mg) should be taken within 5 d since UPSI. Micronised UPA 30 mg is equivalent to un-micronised UPA 50 mg used in previous trials [12,37].

UPA binds to progesterone receptors and inhibits the pro-gestational effects of progesterone in the same way as does Mifepristone (RU486). Their molecules are quite similar.

HRA-Pharma states that ellaOne[®], administered in the fertile period of the cycle, can delay ovulation and hence prevent fertilisation: ellaOne[®] would postpone follicular rupture up to 5 d even when taken immediately before ovulation is scheduled to occur and its efficacy would be consistently over 80%, even when it is taken up to five days since UPSI [12]. This statement, basing on Brache’s paper [25], is fully endorsed and shared by the EMA [14].

Nevertheless, the table at page 7 of the EMA-CHMP AR on ellaOne[®] ‘EMA/73099/2015’ [38] evidences that the above statement is untrue.

EMA reports the HRA2914-554 study, that examined the effect on ovulation of single doses of ellaOne[®] taken weekly (Q7D) or every 5 d (Q5D) for 8 consecutive weeks, starting from the first day of the menstrual cycle. Ovulation was observed at least once in 91.7% (twice in 50%) of the women in the group Q7D and in 72.7% of those in the group Q5D. The pre-ovulatory cervical mucus was always favourable to sperm penetration and the endometrium, evaluated at the end of the treatment, was quite

unsuitable for implantation: it was morphologically altered in 50% of women. Of course, using UPA on an ongoing base does not represent the one-time use suggested for EC.

Anyway, nowhere in the official information on UPA-ECs is written that frequently repeated UPA assumption reduces its contraceptive effectiveness in any way or is unsafe. On the contrary, the ongoing assumption of ellaOne[®] is proposed as acceptable by HRA Pharma and EMA: based on the study HRA2914-554, in fact, they removed the warning against its repeated assumption within the same menstrual cycle (EMA/73099/2015, page 9, point '2.2.2.1.2. HRA2914-554') [38].

These data themselves, in our opinion, might close any discussion on UPA's MOA definitively. Nevertheless, we will discuss the primary literature dealing with this topic in women.

Anti-ovulatory effects

Brache evaluates the effects of ellaOne[®] on ovulation when it is taken in the different days of the fertile period [25]. She suggests that ellaOne[®] inhibits or significantly delays follicular rupture for over 5 d even when is taken immediately before ovulation, a point that is emphasised in the title, in the abstract and in the paper conclusions.

Thirty-four women are included. Overall, ellaOne[®] inhibits or delays ovulation in 58.8% of the women, while 41.2% ovulate regularly and fertilisation can ensue. The effects of UPA result highly dependent on the levels of LH at the time of administration, in the three subsequent phases of the fertile period. Ovulation is consistently delayed (100%) only in eight women who took ellaOne[®] before LH-levels increase. After the onset of LH-surge but prior to its peak, ovulation is delayed in 11 women out of 14 (78.6%). In the patients treated at the LH-peak ovulation is delayed in only one woman out of 12 (8.3%).

Moreover, in the *results* section, the authors state verbatim that 'when UPA was given at the time of the LH-peak, the time elapsed (from intake) to (follicular) rupture was similar to placebo (1.54 ± 0.52 days versus 1.31 ± 0.48 days)'. The one-two days before ovulation are the most fertile in the cycle, those in which fertilisations mostly occur. These are the days in which UPA, credited with a steadily high contraceptive efficacy ($\geq 80\%$), should prevent ovulation with the highest efficacy if its MOA were truly anti-ovulatory.

On the contrary, ellaOne[®] taken in these days has no (or placebo-like) anti-ovulatory effects. Some authors, nonetheless, quoting Brache in two papers, at pages 302 [39] and 93 [40], sentence that 'Even on the day of the LH-peak, UPA could delay ovulation for 24 to 48 hours after administration'. That represents incorrect information.

EllaOne[®]'s ability to delay ovulation decreases sharply from the first fertile day and becomes placebo-like (8%) 36 h before ovulation. On the contrary, its effectiveness in preventing pregnancy-appearance remains very high ($\geq 80\%$) and does not decrease depending on which of the 5 d it is taken after UPSI [5,28,37,41]: its sharply decreasing anti-ovulatory effect cannot explain its persistently high effectiveness [36].

Lira-Albarrán [42], as well, administered ellaOne[®] in the one-two pre-ovulatory days, 'at a time in which the

probability of pregnancy is highest': ovulation occurred regularly when expected.

At last, Stratton administered 10-50-100 mg of un-micronised UPA to women in their mid-follicular phase, before the fertile period, and reported a delay in ovulation that was greatest with the highest doses: 50 mg (ellaOne[®]) and 100 mg. On the contrary, the luteal phase endometrial maturation was inhibited similarly at all the doses, evidencing that UPA-threshold for altering endometrial morphology was lower than that for altering folliculogenesis [43].

Endometrial effects

UPA's negative effects on the endometrium appear consistently in the luteal phase [43], both when UPA delays ovulation and when it does not after its lowest dose (10 mg). When ovulation occurs and fertilisation ensues, the endometrium will always be unsuitable for embryo-implantation.

