EMERGENCY CONTRACEPTION

Position Paper on the Mechanism of Action

LONG SUMMARY

Emergency contraception (EC) is defined as the use of any drug, or the intrauterine insertion of devices, after unprotected intercourse in the fertile days with the aim of preventing an unwanted pregnancy. Unprotected intercourse can lead to pregnancy only if it occurs in the fertile period of the cycle, that is, in the four-five days preceding ovulation and on the ovulation day itself. Only in these days, in fact, does the cervical mucus allow the sperms to enter female internal genitalia. Among the fertile days, the pre-ovulatory day is the day on which the probability of conception is highest, followed by the ovulation day itself and by the second day preceding ovulation. The use of EC must face two facts: the sperms already entered and ovulation is imminent.

The emergency contraceptives (ECs) currently used are Levonorgestrel (LNG; Norlevo®, Levonelle® and Escapelle®), which is a potent synthetic progestogen, and Ulipristal Acetate (UPA; ellaOne®), a potent anti-progestagen quite similar to Mifepristone (RU486, Myfegyne®).

The producer (HRA Pharma), the Food and Drugs Administration (US-FDA, the European Medicines Agency (EMA), the most highly reputed international and national gynecological Scientific Societies affirm that emergency contraceptives work by either inhibiting or delaying ovulation and therefore preventing fertilization without affecting implantation in any way.

In this *Position Paper* it will be evidenced that the main mechanism of action (MOA) of these drugs is, on the contrary, the inhibition of embryo implantation, which is in sharp contrast with the Maltese laws that protect human life from conception.

Levonorgestrel - The EMA's EPAR on EllaOne®, updated 29/06/2017, shows that LNG taken in the most fertile days of the cycle never inhibits ovulation, which takes place regularly, and fertilization can ensue. LNG, on the contrary, affects the function of the corpus luteum with a severe impairment in the production of progesterone, the pro-gestational hormone that should prepare the endometrium for embryo-implantation. This makes it impossible for the embryo to implant.

Ulipristal Acetate - EllaOne® can inhibit or delay ovulation only when it is taken in the first fertile days. In the 36 hours preceding ovulation and later (the most fertile days, in which over 70% of fertilization do occur) it is unable to affect ovulation in any way, as evidenced in Brache's paper. On the contrary, in whichever day it is taken during the cycle, UPA consistently impairs endometrial development even at doses much lower than those that are present in ellaOne®.

Moreover, ovulation was observed even after a repeated regular intake of ellaOne®: in 91.7% of the women taking the drug every week for eight weeks and in 72.7% of those taking it every fifth day for eight consecutive weeks. This is reported by EMA (EMA/73099/2015) and further confirms that no anti-ovulatory effect can be claimed as the main contraceptive MOA for ellaOne®.

EMA acknowledges (EMEA-261787-2009) that "*Ulipristal acetate 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*." This means that UPA can prevent embryo implantation and can even terminate ongoing pregnancies, as EMA acknowledges after off-label use. In fact (ibidem) UPA is able "*to terminate pregnancy, as well as mifepristone does"* and "*when using intramuscular administration of 0.5 mg/kg, 4/5 fetuses were lost in UPA treated macaques*". This means that 50 mg unmicronized UPA (equivalent to ellaOne®) can terminate pregnancies in a 100kg primate. Still more, EMA acknowledges that "*The threshold for altering endometrial morphology appears lower than for inhibition of ovulation*": i.e., anytime ovulation occurs and fertilization ensues (as usually), the endometrium will not allow the embryo implantation.

The data from medical literature (Brache) evidence that UPA ability to delay ovulation is highest (100%) only at the start of the fertile period; thereafter it decreases sharply and becomes almost null (8%) in the one to two days before follicular rupture. In spite of this, its effectiveness in preventing pregnancies is very high (≥80%) and does not decrease depending on which of the five days it is taken after unprotected intercourse. This appears surprising if UPA effectiveness is assumed to be due to its anti-ovulatory action. If it were so, the sharp decrease in UPA anti-ovulatory action should lead to a progressive reduction in its effectiveness as the pre-ovulatory days elapse. On the contrary, its efficacy remains very high, consistently over 80%.

The lack of any anti-ovulatory effects when ellaOne® is taken in the most fertile days of the cycle points out that its contraceptive MOA must be due to something else, that is, to its inhibitory endometrial effects. As expected, whenever it is taken in the menstrual cycle, the pro-gestational effects of Progesterone on the endometrium are lost, included the expression of those proteins that make the maternal uterus hospitable for the embryo. Embryo-implantation becomes impossible.

The definitive demonstration of the anti-implantation MOA of ellaOne® has been given, quite recently, by Lira-Albarràn et Al.: they administered a single dose of ellaOne® in the most fertile days of the cycle to 14 women carefully studied in the previous, untreated, control cycle. They evidenced that ovulation took place regularly after the pre-ovulatory intake of ellaOne®, excluding any anti-ovulatory effect when it is taken in the most fertile days of the cycle.

After ovulation, at the day LH+7, i.e. when the endometrium should be prepared for implantation, an endometrial biopsy was taken from all the women in both the control and the treated cycles. On this tissue the expression of 1183 genes was determined.

Despite the luteal progesterone plasma levels were normal, ellaOne® showed its clear anti-progestin activity at the tissue level: the genes that were activated in the hospitable pro-gestational endometrium were, on the contrary, inactivated in the ellaOne®-treated endometrium and vice versa, leading to a non-receptive endometrial phenotype, i.e. to an endometrium unsuitable for embryo-implantation.

Conclusions - ECs do not respect human life from conception as they mainly prevent embryo implantation. The people and the health-operators are intentionally deceived by false information.

INTRODUCTION

Procreation and sexuality are among the most sensitive aspects of human life. Their expression should be conscious and oriented to safeguarding the dignity, life and health of the adults involved and of their offspring since fertilization.

Currently, both the dignity of the partners and the life of the embryo appear to be threatened by emergency contraceptive drugs (ECs), as their mechanism of action (MOA) is described as pre-fertilization, while scientific research shows that they are effective prevalently after fertilization.

It is crucial to understand that the unavailability of correct or complete information on this issue severely hinders the capacity of women and their doctors to take conscious personal and professional decisions, therefore impairing their freedom of choice.

Correct information on the MOA of these drugs is dutiful and is the essential requirement for the woman to express a fully free and informed consensus to their use and for the doctors' decision to prescribe or not.

Several are the papers evidencing that the MOA is one of the main criteria that determine the choice among the different contraceptives. [1-4]

This is true for the women, the doctors and all the health-operators. Understanding whether the ECs do, or do not, prevent fertilization and respect human life since fertilization is highly important in order to choose.

Besides, information is essential to evaluate whether or not these drugs are compatible with National Laws of the Countries that protect human life since fertilization.

DEFINITION

Emergency contraception (EC) is defined as the use of any drug, or the intrauterine insertion of devices, after unprotected intercourse with the aim of preventing an unwanted pregnancy. (Slide 1) Unprotected intercourse can lead to pregnancy only if it occurs in the fertile period of the cycle, that is, in the four-five days preceding ovulation and on the ovulation day itself. (Slide 2) Only in these days, in fact, does the cervical mucus allow the sperms to enter female internal genitalia. Among the fertile days, the pre-ovulatory day is the day on which the probability of conception is highest, followed by the ovulation day and by the second day preceding ovulation.[5-9] On these same days, the frequency of both protected and unprotected intercourse peaks,[6,10] that is, most of the intercourse takes place in the three last fertile days. (Slides 3-6)

The use of EC to prevent pregnancy, after unprotected sex intercourse in the fertile days, is an attempt that must face at least two facts.

- the sperms have already entered. Thanks to the fertile mucus they already passed through the cervical channel and many have already reached the tube;[11] there they await, resting, the oocyte release. No day-after drug can of course inhibit their ascent to the inner female genitalia, given the fact it has already happened.

- ovulation is imminent.

At this point in time, everything in the female body is arranged for fertilization and for the subsequent embryo-implantation into the endometrium, which will be made hospitable by the luteal hormones which are produced and released, after ovulation, by the corpus luteum (the gland deriving from the lining of the former ovarian follicle, the receptacle which held the oocyte before release) (Slides 7-11)

Within this setting, a clinical appearance of pregnancy can only be avoided in two ways: by preventing *in extremis* the occurrence of ovulation and thereby preventing fertilization, or by making sure that the embryo will not find the fertile ground he needs to implant within the uterus. The substantial difference between the two hypotheses is evident: in the former fertilization is avoided, while in the latter the embryo is actively eliminated before he/she can implant and disclose his/her presence.

