ELLAONE (ULIPRISTAL ACETATE): AN ABORTION PILL USED FOR EMERGENCY CONTRACEPTION

Position Paper on Mechanism of Action and Toxicity

EllaOne is an abortifacient drug that contains Ulipristal Acetate (UPA) which binds with high affinity to the Progesterone receptor and consequently prevents Progesterone from acting. It is very similar to the abortion pill Mifepristone (RU486) and, like the latter, has been shown to be effective in terminating pregnancy up to the ninth gestational week in medical abortion procedures.

It is currently distributed freely, without a prescription, as an emergency contraceptive. EMA and AIFA present it as a means of preventing or delaying ovulation in order to avoid conception after unprotected sexual intercourse.

In reality, ellaOne does not prevent ovulation when taken on the most fertile days of the cycle, but it does prevent the embryo from implanting. The woman, then, ovulates and can conceive, but the endometrium is profoundly altered by Ulipristal and does not allow implantation.

Repeated intake of ellaOne can seriously compromise a woman's health: the drug accumulates in the tissues, particularly in the liver, causing even irreparable damage.

LONG SUMMARY

Abortifacient drug

EllaOne (Ulipristal Acetate, UPA) is a powerful anti-progestin very similar to Mifepristone (RU486, Myfegyne®) and like Mifepristone it can be used for abortion, as confirmed by a recent study.

In the protocol for medical abortion it has proven to be as effective as Mifepristone, ending the pregnancy in 97% of cases at a dose of only two tablets. The use of a single tablet has not been tested.

Used as an emergency contraceptive

This drug, capable of causing abortion up to the ninth gestational week, has been proposed and has been used for over 15 years as an emergency contraceptive and is claimed to be able to inhibit or delay ovulation if taken within five days of risky sexual intercourse.

Emergency Contraception (EC) means the use of any drug, or the insertion of an intrauterine IUD, after unprotected sexual intercourse on the fertile days of the cycle, for the purpose to prevent an unwanted pregnancy. It should be emphasized that unprotected intercourse can result in pregnancy only if it occurs in the fertile period of the cycle, i.e. in the four to five days preceding ovulation and on the day of ovulation itself. Only in these days, in fact, the cervical mucus allows the entry of spermatozoa inside the female genitals. Among fertile days, the pre-ovulatory is the day on which the

probability of conception is highest, followed by the day of ovulation itself and the second-last day before ovulation

The resort to the EC has to face two facts: the spermatozoa have already entered and ovulation is imminent.

As mentioned, the manufacturer of ellaOne (HRA Pharma), the Food and Drugs Administration (US-FDA), the European Medicines Agency (EMA), the most famous national and international Gynaecological Societies affirm and spread that UPA acts by inhibiting or delaying ovulation and therefore preventing conception, without in any way interfering with implantation.

On the contrary, it has been shown that the main mechanism of action (MOA) of ellaOne is the inhibition of embryo implantation in the uterus and the very recent article by Winikoff et al. published in NEJM Evidence (Jan 23rd 2025) has demonstrated its ability to terminate pregnancy with high efficacy , greater than 97%, closing any discussion on its abortifacient effects.

In clinical practice, ellaOne - used as an emergency contraceptive - can only inhibit or delay ovulation when it is taken in the very first fertile days. In the 36 hours preceding ovulation and, of course, in the following day of ovulation (the most fertile days in which more than 70% of conceptions occur) ellaOne is unable to interfere with ovulation, as highlighted in Brache's article. On the contrary, on any day it is taken during the menstrual cycle, UPA invariably alters the development of the endometrium, even at doses much lower (one fifth) than those contained in ellaOne.

It should be emphasized, as proof of its very poor anti-ovulatory efficacy, that ovulation occurs almost normally even after regular and repeated intake of ellaOne: in 91.7% of women who took the drug weekly for eight consecutive weeks and in 72.7% of those who took it every five days for the same period. These data are reported by the EMA (EMA/73099/2015) and further confirm that it cannot be argued in any way that the main MOA of ellaOne is the anti-ovulatory effect.

EMA acknowledges (EMEA-261787-2009) that "*Ulipristal acetate prevents progesterone from occupying its receptor, so the gene transcription normally activated by progesterone is blocked and the synthesis of proteins necessary to initiate and maintain pregnancy are not synthesized*".

This means that, in addition to preventing implantation, UPA is also able to terminate a pregnancy.

It is known, but it has always been kept hidden.

EMA, moreover, explicitly admits that the termination of pregnancy is possible following "*off-label" use* of the drug. In fact (ibidem), it reports that UPA is able to "*terminate pregnancy, as well as mifepristone does"* and that "by *administering 0.5 mg/kg intramuscularly, 4/5 fetuses were aborted in macaques treated with UPA*".

This means that 50 mg unmicronized UPA (equivalent to ellaOne) can terminate pregnancy in a macaque weighing up to 100kg. Furthermore, EMA recognizes that "*The threshold for altering endometrial morphology appears lower than for inhibition of ovulation*"): that is, every time ovulation occurs and conception follows, the endometrium will never allow the embryo to implant.

As anticipated, the article by Winikoff et al. published in NEJM Evidence has definitively demonstrated its abortion efficacy, which can be superimposed on that of Mifepristone.

Returning to its use as an emergency contraceptive, data in the medical literature (Brache) show that ellaOne's ability to delay ovulation is maximum (100%) only at the beginning of the fertile period; then it decreases and becomes almost zero (8%) one or two days before ovulation. Nevertheless, its effectiveness in preventing the onset of pregnancy is very high (≥80%) and does not decrease in any of the five days after risky intercourse the drug is taken. This is surprising if we assume that the effectiveness of ellaOne is due to its anti-ovulatory effect. If this were the case, the abrupt reduction in the anti-ovulatory effect of ellaOne described in the literature should lead to a progressive reduction in its efficacy, which should be reduced to zero when the drug is taken on the most fertile pre-ovulatory days. On the contrary, its effectiveness remains very high, constantly above 80%.

The absence of any anti-ovulatory effect when ellaOne is taken on the most fertile days of the cycle highlights that its MOA must be due to something else, i.e., its inhibitory effects on the endometrium. As expected, at any time the drug is taken in the menstrual cycle, the pro-gestation effects of progesterone, including the expression of those proteins that make the mother's uterus hospitable to the embryo, are lost. Embryo implantation becomes impossible.

The definitive demonstration of the anti-implantation effect of ellaOne is given by Lira-Albarràn et al. who administered a single dose of ellaOne in the most fertile days of the cycle to 14 women evaluated with extreme care in the previous, untreated cycle, considered a control cycle.

These researchers have shown that ovulation occurs regularly after pre-ovulatory intake of ellaOne, thus further ruling out any anti-ovulatory effect of the drug when taken on the most fertile days of the cycle.

After ovulation, on day LH+7, i.e. when the endometrium (the tissue that lines the inside of the uterus and prepares to host the child every month) should be prepared for implantation, each of the 14 women underwent an endometrial biopsy, both in the control cycle and in the cycle treated with ellaOne. On endometrial tissue, the expression of 1183 genes was determined.

Though the plasma luteal (post-ovulatory) levels of progesterone were normal, ellaOne confirmed its known and clear anti-progestogen activity at the tissue level: the genes that were activated in the endometrium made hospitable by Progesterone were, on the contrary, inactivated in the endometrium of women treated with ellaOne and vice versa. It follows that ellaOne determines a non-receptive endometrial phenotype, i.e. an endometrium unsuitable for embryo implantation.

The confirmation that the anti-implantation effects of ellaOne occur even when the drug is taken after ovulation and eventual conception – in perfect and logical continuity with the abortifacient effect – comes from the study by Jimenez Guerrero et al. who administered a single dose to a group of 4 women in the early luteal phase of the cycle. Five days later, in the implantation window, each of them underwent an endometrial biopsy. A similar sampling, again in the implantation window, had been obtained from the same patients in the previous, untreated (control) cycle, and in the second cycle following the administration of ellaOne. On the endometrium, the expression of a

group of genes that are essential for its secretory differentiation was evaluated.

The analysis of the results obtained shows that the administration of ellaOne after ovulation depresses the expression of genes associated with endometrial receptivity, i.e. those genes that are particularly involved in determining the preparation of the endometrium for implantation and that make it able to "dialogue" with the embryo in the very delicate mechanisms of implantation in the uterus. This anti-implantation effect would not be limited to the cycle in which ellaOne is taken but would seem to last for over two months. The data is entirely consistent with the recently proven abortifacient effect of ellaOne .

Safety profiles - hepatotoxicity

A review of the safety profiles of Esmya (28 UPA 5 mg tablets) highlighted the possibility of life-threatening liver damage. Following subsequent and repeated reevaluations, the drug was withdrawn from trade and, finally, its use was limited only to inoperable patients without therapeutic alternatives, but always with rigorous controls of liver function before, during and after UPA.

No recommendation or request for controls is envisaged, however, for ellaOne, with very serious potential dangers for the female population, which resorts to its use in an increasing and indiscriminate way, uninformed about the mechanism of action, unaware of the risk to which it is exposed and indeed reassured by EMA on its harmlessness even in the event of frequent and repeated intake, even during the same menstrual cycle.

Conclusions - EllaOne is a frankly abortifacient drug. In its use as an emergency contraceptive, its main mechanism of action is the inhibition of embryo implantation, therefore a post-conceptional effect. Recently, evidence has emerged of very serious liver damage resulting from the intake of UPA, which requires supervision and control by the doctor. No mention of these risks appears, however, in the official information on ellaOne, with serious potential risks for women's health.

INTRODUCTION

Responsible procreation and contraception - The exercise of free and conscious choices in the field of responsible procreation presupposes an adequate knowledge of reproductive physiology and of what are the tools currently available to temporarily separate sexuality from procreation[(1)].

In Italy the national legislation in force – in particular Law No. 405 of 29 July 1975 on the "Institution of Family Counselling Centres" and Law No. 194 of 22 May 1978 on "Regulations for the social protection of maternity and the voluntary interruption of pregnancy" – *"give to the responsible procreation the purpose of protecting and promoting the health of both the woman and the product of conception*", " *protect human life from its beginning*" and "*exclude that abortion is a means of birth control*."

The protection of human life from its beginning implicitly excludes post-conceptional contraceptives from the list of licit contraceptives. The European Court of Justice itself (Grand Chamber), moreover, in the Judgment of 18. 10. 2011 — Case C-34/10 (Brüstle v Greenpeace) acknowledges that "*from the stage of its fertilisation, any human ovum must be regarded as a 'human embryo', since fertilisation is such as to initiate the process of development of a human being*".

Knowledge of the mechanism of action (MOA) is one of the fundamental criteria on which the choice between the different contraceptive methods is based [(1-6)]. It is the basis of informed consent, as is the knowledge of harmful side effects (by definition a contraceptive must be harmless).

EllaOne - Offered to the public as an emergency contraceptive, it has been available for 16 years and for 10 years its sale has been free from a medical prescription.

