THE QUESTION OF EMERGENCY CONTRACEPTION

From the Realm of Law to the Realm of Scientific Evidencies

INTRODUCTION

I am Bruno Mozzanega, an Assistant Professor of Gynecology at the University of Padua, and teach "Family Planning" in the post-graduate School of Gynaecology and Obstetrics. I am the the Chairman of SIPRe (Societa'Italiana Procreazione Responsabile). In its website (http://www.sipre.eu/the-association/) SIPRe presents a Position Paper titled *Emergency Contraception - Position Paper on the Mechanism of Action*, of which I am the author. The full text of this paper may be viewed at the following link: http://www.sipre.eu/wp-content/uploads/2014/12/POSITION-PAPER-SIPRe-English.pdf

In a nutshell, this position paper highlights that the effects of Emergency Contraceptive Pills (ECPs) occur mostly through damages to the endometrium/decidua that affect the processes of embryo-implantation and pregnancy. It also explains how the information released by the European Medicines Agency (EMA) and by renowned authors in medical literature is deceiving the policy-makers, healthcare professionals and, worst of all, the women: without a correct knowledge, in fact, no free responsible and conscious choice is possible.

Apart from this position paper I also was the author and co-author of various studies in recognized international medical journals, in which I explained that the prevalent action of emergency contraceptives takes place after conception and not before.

SIPRe is an interdisciplinary Scientific Association with scientific, social and cultural aims. It promotes and favours fully conscious and responsible procreative choices. SIPRe respects human life since conception and, accordingly, considers acceptable all the birth-control methods that consistently prevent fertilization.

To this aim SIPRe promotes and directly implements both the divulgation of knowledge concerning human reproductive physiology, prerequisite to free procreative choices that base on correct information, and the divulgation of scientific information concerning the mechanism of action (MOA) of the birth-control methods.

The Association is open to all the professionals who share its purposes (doctors, chemists, lawyers, nurses, midwives, teachers, etc) independently of political and religious orientations.

Following is a summary and less technical version of SIPRe's Position Paper.

SUMMARY OF THE POSITION PAPER

Unprotected intercourse can lead to pregnancy only if it occurs in the fertile period of the cycle, that is, in the four/five days preceding ovulation and on the ovulation day itself. Only on these days, in fact, the lining of the cervix allows the sperms to enter female reproductive organs.

Among the fertile days, the pre-ovulatory day is that on which the probability of conception is highest, followed by the ovulation day and by the second day preceding ovulation. On these same days, the frequency of both protected and unprotected intercourse peaks.

The use of ECs is an attempt to prevent pregnancy that must face two facts. *The First One:* the sperms have already entered. Thanks to the fertile mucus they already passed through the cervical channel and many are already resting in the tube, where they wait the egg release. No drug of the Day-After can inhibit their ascent, given the fact, that it has already happened.

The Second One: Ovulation is imminent. At this point in time, everything in the female body is arranged for fertilization and for the subsequent embryo-implantation into the endometrium that pro-gestational hormones will make hospitable after ovulation. Within this setting, pregnancy can only be avoided in two ways: by preventing ovulation *in extremis* and thereby preventing fertilization, or by avoiding that the embryo finds within the uterus the fertile ground he needs to implant. The substantial difference between the two hypothesis is evident: in the former, fertilization is avoided, while in the latter, the embryo is actively eliminated before he implants.

Mechanism of Action (MOA) of Emergency Contraceptives (ECs)

The drugs currently used are **Levonorgestrel (LNG),** a potent synthetic progestogen, and **Ulipristal-Acetate (UPA),** a potent anti-progestagen quite similar to **Mifepristone (RU486),** the abortion drug. The two drugs will be dealt with separately.

The producer, HRA-Pharma, the Food and Drugs Administration (U.S.FDA), the EMA and other international bodies affirm that ECs work by either inhibiting or delaying ovulation, and therefore preventing fertilization without affecting implantation in any way.

Scientific and experimental evidence, on which SIPRE's Position Paper is based, leads to a quite different conclusion: these drugs prevent fertilization consistently only when they are taken at the very beginning of the fertile period; subsequently, instead, and mainly in the most fertile days closest to ovulation, both ECs have no longer any effects on either ovulation or fertilization, while they transform the endometrium into an inhospitable environment for the embryo.

Levonorgestrel (LNG,Norlevo)

This pill is taken in a 1.5mg oral dose within 72 hours after unprotected intercourse.