BIOLOGICAL PREMISES

Before discussing the papers on ECs MOA in the medical Literature, it is useful to describe synthetically what a menstrual cycle is and how it is regulated. (Slide 2)

The menstrual cycle is a complex of events that involve the ovaries and their follicles (the small structures that contain each one an oocyte), (Slide 12) as well as the hypophysis (or pituitary gland),

a gland hanging from the base of the brain: (Slide 13) both these glands produce hormones. In particular, the hypophysis usually regulates the production of estrogens by ovarian follicles thanks to its hormones: the Follicular Stimulating Hormone (FSH) and the Luteinizing Hormone (LH) (in the male the same hormones stimulate the functions of the testis). As they stimulate the gonads, i.e. the ovaries and the testis, they are also described as pituitary gonadotropins. Also the hypophysis is further regulated by substances produced in other superior brain centers, but to our current discussion we can limit to explain the continuous dialogue between the hypophysis and the ovary.

It is dutiful to state immediately what is a hormone and how it works: it is a substance produced in a gland and put into the circulatory system so that it can reach the organ in which it must be effective. In order to exert its effect, the hormone must links to the target cell through a specific structure that is named hormonal receptor. The hormone cannot work on a cell if this cell is not endowed with the specific receptor for that hormone. As well, a hormone cannot work on a cell which is endowed with the specific receptor for that hormone if the receptor is occupied or made unavailable by other substances.

Every cycle begins when in the woman's blood the levels of estrogens are very low: this happens at the end of the previous menstrual cycle. It is the situation observable at the left side of the slide 2.

The hypophysis, through its receptors, "understands" that the level of estrogens is low and stimulates a group of follicles to work. In the slide 2 the follicles can be seen on the left side: great amounts of FSH and LH push them to work (great blue and light-blue arrows).

The recruited follicles start the production of estrogens (red arrows) in growing amounts and their levels increase in the woman's blood (underlying red area). As estrogens increase, the hypophysis reduces its stimulation (smaller arrows) and from the 5th day onward one only follicle remains active and will grow and mature until the release of its oocyte. It is the *dominant follicle* of the cycle.

During its growth, it increases the number of its cells and produce greater and greater amounts of estrogens: the oocyte inside it completes its maturation.

When the hypophysis "understands" that estrogen levels are becoming very high, it increases its production of FSH and, mainly, LH (*LH surge*) until it reaches a peak (*LH peak*). LH peak triggers the rupture of the dominant follicle and the release of the oocyte. The release, i.e. *ovulation*, takes place about 36 hours after the LH peak and sometimes still later.

The oocyte can be fertilized by the sperm within 24 hours from its release.

After the release of the oocyte, the cells that constituted the wall of the dominant follicle and are strongly supported by a rich vascularization, increase their content in lipids and give origin to a yellow structure, the *corpus luteum* (luteum in Latin means yellow). (Slide 2) The corpus luteum is a

temporary gland that exists only after the release of the oocyte: it still produces estrogens, but – above all – it produces progesterone, the pro-gestational hormone, the hormone that prepares the uterus and the whole woman's body to gestation. All the ovarian cyclic events, from follicle recruitment to the expiry of the corpus luteum, can be easily followed in sequence, as illustrated in Netters' Atlas. (Slide 12)

In the lower layer of slide 2 is represented the endometrial tissue, the internal surface of the uterus, the "bed" in which everyone implanted in one's first days of life after fertilization. The endometrium is a tissue that completely depends on estrogens: if estrogens are present in the woman's blood the endometrium is well nourished and stands; otherwise, when estrogens are absent, the vessels that nourish it close and the tissue die: it is expelled by the menstrual flow that is the sign of the end of the menstrual cycle and of the beginning of a new one.

We already know that, at the beginning of the cycle, the ovarian follicles are stimulated by the hypophysis and start producing estrogens in increasing amounts; these estrogens – through their specific receptors on the endometrial cells – stimulate the reconstruction of the endometrial layer that is complete around ovulation, as can be seen in the slide 2. After ovulation, the corpus luteum maintains the production of estrogens and produce progesterone, which modifies significantly the qualities of the endometrium and prepare it to embryo-implantation and pregnancy.

Due to the action of progesterone – through its specific receptors on the endometrial cells – the endometrial vessel support is increased, so that the tissue is intensely nourished; besides, the endometrial glands become more and more dilated and filled by an extraordinary amount of nutrients secreted by the endometrial cells: in the glandular lumen the embryo will find all what is needed to develop and grow before the establishment of the embryo-maternal circulation. (Slide 7)

Besides, progesterone – always through its own receptors – deeply modifies the immunological asset of the endometrium depressing any possible reject reaction against the host (the embryo is quite another individual) and transforming it into a hospitable environment. (Slide 7)

The corpus luteum works for two weeks. In the absence of fertilization it will degenerate (Slide 2,12) and will produce no more hormones, neither estrogens nor progesterone. The endometrium, no longer nourished, will die and menstrual flow will appear.

A new cycle is ready to start in the same way already described: the hypophysis will stimulate new ovarian follicles and everything will be repeated and repeated cyclically. (Slide 2,12)

In case of fertilization – that occurs in the tube – everything changes. The embryo, at the stage of the first cell, immediately starts to send to the mother substances that modulate her immune defenses. (Slide 8) Cell reproduction starts and after about three days the embryo enters the uterus; around the fifth day the blastocyst is ready to implant. The aspect of the embryo is now cyst-like, with the inner cells destined to form the body and the peripheral cells to constitute the trophoblast, i.e. the cells through which the embryo will be in contact with the mother and

nourish, the future placenta. (Slide 9) Until now, the embryo used all the nutrients present in the great oocyte to grow: as can be seen, the cells while increasing in number do decrease in volume, but the total volume of the embryo does not change. (Slide 9)

At this point, the initial endowment is used up and the embryo needs more and more nutrients: he will deepen into the endometrium and reach the glands to access to their content. (Slide 10,11)

Since the early stages of life the embryo is very active. At the stage of 8 cells he already produces a gonadotropin of his own: the human Chorionic Gonadotropin (hCG): it is similar to LH but more potent: when the embryo is implanted, hCG enters maternal blood and finally reaches the corpus luteum stimulating it to increase its volume to become the pregnancy corpus luteum and go on with hormone production (Slide 14). This cycle will not end and no menstrual flow will be observed: estrogens and, mainly, progesterone will maintain the endometrium rich and suitable to the embryo needs. The ovary is no longer under the control of the woman: her hypophysis is now replaced by the embryo, which will produce hCG with the chorionic cells, the ones that shortly later will become the placenta.

One last information before closing this premises of physiology: the increasing estrogens that finally lead to the follicle rupture and the release of the oocyte, do progressively modify the characteristics of the cervical mucus so that only in these days – the fertile ones – the sperms can enter the female genitalia. (Slide 15)

The endocrine processes that lead to ovulation and to the appearance of a fluid cervical mucus are simultaneous expressions of the same biological event: the increase of estrogen levels. Consequently, the appearance of the fertile mucus usually and reliably foresees ovulation and allows any woman to recognize her fertile days and be fully aware of her fertility. The fertile days in the slide 2 are evidenced and numbered inversely as they approach ovulation, with the most fertile in greater characters. (Slides 2,4)

MECHANISM OF ACTION OF EMERGENCY CONTRACEPTIVES

The drugs currently used for EC are two: Levonorgestrel (LNG - active ingredient of Norlevo®, Levonelle® and Escapelle®), which is a potent synthetic progestogen, and Ulipristal Acetate (UPA - active ingredient of ellaOne®), a potent anti-progestagen quite similar to Mifepristone (RU486 - active ingredient of Myfegyne®). The two drugs will be dealt with separately.

First of all, an overview will be given to what is reported on ECs' MOA at the international level.

The producer (HRA Pharma),[12] the Food and Drugs Administration (US-FDA),[13] the European Medicines Agency (EMA),[14] the most highly reputed international and national gynecological Scientific Societies[15] report and affirm that ECs work by either inhibiting or delaying ovulation and therefore preventing fertilization without affecting implantation in any way.