Presented as a drug capable of preventing or delaying ovulation, and therefore preventing conception, ellaOne has instead been shown to be frankly abortive [(7)] (Fig. 1a-1b) at least until the ninth week of gestation, comparable in efficacy to its twin molecule RU-486 (Mifepristone) used for medical abortion. Its distribution in pharmacies, parapharmacies and in the health departments of supermarkets is completely incompatible with Italian current legislation.

In liberalizing its distribution, in 2015, EMA [(8)]wrote that it was not known whether ellaOne could induce abortion: although invited to document that the drug could not induce abortion, in fact, in the six years since its marketing (from 2009 to 2014) the manufacturer HRA Pharma had been careful not to produce studies that answered the question. In spite of this, EMA removed the need for a prescription and reiterated that its mechanism of action was to prevent or delay ovulation, thus preventing conception, without interfering with implantation in any way.

Now, however, the answer has arrived – certainly not from HRA Pharma, but from an independent group – and indicates that ellaOne is an abortifacient drug.

Emergency contraception - Emergency contraception means taking medication or inserting IUDs into the uterus following unprotected sexual intercourse that has occurred during the fertile period of the menstrual cycle (Fig.s 1c-2), i.e. in the 4-5 days preceding ovulation and on the day of ovulation itself: only in them, in fact, does the cervical mucus allow the passage of spermatozoa. Among them, the most fertile day, i.e. the day on which the probability of conceiving is highest, is the day before ovulation, followed by the day before and the day after: the day of ovulation itself [9-11]. In these three days, the incidence of sexual intercourse, both protected and unprotected, is also highest [10] (Fig.s 3-6).

Taking these drugs is, consequently, an extreme attempt that has to deal with at least two facts.

- The sperm have already entered. Thanks to the fertile mucus they have already passed through the cervix and in large part they have already reached the fallopian tube [12]; there they wait, quiescent, for the release of the egg. No drug the next day will obviously be able to prevent their ascent, since it has already happened.
- Ovulation is now impending.

At this point, in the female body, everything is predisposed towards conception and the subsequent implantation of the embryo in the endometrium which, after ovulation, will be made hospitable by the hormones produced by the corpus luteum (the gland that derives from the cells of the follicle after it has released the egg) (Fig.s. 7-11).

There are only two ways to prevent the occurrence of a clinically evident pregnancy: to prevent ovulation from occurring *in extremis*, i.e. to prevent conception, or to ensure that the conceived embryo does not find the fertile ground he needs inside the uterus.

The substantial difference between the two hypotheses is clear: in the first case conception does not occur, in the second the embryo is actively suppressed even before its presence manifests itself.

PREMISES OF PHYSIOLOGY

Before discussing the scientific articles that deal with the mechanism of action of ellaOne, an abortifacient drug – as we will see – sold and presented for 15 years as an anti-ovulatory drug, it is useful to describe, albeit briefly, what a menstrual cycle is and how it is regulated [13] (Fig. 2).

The menstrual cycle is a series of events involving the ovary with its follicles (the small structures each of which contains an egg cell) (Fig. 12) and the pituitary gland, a gland hanging at the base of the brain (Fig. 13): both of these glands produce hormones. In particular, the pituitary gland normally regulates the production of estrogen by ovarian follicles thanks to its hormones: Follicular Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (in males, the same hormones stimulate testicular functions). Since they stimulate the gonads, i.e. the ovary and testicle, these pituitary hormones are also referred to as pituitary gonadotropins.

The pituitary gland, in turn, is also regulated by substances produced in other higher brain centers, but for the current description it is enough to illustrate and explain the continuous dialogue between the pituitary gland and the ovaries.

It is necessary to immediately clarify what a hormone is and how it works: it is a substance produced by a gland and introduced into the circulatory system (in the blood) so that it can reach the organ in which it must perform its function. To exert its effect, the hormone must bind to the target cell through a specific structure called a **"hormone receptor".** A hormone cannot activate a cell if this cell does not have the specific receptor for that hormone. Similarly, a hormone cannot activate a cell, even if it has its own specific receptor, if the receptor is occupied or made inaccessible by other substances.

The cycle begins when the estrogen levels in the woman's blood are very low, which occurs at the end of the previous cycle. This can be seen in the left margin of Figure 2.

The pituitary gland, through its receptors, "understands" that the estrogen level is low and stimulates a group of follicles to activate. In Figure 2 you can see the follicles on the left side: large amounts of FSH and LH stimulate them to activate (blue and blue arrows).

The recruited follicles begin to produce estrogen (red arrows) in increasing quantities, and in the woman's blood their levels increase (red area underneath). As estrogen increases, the pituitary gland reduces the sending of its messengers (smaller arrows) and from day 5 onwards only one follicle remains active and will grow and mature until the egg is released. It is the *dominant follicle* of the cycle.

During its growth, the follicle increases the number of its cells and produces increasing amounts of estrogen: the egg inside completes its maturation.

When the pituitary gland "understands" that estrogen levels are becoming particularly high, it increases the release of FSH and, above all, LH (*LH surge*) until it reaches its peak (*LH peak*). The LH peak causes the dominant follicle to rupture and the egg cell to be released, i.e. *ovulation*. Ovulation occurs about 36 hours after the LH peak and sometimes even later [(14)].

The egg can be fertilized by the sperm within 24 hours of its release.

After ovulation, the cells that made up the wall of the dominant follicle and which are supported by rich vascularization, increase their lipid content and give rise to a yellow structure, the *corpus luteum* (luteum in Latin means yellow) (Fig. 2). The corpus luteum is a temporary gland that exists only after ovulation: it continues to produce estrogen, but – above all – it produces progesterone, the pro-gestation hormone, the hormone that prepares the uterus and the entire female body for pregnancy. All the events of the ovarian cycle, from the recruitment of follicles to the exhaustion of the corpus luteum, can easily be observed sequentially in the image taken from the Netter Atlas (Fig. 12).

The lower part of Figure 2 shows the endometrial tissue, the inner surface of the uterus, the "bed" in which each of us has nested in our first days of life after conception.

The endometrium is a tissue that is totally dependent on estrogen: if estrogen is present in the woman's body, the endometrium is well nourished and stable; on the contrary, when estrogen is absent, the vessels that nourish it do obliterate and the tissue dies: it is expelled through the menstrual flow which is the visible sign of the end of the menstrual cycle and the beginning of a new one.

We already know that, at the beginning of the cycle, ovarian follicles are stimulated by the pituitary gland and begin to produce estrogen in increasing quantities; these estrogens – through their specific receptors on endometrial cells – stimulate the reconstruction of the endometrium, which is completed around ovulation, as can be seen from Figure 2.

After ovulation, the corpus luteum maintains the production of estrogen and produces progesterone, which significantly changes the characteristics of the endometrium and prepares it for embryo implantation and pregnancy.

Thanks to the action of progesterone – through its specific receptors on endometrial cells – the vascular support to the endometrium is increased, so that the tissue is intensely nourished; moreover, the endometrial glands dilate more and more and accumulate within them an extraordinary amount of nutrients secreted by the endometrial cells: in the lumen of these glands the embryo will find everything it needs to grow and develop until the establishment of the feto-placental circulation (Fig. 7,10,11).

In addition, progesterone – again through its receptors – profoundly modifies the immune structure of the endometrium, avoiding any possible rejection reaction towards the host (the embryo is an individual totally different from the mother), and transforming the endometrium into a hospitable environment (Fig. 7).

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

A new cycle is about to begin in the same way as the one just described: the pituitary gland will stimulate new ovarian follicles and everything will be repeated, and repeated again, cyclically (Fig.s 2,12).

In the case of conception – the meeting between egg and sperm, which takes place in the fallopian tube – everything changes.

The embryo, just at the stage of the first cell, immediately begins to send substances to the mother that modulate her immune defenses (Fig. 8). Cell reproduction begins and after about three days the embryo enters the uterus; around the fifth day, the blastocyst is ready to implant: the appearance of the embryo is now similar to a cyst, with the internal cells destined to form the body and the peripheral cells that make up the trophoblast, i.e. the cells through which the embryo will make

contact with the mother's uterus and feed itself, the future placenta (Fig. 9).

Up to this point, the embryo has used all the raw materials present in the large egg-cell to grow: as can be seen, as they increase in number, its cells reduce in size, but the total volume of the embryo remains constant (Fig. 9).

Now, however, the initial endowment of resources is exhausted and the embryo has an increasing need for nutrients: it will deepen into the endometrium until it reaches its glands to finally access their contents (Fig.a 10,11).

Since the first moments of life, the embryo is very active.

At the 8-cell stage, it already produces a gonadotropin of its own: the human chorionic gonadotropin (hCG): it is a hormone similar to LH, but much more powerful; when the embryo is implanted, hCG passes into the mother's blood and reaches the corpus luteum, which is in the mother's ovary. By binding to LH receptors, it stimulates the corpus luteum to increase in volume and become gravid corpus luteum: the production of luteal hormones will increase and continue (Fig. 14).

This menstrual cycle will not end and no menstrual flow will appear: estrogen and, mainly, progesterone will keep the endometrium rich and adequate to meet all the needs of the embryo.

The ovary – the corpus luteum is part of it – is no longer under the woman's control: her pituitary gland is now replaced by the embryo that will produce hCG with its own peripheral cells, the chorionic ones, which will soon form the placenta.

One last piece of information before concluding these long physiological premises: the increase in estrogen that eventually leads to ovulation, progressively modifies the characteristics of the cervical mucus so that – precisely and only in these days, the fertile days – the spermatozoa can enter the female genitals (Fig. 15).

Both the endocrinological processes that lead to ovulation and the appearance of fluid mucus are simultaneous expressions of the same biological event: the increase in levels of estrogen hormones. As a result, the appearance of fertile mucus usually reliably predicts ovulation and allows every woman to recognize fertile days and be fully aware of her fertility. The fertile days in Figure 2 are highlighted and numbered in reverse order as they approach the day of ovulation, with the most fertile ones being distinguished by a larger character (Fig.s 2,4).

USE OF ELLAONE IN MEDICATION ABORTION

As mentioned in the introduction, a recent study carried out in Mexico (7) demonstrated the full efficacy of ellaOne in inducing the termination of pregnancy by the ninth gestational week.

The study was designed by the teams of the Gynuity Health Projects and the National Autonomous University of Mexico and it is made explicit that the decision to publish the results was taken unanimously by all the authors, in full autonomy with respect to external influences.

The administration of two tablets of ellaOne followed by 800 μg of oral misoprostol to 133 patients resulted in a complete abortion in 129 of them, with an efficacy of 97%, completely comparable to that of Mifepristone.

The use of a single tablet has not been tested. However, it is worth underlining, although it is obvious, that obtaining two tablets freely from the pharmacy or para-pharmacy is extremely easy, since the drug can be dispensed without a prescription even to minors. Just go to two different stores.

