Ulipristal acetate.
An emergency contraceptive?

Justo Aznar*, Julio Tudela**

Introduction

There is no doubt that the issue of unwanted pregnancies, and on many occasions consequent abortion, is a serious social problem. To confirm this, one only has to refer to the data provided in the bibliography. Indeed, the number of pregnancies in adolescents (girls aged between 15 and 19 years) in the world between 2000 and 2002 was 14,020,000, which was 10.5% of all pregnancies. Of these, 494,000 (7% of the total) were in Europe; the highest percentage occurred in Africa with 4,985,000 pregnancies (15.8% of the total) and Latin America and the Caribbean with 1,904,000 (16.3% of the total).1 In the United States, around 970,000 teenage pregnancies occur every year.2 In Europe, these figures vary between countries, although Eastern countries generally have higher rates than Western Europe, with the United Kingdom having the highest.3 Many times, teenage pregnancies end in abortion. Thus, in 2008, there were 338,217 abortions in adolescents in Europe and 170,932 in the 27-state-EU,4 all of which indicates the social importance of this problem and the need to combat it.

* Medical Doctor, Director of the Institute of Life Science of the Catholic University of Valencia, Spain; ** Member of the Institute of Life Sciences of the Catholic University of Valencia, Spain (e-mail: justo.aznar@ucv.es).

Although various methods are used for this purpose, one of the more widely accepted is emergency contraception.

**Definition**

Emergency contraception can be defined as the use of various drugs or mechanisms to prevent pregnancy after unprotected sexual intercourse. Unprotected sexual intercourse is considered to be intercourse in which no contraceptive method was used or the method used failed.

**Methods used**

Before the development and marketing of ulipristal acetate, various methods had been used for emergency contraception, and in fact are still in use today. The first of these is the Yuzpe method, in which 100 µg of ethinylestradiol and 500 µg of levonorgestrel are administered in two doses, the first as soon as possible after sexual intercourse and the second after 12 hours. The second is called the morning-after pill, in which a first dose of 750 µg of levonorgestrel is administered, likewise as soon as possible after sexual intercourse, followed by a second dose after 12 hours; a single dose of 1500 µg of levonorgestrel is also being used. Mifepristone, danazol and the IUD have been used as well, albeit to a lesser degree, although undoubtedly levonorgestrel administered alone and the so-called morning-after pill are used more often.

The use of ulipristal acetate has recently been approved as an emergency contraceptive, which can be used up to 120 hours after unprotected sexual intercourse; marketing authorisation for its clinical use was granted by the European Medicines Agency (EMEA) on 19 March 2009.

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5 OKEWOLE IA, AROWOJU AO. Single dose of 1.5 mg Levonorgestrel for emergency contraception. Int J Gynaecol Obstet. 2005; 89: 57-64.
Ulipristal acetate, developed by HRA Pharma (UK Limited, Kensal Green, London), contains 30 µg of micronised ulipristal acetate and is distributed under the commercial name of EllaOne.7

Chemical composition and pharmacological action

Ulipristal, 17α-acetoxy-11,-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, also known as CD8-2914, VA-2914, HRP-2000 and RTI-3021-012, is a derivative of 19-norprogesterone, with an 11α-aryl substitution, similar to mifepristone.

From a pharmacological point of view, ulipristal acetate acts as a progesterone receptor antagonist with no agonist activity.8

Clinical efficacy

Clinical efficacy studies on ulipristal acetate have focused on its anticonceptive or interceptive activity, generally comparing it with another emergency contraceptive, as a reference parameter.

To evaluate its clinical efficacy, the pregnancy index or rate is used, understanding as such the ratio between the number of pregnancies observed and the total number of women entered in a particular clinical trial. This index reflects the proportion of pregnancies prevented by the administration of the drug evaluated.

With respect to the clinical efficacy of ulipristal acetate, we con-
sider that there are three well-designed studies on the topic. In the first of these, Creinin et al. conducted a randomised, double-blind, placebo-controlled phase II clinical trial, which included 1672 women aged between 18 and 44 years, giving them 50 µg of non-micronised ulipristal or 750 µg of levonorgestrel, in two doses 12 hours apart, administered between 0 and 72 hours after sexual intercourse.