Scientific and experimental evidence, on which this *Position Paper* is based, leads to a very different conclusion: in fact, these drugs consistently prevent fertilization only when they are taken at the very beginning of the fertile period; in the subsequent fertile days, instead, and mainly in the days closest to follicular rupture (the rupture of the ovarian follicle holding the oocyte and the release of the oocyte itself), both ECs no longer have any effects on either ovulation or fertilization. Evidence shows that in the days closest to ovulation ECs transform the endometrium into an inhospitable environment for the embryo. The fertile days closer to ovulation are the most fertile ones in the menstrual cycle and they are also the days in which, statistically, most intercourse and most fertilizations do occur.[5-7,12] (Slides 3-6)

Given these premises, the evaluation of the two types of EC Pills will be detailed.

- ***LEVONORGESTREL (LNG; Norlevo®, Levonelle® and Escapelle®)***

Each tablet contains Levonorgestrel 1.5 mg, to be taken in a single oral dose. The drug is presented as an EC to be used within 72 hours from unprotected intercourse;[17,18] however, the treatment efficacy seems to persist up to 96 hours without any significant reduction.[18] (Slides 15-17) Of course, we will discuss of a tablet-intake occurring after unprotected intercourse in the fertile days (out of them no intercourse can lead to pregnancy), that is, in the pre-ovulatory phase.

Anti-ovulatory effects

LNG is reported to delay or inhibit ovulation and consequently to prevent fertilization without affecting embryo-implantation in any way.

This is stated by the International Consortium for Emergency Contraception (ICEC) and the International Federation of Gynecology & Obstetrics (FIGO) in their 2008, 2011 and 2012 joint Statements "*How do Levonorgestrel-only emergency contraceptive pills (LNG-ECPs) work to prevent pregnancy*?".[15] (Slide 18)

Actually, in the studies quoted in support to the above statements,[15,19-23] (Slide 19) a delay in ovulation can be observed in 80% of the treated women when LNG is taken in the first fertile day and that is 4-5 days before ovulation. (Slide 20) Of course, a woman taking the drug on the first fertile day, following unprotected intercourse which has occurred one to three days earlier, would likely take the drug unnecessarily, as that intercourse likely occurred in a still infertile period.

Ovulation, on the contrary, is never inhibited when the women take LNG in the advanced pre-ovulatory phase, that is in the most fertile days of the cycle. (Slide 21) In these women, however, the studies quoted in the FIGO Statement [15,19-23] evidence that LNG affects the function of the corpus luteum (the gland deriving from the lining of ovarian follicle after ovulation). This impairs severely the production of the luteal hormones, Progesterone above all, that shall prepare the endometrium for embryo-implantation, and therefore makes it impossible for the embryo to implant. (Slides 22-24)

It is appropriate to specify, at this point, that pregnancy becomes clinically evident 10-14 days after fertilization, when the human Chorionic Gonadotropin (hCG) – a hormone produced by the developing embryo since the early stage of eight-cells – can enter the maternal blood after implantation. (Slide 21) At that time pregnancy becomes clinically detectable through the assay of the beta sub-unit of this hormone, the β-hCG, in the maternal blood.

The detection of β-hCG confirms us that the woman is pregnant (the commonly available pregnancy tests detect the β-hCG in the mother's urine). If the embryo is not allowed to implant and dies, no evidence of its presence and no clinically evident pregnancy will ever be detectable.

As reported, LNG is unable to prevent ovulation.

However, it is highly effective in avoiding the appearance of pregnancy: when unprotected intercourse occurs in the fertile period of the cycle and LNG is taken in the subsequent days, which are the most fertile ones, before ovulation, it prevents the clinical appearance of 70% of pregnancies.[24] These data have been clearly confirmed by Gabriela Noè: in her study, [25] ovulation was observed in 66% (57 out of 87 *total* cases) of patients who have taken LNG in the fertile pre-ovulatory phase, following unprotected intercourse in the fertile period; this percentage rose to 79% (57 out of 72 *evaluable* cases) if we exclude the 15 patients that dropped out of the study.

Noè pointed out that ovulation occurred, but no clinically evident pregnancies were observed out of the 13 expected to appear clinically. (Slides 25,26)

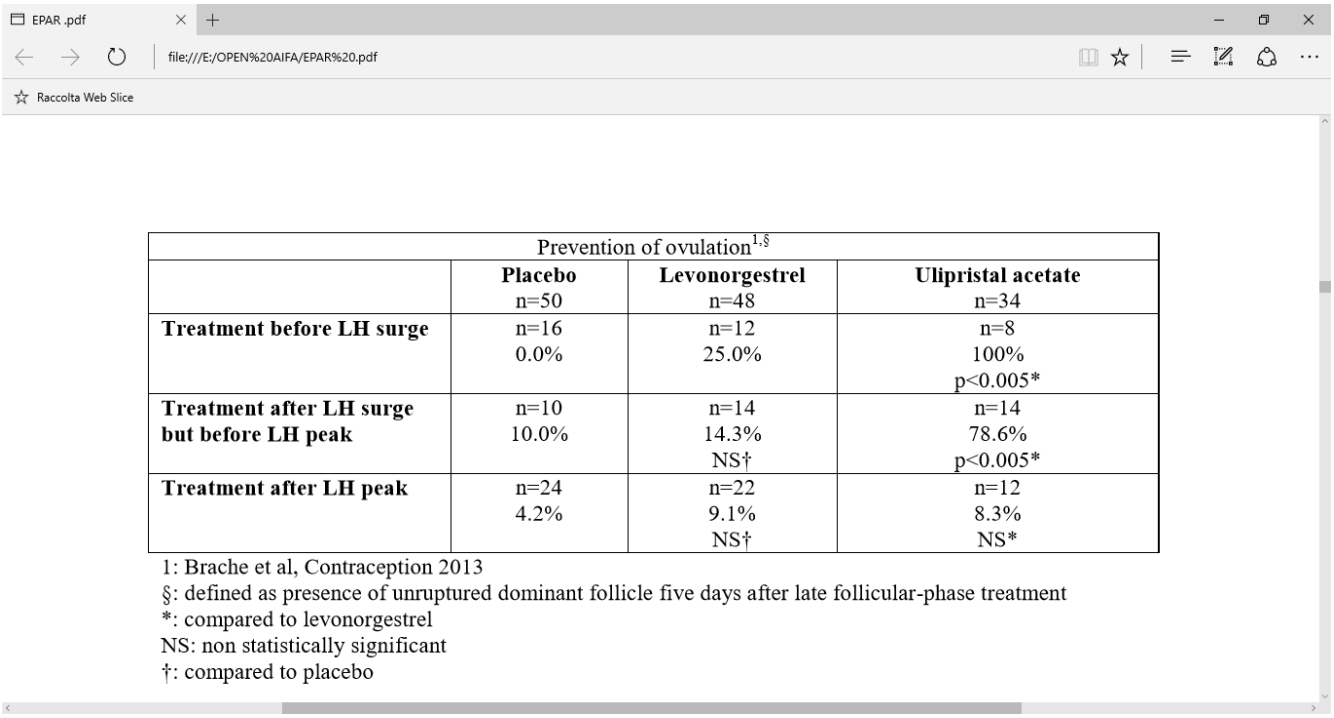
On the contrary, if LNG is taken after ovulation it seems unable to avoid the appearance of pregnancy: 6 pregnancies were observed out of the 7 expected. (Slide 26)

All these data evidence clearly that the ability of the day-after pill to prevent the clinical appearance of pregnancies, expressed by the ratio between observed (0) and expected (13) ones, cannot be due to any anti-ovulatory effect, which is absent, but must be due to something else: namely, to the alterations in the endometrial tissue which are due to the above described inadequate levels of Progesterone in the luteal phase.

Cohort studies further confirm this suggestion, as they clearly evidence that it is exactly the pre-ovulatory administration of LNG that prevents the clinical appearance of pregnancies. [26,27] The fact that sperms are already waiting inside the tubes, ovulation normally occurs, fertilization can follow, but no pregnancies do appear indicates that LNG effect necessarily is a post-fertilization one.

Finally, *ad abundantiam*, the European Public Assessment Report (EPAR) on ellaOne by the EMA updated 29/06/2017(14) evidences that in the fertile days LNG is never able to inhibit ovulation: its anti-ovulatory ability is only 25% in the first fertile days before LH surge, while subsequently it decreases further to only 10%, which is a placebo-like anti-ovulatory effect.