We therefore believe that ellaOne, as an abortifacient, should be subjected to a restricted administration regimen, which limits it to hospital use only, as is the case for the sister drug Mifepristone. The DE 2001/83 in art. 4, paragraph 4 allows it and our laws require it.

This article [7] appears ten years after the publication of the CHMP Assessment Report on ellaOne (EMA/73099/2015) in which EMA writes, verbatim, on page 35, that "*During the evaluation process of the ellaOne registration dossier, the MAH applicant (HRA-Pharma) was asked to study any potential off-label use of ellaOne, particularly in pregnancy, possibly as an abortifacient. No clinical study has been carried out with ulipristal-acetate as an abortifacient, and it is therefore unknown whether it can be used for abortion*".

HRA-Pharma has been careful not to answer the question, probably counting on the condescension of Bodies and Institutions – such as EMA and the subordinate AIFA – willing to close both eyes in order to accredit ellaOne with an anti-ovulatory mechanism of action.

The discussion that follows, on the mechanism of action of ellaOne in emergency contraception, amplifies and substantiates the considerations that the authors of the article clearly explain in their introduction [7] and that led them to believe that ellaOne is substantially superimposable to Mifepristone, and as such usable for medical abortion. These are the same data that have always been known to the regulatory bodies.

MECHANISM OF ACTION OF ELLAONE IN EMERGENCY CONTRACEPTION

First of all, let's see what is being declared internationally in relation to this frankly abortifacient drug.

The manufacturer (HRA Pharma), the European Medicines Agency (EMA) [15], the United States Food and Drugs Administration (US-FDA) [16], the most representative international and national scientific societies of gynecologists support and disseminate that ellaOne prevents or delays ovulation and therefore prevents conception, without interfering in any way with implantation.

In reality, however, experimental studies show – and illustrating this is one of the aims of this report – that ellaOne is not able to prevent ovulation and conception with certainty, except when it is taken at the very beginning of the fertile period.

In the following fertile days, however, and especially in the days closest to the release of the oocyte, it no longer has any effect on ovulation and conception, but makes the endometrium inhospitable to the embryo.

The fertile days closest to ovulation are, moreover, the most fertile days of the menstrual cycle and are also those in which statistically the greatest number of sexual intercourse seems to be concentrated and in which the greatest number of conceptions occur [9-11,13] (Fig.s 3-6).

Having made these clarifications, let's delve into the knowledge and detailed evaluation of ellaOne.

Each ellaOne tablet contains 30 mg of Ulipristal Acetate in its micronized form, to be taken orally in a single dose. It is unanimously recognized that 30 mg of micronized UPA is equivalent to 50 mg of non-micronized UPA, the active ingredient administered in gelatine capsules that was used in previous clinical trials [14,17] (Fig. 16-18).

UPA binds to the progesterone receptor, the pro-gestation hormone. It works in the same way as Mifepristone, better known as RU486 (the pill used to terminate pregnancy), and their molecules are very similar (Fig. 19).

The manufacturer, HRA Pharma, claims that ellaOne, administered in the fertile period of the menstrual cycle, has the ability to postpone ovulation and therefore prevents the meeting of egg and sperm. The drug would have the ability to inhibit ovulation or postpone it by five days even when it is taken immediately before ovulation, and would act with consistently high efficacy, greater than 80%, even if taken up to five days after unprotected intercourse (Fig. 20,21).

This statement, based on the article by Vivian Brache [18,19], is fully supported and shared by the EMA [15] (Fig.s 22,23).

The data reported in Table 2 below, published by the EMA itself, should, however, be sufficient to demonstrate the groundlessness of the above and to close any discussion.

This table is published in the EMA-CHMP Assessment Report on ellaOne "EMA/73099/2015", exactly on page 7/76 [8].

It refers to a study reporting the effects on ovulation of a single dose of ellaOne taken weekly (Q7D) or every 5 days (Q5D) for 8 consecutive weeks; 12 women were treated every 7 days (Q7D) and 11 every 5 days (Q5D).

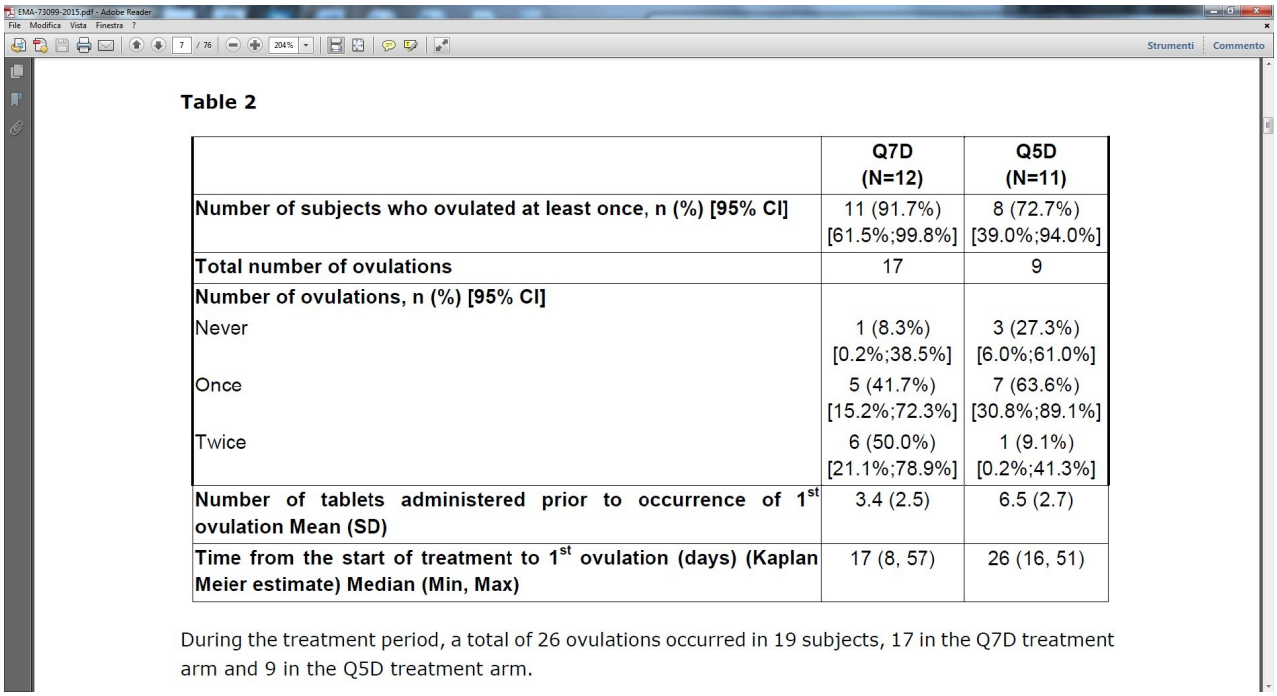

Table 2

	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.

The study, HRA2914-554, was presented directly by the manufacturing company, HRA Pharma.

The table shows that ovulation occurred regularly in 91.7% of women who took ellaOne every 7 days for eight consecutive weeks and in 72.7% of those who took ellaOne every 5 days, again for eight consecutive weeks.

Fifty percent of the women treated weekly even ovulated twice, as is usually the case over the course of eight weeks.

In both groups, the qualitative evaluation of cervical mucus (carried out in the treatment period when the follicle measured more than 15 mm, i.e. in the fertile period) indicated the presence of cervical mucus favorable to sperm passage and conception.

Despite the evidence of these data by EMA, which exclude any significant effect of ellaOne on ovulation and conception, we believe it is our duty to continue with the discussion of all experimental studies carried out on women in this regard.

It should be remembered that conception can only occur if coitus has occurred in the four to five fertile days before ovulation, during which cervical mucus allows sperm to enter the female genitalia, and that conception usually occurs within 24 hours of the release of the egg.

On fertile days, the phenomena that prepare and determine ovulation occur in the ovary and pituitary gland (Fig. 2):

- First, in the ovary, the dominant follicle increases the secretion of estrogen, which immediately induces the production of an increasingly fluid mucus, favorable to sperm penetration (Fig. 15).
- Ovarian estrogens, in turn, cause a progressive increase in LH levels (LH surge) released by the pituitary gland.
- Finally, LH reaches its peak (LH peak) which is maintained for hours and induces ovulation
- Ovulation usually occurs 36 hours (24-48) after the peak, but sometimes it occurs later [14].
- If we visualize these hormonal variations on a graph that represents the fertile days of the menstrual cycle, we realize that the period preceding the rise in LH is identified with the beginning of the fertile period; the period during which LH increases probably coincides with the second-third fertile day of the cycle, while the peak days (the 24-48 hours pre-ovulation) and the following day of ovulation are the last fertile days. the most fertile of the menstrual cycle (Fig.s 2,4-6).

Anti-ovulatory effects

That said, there is only one study evaluating the effect of ellaOne on ovulation when administered in the fertile period of the cycle. This is the one already mentioned by Vivian Brache in which it is insistently stated that ellaOne is able to postpone ovulation for more than five days, even when it is administered immediately before ovulation [18]. This conclusion is emphasized both in the title of the study itself, in the summary, and in the conclusions (Fig.s 24-25).

The number of women evaluated is small: 34. They are considered first as a whole and then separately: stratified into three groups according to whether they receive Ulipristal before LH begins to increase, or during the LH increase phase, or after the LH peak has been reached (Fig. 26).

The first evaluation shows that taking ellaOne in the fertile period of the menstrual cycle inhibits or postpones ovulation in a total of 58.8% of women. This means that 41.2% of women treated in the fertile period ovulate regularly and can conceive (Fig. 27).

The evaluation of the anti-ovulatory efficacy of ellaOne in relation to the time of taking the drug, in the three different phases of the fertile period, shows that the effects of UPA on ovulation are strongly dependent on LH values. Ovulation, in fact, is consistently delayed (100%) only in the eight women treated at the beginning of the fertile period, before LH begins to increase. If the LH level has already started to grow, ovulation is delayed in eleven out of fourteen women (78%): three women ovulate and can conceive. In patients in whom the LH peak has already been reached, ovulation is delayed in only one case out of twelve: 92% of the women studied ovulate and can conceive (Fig. 28).

Furthermore, in the paragraph of the *results*, the author herself specifies that at the LH peak, one or two days before ovulation, the drug no longer has any ability to prevent it and works 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)*" (Fig. 29).

These are, as mentioned, the most fertile days of the cycle, those in which unprotected intercourse is followed by the highest number of conceptions (Fig. 30). These are the days in which UPA, credited with a "contraceptive" efficacy constantly above 80%, should inhibit ovulation with maximum effectiveness if its effect were attributable to an anti-ovulatory action.