The results showed that in the group of women treated with CDB-2914 (Ulipristal), the pregnancy rate was 0.9% (95% CI: 0.2%-1.6%) and in the control group (levonorgestrel) was 1.7% (95% CI: 0.8%-2.6%).

In the second study, Glasier et al. used 30 µg of micronised ulipristal acetate in the test group and 1500 µg of levonorgestrel in a single dose in the control group. This study included 1899 women, distributed in two groups of 1696 and 203 women. In the first group, all the subjects received the corresponding drug within 72 hours of unprotected sexual intercourse. Of these, 844 women were included in the ulipristal group and 852 in the levonorgestrel group. The pregnancy rate was 1.8% in the ulipristal group (95% CI: 1.0%-3.0%) and 2.6% (95% CI: 1.7%-3.9%) in the levonorgestrel group. The second group of 203 women were administered the contraceptive pill between 72 and 120 hours after unprotected sexual intercourse. Three pregnancies were detected in this group, all using levonorgestrel. Considering these data overall, i.e. during the period from 0 to 120 hours, the pregnancy rates for ulipristal acetate and levonorgestrel were 1.8% and 2.6%, respectively, although the differences observed were not statistically significant; however, those obtained in the group of women who received the contraceptive between 72 and 120 hours were statistically significant.


10 Creining et al. Progesterone receptor modulator...

The third study, by Fine et al., was a multicentre, non-placebo controlled phase III clinical trial, in which a single dose of 30 µg of micronised ulipristal acetate was administered between 48 and 120 hours after unprotected sexual intercourse to 1533 women, of which 1241 were finally evaluated. The overall pregnancy rate for the whole period of 48 to 120 hours was 2.1% (95% CI: 1.4%-3.1%), having observed 26 pregnancies among 1241 women, which in relation to the 5.5% of pregnancies expected, means an overall preventive efficacy of 62%.

**Side effects**

According to data from a report drawn up by the EMEA, the side effects observed with the use of ulipristal acetate, when 30 µg micronised are administered, are mild or moderate and remit spontaneously. The most common were headache, nausea and abdominal pain, which were experienced by around 10% of users. However, in the study by Glasier et al., which includes the side effects of both ulipristal acetate and levonorgestrel, the percentage of negative side effects were objectively higher than those in the EMEA report, as they detected headache in approximately 19%, dysmenorrhoea and nausea in 17%, fatigue, dizziness and abdominal pain in approximately 5% and back pain in 3%.

**Contraceptive mechanism of action**

The first studies on the contraceptive mechanism of action of ulipristal acetate were conducted using the product known as CDb-
2914. In the first of these,\textsuperscript{16} the drug was administered in the pre-ovulatory phase, when the follicle size ranged between 14 and 16 mm. In all cases there was a delay in ovulation which was greater with the higher doses of the drug, ovulating in this case up to 7 days after its administration. In the luteal phase, it could be seen that it inhibited endometrial maturation.

In 2003, Passaro et al\textsuperscript{17} also evaluated the effect of C\textsubscript{DB}-2914, but in this case administering it on the sixth day of the luteal phase, showing that it caused premature endometrial bleeding, undoubtedly an indicator of a direct effect on the endometrium, an action similar to that produced by mifepristone.

In a third study, in which VA-2914 was used, Mutter et al\textsuperscript{18} found objective modifications in the endometrium which they classed as “PRM-associated endometrial changes”.

Ravet et al,\textsuperscript{19} also after administering low doses of VA-2914 for 12 weeks, performed an endometrial biopsy six or eight days after the LH peak, showing the existence of endometrial atrophy.