The Table 1 shows the charting exactly as provided by the EPAR at page 9. The central column reports the rates of ovulation prevention by Levonorgestrel in the fertile period.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Raccolta Web Slice

Prevention of ovulation[1,§]			
	Placebo n=50	**Levonorgestrel** n=48	**Ulipristal acetate** n=34
Treatment before LH surge	n=16 0.0%	n=12 25.0%	n=8 100% p<0.005*
Treatment after LH surge but before LH peak	n=10 10.0%	n=14 14.3% NS†	n=14 78.6% p<0.005*
Treatment after LH peak	n=24 4.2%	n=22 9.1% NS†	n=12 8.3% NS*

1: Brache et al, Contraception 2013
§: defined as presence of unruptured dominant follicle five days after late follicular-phase treatment
*: compared to levonorgestrel
NS: non statistically significant
†: compared to placebo

Its highest rate is only 25% at the very beginning of the fertile period (likely the 5th day before ovulation), before the LH levels start to rise. Thereafter it is null, like that of placebo.

Endometrial effects

We reported above that the studies quoted in the FIGO Statements,[15,19-23] evidenced that most women do ovulate regularly when LNG is taken in the pre-ovulatory fertile period. We add now that exactly in those same women who ovulated LNG prevents the formation of an adequate corpus luteum.[20-23] This impairs the production of those hormones (Progesterone above all) that shall prepare the endometrium to embryo-implantation and therefore leads to the impossibility for the embryo to implant.

The FIGO Experts, however, affirm that Levonorgestrel does not prevent implantation and repeat this in all the three subsequent Statement editions.[15] In support of this they report two studies which use cultures of endometrial tissue obtained from fertile women with normal cycles, who had received no hormonal treatment previously.[28,29]

In particular, in the two studies, they use cultures of luteal endometrium obtained five days after ovulation, that is when its receptivity is highest. Embryos are placed in this absolutely hospitable endometrium. In the presence of Progesterone 10 embryos out of 17 do attach (57%), while in the presence of LNG the percentage of attachments is lower: 6 out of 14 succeed (43%). The difference

is presented as non-significant, even if the number of cases evaluated is quite insufficient to allow any conclusion.

However, even if we were to accept that Levonorgestrel, added in the culture, cannot inhibit human blastocyst attachment, it must be stressed that these studies use normal luteal endometrial tissue obtained from patients who had not been pre-treated with any hormonal treatment.

These studies should have used endometrium obtained from women given Levonorgestrel in the pre-ovulatory fertile days. In reality the only thing that can be concluded from these studies is that Levonorgestrel, taken five days after fertilization, during a normal luteal phase, cannot impair an embryo-implantation already in progress. These are surely not the days in which ECs are usually recommended.[30,31]

At this point further information is indispensable to ascertain the reliability of FIGO and ICEC joint Statements.[32]

The names of the Statements' authors – Brache, Faundes, Fraser (gynecologists) and Trussell (statistician) – are reported in the official website of the European Society of Contraception and Reproductive Health (http://www.escrh.eu/about-esc/news/how-do-levonorgestrel),[33] where they are thanked "*for their incredible attention to detail and persistence in making sure this statement was accurate and fully reflected the most recent studies*". (Slides 27,28)

Brache is the first author of a paper on ellaOne® (UPA) supported by HRA Pharma.[34] At the end of the paper she compares the efficacy of UPA and LNG and concludes that when LNG is taken in the advanced pre-ovulatory phase it "*resulted in follicle rupture inhibition in 7/48women (14.6%) of the LNG studied cycles*". (Slides 29-31)

This evidence comes from the combined evaluation of the data from two similar trials performed by Brache herself and Faundes, wherein they stress that LNG is not able to inhibit ovulation in the most fertile days of the cycle[35,36] and this conclusion is reaffirmed, even recently, in a further paper where Brache compares different ECs.[37]

On the contrary, in the Statements, Brache and Faundes – in concert with the other two FIGO Experts – do state exactly the opposite of what is evident in their own studies. On behalf of all the world's gynecologists (FIGO), they state officially and dogmatically "*that inhibition or delay of ovulation is LNG ECPs' principal and possibly only mechanism of action*". (Slide 18)

This Statement appears as the official truth, unanimously shared by all the world gynecologists.

On it the doctors will base their professional and ethical choices.

On it the women will base their personal choices, believing that LNG does prevent fertilization.

On it the Nations and Governments will rely when they will legislate on these vital topics.

- ***ULIPRISTAL ACETATE (UPA; ellaOne®)***

Each tablet of ellaOne® contains 30 mg of micronized Ulipristal Acetate, to be taken in a single oral dose. It is unanimously acknowledged that 30 mg of micronized UPA are equivalent to 50 mg of unmicronized UPA (the drug used in previous clinical trials, in which it was administered in gelatin capsules).[12,38] (Slides 32-34)

UPA binds to Progesterone Receptors and inhibits the effects of Progesterone, the pro-gestational hormone. It works in the same way as does Mifepristone, which is better known as RU486, and their molecules are quite similar. (Slide 35)

The producer, HRA Pharma, affirms that ellaOne®, administered in the fertile period of the menstrual cycle, is able to delay ovulation and prevent the entrance of the sperm into the oocyte. EllaOne® would be able to postpone follicular rupture up to five days even when taken immediately before ovulation is scheduled to occur and its efficacy would be consistently high, over 80%, even when the drug is taken up to five days since unprotected intercourse.[12] (Slides 36,37) This statement, basing on the just mentioned Brache's paper,[34] is fully endorsed and shared by the EMA.[14] (Slides 38,39)

The data in the following Table 2, however, published by EMA itself, should be enough as evidence that the above statement is untrue and to close any discussion.

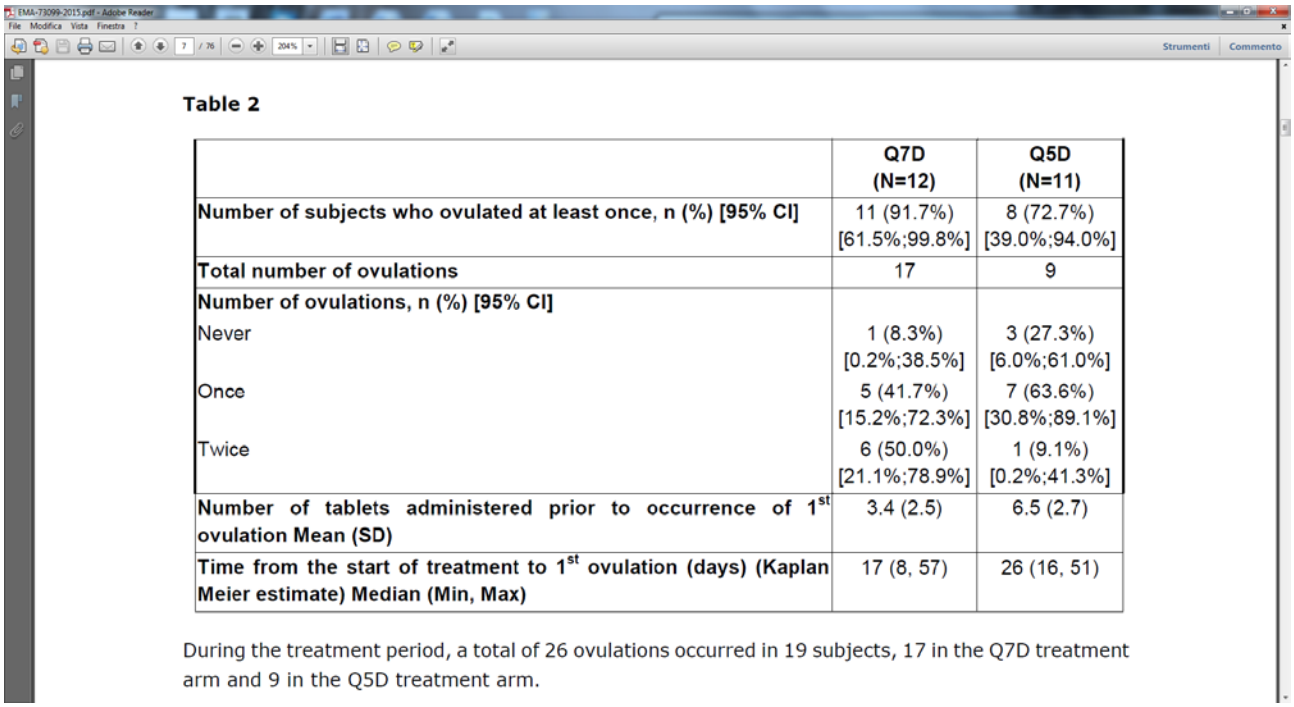

Table 2

	Q7D (N=12)	Q5D (N=11)
Number of subjects who ovulated at least once, n (%) [95% CI]	11 (91.7%) [61.5%;99.8%]	8 (72.7%) [39.0%;94.0%]
Total number of ovulations	17	9
Number of ovulations, n (%) [95% CI]		
Never	1 (8.3%) [0.2%;38.5%]	3 (27.3%) [6.0%;61.0%]
Once	5 (41.7%) [15.2%;72.3%]	7 (63.6%) [30.8%;89.1%]
Twice	6 (50.0%) [21.1%;78.9%]	1 (9.1%) [0.2%;41.3%]
Number of tablets administered prior to occurrence of 1st ovulation Mean (SD)	3.4 (2.5)	6.5 (2.7)
Time from the start of treatment to 1st ovulation (days) (Kaplan Meier estimate) Median (Min, Max)	17 (8, 57)	26 (16, 51)

During the treatment period, a total of 26 ovulations occurred in 19 subjects, 17 in the Q7D treatment arm and 9 in the Q5D treatment arm.