The International Consortium for Emergency Contraception (ICEC) and the International Federation of Gynecology & Obstetrics (FIGO) in their 2008, 2011 and 2012 joint Statements *"How do Levonorgestrel-only emergency contraceptive pills (LNG-ECPs) work to prevent pregnancy?"* state that LNG either delays or inhibits ovulation, and consequently prevents fertilization, without affecting embryo-implantation.

On the contrary, in the studies quoted in support to the Statements, ovulation is never inhibited when LNG is taken in the advanced pre-ovulatory phase, a phase that encompasses

the most fertile days of the cycle: when LNG is taken in these days, most women have normal ovulation but a severe functional impairment of the corpus luteum, the gland that produces Progesterone, the pro-gestational hormone that prepares the endometrium to embryo-implantation. This impairment leads to the impossibility for the embryo to implant

Nonetheless, LNG is highly effective; it prevents the appearance of 70% of pregnancies, though it is unable to prevent ovulation. Evidently, LNG effectiveness is due to something else: namely, to the alterations in the endometrial tissue.

Are the ICEC and FIGO Statements reliable?

The Statements' authors conclude that *"inhibition or delay of ovulation is LNG ECPs's principal and possibly only mechanism of action"*. Their names - Brache, Faundes and Fraser (gynaecologists), Trussell (statistician) - are reported in the website of the European Society of Contraception and Reproductive Health (http://www.escrh.eu/about-esc/news/how-do-levonorgestrel): they are thanked *"for their incredible attention to detail and persistence in making sure this statement was accurate and fully reflected the most recent studies".*

Brache is the first author of a paper (Hum Reprod 2010;25:2256-2263) at the end of which she deals with the anti-ovulatory efficacy of LNG and concludes - quoting studies by herself and Faundes - that LNG administration in the advanced follicular phase (the most fertile days) *"resulted in follicle rupture* (ovulation) *inhibition in 7/48women (14.6%)"*, evidencing that LNG effectiveness is placebo-like.

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

Their Statements are considered Holy Writ, unanimously shared by all the World's gynaecologists. According to these Statements, medical doctors base their professional and ethical choices. On them, women, base their personal choices, believing that LNG *does* prevent fertilization. On these Statements, nations and governments rely when they legislate on these vital topics.

Additionally, *ad abundantiam*, the European Public Assessment Report (EPAR) on ellaOne by the EMA – Product Information/human/001027/WC500023670, updated 09/08/2016 states that in the fertile days LNG is never able to inhibit ovulation: its anti-ovulatory ability is only 25% in the first fertile days, while subsequently it decreases further to only 10%, a placebo-like anti-ovulatory effect (Table, page 9).

Ulipristal-Acetate (UPA,ellaOne)

Each tablet contains 30mg of micronized (broken down to very small particles) Ulipristal-Acetate, to be taken in a single oral dose. It is acknowledged that 30 mg of micronized UPA are equivalent to 50 mg of un-micronized UPA, the drug used in previous clinical trials.

"Ulipristal-acetate prevents progesterone from occupying its receptor (omissis) and the proteins necessary to begin and maintain pregnancy are not synthesized." This is reported (page 8) in the EMA-*CHMP Assessment Report for ellaOne*" (EMEA-261787-2009), the Report leding to ellaOne Marketing Authorisation. It should be enough, by itself, to qualify ellaOne abortifacient ability.

The producer, HRA Pharma, claims that if administered in the fertile period of the menstrual cycle, it is able to delay ovulation, so preventing fertilization. The claim bases on the above-mentioned Brache's paper and is endorsed and shared by the ICEC and FIGO.

Anti-ovulatory effects

Brache's study is the only one that evaluates the effects of ellaOne on ovulation, when it is taken during the different days of the fertile period. The study suggests that UPA is able to inhibit, or delay ovulation for over five days, even when it is administered immediately before ovulation. This point is emphasized in the title, in theory and in the paper's conclusions.

The number of the Study's subjects is small, 34. Overall, 41.2% women do ovulate regularly, and so fertilization can occur. Only in the 8 women treated at the beginning of the fertile period a consistent delay in ovulation was observed. Instead, among the patients treated at the LH peak, ovulation is delayed in only 8% of subjects: 92% of women *do* ovulate and fertilization can follow.

In the results section, the author states this clearly: when UPA is taken at LH peak (LH is a hormone which triggers ovulation and development of the corpus luteum), 24-48 hours before follicular rupture, the drug has no ability to either avoid or delay ovulation. These days are the most fertile in the cycle, those in which most fertilizations occur; those days in which a drug with a steadily high contraceptive efficacy consistently above 80%, should prevent ovulation with the highest efficacy, were its efficacy due to an anti-ovulatory effect.