Finally, of the studies conducted with pharmacological variants of ulipristal acetate other than EllaOne, the latest by Stratton et al\textsuperscript{20} found that administering the drug one or two days after the LH peak caused a significant reduction in endometrial thickness in the group of women who received the drug compared with the placebo group. They observed endometrial atrophy and persistence of the proliferative endometrium in the luteal phase of the cycle less often, when the highest doses of C\textsubscript{DB}-2914 (100 mg) were used.

\textsuperscript{17} PASSARO MD, PIQUION J. Luteal phase dose-response relationships of the antiprogestin C\textsubscript{DB}-2914 in normally cycling women. Human Reproduction 2003; 18 (9): 1820-1827.
\textsuperscript{18} MUTTER GL, BERGERON C ET AL. The spectrum of endometrial pathology induced by progesterone receptor modulators. Modern pathology 2008; 21: 591-598.
\textsuperscript{20} STRATTON O, LEVENS ED ET AL. Endometrial effects of a single luteal dose of the selective progesterone receptor modulator C\textsubscript{DB}-2914. Fertility and Sterility 2010; 93 (6): 2035-2041.
From all the aforementioned data, it can be concluded that ulipristal acetate, in its CDB-2914 and VA-2914 denominations, has an objective effect on the endometrium of the woman receiving it, which without doubt supports the important role played by the anti-implantation effect in its contraceptive mechanism.

In relation to ulipristal acetate (UPA) in its EllaOne presentation, the five-day morning after pill, we have already specifically referred to the mechanism by which it prevents unwanted pregnancies in one of our previous studies, a paper written using reports from the company which produces the drug (HRA Pharma), the European Medicines Agency and the report written by the United Kingdom Royal College of Obstetricians and Gynaecologists. In said study, it was observed that ulipristal acetate acts by anti-implantation mechanism between 50% and 70% of the time.

Since the publication of our paper to date, we are only aware of three published studies which in some way evaluate the mechanism by which ulipristal acetate prevents unwanted pregnancy.

In the first of these, Glasier et al, already mentioned, referring to the mechanism of action by which levonorgestrel prevents unwanted pregnancies, state that it “acts, quoting Croxatto’s opinion, by interfering with ovulation, although, in their opinion, the inhibition of ovulation occurs in only 50% of menstrual cycles, and is most likely to occur when emergency contraception is given early in the cycle, at a time when risk of conception is low”, which clearly means that if it only acts by an anovulatory mechanism in 50%, in the remaining cases it will have to do so by another mechanism, which cannot be anything but anti-implantation.

Glasier et al, referring specifically to the mechanism of action by which ulipristal acetate prevents unwanted pregnancy, and although this is not the specific aim of their study, state that “although an endometrial anti-implantation effect...
effect, and therefore an additional post-ovulatory mechanism of action cannot be excluded, the dose of ulipristal acetate used in this trial was specifically titrated for emergency contraception on the basis of inhibition of ovulation and might be too low to inhibit implantation”.

All of the above indicates that although ulipristal acetate has an anovulatory effect depending on the dose of the drug and the day on which it is taken after sexual intercourse, the anti-implantation effect cannot be excluded.

In the second of the studies considered, by Fine et al,26 Ulipristal is more effective preventing pregnancies when is used later after the unprotected intercourse, in the 96-120 hours interval. In our study, according with the contraceptive effect of the drug evaluated in the Table 1, the mean overall anovulatory activity, when the drug is taken 72 hours after sexual intercourse, is 12.4%, but if it is taken after 96 hours it is only 1.2%, and if taken after 120 hours is 0%, so that the mean overall anti-implantation effect of ulipristal acetate when taken between 72 and 120 hours after sexual intercourse is 83.7%.

In the third study, the most recent, Brache et al from Croxatto’s group made a more thorough evaluation of the effect of ulipristal acetate, detecting an anovulatory or ovulation-delaying effect which varied according to the day of sexual intercourse with respect to the day of ovulation and the time since sexual intercourse to intake of the drug.