This table is published in the EMA-CHMP Assessment Report on ellaOne® "EMA/73099/2015", shown in page 7/76.[39]

It refers to a study that examined the effect on ovulation of single doses of ellaOne® taken weekly (Q7D) or every 5 days (Q5D) for 8 consecutive weeks; 12 and 11 subjects were included in the Q7D and the Q5D treatment arms, respectively.

The study, HRA2914-554, has been presented directly by the producer, HRA Pharma.

The table evidences that ovulation was observed in 91.7% of the women who took ellaOne® every week for eight weeks and in 72.7% of those taking the drug every fifth day, always for eight consecutive weeks.

In both treatment arms, the mean overall scores for the cervical mucus evaluation (performed during treatment period if follicle ≥15 mm, that is in the fertile period) indicated cervical mucus normally favorable to sperm penetration and fertilization.

In spite of these data from EMA, that rule out any possible significant effect of ellaOne® on ovulation and fertilization, we are going to discuss all the experimental papers dealing with this topic in women.

It must be reminded that fertilization can occur only when intercourse occurs in the 4-5 pre-ovulatory days and in the day of ovulation, during which the cervical mucus allows the sperms to enter female genitalia, and that it usually occurs within 24 hours from ovulation.

In the fertile days, in the ovaries and pituitary, several events can be observed that modify the cervical mucus characteristics, prepare ovulation and finally lead to follicular rupture and the release of the oocyte: (Slide 2)

- Firstly, in the ovary, the dominant follicle increases the secretion of estrogens, which immediately begin to induce the production of an increasingly fluid cervical mucus, favorable to sperm penetration. (Slide 15)
- Ovarian estrogens, in turn, lead to a progressive increase in LH levels (LH *surge*) by the hypophysis.
- LH, finally, reach its *peak* that persists for hours and triggers ovulation.
- Ovulation normally occurs 36 hours (24-48) after the LH peak, but sometimes it does occur also later.[8]

If these events are put on a chart representing the fertile days of the menstrual cycle, it is easy to realize that the period preceding the LH surge – the one in which only estrogens increase – coincides with the beginning of the fertile period; the period in which LH levels rise coincides with the second-third fertile days; while the days of LH peak (24-48 pre-ovulatory hours) and the following day, the day in which ovulation occurs, are the last fertile days, the most fertile of the menstrual cycle. (Slide 2,4-6)

Anti-ovulatory effects

In the medical Literature only one study evaluates the effects of ellaOne® on ovulation when it is taken in the different days of the fertile period. It is that by Vivian Brache, mentioned above. The authors suggest that UPA is able to inhibit or significantly delay follicular rupture for over 5 days, even when it is administered immediately before ovulation,[34] a point that is emphasized in the title, in the abstract and in the paper conclusions. (Slides 40,41)

The number of the study-subjects is small: 34 women. At first they are evaluated as a whole and then separately, categorised into three groups according to whether they took Ulipristal before LH levels start to increase, or during LH surge, or when LH peak levels are reached. (Slide 42)

The first overall evaluation evidences that ellaOne® taken in the fertile period of the cycle inhibits or delays ovulation in 58.8% of the women. This means that 41.2% of the women treated in the fertile period do ovulate regularly and hence fertilization can ensue thereafter. (Slide 43)

The effects of UPA are reported to be highly dependent on the levels of luteinizing hormone (LH) at the time of administration, that is, in the three different phases of the fertile period. Ovulation is consistently delayed (100%) only in eight women who took UPA before LH levels start to increase. After the onset of LH surge but prior to its peak, ovulation is delayed in eleven women out of fourteen (i.e. 78.6%), as three women do ovulate. In the patients treated at the LH peak ovulation is delayed in only one woman out of twelve, thus 92% of women do ovulate and fertilization can follow (this data is also reported in the table at page 10 of this *Position Paper*, in the right column, from Brache's paper). [37] (Slide 44)

Moreover, in the *results* section of the same paper, the authors state that when UPA is taken at the LH peak, that is one to two days before follicular rupture, the drug has no ability to either avoid or delay ovulation and behaves exactly like a placebo ["*when UPA was given at the time of the LH peak, the time elapsed to rupture was similar to placebo (1.54±0.52 days versus 1.31±0.48 days)*."]. (Slide 45) These days are known to be the most fertile in the cycle, those in which most fertilizations do occur (Slide 46). These are the days in which UPA, which is demonstrated to have a steadily high contraceptive efficacy (over 80%), should prevent ovulation with the highest efficacy if its MOA were truly anti-ovulatory.

On the contrary, as just shown, when ellaOne® is taken in the most fertile days of the cycle, that is one-two days before ovulation, it does not exhibit any anti-ovulatory effect.

UPA ability to delay ovulation is highest (100%) only at the start of the fertile period; thereafter it decreases sharply and quickly and becomes almost null (8%) in the one to two days before follicular rupture. In spite of this, its effectiveness in preventing pregnancies is very high (≥80%) and does not decrease depending on which of the five days it is taken after unprotected intercourse.[38,40-42] This appears surprising if UPA effectiveness is assumed to be due to its anti-ovulatory action, that decreases sharply as LH levels approach to peak: (Slide 47) if it were so, the

sharp decrease in UPA anti-ovulatory action should lead to a progressive reduction in its effectiveness as the pre-ovulatory days elapse. On the contrary, as repeatedly shown, its efficacy remains very high.[32] (Slide 48)

A further confirmation that ellaOne® cannot delay ovulation when administered in the one to two days preceding follicular rupture comes from the recent paper of Lira-Albarràn et Al [43]. (Slide 49) The research paper shows that the drug, intentionally given at a time of the cycle in which the probability of pregnancy is highest, (Slide 50) had no effect on the ovulation that normally occurred when it was physiologically expected. (Slide 51) Moreover, the endometrium, analyzed in the midluteal phase – that is the phase in which implantation takes place, about 5-6 days after fertilization – proved to be absolutely inhospitable.

At last, Stratton administrated 10, 50 and 100 mg of unmicronized UPA to women in their mid-follicular phase of the cycle: they caused a delay in ovulation that was greatest at the highest doses, but they inhibited luteal phase endometrial maturation similarly at all doses, evidencing that the threshold for altering endometrial morphology was lower than that for altering folliculogenesis, that is the process that – starting from the stimulation of several ovarian follicles at the beginning of the cycle – progressively leads to the maturation of a single follicle and to its rupture with the release of the oocyte.[44] (Slides 2,13)

We know that unmicronized UPA 50 mg is equivalent to the micronized UPA 30 mg of ellaOne®. The fact that ellaOne® can delay ovulation before the start of the fertile period (mid-follicular) is not surprising, as we know from Brache's paper that it delays ovulation even when it is taken in the first fertile day. What we learn from this study is that UPA's negative effects on the endometrium do appear consistently in the post-ovulatory luteal phase, even when UPA succeeds in delaying ovulation. We also understand and learn that, once ovulation occurs and fertilization can ensue, the endometrium will always be unsuitable for embryo-implantation.

The lack of any anti-ovulatory effects when ellaOne® is taken in the most fertile days of the cycle, as well as the anticipations from the last two mentioned studies, [43,44] point out that its contraceptive MOA must be due to something else and particularly to its inhibitory endometrial effects.

However, before passing to describe UPA endometrial effects, we want to report and put in evidence that some authors [45,46] offer a comment to Brache's results that is quite different from ours.

As was evidenced, Brache details verbatim that "*when UPA was given at the time of the LH peak, the time elapsed (from UPA intake) to rupture was similar to placebo (1.54±0.52 days versus 1.31±0.48 days)*". It means that UPA behaves exactly like a placebo when it is taken at the LH peak. (Slide 52) Neither ellaOne®, nor, evidently, the placebo, when administered at the LH peak have any effects on ovulation, which occurs physiologically one-two days later.