It is evident, however, as we have seen, that ellaOne, taken in the most fertile period of the cycle, i.e. one or two days before ovulation, does not demonstrate any anti-ovulatory efficacy. [20,21]

Its ability to inhibit ovulation is maximum (100%) only at the beginning of the fertile period; subsequently it decreases rapidly and progressively until it is almost zero (8%) in the two pre-ovulatory days. Despite this, its "contraceptive" efficacy, greater than 80%, does not decrease over time: whether the drug is taken on the first day after risky intercourse, or whether it is taken on the second, third, fourth or even fifth day after intercourse itself, the "contraceptive" efficacy remains constantly high. [17,21-23]

If the contraceptive mechanism of ellaOne were really related to its anti-ovulatory effect, which – as seen – vanishes as the LH peak approaches (Fig. 31), one would expect a progressive decline in its effectiveness as the days go by, as the time of ovulation approaches. On the other hand, the efficacy of ellaOne remains consistently high [20,21] (Fig. 32).

Further confirmation that ellaOne is not able to delay ovulation when taken in the 24-48 hours prior to ovulation comes from the recent study by Lira-Albarràn et Al [24] (Fig. 33). The study shows that the drug, intentionally administered at the time of the cycle when the probability of pregnancy is highest (Fig. 34), has no effect on ovulation, which normally occurs when it is physiologically expected (Fig. 35).

Ovulation, therefore, always occurs, but the endometrium, as we will see, analyzed in the mid-luteal phase – the phase in which implantation occurs, about 5-6 days after conception – has proven to be absolutely inhospitable.

Finally, Stratton administered 10, 50 and 100 mg of non-micronized UPA to women in the mid-follicular phase of the cycle, seven days before ovulation: UPA causes a delay in ovulation that is greater with higher dosages, but inhibits endometrial maturation in the luteal phase in a similar way even with lower doses (Fig.s 36,37). This highlights that the threshold for altering endometrial morphology is lower than that necessary to alter folliculogenesis, i.e. the process that – starting from the stimulation of several follicles at the beginning of the cycle – progressively leads to the maturation of a single follicle and its rupture with the release of the egg [25] (Fig. 2,12).

We know that 50 mg of non-micronized UPA is equivalent to the 30 mg of micronized UPA that is present in ellaOne [17] (Fig. 18).

The fact that ellaOne can delay ovulation before the fertile period begins (mid-follicular phase) is not surprising, since Brache's article already shows us that ellaOne can delay ovulation even when it is taken on the first of the fertile days.

What this study teaches us, however, is that the negative effects of UPA on the endometrium appear consistently in the post-ovulatory luteal phase, even after delayed ovulation by UPA. We also understand, and learn, that once ovulation occurs and conception follows, the endometrium will never allow the embryo to implant.

The absence of any anti-ovulatory effect when ellaOne is taken on the most fertile days of the cycle, and the anticipations from the last two studies mentioned [24,25], show that its "contraceptive" MOA is necessarily due to something else and in particular to its inhibitory effects on endometrial maturation.

However, before even going into the description of them, we would like to point out and report that some authors [26,27] propose an interpretation of Brache's data that is very different from ours.

As we know, in his study on ellaOne, Brache reports verbatim that "*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* ".

This means that Ulipristal Acetate, when administered at the LH surge, a day and a half before ovulation, behaves exactly like placebo (Fig. 38).

Neither ellaOne, nor evidently placebo, when administered at the LH surge, have any effect on ovulation, which physiologically occurs one or two days later.

Citing these same data from Brache [18], Gemzell-Danielsson and Lalitkumar, in two articles from 2013, respectively on pages 302 [26] (Fig.s 39,40) and 93 [27] (Fig.s 41,42), state verbatim: "*Even on the day of the LH peak, UPA could delay ovulation for 24 to 48 h after administration*" and that is, that ellaOne, at that point, would still be effective and able to delay ovulation.

It is the exact opposite of what Brache reports, which documents – as seen – an effect similar to placebo.

It is incomprehensible why these authors repeat twice the same statement, manifestly contrary to scientific evidence.

Endometrial effects

Let's come to the endometrium. A single dose of non-micronized Ulipristal (10, 50 and 100 mg) constantly results in a reduction in endometrial thickness and profoundly alters tissue receptivity, at whatever time of the cycle it is taken: in the middle of the follicular phase, even before the fertile days begin [25] (Fig.s 43-45); in the middle of the cycle, in the days immediately following ovulation [28] (after conception has occurred) (Fig.s 46-52); and in the middle of the luteal phase [29], precisely on the days when the embryo should implant (Fig.s 53-55). The effect of Progesterone on the endometrium is lost and, with it, the expression of those proteins that make the maternal body hospitable towards the embryo. In particular, Stratton et al. [28] administer doses of 50 mg (equivalent to ellaOne) and 100 mg in the initial luteal phase, immediately after conception, and show that they increase endometrial receptors for Progesterone and significantly reduce the expression of tissue markers of endometrial receptivity (Node-Addressin) (Fig.s 47-50). Embryo implantation becomes impossible.

These effects are quite similar to those observed after administration of 200 mg of Mifepristone (RU486), the dose used for abortion, but UPA is effective at even lower doses: 10 mg, one-fifth of the dose (50 mg) equivalent to ellaOne [20,21,28] (Fig. 51).

The inhibitory effect on endometrial maturation is direct and is linked to the inhibition of tissue receptors for Progesterone (it is exactly the same mechanism by which the RU486 pill works) [30-35]. In essence, ellaOne occupies those cellular structures to which Progesterone should bind in order to perform its pro-gestational function.

Progesterone is present but cannot act and the endometrium will not become a hospitable environment.

This inhibition is also observed when the woman is given significantly lower dosages of Ulipristal than what is contained in the ellaOne pill: in fact, doses even five times lower than those taken, with little success, for anti-ovulatory purposes, are enough to make the endometrium hostile to the embryo. It is documented that the dose of UPA sufficient to alter the endometrium is lower than that required to interfere with the normal development of ovarian follicles [28,29] (Fig. 45). After taking ellaOne, therefore, the endometrium will always be inhospitable and every time fertilization takes place, the embryo, inevitably, will not be able to survive.

All the studies performed on women, therefore, strongly and significantly support the evidence that ellaOne acts predominantly with a post-conceptional mechanism.

However, the definitive demonstration of this anti-implantation mechanism of action comes from the study by Lira-Albarràn et Al. [24], already cited (Fig. 56). In fact, these authors demonstrate that ellaOne, when taken in the most fertile days of the cycle, consistently allows ovulation, but induces changes in the luteal endometrium that are associated with a non-receptive phenotype, i.e. an endometrium that is not suitable for embryo implantation.

The study longitudinally followed 14 fertile and healthy women over the course of two consecutive menstrual cycles, in which each individual woman served as a control of herself: her parameters assessed in the first cycle, before treatment, were compared with her own parameters reassessed in the next cycle, after taking ellaOne. In the first cycle, which was not treated and served as a control, the main characteristics of the cycle were determined. In the next cycle each woman received a single dose of ellaOne when the follicle diameter reached 20 mm, intentionally on the most fertile days of the cycle (Fig. 57).

Both in the control cycle and in the cycle treated with ellaOne, ovulation occurred regularly, with no difference between the two cycles: in no case was ovulation inhibited or delayed (Fig. 58).

On day LH+7 (7 days after the LH surge), both in the control cycle and in the treated cycle, an endometrial biopsy was performed in each woman. The expression of 1183 genes was evaluated in the collected tissue (Fig. 57).

Although plasma levels of Progesterone were normal (Fig. 58), ellaOne exerted a direct anti-progestogen effect on the endometrium.

As shown in Figure 1 on page 4 of Lira-Albarràn's article, which is reproduced on the following page, the genes that were over-expressed (activated) in the progestational hospitable endometrium, were, on the contrary, repressed (inactivated) after the intake of ellaOne. Conversely, genes repressed in the pro-gestational hospitable endometrium were over-expressed after ellaOne was taken.

The gene expression normally observed in the pro-gestational receptive endometrium changes completely after taking ellaOne and goes in the diametrically opposite direction (Figure is taken from the original article). The detailed analysis of the results (Fig. 59-62,64) leads the authors to predict with certainty that the implantation of the embryo (of the blastocyst) will be inhibited.

As further confirmation of the anti-implantation effect, the authors document that among the genes whose expression is subverted by ellaOne is included a large part (two thirds) of those unanimously considered markers of fertility [36] (Fig.s 65,66).

We report just one of the many significant results commented by the authors themselves: it concerns the PAEP gene, a gene regulated by Progesterone, which plays a key role in the process of embryo adhesion to the endometrium. Out of all the genes evaluated, its expression is the most repressed after treatment with ellaOne (Fig. 62).

In summary, the study by Lira-Albarràn et Al. [24] and his further study [36] show that women who take ellaOne after unprotected intercourse on fertile days, and in particular on the most fertile days before ovulation, ovulate normally and can conceive, since the spermatozoa have already risen into the fallopian tubes and can fertilize the egg that is released. The drug, in fact, does not interfere in any way with the fertilizing capacity of spermatozoa [37] (Fig. 63).