One single dose of un-micronised UPA (10,50,100 mg) leads to a reduction in endometrial thickness consistently, at whichever time it is given: mid-follicular [43]; mid-cycle, following ovulation and fertilisation [44]; mid-luteal [45], in the implantation-window. The pro-gestational effects of progesterone on the endometrium are lost. In particular, taken in the early luteal phase [44], the doses of 50 mg (ellaOne[®]) and 100 mg increase endometrial progesterone receptors and reduce significantly the markers of endometrial receptivity (Node-Addressins), potentially affecting embryo-implantation.

Some authors [46,47], quoting the above Stratton et al.'s data [44], acknowledge that un-micronised UPA 50 mg (ellaOne[®]) and 100 mg reduce significantly endometrial receptivity, but affirm that 'in the doses relevant for EC use (30mg) UPA has no significant effect on the endometrium'. This information appears deceiving, as ellaOne[®] is quite equivalent to un-micronised UPA 50 mg.

Stratton, besides, evidences that in women's endometrium UPA induces effects that are identical to those observed with Mifepristone 200 mg (the dose used for pregnancy termination), but that UPA is effective at a much lower doses: 10 mg (one fifth of ellaOne[®]) [44], as we previously reported [36].

Endometrial inhibition is direct: ellaOne[®] occupies progesterone receptors [48–52]: progesterone is present but cannot work and the endometrium will be not-receptive. UPA effects on the endometrial tissue are consistent with UPA acting as a progesterone receptors antagonist [52].

The decisive demonstration of the anti-implantation MOA comes from the above-mentioned study by Lira-Albarrán [42]. He administered ellaOne[®] in the most fertile days: ovulation was always observed, but the luteal endometrium became non-receptive.

Fourteen women were evaluated in two consecutive cycles: each woman served as control of herself [42]. In the untreated cycle the major characteristics of the cycle were determined. In the following cycle a single dose of ellaOne[®] was administered when the follicle reached 20 mm diameter, intentionally *when the probability of pregnancy is high*. In both the control and the treated cycles ovulation took place regularly. At the day LH + 7 of both cycles an endometrial biopsy was taken from all women.

The endometrial expression of 1183 genes was determined. Despite normal luteal progesterone levels, ellaOne[®]

showed an anti-progestin effect in the endometrium. The genes that were up-regulated in the receptive pro-gestational endometrium were, on the contrary, down-regulated in the UPA-treated endometrium, and vice-versa. The physiological gene expression observed in the receptive endometrium changed completely after ellaOne[®], showing a quite opposite directionality. The author concludes that the ‘changes observed in gene expression in endometrial samples from women exposed to UPA are associated with a non-receptive endometrial phenotype’.

Taking ellaOne[®] after UPSI in the most fertile days allows ovulation [25,27,42]. UPA cannot interfere with sperm fertilising ability and nothing can prevent fertilisation [53,54]. The endometrium, however, is non-receptive and the embryo has no chance of surviving.

Scientific evidence is strong, but simple reasoning confirms. We all know that the pre-ovulatory day is the most fertile day of the cycle: the one in which most intercourse and most UPSI do occur, leading to most fertilisations [1–5]. We will use it correctly to exemplify.

If a woman has UPSI in the pre-ovulatory day, with ovulation within the next 24 h, fertilisation will follow within 24 further hours, that is within 48 h since intercourse.

EllaOne[®] can be taken – with a consistent efficacy higher than 80% – up to 5 d since that UPSI, that is up to 4 d since ovulation and up to 3 d since the eventual fertilisation.

How can any anti-ovulatory effect be claimed? By the way, given the fact that in the pre-ovulatory day ellaOne[®]'s anti-ovulatory effectiveness is placebo-like [25,27,42], not even taking ellaOne[®] during UPSI itself would lead to any ovulation delay.

Again some authors try to demonstrate that ellaOne[®] does not affect human embryo-attachment *in vitro* and conclude that ellaOne[®] does not disrupt the *implantation process* [55].

Unfortunately, they used fully receptive luteal endometrium already endowed with the machinery for embryo-attachment. They did not use luteal endometrium from ellaOne[®] pre-treated women, like that, quite inhospitable, reported by Lira-Albarrán.

Moreover, the cultures [55] might not reproduce *in vivo* conditions: UPA-concentration *in vitro* (200 ng/ml) was similar to that observed in the women's blood 1 h after ellaOne[®] intake (176 + 89 ng/ml), while the tissue concentration *in vivo* is higher than that in the women's blood. We acknowledge that we currently have no data on the actual tissue concentration and this makes it impossible to draw any conclusion – either favourable or unfavourable – as to validity of that [55] *in vitro* model and its correspondence with what may happen *in vivo*.

Lastly, only the initial step, the embryo-attachment, might be reproducible *in vitro*. Implantation cannot be tested, as the authors acknowledge. Nevertheless, they conclude that ‘the mechanism of action of UPA when used as an EC does not disrupt the *implantation process*’, and always refer to *implantation* in the abstract's Study Question, Summary Answer and Conclusions [55]. This, again, does not appear correct information.