Quoting the above Brache's data,[34] Gemzell-Danielsson and Lalitkumar, in two papers, respectively at pages 302[45] (Slides 53,54) and 93[46] (Slides 55,56), detail verbatim: "*Even on the day of the LH peak, UPA could delay ovulation for 24 to 48 hs after administration*". Supported by the prestige of the Karolinska Institute, they affirm that ellaOne® is still effective when is taken at LH peak and could delay ovulation even at that point, a conclusion that is the exact opposite of Brache's results and comment.

It is hard to understand why such renowned authors repeat twice this sentence, that is patently contrary to the scientific evidence.

Endometrial effects

Let's come to the endometrium. One single dose of unmicronized UPA (10, 50, 100 mg) leads to a reduction in endometrial thickness consistently and modifies deeply endometrial receptivity, at whichever time it is given: either in the mid-follicular phase, before the beginning of the fertile days;[44] (Slides 57-59) at mid-cycle, in the days that follow ovulation (and the eventual fertilization);[47] (Slides 60-66) and in the mid-luteal phase,[48] just in the days in which the embryo should implant. (Slides 67-69) The pro-gestational effects of Progesterone on the endometrium are lost and, among them, the expression of those proteins that make the maternal uterus hospitable for the embryo. In particular, taken in the early luteal phase,[47] after the eventual fertilization, the doses of 50 mg (which is equivalent to ellaOne®) and 100 mg increase endometrial Progesterone receptors and reduce significantly the markers of endometrial receptivity (Node-Addressin). (Slides 63-66) Embryo-implantation becomes impossible.

These effects are just identical to those observed after the administration of 200 mg of Mifepristone (RU486), the dose used for pregnancy termination, but UPA is effective even at a much lower doses: 10 mg. [32,47] (Slide 65)

Endometrial inhibition is direct and is due to the inhibition of endometrial Progesterone receptors (the same MOA of the pill RU486).[49-54] Essentialy, ellaOne® occupies those cell structures – the specific receptors – to which Progesterone must necessarily link in order to perform its pro-gestation functions. Progesterone is present but it cannot act and the endometrium will not transform into a hospitable ground.

Such inhibition is observed even after the administration of UPA at doses which are much lower – even five times lower – that those equivalent to ellaOne®. It is well documented that the threshold for altering endometrial morphology is lower than that required for altering folliculogenesis.[44,47,48] (Slide 59) EllaOne®, consequently, will lead consistently to an inhospitable endometrium and, as said above, whenever fertilization will occur the embryo will not be allowed to implant and survive. The indications from all the studies performed in women are really significant and strongly support the evidence of a prevalent post-fertilization MOA for ellaOne®.

However, the definitive demonstration of this anti-implantation MOA comes from the above mentioned study by Lira-Albarràn et Al.[43] (Slide 70). They demonstrated, in fact, hat ellaOne® allows ovulation consistently when it is taken in the most fertile days, but induces in the luteal endometrium changes associated with a non-receptive phenotype, i.e. an endometrium unsuitable for embryo-implantation.

Fourteen healthy fertile women were longitudinally followed in two consecutive menstrual cycles in which each woman served as control of herself, i.e. her parameters evaluated before treatment were compared with her same parameters evaluated after the intake of ellaOne® . In the first cycle, that was untreated and served as control, the mayor 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 in the most fertile days of the cycle. (Slide 71)

In both the control and the treated cycle follicular rupture took place regularly, with no significant differences between the cycles: in no case ovulation was either inhibited or delayed. (Slide 72)

At the day LH+7 (7 days after LH peak) of both the control and the treated cycles an endometrial biopsy was taken from all the participants. On this tissue the expression of 1183 genes was determined. (Slide 71)

Despite the luteal progesterone plasma levels were normal, UPA showed an anti-progestin like activity in the endometrium. As is evident in the Figure 1 at page 4 of Lira-Albarràn's paper, which is reproduced in the next page, the genes that were over up-regulated (activated) in the hospitable pro-gestational endometrium were, on the contrary, down-regulated (inactivated) in the UPA-treated endometrium. Vice versa, the genes that were down-regulated in the hospitable pro-gestational endometrium were up-regulated in the UPA-treated endometrium.

The gene expression that is normally observed in the receptive endometrium does change completely after UPA administration and goes in a quite opposite direction, as is evident from the original Figure by the authors. (Slides 73-78)

The detailed analysis of the results leads the authors to predict that the embryo and blastocyst implantation are inhibited. One can just report one of the many significant results commented by the authors: it regards the PAEP, a Progesterone-regulated gene that is a key-gene in the process of attachment of the embryo to the endometrium. Amongst all of the evaluated genes, its expression was the most down-regulated after UPA treatment. (Slide 76)

In summary, the study of Lira-Albarràn et Al.[43] evidences that the women who take Ulipristal after unprotected intercourse in the fertile days, and particularly in the most fertile days, do experience ovulation and fertilization can follow as the sperms, at that point, are already inside the tube and can fertilize the released oocyte. UPA cannot interfere with human sperm fertilizing ability in any way [55] (Slide 79) and nothing can prevent fertilization. Unfortunately, the endometrium is quite unhospitable and the embryo will not have any possibility of surviving.

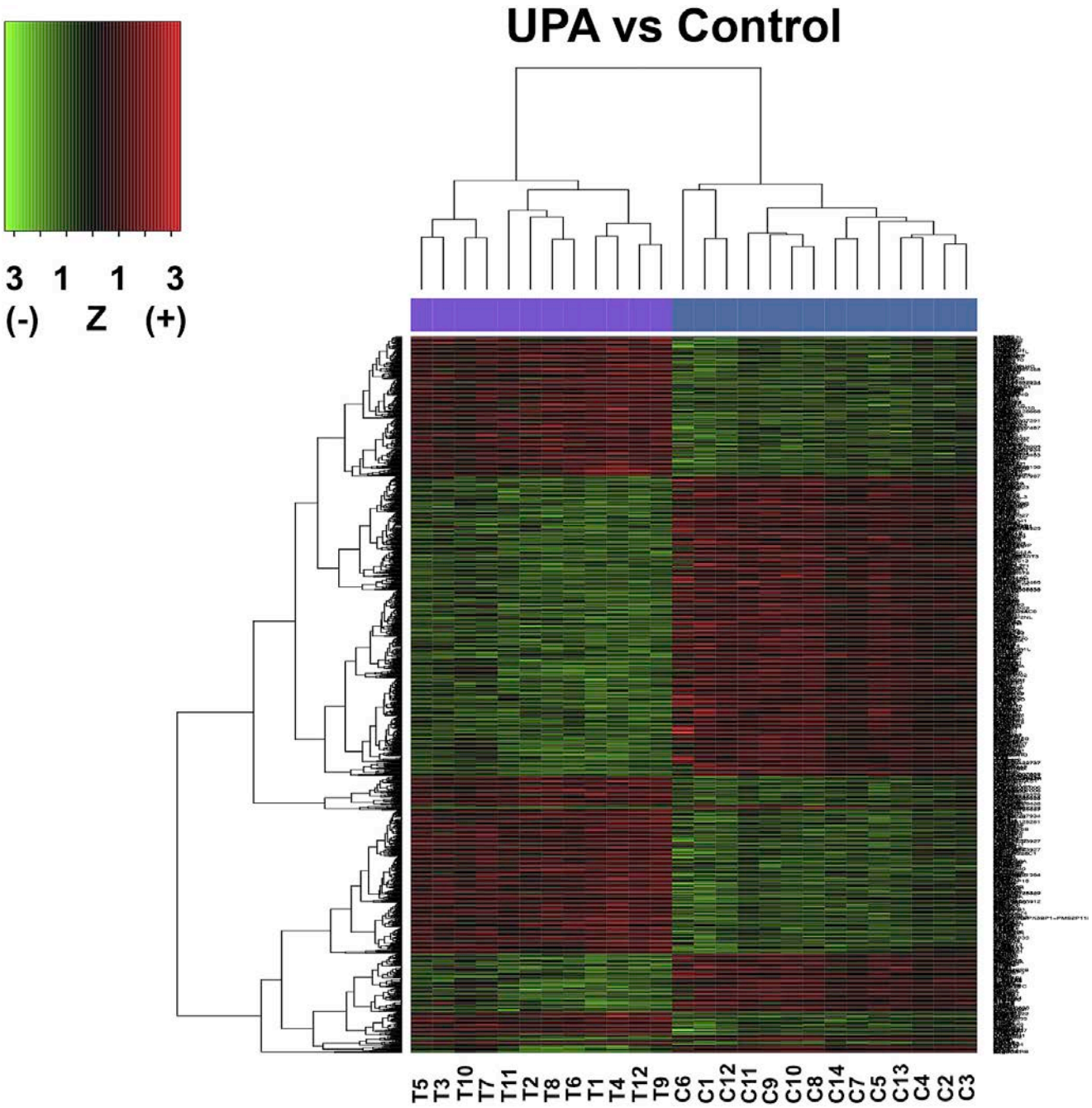

Fig. 1. Gene clustering of the GeneChip® Human Gene 2.0 ST Array (Affymetrix) data showing pairwise comparison of: **UPA-treated (T) *versus* non-treated (Control, C)** endometrial samples. The heat map corresponds to one sample for each column and one gene for each horizontal line. Color indicates gene expression value intensities (Z-score); **red signifies up-regulation, green down-regulation** and black unchanged