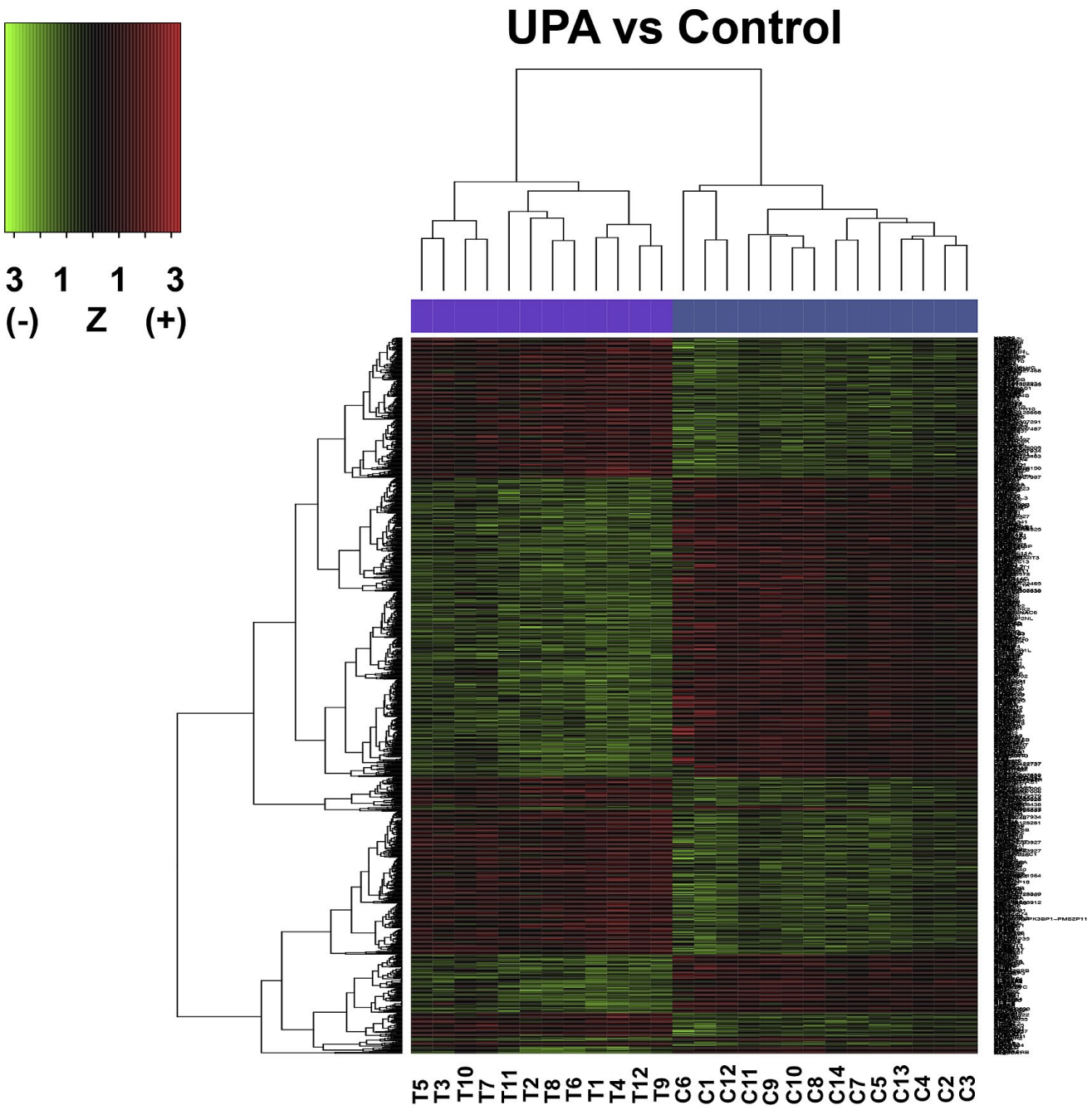

Fig. 1. Gene clustering of the GeneChip® Human Gene 2.0 ST Array (Affymetrix) data showing pairwise comparison of: **UPA-treated (T)** ***versus*** **non-treated (Control, C)** endometrial samples. The heat map corresponds to one sample for each column and one gene for each horizontal line. Color indicates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

The endometrium, however, is irreparably compromised and the embryo will have no chance of implanting and surviving.

At the end of their examination, the authors conclude verbatim that "*the observed changes in gene expression in endometrial samples obtained from women exposed to UPA are associated with a non-receptive endometrial phenotype*" (Fig. 64).

To further confirm the inhibitory effect of ellaOne on endometrial receptivity, at any time of the cycle it is administered, Jimenez Guerrero et al. [38] (Fig. 67) have shown *in vivo* that even its post-ovulatory administration depresses the expression of genes associated with endometrial receptivity, i.e. those genes that are particularly involved in determining the preparation of the endometrium for implantation and that make it able to "dialogue" with the embryo in the very delicate mechanisms of implantation in the uterus. The same authors, previously [39], had already demonstrated in mice that post-ovulatory administration of UPA compromises pregnancy, probably due to interference with endometrial receptivity.

In their study [38] they longitudinally followed 4 fertile and healthy women during three menstrual cycles in which each individual woman served as a control of herself: her parameters evaluated in the first cycle, before treatment, were then compared with her same parameters reevaluated in the next cycle, after taking ellaOne, and finally in the second cycle following the intake of the drug. In the first cycle, which was not treated and served as a control, the main characteristics of the cycle were determined. In the following cycle, each woman received a single dose of ellaOne two days after the LH peak, after documenting by ultrasound the signs that ovulation occurred, i.e. a 50% reduction in the size of the dominant follicle.

On the endometrial tissue, taken from each individual woman on day LH+7 of each of the three cycles studied, i.e. at the implantation window (Fig. 68), they evaluated the expression of 192 genes, carefully selected, that are associated with endometrial receptivity and maternal immune response (Fig. 69). The intake of ellaOne causes a decrease in the expression of these genes compared to the control untreated cycle, which is also reduced in the second untreated cycle following the administration of ellaOne.

Jimenez Guerrero's results agree with what was already reported by Stratton in 2010 [28] and confirm that the anti-implantation effects of ellaOne occur even when the drug is taken after ovulation and eventual conception. These effects would not be limited to the cycle in which ellaOne is taken but would seem to last for more than two months (Fig. 70).

The study by Li et al. seems to reach partially different conclusions [40]: they indicate a significantly greater ability to avoid the onset of pregnancy for the intake of ellaOne in the pre-ovulatory phase, compared to the intake in the luteal phase (Fig. 71). Here we don't discuss the mechanism of action: we have seen it cannot be anti-ovulatory in the most fertile pre-ovulatory days. Here we point out the effectiveness of ellaOne even when it is taken in the luteal phase: it is recognized and certainly does not depend on anti-ovulatory effects.

The study has obvious limitations: the classification of each patient as pre- or post-ovulatory at the time of taking the drug is retrospective, inevitably. It is also approximate, although accompanied by a hormonal dosage and a punctual ultrasound check. It is basically based on menstrual history. It recognizes the difficulty of identifying the fertile period and does not indicate whether the intercourse took place in it or not. Statistically, basing on the frequency of unprotected intercourse [10], it is more likely that they took place on the most fertile days, with a

higher number of expected pregnancies when ellaOne is taken in the initial luteal phase, just after the end of the most fertile period. On the contrary, Li's study indicates that when ellaOne is taken in the luteal phase, the number of expected pregnancies is considerably lower: even half (Fig. 72). Finally, the percentages of expected pregnancies reported in this study differ markedly from those reported by Noè et al. (41) in a similar study: while Li reports a percentage of expected pregnancies of 6.2% and 3.3% depending on whether the woman takes the drug in the pre- or post-ovulatory phase, the percentages reported by Noè are, respectively, 17% (pre-) and 20% (post-) (Fig. 73). Finally, there is no reference to the time elapsed between the intercourse and the intake of ellaOne. Anyway, there remains evidence of a reduction in the number of clinically observed pregnancies even after luteal intake of ellaOne (Fig. 74), which clearly contrasts with the alleged and unique anti-ovulatory mechanism.

The scientific evidence appears irrefutable, but even a simple reasoning [21] could be enough to understand that the prevailing effect of ellaOne is post-conceptional.

In fact, ellaOne is presented as "the five-day-after pill", being shown that it is totally effective even if taken five days (120 hours) after sexual intercourse that occurred in the fertile period of the cycle [22,23] and, that is, when it is taken even after ovulation has occurred.

It is known that the pre-ovulatory day is the most fertile day of the cycle and is also the day on which the highest number of sexual intercourse occurs (Fig.s 3-6).

Let's imagine sexual intercourse that took place on the day before ovulation (this is the most frequent situation), with ovulation occurring in the following 24 hours and conception within the next 24 hours (and therefore 48 hours after that sexual intercourse) (Fig. 75). EllaOne can be taken with unchanged and very high efficacy up to five days after that intercourse and therefore up to four days after ovulation and up to three days after conception.

How, in this scenario, can an anti-ovulatory and contraceptive action be invoked for ellaOne? It would not only be contrary to scientific evidence, amply illustrated, but also to simple logical reasoning.

There will only be an anti-implantation action, [20,21,24] but it is not even mentioned in the official information provided to people, which is – consequently – deliberately misleading both for women, for doctors and pharmacists, and for the Authorities themselves.

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

In particular, Gemzell-Danielsson of the Karolinska Institute in Stockholm in a 2013 article [42] discusses the effects of Ulipristal on the endometrium reported by Stratton, [28] when it is taken in the initial luteal phase, i.e. after conception (Fig. 76).

The author correctly reports, as we have done in this same text, that non-micronized UPA, at doses of 50 and 100 mg determines a reduction in endometrial thickness and an increase in endometrial receptors for Progesterone. This environment is the expression of an unopposed estrogenic stimulation, given the impossibility for Progesterone to function, since UPA occupies all its receptors. In this environment, the embryo cannot implant.

This is exactly the data of Pamela Stratton. [28] At the same time, however, Gemzell-Danielsson adds that the dosage used for emergency contraception would not be able to change the endometrium ("*Yet, in the doses relevant for EC use (30 mg) UPA has no significant effect on the endometrium*"). It is on page 5 [42] (Fig. 77).

Gemzell-Danielsson seems to forget that ellaOne, 30 mg of micronized UPA, is exactly the same as the 50 mg of non-micronized UPA [17] that was administered in Stratton's study, and that, as a result, ellaOne can only have the same anti-implantation effects on the endometrium.

But what is most striking, in this singular sequence, is that in the same article, a few pages later, on page 9, Gemzell-Danielsson herself shows that she knows well that 30 mg of micronized UPA (ellaOne) is equivalent to 50 mg of non-micronized UPA, although she admits it only within two parentheses (Fig. 78). Nor, on the other hand, could she ignore it, being an expert on the subject and having been part of the medical advisory board of HRA Pharma, as she points out at the end of the same article.

Despite this awareness, a year later, in a 2014 Review [43] in which she again cites Pamela Stratton's data, [28] 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*". It is in the first paragraph of p. 687 (Fig.s 79,80).

In the same Review, [43] anticipating the results illustrated in a subsequent article in 2015, [44] Gemzell-Danielsson writes:

"*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 the 2015 article [44] the author tries to demonstrate that ellaOne does not interfere with the process of adhesion of the human embryo to human endometrial tissue (Fig. 81).

The experiment, however, does not support its conclusions for three main reasons.

- The endometrial tissue used to build a 3D endometrial model was obtained from healthy volunteers with normal, non-hormone-treated menstrual cycles and documented fertility on the day of the LH+4 cycle. It was, therefore, a normal hospitable luteal endometrium, already endowed with the necessary and sufficient biochemical characteristics for embryo adhesion. It was an endometrium entirely prepared by Progesterone. The author did not use luteal endometrium from women previously treated with ellaOne, a drug that prevents the action of Progesterone on the endometrium.

- The treated endometrial samples were continuously exposed to 200 ng/ml of UPA, a concentration of drug comparable to that observed in the woman's serum one hour after taking ellaOne (i.e. 176+89 ng/ml), which is the maximum average concentration of UPA in the serum (UPA Cmax) (Fig. 82). It is well known, however, that the concentration of UPA present in the endometrium of women taking ellaOne is higher than that found in their blood and, consequently, higher than the amount used in 3D in vitro models. The conditions of the experiment probably do not reproduce the situation in vivo.

- In the in vitro model, one can imagine simulating and evaluating in vitro only the very initial moment of adhesion, while the implantation process cannot be tested in any way in the 3D model, as the author herself acknowledges.

Despite this, Gemzell-Danielsson concludes by writing verbatim that "the mechanism of action of UPA when used as an EC does not disrupt the *implantation process*".

Furthermore, in the abstract, both the main question (*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" refer to the implantation process that has never been evaluated (Fig. 83).

Finally, the conclusion of the abstract is again, verbatim (Fig 83): "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." As if the study had evaluated the implantation and viability of the embryo.