On the contrary, UPA's ability to delay ovulation is highest (100%) only at the start of the fertile period; thereafter, it drops sharply and becomes almost null (8%) in the two pre-ovulatory days. In spite of this, its effectiveness in preventing pregnancies is very high (>80%) and does not decrease depending on which of the five days it is taken, after unprotected intercourse.

Ad abundantiam again, in the EMA/73099/2015 is reported a study evaluating the effects of repeated dose of ellaOne on ovulation and on the endometrium. The subjects were treated for 8 weeks. A group was treated every 5 days, while the other every 7 days: normal ovulation was observed in 72.1% of the former and in 91.7% of the latter. The cervical mucus was consistently permeable to sperms.

Ovulation occurs, so the "contraceptive" efficacy must be due to a different MOA: namely, to UPA inhibitory endometrial effects.

Endometrial Effects

One single dose of Ulipristal-Acetate modifies deeply endometrial receptivity at whichever time it is administered. It blocks endometrial Progesterone-receptors: the pro-gestational effects of Progesterone are lost and, among them, the expressions of those proteins that make the maternal endometrium hospitable for the embryo. These effects are identical to those of Mifepristone (RU486), but UPA is effective even in lower doses.

EllaOne leads consistently to an inhospitable endometrium and whenever fertilization occurs the embryo will not be allowed to implant and survive. In fact, *"the threshold for altering endometrial morphology appears lower than for inhibition of ovulation"* (EMEA/261787/2009, page 22).

In short, women who take Ulipristal after unprotected intercourse during their fertile days, mostly do ovulate and fertilization follows. Unfortunately, the endometrium is irreversibly damaged, independently of the period when UPA is taken.

The single-dose UPA effects on human endometrium are reported by Stratton (Hum Reprod 2000;15:1092-1099 and Fertil Steril 2010;93:2035-2041) and Passaro (Hum Reprod 2003;18:1820-1827).

The repeated-administration ellaOne effects on the endometrium are reported in EMA/73099/2015: morphological alteration are evident in 50% of patients.

We conclude that ellaOne consistently high efficacy is explained only by the consistent endometrial impairment, that is by its anti-implantation MOA.

Ulipristal as an abortifacient

Besides working prevalently with an anti-implantation MOA, UPA is acknowledged as an abortifacient drug: EMEA/261787/2009 clearly reports that "*When using intramuscular administration of 0.5 mg/kg 4/5 foetuses were lost in Ulipristal-Acetate treated animals."* This means that the intramuscular administration of UPA 50mg, equivalent to ellaOne micronized 30mg, induces abortion in 80% of cases (the sub-lingual route is similar to the intramuscular).

UPA can be used for pregnancy-termination and this is presented as a "safety concern" in the EMEA/261787/2009, but the strategic choice for the "risk minimization" was "Omit any sentence in the literature accompanying this pharmaceutical (SPC & PIL) suggesting that the product could be used as an abortifacient.".

At last, EMA and HRA-Pharma agree that all of the approaches to avoid ellaOne use of as an abortifacient suffer from inevitable limitations; the only way may be prescription registries. However, the prescriptions were abolished by EMA.

"*During the evaluation process of the ellaOne registration dossier the MAH* (HRA-Pharma) *was requested to study any potential off-label use of ellaOne, in particular during pregnancy, possibly as an abortifacient. No clinical studies have been performed with Ulipristal-Acetate*

as an abortifacient, and it is therefore also unknown whether it is possible to use it for abortion" (EMA/73099/2015).

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

Ulipristal and Mifepristone: twin molecules

Mifepristone (RU486) 200mg is the drug administered for pregnancy termination (chemically-induced/non-surgical abortion). UPA and RU486 share many effects in the female reproductive system. Both, in the same doses, decrease fibroid size and reduce uterine haemorrhage.

Currently, micronized UPA is marketed for fibroid reduction prior to surgery: Esmya (5mg tablets in blister of 28, for the total amount of 140mg). EllaOne contains 30mg. We remember that 120mg of micronized UPA are equivalent to 200mg of un-micronized UPA which, in turn, correspond to 200mg of Mifepristone: the dose for pregnancy termination. Both drugs, at these doses, taken seven days after ovulation and fertilization - the time when the embryo starts implantation - consistently anticipate uterine bleeding.

This should carefully be considered when deciding prescription regulations and limitation of UPA-containing drugs. It is a question of conscience for all concerned.