At the end of their discussion, the authors conclude verbatim that the *"changes observed in gene expression in endometrial samples from women exposed to UPA are associated with a non-receptive endometrial phenotype"*. (Slide 80)

The described scientific evidences appear very strong, but also simple and basic reasoning should be sufficient to indicate that the main MOA of ellaOne® is post-fertilization.

In fact, ellaOne® is advertised as the "five days-after pill", showing that it is quite effective even when it is taken up to five days (120 hours) after an intercourse which has occurred in the fertile period, that is, when it is taken after ovulation has already occurred.

It is acknowledged that the pre-ovulatory day is the most fertile day and is also the day in which most intercourses do occur.

In the case of having unprotected intercourse on the pre-ovulatory day, with ovulation within the next 24 hours, fertilization would occur within 24 further hours, that is within 48 hours from intercourse. EllaOne® can be taken with an unchanged and consistently high efficacy up to five days from intercourse, in this case – that is the most frequent – it would be up to four days since ovulation and up to three days since fertilization.

In such scenario, it is impossible to conceive any anti-ovulatory MOA, since ovulation have already occurred: advocating a prevalent anti-ovulatory MOA for EllaOne® is not only countering the scientific evidences illustrated above, but counters logic itself, which is the very basis and foundation of all scientific disciplines.

The only possible MOA – both in the mentioned example and in scientific evidence – is anti-implantation,[32,43] but this MOA is not even mentioned in the officially delivered information which, consequently, results to be intentionally deceiving for women, doctors, chemists and authorities. Besides, its anti-implantation MOA makes ellaOne® totally incompatible with the National Laws of Countries that protect human life as from fertilization.

Again, some authors offer a different interpretation of the data published on UPA's endometrial effects.

In particular, Gemzell-Danielsson from the Karolinska Institute, in a 2013 paper,[56] discusses the endometrial effects of UPA taken in the early luteal phase, that is after the eventual fertilization.[47] (Slide 81) She correctly reports, as we did, that unmicronized UPA, at the doses of 50 and 100 mg, leads to a reduction in endometrial thickness and to an increase in endometrial Progesterone receptors. This environment is the expression of an estrogen unopposed activity due the impossibility for Progesterone to work, as its own receptors are masked by UPA, and makes the embryo-implantation impossible.

These are exactly the data published by Pamela Stratton.[47] At the same time, however, Gemzell-Danielsson adds that the dose used for EC cannot affect the endometrium. She details verbatim: "*Yet, in the doses relevant for EC use (30 mg) UPA has no significant effect on the endometrium*" (at the page 5).[56] (Slide 82) She seems to forget that ellaOne®, 30 mg of micronized UPA, is quite equivalent to the 50 mg of unmicronized UPA [12,40] which were administered in Stratton's study

and, consequently, must necessarily have the same anti-implantation effects on the endometrium. But what is most surprising, in this sequence, is that in the same paper, at the page 9, Gemzell-Danielsson herself acknowledges (though within brackets) that 30 mg of micronized UPA (ellaOne®) are quite equivalent to 50 mg of unmicronized UPA. (Slide 83) On the other hand, she could never ignore this, as she is a renowned expert of EC and served on medical advisory board for HRA Pharma, as she declares at the end of the same paper.

In spite of this acknowledgment, one year later, in a 2014 Review [57] in which she quotes again the data from Pamela Stratton,[47] she repeats verbatim that "*UPA given in early-luteal phase shows dose-dependent effects with no significant endometrial effects observed following exposure to doses relevant for EC*" (in the first paragraph of page 687). (Slides 84,85)

In the same Review,[57] anticipating the findings illustrated in a 2015 paper of her own,[58] Gemzell Danielsson details verbatim: "*To be able to study the effect of EC on human implantation, an in vitro three-dimensional implantation model has been developed. In this model it has been demonstrated that LNG or UPA at EC concentrations have no effect on the human embryos or endometrial receptivity and cannot impair or prevent implantation*".

In her 2015 paper [58] the author tries to demonstrate that ellaOne® does not affect the process of human embryo attachment to human endometrial tissue. (Slide 86) The experiment, however, does not support her conclusions for three main reasons that will be exposed.

- The endometrial tissue used to construct the 3D endometrial model was obtained from healthy volunteers with normal untreated menstrual cycles and proven fertility, in the cycle day LH+4. It was, consequently, a normal and hospitable endometrium, already endowed with the full machinery that is necessary and sufficient for embryo attachment. It was an endometrium fully prepared by progesterone. She did not use endometrial tissue obtained in the luteal phase from women previously treated with ellaOne®, a drug that prevents progesterone action on the endometrium.

- The treatment group of cultures were continuously exposed to UPA 200 ng/ml, an amount of drug quite similar to that observed in the women's blood one hour after the oral administration of ellaOne®, namely 176+89 ng/ml, which is UPA maximum mean serum concentration (Cmax). It is well known, however, that the concentration of UPA measured in the endometrium of the women who take ellaOne® is higher than that observed in their blood and, consequently, higher than the amount of UPA used in the in vitro 3D model. (Slide 87) The conditions of the experiment probably did not reproduce what happens in vivo.

- Only the very initial step of tissue-attachment could be imagined as reproducible in vitro and evaluable, while the process of implantation is in no way testable in this model, as she herself acknowledges.

In spite of this, the author concludes writing verbatim that "the mechanism of action of UPA when used as an EC does not disrupt the *implantation process*".

Moreover, in the abstract, both the Study Question: "Does UPA used for emergency contraception interfere with the human *embryo implantation* process?" and the Summary Answer: "UPA, at the dosage used for EC, does not affect human *embryo implantation* process, in vitro" do refer to the implantation process which in reality has never been tested. (Slide 88) Finally, the abstract conclusion is, again verbatim, "that the study provides new insights on the mechanism of action of UPA on human *embryo implantation*, demonstrating that UPA in a dosage used for EC does not affect embryo viability and the *implantation* process of embryo." (Slide 88)

At this point of our discussion it should be quite clear that the prevalent MOA of ellaOne® is linked to its anti-progestational effect on the endometrium and not to any effect on the process of ovulation: the women regularly ovulate when they take the drug in the most fertile days and fertilization can regularly follow, as the sperms already accessed and are waiting within the tubes. The embryo, however, will not implant and will die because the UPA-treated endometrium is absolutely inhospitable.

All this information, however, was already evident when ellaOne® was introduced into the market in 2009: the papers that describe the effects of UPA in women are the same discussed above in this *Position Paper*. HRA2914-505*: Stratton*.[44] HRA2914-506: *Stratton*.[47] HRA2914-503. *Passaro*.[48]

In fact, in the *CHMP Assessment Report for Ellaone®*" (EMEA-261787-2009)[59] that led to ellaOne® Marketing Authorisation, (Slide 89,90) EMA acknowledges explicitly many important issues:

1. "Ulipristal acetate 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." This is reported at point 2.3 page 8: "Non-clinical aspects - Pharmacology". (Slide 91) It means clearly that UPA can prevent implantation and also terminate ongoing pregnancies.