At this point it should be clear that the prevalent MOA of ellaOne is related to its anti-progestogen effect on the endometrium and not to any effect on the ovulatory process: women ovulate regularly when they take the drug on their most fertile days and conception can occur without impediment, since the spermatozoa have already entered and are waiting in the fallopian tubes.

The embryo, however, will not be able to implant and will die because UPA has made the endometrium inhospitable.

The official documents of the EMA, the European Medicines Agency

All this information, however, was already available and evident when ellaOne was placed on the market in 2009: the studies describing the effects of Ulipristal in women are the same as those discussed in this report. HRA2914-505*: Stratton*,[25] HRA2914-506: *Stratton*,[28] HRA2914-503: *Passaro*. [29]

In fact, in the *CHMP Assessment Report for ellaOne* (EMEA-261787-2009)[45] which led to the "Marketing Authorisation" for ellaOne (Fig. 84), EMA explicitly acknowledges many important points:

1. "*Ulipristal acetate prevents progesterone from occupying its own receptors, so the gene transcription normally activated by progesterone is blocked and the proteins needed to initiate and maintain pregnancy are not synthesized.*" It is reported in point 2.3 on page 8 under the heading "Non-clinical aspects - Pharmacology" (page 8) (Fig. 85). It clearly means that ellaOne can prevent implantation and even terminate a pregnancy that has already begun.

2. *"The efficacy of Ulipristal Acetate (UPA) in terminating pregnancy has been evaluated. Ulipristal and Mifepristone (RU486) are equipotent in primates"* (page 10) (Fig. 86).

3. "When 0.5 mg/kg is administered intramuscularly, 4/5 fetuses are aborted in treated animalswith ulipristal acetate" (in macaques, page 10) (Fig. 86). It means that 50 mg of not micronized UPA (0.5 mg/kg = 50mg/100kg), the dose equivalent to ellaOne, is able to terminate pregnancy in a primate weighing 100 kg [46] and we know that sublingual administration is similar to parenteral administration, although it cannot be proposed in monkeys (they should understand to keep it under the tongue until dissolved and behave accordingly).

4. "*The threshold for altering endometrial morphology appears lower than that for inhibiting ovulation*" (page 22). This is the result of Stratton's study HRA2914-505 [25] (Fig. 87).

5. "*In the early luteal phase, a significant delay in endometrial maturation was observed in women treated with non-micronized UPA 50 mg (ellaOne) and 100 mg, compared to women treated with 10 mg or placebo*" (also on page 22). These are the results of study HRA2914-506, also by Stratton [28] (Fig. 87). This means that the delay in endometrial maturation caused by 50 mg (ellaOne) and 100 mg UPA was known and statistically significant compared to what was observed with 10 mg and placebo.

6. When using UPA for emergency contraception, "changes to the endometrium may contribute to the effectiveness of the product" (page 23). This means acknowledging a post-conceptional mechanism that is never mentioned in the ellaOne package insert (Fig. 88).

7. In addition, at the end of page 22 it is reported verbatim that "the 50 mg dose of ulipristal (non-micronized) was chosen in phase II studies, since it is the minimum dose that alters endometrial maturation and induces inhibition of ovulation" (Fig. 87).

   We know well from point 4 above that endometrial damage is always present after taking non-micronized UPA, even at the lowest dosage of 10 mg [25] (one fifth of ellaOne).

   We also know that ovulation is never inhibited when ellaOne (equivalent to a higher dose, 50 mg, of non-micronized UPA) is taken after unprotected intercourse on the most fertile days.

   As a result, conception is always possible, but the endometrium will never allow the embryo to implant.

8. the possibility that UPA is used "off-label" to terminate pregnancy is concrete and is presented as a "safety concern" in the Table "Summary of the risk management plan for Ellaone" (p. 41 - second space on the left), but the strategic choice to minimize the risk was not to talk about it ("Omit any sentence in the SPC and the PL suggesting that the product could be used as an abortifacient." (Fig. 89).
9. Finally, EMA and HRA Pharma agree that all approaches to prevent ellaOne from being used to terminate pregnancy have unavoidable limitations, and that the only way can be a register of prescriptions (pages 45 and 46) (Fig.s 90,91), those prescriptions that EMA eliminated in 2015 [8].

Based on the content of the document (*CHMP Assessment Report for ellaOne*), the EMA-CHMP recommended that it be granted marketing authorisation with the indication of emergency contraception (Fig. 92); ellaOne is marketed as an anti-ovulatory medicine.

Despite all the above information and aware of the fact that women ovulate normally even if they take ellaOne regularly for 8 weeks (see the table reproduced on page 11 of this text), on 30 September 2014 (EMA/631408/2014) [47] the EMA CHMP repeated, as it has always been since 2009, that "*Emergency contraceptives work by stopping or delaying ovulation*.

In the subsequent Assessment Report "EMA/73099/2015" [8] (Fig. 93), the one that decided the free sale of ellaOne in Pharmacies, on page 35 it is reported that "*During the evaluation process of the ellaOne registration dossier, the MAH applicant (HRA-Pharma) was asked to study any potential off-label use of ellaOne, particularly during pregnancy, possibly as an abortifacient. No clinical study has been carried out with Ulipristal-Acetate as an abortifacient, and it is therefore unknown whether it can be used for abortion"* (Fig. 94).

Any further comment seems superfluous, all the more so now that a group of independent researchers has highlighted the absolute and indisputable effectiveness of only two tablets of ellaOne [7] in inducing abortion up to the ninth week of pregnancy.

However, it should be added that in order to exclude a possible "off-label" use, in the total absence of reassuring scientific evidence, the EMA felt satisfied with the result of an interview to 75 doctors

from Poland and Sweden (HRA2914-544a), evidently representative of all European doctors.

These doctors replied that they had never prescribed ellaOne for abortion: 20% of them, however, prescribed the drug more than 5 days after unprotected intercourse and 2.7% of them in more than one dose (Fig. 95).

Study HRA2914-544a is reported on page 31 of the same Assessment Report "EMA/73099/2015" [8] and was considered a "*reliable demonstration that the off-label prescription of ellaOne for abortion does not occur in the real world, dispelling the concern that existed before the approval of the original marketing authorisation"* (Fig. 95).

Finally, in the same 2015 Assessment Report [8] in the table on page 64, the "*Effect on continuation of pregnancy / Off-label use as an abortifacient"* is still presented as a Health Concern, indicating that ellaOne may threaten pregnancy. Nevertheless, the EMA's CHMP recommended that the contraindication "*pregnancy*" be removed from the drug information (Fig. 96).

On 23 September 2024, the EMA again updated the European Public Assessment Report (EPAR) on ellaOne:[15] this happened more than six years after the publication of the Lira-Albarràn articles that we commented on [24,36] and three years after the publication of the Jimenez Guerrero article [38]. We only recall that the former administered ellaOne in the most fertile days of the cycle and reported that all the treated women ovulated regularly, but the analysis of the expression of 1183 genes in the luteal endometrium showed that ellaOne transforms it into a tissue completely inhospitable to the embryo. The latter, in turn, administered ellaOne in the early luteal phase - i.e. after ovulation and eventual conception - showing that the expression of 192 selected genes, associated with endometrial receptivity, was depressed in the mid-luteal endometrium after taking the drug.

Despite these data and all the information previously available, on 23 September 2024 the CHMP repeats again, on page 8 of the EPAR, that "*When used for emergency contraception the mechanism of action is inhibition or delay of ovulation*" and reports that "*ellaOne Works by Postponing Ovulation*" in the *Leaflet: informationfor the user* at page 39 (https://www.ema.europa.eu/en/documents/product-information/ellaone-epar-product- information_en.pdf).

This information is exactly the opposite of what clearly emerges from the experimental data, and the individual National Medicines Agencies have probably been inattentive and distracted when they passively accepted that an anti-implantation and potentially abortifacient drug, such as ellaOne, be marketed in their countries.

In presenting UPA as an anti-ovulatory drug, EMA was well aware of its prevalent anti-implantation effect and, moreover, of its ability to terminate pregnancy as effectively as Mifepristone (RU486), but chose to remain silent on these data and maintained intentionally misleading information.

Its abortifacient efficacy has now been demonstrated. [7]

Ulipristal and Mifepristone: the twin molecules

Ulipristal and Mifepristone have extremely similar molecules (Fig. 19) and share multiple effects in the female reproductive system. [20,21,45,48-52]

Mifepristone is also used as an emergency contraceptive at doses of 25–50 mg in China. [48]

When administered in the middle of the follicular phase, before fertile days begin, its effects on ovulation are similar to those of UPA, [50] although UPA is effective at much lower doses· [25]

Similarly, in the early luteal phase, 200 mg of mifepristone is highly effective in preventing the clinical onset of pregnancy; [53-56] needless to say, ovulation and conception have already occurred at that stage of the cycle. This is the same effect found with much lower dosages of Ulipristal. [28]

Finally, both Mifepristone and non-micronised Ulipristal, at the same dose of 200 mg, administered in the mid-luteal phase, seven days after ovulation and conception, exactly on the days when implantation is completed, constantly lead to early endometrial bleeding [29] (Fig.s 53-55).

While Mifepristone (RU486), at a dose of 200 mg, is the drug used to terminate pregnancy, Ulipristal had never been tested for the termination of pregnancy in women, despite explicit requests from EMA to HRA-Pharma, the manufacturer. [8] At Last, the final answer comes from Winikoff et al. who have successfully tested ellaOne as an abortifacient drug, with a very high effectiveness: 97%. [7]

The two drugs also share other activities, both on the development of ovarian follicles and on the differentiation of the endometrium, at dosages that are substantially overlapping. [32-35]

In addition, both Ulipristal [57.58] and Mifepristone,[59.60] always at the same doses (5 mg per day for three-month treatments), are able to reduce the volume of uterine fibroids and reduce the intensity of uterine haemorrhages, which are frequent gynaecological diseases.

Micronized ulipristal has been available in pharmacies in Western Europe for the pre-operative treatment of uterine fibroids, which are benign tumors of the uterus. The name of the commercial preparation is Esmya: one pack contains a blister pack with 28 tablets of 5 mg each, for a combined total of 140 mg (ellaOne contains 30 mg).

ULIPRISTAL ACETATE TOXICITY – SERIOUS SIDE EFFECTS

Due to the occurrence of severe liver lesions in patients treated with Esmya, in December 2017 the EMA (Pharmacovigilance Risk Assessment Committee) initiated a re-evaluation of the medicine (EMA/791062/2017) [61] (Fig. 97) believing that Esmya□ could be the cause. The conclusions were sent to EMA's Committee for Medicinal Products for Human Use (CHMP) and finally to the European Commission (EMA/355940/2018) [62] (Fig.s 98-100).

This resulted in a ban on prescribing Esmya (UPA) to patients with liver disorders and in the requirement for serial liver function checks before, during and after treatment. The patients, who were already normally followed by hospital gynaecologist specialists, should also have been informed about the signs and symptoms of liver damage and the actions to be taken in case these occurred.