All the data we exposed make us believe that the prevalent MOA of ellaOne[®] is linked to its anti-progestational effect on the endometrium [52].

Discussion

The information on which we rely was already available in the EMA-CHMP AR for Ellaone[®] (EMA/261787/2009) [56] leading to ellaOne[®] marketing authorisation. We discuss the same papers: HRA2914-505, Stratton et al. [43]; HRA2914-506, Stratton et al. [44]; HRA2914-503, Passaro et al. [45]; HRA2914-511, Brache et al. [25].

The EMA-AR [56] acknowledges what we reported above and adds many important issues:

1. ‘UPA prevents progesterone from occupying its receptor, thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized’. (page 8).
This led EMA to consider the possibility that UPA is effective as an abortifacient. EMA itself went on this evaluation and further reported that:
2. ‘The ability of UPA to terminate pregnancy was investigated. Ulipristal and mifepristone were approximately equipotent’ (page 10)
3. ‘When using intramuscular administration of 0.5mg/kg, 4/5 fetuses were lost in UPA treated animals (macaques)’ (page 10) [57]. Un-micronised UPA 0.5 mg/kg means 50 mg/100 kg: 50 mg is the dose equivalent to ellaOne[®] and can terminate pregnancy in a 100 kg primate and the parenteral administration is similar to the sublingual one. We acknowledge that this observation is purely speculative: macaques never reach 100 kg weight. However, they are tested because of their similarities with the humans, who can use the sub-lingual way easily.
4. The possibility that UPA is used *off-label* for pregnancy termination is presented as a ‘safety concern’ in the table ‘Summary of the risk management plan for Ellaone[®]’ (page 41). The strategic choice to get the ‘proposed risk minimization’ is ‘Omit any sentence’.
5. EMA and HRA-Pharma agree that all of the approaches to avoid *off-label* use suffer from inevitable limitations; the only way seemed monitoring prescription registries (pages 45–46), but EMA abolished prescriptions in 2015 [38].

In spite of all the above information, the EMA-CHMP holds that ‘Emergency contraceptives work by stopping or delaying ovulation’ [58].

In the AR ‘EMA/73099/2015’ [38], EMA concludes (page 32, first sentence) that ‘an abortifacient image is not the hallmark of all SPRMs. It is specifically and strongly associated with mifepristone’ and that ‘No abortifacient effects have been reported at any dose or with any duration of therapy in the clinical setting’. However, three pages later (page 35), EMA emphasises that ‘During the evaluation process of the ellaOne[®] registration dossier the MAH (HRA-Pharma) was requested to study any potential off-label use of ellaOne[®], in particular during pregnancy, possibly as an abortifacient. No clinical studies have been performed with UPA as an abortifacient, and it is therefore also unknown whether it is possible to use it for abortion’.

It would be easy to assume that ‘no abortifacient effects have been reported’ just because ‘no clinical studies have

been performed with UPA as an abortifacient'. Further comment appears unnecessary.

However, to rule out any possible *off-label* use, in the absence of reassuring scientific evidences, EMA accepted the results of an interview to 75 prescribers from Poland and Sweden (HRA2914-544a) (page 31), *evidently* representative of the European doctors: requested, they answered they never used UPA for abortion. This was considered a reliable 'demonstration that off-label prescription of ellaOne[®] for abortion does not happen in the real world' [38].

At last, in the table at page 64 of the same AR [38], the 'Effect on pregnancy maintenance/Off-label use as an abortifacient' is still presented as a Safety Concern. Nevertheless, the EMA-CHMP recommended that the contraindication 'pregnancy' be removed from the information.

EMA is aware of UPA post-fertilisation effect and of its ability to terminate pregnancy with the same efficacy as Mifepristone: the two molecules, administered at similar dosages, share similar effects in the female reproductive tract [16,56,59–72], for instance in the medical treatment of uterine fibroids with Esmya[®] (UPA 5mg tablets in monthly blisters of 28 tablets).

Esmya[®], by the way, and just to think about, has been shown to be severely hepatotoxic and currently its prescription is possible only after an overall evaluation of liver function (EMA/482522/2018) [73]. As we reported above, the EMA-CHMP (requested by HRA-Pharma) removed the warning against repeated administration of ellaOne[®] within the same menstrual cycle: basing on the study HRA2914-554, that warning was considered out-of-date (EMA/73099/2015, page 9) [38]. Nonetheless, we observe that the amounts of UPA assumed in HRA2914-554 study and considered safe were similar (270 mg in Q7D) to, or even greater (360 mg in Q5D) than, the potentially dangerous amounts assumed through Esmya[®] (280 mg) in the same 8 weeks, without any recommendation to screen the liver function before assuming ellaOne[®] repeatedly.

Conclusions

Neither LNG nor UPA EC-pills can prevent or delay ovulation when they are taken in the most fertile days of the cycle. Their prevalent effects are post-fertilisation. Ovulation occurs, fertilisation can ensue, but the endometrium will be non-receptive. This is strongly suggested for LNG and is clearly demonstrated for UPA.

The women, the doctors and health-operators must receive whole, accurate and correct information.

Disclosure statement

The authors report no conflicts of interest.

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