2. "*The ability of Ulipristal Acetate (UPA) to terminate pregnancy was investigated. Ulipristal, mifepristone and lilopristone were approximately equipotent*" (page 10) (Slide 92)

3. "*When using intramuscular administration of 0.5 mg/kg, 4/5 foetuses were lost in ulipristal acetate treated animals*" (in macaques, page 10).[60] It means that 50mg unmicronized UPA, the dose equivalent to ellaOne®, is able to interrupt pregnancy in a primate weighing 100 kg, and we know that the sublingual administration is similar to the parenteral one, even if it cannot be used easily in monkeys (they should understand that the tablet must be taken under the tongue until dissolved and behave accordingly). (Slide 92)

4. "*The threshold for altering endometrial morphology thus appears lower than for inhibition of ovulation*", at page 22. These are the results of the study HRA2914-505 by Stratton.[44] (Slide 93)

5. "*At early-luteal phase significant delay in endometrial maturation occurred in the 50 (ellaOne®) and 100 mg groups compared to the placebo and 10 mg groups*", always at page 22. These are the results of the study HRA2914-506, again by Stratton.[47] (Slide 93) This means that there was statistical and well known significance between the delay in endometrial maturation caused by the 50mg (ellaOne®) and 100mg dose and the absence of delay observed with the 10mg and placebo.

6. In UPA use for emergency contraception "*alterations to the endometrium may also contribute to the efficacy of the product*" (page 23). This means acknowledgment of a post-fertilization MOA that is never mentioned in the package leaflet of ellaOne®. (Slide 94)

7. Besides, at the end of page 22, it is reported verbatim that "*The dose of 50 mg unmicronized ulipristal acetate was chosen in the phase II studies, since this was the minimal dose that alters endometrial maturation and induces inhibition of ovulation.*" (Slide 93) We know well from the above point 4 that the endometrial damage is always present after the intake of unmicronized UPA, even at the lowest dosage of 10 mg.[44] We also know that ovulation is never inhibited when ellaOne® (equivalent to the higher dose 50 mg of unmicronized UPA) is taken after unprotected intercourse in the most fertile days. Consequently, fertilization is always possible, but the endometrium will never accept the embryo.

8. The possibility that UPA is used *off-label* for pregnancy termination is real and is presented as a "safety concern" in the Table "Summary of the risk management plan for Ellaone®" (page 41- second box on the left), but the strategic choice for the "proposed risk minimization" has been "*Omit any sentence in the SPC and the PL suggesting that the product could be used as an abortifacient.*" (page 41 - second box on the right). (Slide 95)

9. At last, EMA and HRA Pharma agree that all of the approaches to avoid this abuse suffer from inevitable limitations; the only possible way to limit this abuse seemed to be prescription registries (page 45 and 46). However, the prescriptions were abolished by EMA in 2015.[39] (Slides 96,97)

Based on the review of the whole document (*CHMP Assessment Report for ellaOne®*) the EMA-CHMP recommended the granting of the marketing authorization with the indication of emergency contraception; ellaOne® was marketed as an anti-ovulatory drug. (Slide 98)

In spite of all the above information and aware of the fact that women mostly ovulate even if they take ellaOne® regularly for 8 weeks (see the table reproduced at the page 6 of this *Position Paper*), on September 30th 2014 (EMA/631408/2014)[61] the CHMP of the EMA helds that "*Emergency contraceptives work by stopping or delaying ovulation*".

In the Assessment Report "EMA/73099/2015"[39], at page 35, it was held 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 Ulipristal-Acetate as an abortifacient, and it is therefore also unknown whether it is possible to use it for abortion". (Slides 99,100)

Any further comment appears unnecessary.

However, to rule out a possible off-label use, in the total absence of reassuring scientific evidences, EMA considers sufficient the results of an interview to 75 prescribers from Poland and Sweden (HRA2914-544a), evidently representative of all the European doctors: they answered that they never used UPA for abortion: 20% of them, however, prescribed the drug more than 5 days after the intercourse and 2.7% in more doses. (Slide 101)

The above study (HRA2914-544a) is reported at page 31 of the same Assessment Report "EMA/73099/2015" [39] and has been considered a reliable "*demonstration that off-label prescription of ellaOne for abortion does not happen in the real world, dispelling the concern that existed prior to the approval of the original Marketing Authorization*". (Slide 101)

At last, in the same 2015 Assessment Report [39] in the Table at page 64, the *"Effect on pregnancy maintenance / Off-label use as an abortifacient"* is still presented as a Safety Concern and indicates that ellaOne® can affect pregnancy. Nevertheless, the EMA CHMP recommended that the contraindication "*pregnancy*" be removed from the information. (Slide 102)

At the end of June 2017 the EMA updated the European Public Assessment Report (EPAR) on ellaOne® [14]: (Slides 103-106) this happened well after the online pre-publication (February) and the official publication (May 1st) of tha above discussed Lira-Albarràn's paper.[43]

We recall that Lira-Albarràn administered ellaOne® in the most fertile days of the cycle and reported that all the treated women had normal ovulations, but the analysis of the expression of 1183 genes evidenced that ellaOne® transforms the endometrium into a completely inhospitable tissue for the embryo.

In spite of this and of all the previous information, the CHMP repeats, at page 8, that "*When used for emergency contraception the mechanism of action is inhibition or delay of ovulation*" (Slide 104) and reports that "*ellaOne® works by postponing ovulation*" in the *Package leaflet: Information for the user*, at page 24. (Slide 106)

This information appears to be exactly the opposite of that emerging clearly from the experimental data, and the single National Medicines Agencies were probably careless and inattentive when they passively accepted that such an anti-implantation (and possibly also frankly abortifacient) drug as ellaOne® was marketed in their Countries.

While presenting UPA as an anti-ovulatory drug, EMA was well aware of its prevalent post-fertilization effect and, furthermore, of its ability to terminate pregnancy with the same efficacy of Mifepristone (RU486), but it chose to omit any sentence about this and went on with intentionally deceiving information.

Ulipristal and Mifepristone: the twin molecules

Ulipristal Acetate and Mifepristone have many similar effects in the female reproductive apparatus. [17,32,59,62-65]

Mifepristone is largely used and highly effective for EC in China, at doses of 25-50 mg.[17]

When it is taken in the follicular phase, before the beginning of the fertile period, its effects on ovulation are similar to those of Ulipristal Acetate,[66] though Ulipristal showed to be effective at much lower doses.[44]

When administered in the early luteal phase, 200 mg of mifepristone is highly effective in preventing the clinical appearance of pregnancy.[67-69] Ovulation and fertilization, of course, would already have occurred at that point. These effects are the same observed with lower doses of UPA.[47]

Lastly, when administered in the mid-luteal phase, both Mifepristone and unmicronized Ulipristal, at the same dose of 200 mg, consistently induce a premature endometrial bleeding.[48]

While Mifepristone (RU486) is known for terminating pregnancy (the administered dose is 200 mg) Ulipristal has never been tested for pregnancy termination in women. Nonetheless, UPA and RU486 share the same effects on either folliculogenesis and endometrial differentiation, at doses that are quite the same.[51-54]

Besides, both Ulipristal [70,71] and Mifepristone,[72,73] always at the same doses (5 mg daily for three months), are able to decrease fibroid size and reduce the intensity of uterine haemorrage, which are frequent gynecological pathologies.

Currently, micronized UPA has been licensed, in Western Europe, for fibroid reduction prior to surgery. It is marketed as Esmya®, 5-mg tablets in a blister pack of 28 tablets for a total amount of 140 mg (ellaOne® contains 30 mg).

As to Esmya®, it is important to remind that 120 mg of micronized UPA (a dose which is lower than the 140 mg contained in each Esmya® package and that can be obtained with only four tablets of ellaOne®) are equivalent to 200 mg of unmicronized UPA[38], which, in turn have been shown to be equivalent to 200 mg of Mifepristone: the dose used to terminate pregnancies.

Both Ulipristal Acetate and Mifepristone, at these doses, taken seven days after ovulation and fertilization, exactly in the days when the embryo becomes implanted, consistently lead to a premature uterine bleeding.[48,74]

This should be carefully considered when deciding the authorization and of any UPA-containing drug.[32]

CONCLUSIONS

Neither Levonorgestrel (Norlevo®, Levonelle® and Escapelle®) nor Ulipristal Acetate (ellaOne®), when used for EC, does in anyway prevent or delay ovulation, and when they are taken in the most fertile days of the cycle. Their prevalent effects are on the endometrium. For Levonorgestrel these effects are deduced from the luteal inadequacy induced by the drug. For Ulipristal they have been definitely demonstrated in the recent paper from Lira-Albarràn.

Both drugs allow ovulation and fertilization, but inhibit the process of embryo implantation and this MOA goes against the laws of the Countries that protect human life since fertilization. Moreover, ellaOne® is also able to terminate ongoing pregnancies.

Currently, the women, the doctors and all the health-operators are intentionally deceived by false information on ECs'MOA.

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