On 4 September 2020, a further case review conducted by EMA's PRAC definitively confirmed that UPA 5 mg can cause liver damage so severe that liver transplantation may be required. As it was not possible to identify which patients were most at risk or measures that could reduce the risk, the PRAC concluded that the risks outweigh the benefits and that Esmya should not be marketed in the EU (EMA/455818/2020)[63] (Fig.s 101,102). The EMA CHMP, while agreeing with the analysis, considered that it would maintain limited availability for patients who have already been operated on without success, or are inoperable, for whom there is no therapeutic alternative (EMA/524073/2020 and EMA/24778/2021).[64,65]

Only through close post-marketing surveillance was it possible to correlate the administration of Esmya with side effects. The time between the start of taking Esmya and the onset of liver failure ranged from a few days to six months [66] (Fig. 103).

All this caution appears necessary in relation to the liver risks associated with the intake of UPA. After all, it has been known for over a decade that Ulipristal Acetate, the active ingredient, progressively accumulates in tissues, particularly in the liver with potentially toxic effects, as EMA reports on page 1. 13 of the Assessment Report (EMEA/271787/2009) [45] with which it introduces the drug on the market (Fig. 104).

On the contrary, the drug ellaOne, which contains the same active ingredient, is distributed freely, without any limitation and prudence, without information on the risks and without any medical supervision. Furthermore, in all the EMA documents referred to above (from 2017 to 2021) [61-65] which reiterate the dangers associated with taking Esmya (Ulipristal), it is insisted on repeating that taking ellaOne is safe ("*No concern has been raised about liver injury with these single-dose emergency contraception medicines and this recommendation does not affect them.*") (Fig. 105), knowing full well that there are no limits to its use, even repeated in the same menstrual cycle and, therefore, to the quantities that can be ingested.

EllaOne, in fact, had been authorized in 2009 for occasional use (Fig. 104) and was subject to medical prescription, precisely because of the risk of liver accumulation. In 2015, at the request of HRA-Pharma, the need for a medical prescription was removed. [19]

In doing so, EMA assesses the criteria which must be fulfilled for this purpose, as provided for in Article 71 of the European Directive 2001/83/EC.

The *first criterion* is that *a drug must be subject to medical prescription if it can constitute a danger, direct or indirect, even if used correctly, when used without medical supervision* (Fig. 106).

To demonstrate the absence of any danger, EMA and HRA-Pharma refer to a study (HRA2914-554) already mentioned in this same text on page 9: two groups of patients had been treated for eight consecutive weeks with ellaOne administered every 7 days (Group Q7D) or every 5 days (Group Q5D). In eight weeks, the patients in Q7D had received a total dose of 270 mg of UPA, while those in Q5D had taken 360 mg.

It should be noted, first of all, that the amount of UPA taken in eight weeks by those patients is equivalent to or even higher than that (280 mg) that was taken in eight weeks of Esmya and which led some women to fulminant hepatitis and acute liver transplantation[66].

The absence of serious side effects in the 23 patients studied, led EMA and HRA Pharma to exclude the need for a medical prescription even in the hypothesis of repeated and frequent use, a hypothesis considered evidently plausible (Fig. 107) ("*should ellaOne be used more than once in the same cycle, the safety profile is similar to that for a single administration*).

Therefore, though it was aware of the progressive accumulation of UPA in the liver, in 2015, at the request of the manufacturer HRA Pharma, EMA also removed the warning recommending not to take ellaOne repeatedly in the same menstrual cycle (Fig. 108).

Hepatotoxicity due to the intake of Esmya had not yet been reported in 2015, when the EMA's CHPM removed both the need for prescription and, at the same time, the warning against repeated intake of ellaOne.

Today, however, liver damage is known and is officially notified by the official bodies of the EMA, the PRAC and the CHMP [61-65] and it is surprising that EMA reassures and reassures about the safety of ellaOne.

Especially since, although to date no case of hepatotoxicity due to the administration of a single dose of ellaOne has been reported, it is known to the scientific world that a short intake of Esmya (UPA 5mg): from 3 days (15mg, half of ellaOne) to 26 days can be enough to cause fulminant hepatitis. This is the case of patient 2 in the Meunier series [66] (Fig.s 109,110).

Furthermore, it is common knowledge that ellaOne can be taken repeatedly by millions of women each time unprotected sex is repeated, at any time during the cycle, [67] as suggested in the package insert, and that the dosages you take progressively accumulate. The percentage of repeated use appears to be extremely high: 44.2% in the recent study by Jambrina et al. [68]

Finally, while women treated with Esmya were closely monitored and a post-marketing evaluation linking any side effects to the drug was possible (as it happened), the women, mainly minors, taking ellaOne remain unknown: any adverse events could only be attributed with extreme difficulty to self-administration that cannot be documented.

In light of the above, it is easy to conclude that repeated self-administration of ellaOne can lead to a total intake of UPA even higher than those amounts that caused the dramatic liver damage officially attributed to Esmya. Likewise, it is easy to conclude that nothing can discourage or even limit the repeated intake of ellaOne: not only are women not informed of the risk, but they are even reassured that even repeated and close intake is as safe as taking a single tablet (Fig. 107).

In this context, it is absolutely not justifiable that the EMA, which has the mandate to protect the health of Europeans, in banning Ulipristal for serious and manifest damage (Esmya) promotes its free and unlimited use in emergency contraception (ellaOne). This use exposes the woman and, in particular, the adolescent to a very serious risk of which she is not informed and aware, in the absence of any medical supervision. (69)

CONCLUSIONS

Ulipristal Acetate (UPA, ellaOne) is a frankly abortifacient drug, proposed and sold for 15 years as an emergency contraceptive capable of preventing or delaying ovulation.

Taken on the most fertile days of the cycle, ellaOne does not prevent or delay the release of the egg. Its prevalent effect is on the endometrium: the effect of inhibiting endometrial maturation has been reported in the medical literature for years, even before its marketing, and its anti-implantation effect is documented in indisputable terms in the studies of Lira-Albarràn and Jimenez-Guerrero. The drug allows both ovulation and conception, but inhibits the embryo implantation process.

Its ability to terminate a pregnancy up to the ninth week is now unequivocally proven.

Women, doctors, health professionals and authorities are intentionally provided with untruthful information both about its mechanism of action and about its abortifacient effects.

The review of the safety profiles of Esmya, another UPA-based drug, has shown that the molecule is capable of causing very serious and even lethal liver damage. To prevent them, EMA and AIFA limit their use only to patients who have no therapeutic alternatives and provide for close checks of liver function before, during and after taking the drug.

No recommendation or request for controls is envisaged, however, for ellaOne, with very serious potential risks for the female population, largely in adolescence, who resort to its use increasingly, indiscriminately and repeatedly without being in any way informed even of the risks to their health. On the contrary, EMA reassures that even repeated and close intake is as safe as taking a single tablet.

BIBLIOGRAPHY

1. Lopez del Burgo C, Mikolajczyk RT, Osorio A, Carlos S, Errasti T, de Irala J. *Knowledge and beliefs about mechanism of action of birth control methods among European women*. Contraception 2012;85:69-77. doi:10.1016/j.contraception.2011.04.007. Epub 2011 Jun 8.
2. Lopez del Burgo C, Mikolajczyk RT, Osorio A, Errasti T, de Irala J. *Women's attitudes towards mechanisms of action of birth control methods: a cross-sectional study in five European countries*. J Clin Nurs 2013; 22(21-22):3006-15. doi: 10.1111/jocn.12180. Epub 2013 Aug 20.
3. Dye HM, Stanford JB, Alder SC, Kim HS, Murphy PA. *Women and postfertilization effects of birth control: consistency of beliefs, intentions and reported use*. BMC Womens Health 2005; 5:11.
4. de Irala J, Lopez del Burgo C, Lopez de Fez CM, Arredondo J, Mikolajczyk RT, Stanford JB. *Women's attitudes towards mechanisms of action of family planning methods: survey in primary health centres in Pamplona, Spain*. BMC Womens Health 2007;7:10.
5. Lopez-del Burgo C, Lopez-de Fez CM, Osorio A, Guzmán JL, de Irala J. *Spanish women's attitudes towards post-fertilization effects of birth control methods*. Eur J Obstet Gynecol Reprod Biol 2010; 151(1):56-61.
6. Willetts SJ, Mac, MacDougall M, Cameron ST. *A survey regarding acceptability of oral emergency contraception according to the posited mechanism of action*. Contraception 2017; 96:81-88.
7. Winikoff B, Bousiéguez M, Salmerón J, et al. *A proof-of-concept study of ulipristal acetate for early medication abortion*. NEJM Evid 2025; 4(2):1-8. DOI: 10.1056/EVIDoa2400209
8. EMA/73099/2015. *CHMP Assessment Report on ellaOne*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001027/WC500181904.pdf
9. Trussel J, Rodriguez G, Ellertson C. *New estimates of the effectiveness of the Yuzpe regimen of emergency contraception*. Contraception 1998;57:363-369.
10. Wilcox AJ, Baird DD, Dunson DB et al. *On the frequency of intercourse around ovulation: evidence for biological influences*. Hum Reprod 2004; 19:1539-1543.
11. Dunson DB, Baird DD, Wilcox AJ et al. *Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation*. Hum Reprod 1999;14:1835-1839.
12. Gemzell-Danielsson K. *Mechanism of action of emergency contraception*. Contraception. 2010; 82:401-409.
13. Mozzanega B. *From Life to Life - A journey to discover human reproduction*. SEU Ed, Rome, April. 2021; Ch.1:9-29.
14. Behre HM, Kulhage J, Gassner C, Sonntag B. Schem C, Schneider HP et al. *Prediction of ovulation by urinary hormone measurements with the home use ClearPlan Fertility Monitor: comparison with transvaginal ultrasound scans and serum hormone measurements*. Hum Reprod 2000;15:2478-2482.
15. *ellaOne EPAR*, 23 September 2024. https:// www.ema.europa.eu/en/documents/product-information /ellaone-epar-product-information_en.pdf
16. Watson Medical Communication. *Highlights of Prescribing Information* - Ella Tablet. 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf

17. Glasier AF, Cameron ST, Fine PM, et al. *Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and metaanalysis.* Lancet. 2010;375(9714):555-562.
18. Brache V, Cochon L, Jesam C et al. *Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture.* Hum Reprod 2010;25:2256-2263.
19. Breeches V, Cochon L, Deniaud M, Croxatto H. *Ulipristal acetate prevents ovulation more* effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency *contraception regimens.* Contraception. 2013;88:611-618.
20. Mozzanega B, Gizzo S, Di Gangi S, Cosmi E, Nardelli GB. *Ulipristal Acetate: Critical Review About Endometrial and Ovulatory Effects in Emergency Contraception*. Reprod Sci 2014; 21:678-685
21. Mozzanega B, Nardelli GB. *UPA and LNG in Emergency Contraception: the information by EMA and the Scientific Evidences indicate a prevalent anti-implantation effect*. Eur J Contracept Reprod Health Care 2019; 24(1): 4-10. doi: 10.1080/13625187.2018.1555662. Epub 2019 Jan 18
22. Fine P, Mathe´ H, Ginde S, Cullins V, Morfesis J, Gainer E. *Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception.* Obstet Gynecol. 2010; 115(2 pt 1):257-263.
23. Creinin MD, Schlaff W, Archer DF, et al. *Progestin receptor modulator for emergency contraception: a randomized control trial.* Obstet Gynecol. 2006; 108(5):1089-1097.
24. Lira-Albarrán S, Durand M, Larrea-Schiavon MF, González L, Barrera D, Vega C, Gamboa-Domínguez A, Rangel C, Larrea F. *Ulipristal acetate administration at mid-cycle changes gene expression profiling of endometrial biopsies taken during the receptive period of the human menstrual cycle.* Mol Cell Endocrinol. 2017; 447:1-11
25. Stratton P, Hartog B, Hajizadeh N, et al. *A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women.* Hum Reprod 2000;15:1092-1099.
26. Gemzell-Danielsson K, Berger C, Lalitkumar PGL. *Emergency contraception – mechanism of action,* Contraception 2013;87:300-308.
27. Lalitkumar PGL, Berger C, Gemzell-Danielsson K. *Emergency contraception.* Best Practice & Research Clinical Endocrinology & Metabolism 2013;27:91-101.
28. Stratton P, Levens ED, Hartog B, et al. *Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914.* Fertil Steril 2010;93:2035-2041.
29. Passaro MD, Piquion J, Mullen N, et al. *Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women.* Hum Reprod 2003;18:1820-1827.
30. Wagner BL, Polio G, Giangrande P, et al. *The novel progesterone receptor antagonist RTI 3021-3012 and RTI 3021-3022 exhibit complex glucocorticoid receptor activities: implications for the development of dissociated antiprogestins.* Endocrinology 1999;140:1449-1458.
31. Blithe DL, Nieman LK, Blye RP, Stratton P, Passaro M. *Development of the selective progesterone receptor modulator CDB-2914 for clinical indications.* Steroids 2003;68:1013-1017.
32. Attardi BJ, Burgenson J, Hild SA, Reel JR. *In vitro antiprogestational/ antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites and synthetic derivatives of CDB-2914, CDB-4124, and mifepristone.* J Steroid Biochem Mol Biol 2004;88:277-288.

33. Attardi BJ, Burgenson J, Hild SA, Reel JR, Blye RP. *CDB-4124 and its putative monodemethylated metabolite, CDB-4453, are potent antiprogestins with reduced antiglucocorticoid activity: in vitro comparison to mifepristone and CDB-2914.* Mol Cell Endocrinol. 2002; 188:111-123.
34. Gainer EE, Ulmann A. Pharmacologic properties of CDB(VA)-2914. Steroids 2003;68:1005-11.
35. Rao PN, Wang Z, Cessac JW, Rosenberg RS, Jenkins DJ, Diamandis EP. *New 11 beta-aryl-substituted steroids exhibit both progestational and antiprogestational activity.* Steroids 1998;63:523-530.
36. Lira-Albarrán S, Durand M, Barrera D, Vega C, Garcia Becerra R, Diaz L, Garcia-Quiroz J, Rangel C, Larrea F. *A single preovulatory administration ulipristal acetate affects the decidualization process of the human endometrium during the receptive period of the menstrual cycle.* Mol Cell Endocrinol. 2018; 476:70-78
37. Zumoffen C, Gómez-Elíasb MD, Caillea AM, Bahamondesc L, Cuasnicúb PS, Cohenb DJ, Munucea MJ. *Study of the effect of ulipristal acetate on human sperm ability to interact with tubal tissue and cumulus-oocyte-complexes.*Contraception 2017; 95:586-591
38. Jimenez Guerrero M, Fava M, Baccaro LF, Caille AM ,Cuasnicù PS , Horcajadas JA , Cohen DJ , Bahamondes L , Cotàn D, Munuce MJ. *Effect of ulipristal acetate on gene expression profile in endometrial cells in culture and in vivo upon post-ovulatory administration in fertile women.* Eur J Contracept Reprod Health Care 2021;6:1-9. doi: 10.1080/13625187.2021.1975270. Online ahead of print.
39. Gomez-Elìas MD, May M, Munuce MJ, Bahamondes L, Cuasnicú PS, Cohen DJ. *A single post- ovulatory dose of ulipristal acetate impairs post-fertilization events in mice.* Mol Hum Reprod 2019; 25(5):257–264
40. Li HW, Lo SS, Ng EH, Ho PC. Efficacy of ulipristal acetate for emergency contraception and its effect on the subsequent bleeding pattern when administered before or after ovulation. Hum Reprod 2016; 31(6):1200–1207, Advanced Access publication on April 6, 2016 doi:10.1093/humrep/dew055
41. Noé G, Croxatto HB, Salvatierra AM, Reyes V, Villarroel C, Muñoz C, Morales G, Retamales A. *Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation.* Contraception 2010;81:414-420. doi: 10.1016/j.contraception.2009.12.015. Epub 2010 Jan 27
42. Gemzell-Danielsson K, Rabe T, Cheng L. *Emergency contraception.* Gynecol Endocrinol 2013;29(S1):1-14. doi: 10.3109/09513590.2013.774591
43. Gemzell-Danielsson K, Berger C, Lalitkumar PG. *Mechanisms of action of oral emergency contraception.* Gynecol Endocrinol 2014; 30(10):685-687.
44. Berger C, Boggavarupu RN, Menezes J, Lalitkumar PGL, Gemzell Danielsson K. *Effects of ulipristal acetate on human embryo attachment and endometrial cell gene expression in an in vitroco-culture system.* Hum Reprod 2015;30:800-811.
45. EMEA/261787/2009 - CHMP Assessment Report for Ellaone. EMEA/H/C/001027 procedures. https:// www.ema.europa.eu/en/documents/assessment-report/ellaone-epar-public-assessment-report_en.pdf

46. Tarantal AF, Hendrickx AG, Matlin SA, Lasley BL, Gu QQ, ThomasCAA, Vince PM, Van Look PFA. *Effects of Two Antiprogestins on Early Pregnancy in the Long-Tailed Macaque (Macaca fascicularis).* Contraception 1996;54:107-115.
47. EMA/631408/2014. *Levonorgestrel and Ulipristal remain suitable emergency contraceptives for all women, regardless of bodyweight.* http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Emergency_contraceptives_31/WC500176381.pdf
48. Cheng L, Che Y, Gülmezoglu AM. *Intervention for emergency contraception.* Cochrane Database Syst Rev 2012;8:286.
49. Taneepanichskul S. *Emergency contraception with mifepristone 10 mg in Thai women.* J Med Assoc Thai 2009;92:999-1002.
50. Bodensteiner KJ. *Emergency contraception and RU-486 (mifepristone): do bioethical discussions improve learning and retention?* Adv Physiol Educ 2012;36:34-41.
51. Glasier A. *Emergency postcoital contraception.* N Engl J Med 1997;337:1058-1064.
52. Glasier A, Thong KJ, Dewar M, Mackie M, Baird D. *Mifepristone (RU486) compared with high dose estrogen and progestin for emergency postcoital contraception.* N Engl J Med;327:1041-1044.
53. Gemzell-Danielsson K, Marions L. *Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception.* Hum Reprod Update 2004,10:341-348.
54. Hapangama DK, Brown A, Glasier AF, Baird DT. *Feasibility of administering mifepristone as a once a month contraceptive pill.* Hum Reprod 2001;16:1145-1150.
55. Agarwal M, Das V, Agarwal A, Pandey A, Srivastava D. *Evaluation of mifepristone as a once a month contraceptive pill.* Am J Obstet Gynecol 2009; 200:E27-29.
56. Croxatto HB. *Mifepristone for luteal phase contraception.* Contraception 2003;68:483-488.
57. Donnez J, Tatarchuk TF, Bouchard P, et al. *Ulipristal acetate versus placebo for fibroid treatment before surgery.* N Engl J Med 2012;366:409-420.
58. Koskas M , Chabbert-Buffet N, Douvier S, Huchon C, Paganelli E, Derrien J. *Role of medical treatment for symptomatic leiomyoma management in premenopausal women.* J Gynecol obstet Biol Reprod 2011;40:858-874.
59. Esteve JL, Acosta R, Pérez Y, Campos R, Hernández AV, Texidó CS. *Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomized clinical trial.* Eur J Obstet Gynecol Reprod Biol 2012; 161:202-208.
60. Carbonell Esteve JL, Riverón AM, Cano M, Ortiz AI, Valle A, Texidó CS, Tomasi G. *Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery.* Int J Womens Health 2012;4:75-84.
61. EMA/791062/2017. At: http://www.agenziafarmaco.gov.it/sites/default/files/Esmya_EMA_IT.pdf
62. EMA/355940/2018. http://www.agenziafarmaco.gov.it/sites/default/files/IT_Esmya_01.06.2018.pdf
63. EMA/455818/2020 - https:// www.ema.europa.eu/en/documents/referral/ *ulipristal-acetate-5mg-medicinal-products-article-31-referral-prac-recommends-revoking-marketing_en.pdf*

64. EMA/524073/2020 - https:// www.ema.europa.eu/en/documents/referral/ *ulipristal-acetate-5mg-medicinal-products-article-31-referral-chmp-scientific-conclusions-prac_en.pdf*
65. EMA/24778/2021 - https:// www.ema.europa.eu/en/documents/referral/ *ulipristal-acetate-5mg-medicinal-products-article-31-referral-ulipristal-acetate-uterine-fibroids*_en.pdf
66. Meunier L , Meszaros M , Pageaux GP, Delay JM, Herrero A, Pinzani V, Dominique HB. *Case Report. Acute liver failure requiring transplantation caused by ulipristal acetate*. Clin Res Hepatol Gastroenterol 2020; 44: E45-E49. doi: 10.1016/j.clinre.2020.02.008. Epub 2020 Mar 4.
67. Halpern V, Raymond EG, Lopez LM. *Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy*. Cochrane Database of Systematic Reviews 2014; 9, CD007595. DOI: 10.1002/14651858.CD007595.pub3
68. Jambrina AM, Rius P, Gascón P, Armelles M, Camps-Bossacoma, Franch A, Rabanal M. *Characterization of the Use of Emergency Contraception from Sentinel Pharmacies in a Region of Southern Europe*. J Clin Med 2021; 10, 2793. https://doi.org/10.3390/jcm10132793
69. Mozzanega B. Ulipristal Acetate and liver-injuries: while Esmya is revoked, EllaOne is allowed in repeated self-administrations possibly exceeding UPA toxic-dosing with Esmya. J Hepatol 2021;74:750–751. S0168-8278(20)33828-9. doi: 10.1016/j.jhep.2020.11.041. Online Nov 30 ahead of print.