In table 1, the contraceptive effect of the drug is evaluated by looking at two parameters, the day on which the woman has sexual intercourse with respect to the day of ovulation and the time it takes to take the drug after sexual intercourse, observing that, if sexual intercourse takes place 5 days before ovulation and the drug is taken within the following 24 hours, the anovulatory effect, understanding as such the inhibition or delay of ovulation, would be 100%. The same happens if it is taken at 48 hours, but it decreases to 78.6% if taken at 72 hours and to 8.3% if taken at 96 hours. Therefore, the overall anovulatory effect, when sexual intercourse takes place 5 days before ovulation and the drug is taken between 0 and 96 hours afterwards, would be 57.4%.

26 Fine et Al. Ulipristal acetate taken 48-120 hours…
27 Brache V, Cochon L et al. Immediate pre-ovulatory administration of 30 mg. Ulipr-
Following the same reasoning, the overall anovulatory effect when taken up to 48 hours after sexual intercourse would be 37.4%, if it is after 72 hours it is 17.4% and if taken after 96 hours is 1.7%, acting through an anti-implantation effect in all the other cases.

**Final comment**

Undoubtedly, the most interesting ethical aspect to evaluate in relation to the use of ulipristal acetate is to know whether it acts by an anovulatory or anti-implantation mechanism. In the first case, fertilisation would not occur so that no human embryos would have to be destroyed to prevent an unwanted pregnancy. However, if this contraceptive pill acts by an anti-implantation mechanism, it would be achieving its anti-pregnancy objective by destroying the life of a human embryo which has already begun its life course. For this reason, it is fundamental to determine the mechanism of action of ulipristal acetate to make an ethical judgement on its use.

In this ethical debate, we find it interesting to note how, on occasions, it is stated in a categorical, but unfounded manner, that the five-day morning after pill, ulipristal acetate, acts only by impeding ovulation and therefore by an anti-implantation mechanism, which is objectively erroneous.

Equally, some specialists who work in this field, especially Croxatto’s group, show tendencies to highlight the anovulatory activity of the drugs used in emergency contraception, both levonorgestrel and ulipristal acetate, to the detriment of their anti-implantation action. In this respect, it seems interesting to note that in one of their more well-known studies, the paper published in 2004, the authors stated that “levonorgestrel can disrupt the ovulatory process in 93% of the cycles treated when the diameter of the dominant follicle is between 12 and 17 mm”.

However, in their latest study, published in 2010, they specifi-
cally state, on evaluating the mechanism of action of ulipristal acetate, that “current methods of hormonal emergency contraception (EC) are ineffective for preventing follicular rupture when administered in the advanced pre-ovulatory phase. When UPA was given after the LH peak, follicle rupture inhibition was only observed in 1/12 [8.3 %, 95% CI (0.2 – 38.5)] cycles”; in other words, it is sufficient for the follicle to increase from 17 to 18 mm for the contraceptive mechanism to go from being anovulatory in 93% of cases to being anti-implantation.

Furthermore, also in the aforementioned study, it states that, “follicular rupture indeed takes place in most cycles, but later than expected”, which unquestionably could indicate that, in the event of late sexual intercourse, fertilisation could occur, so if it prevented pregnancy in this case, it would always do so by an anti-implantation mechanism.

Moreover, in this study, it is stated that “an intact follicle is still present on the fifth day after UPA administration in almost 60% of women and in none of the placebo”, which means that some authors who are inclined towards defending the anovulatory action of ulipristal acetate as a basis for its interceptive action would be admitting that approximately 43% of the time the action of the drug does not affect ovulation and consequently to prevent an unwanted pregnancy it would have to act by another mechanism, which in our opinion could be none other than by preventing the already created embryo from implanting in its mother.

Summarising the above, we believe that objectively, based on the abovementioned scientific data, there appears to be no doubt that in approximately 60% of cases, ulipristal acetate acts to prevent unwanted pregnancy by a post-fertilisation mechanism, a circumstance that we believe should be taken into account when making an ethical assessment of its use.

30 Ibid.
Evaluation of the contragestive effect of Ulipristal acetate by looking at two parameters, the day on which the woman has sexual intercourse with respect to the day of ovulation and the time it takes to take the drug after sexual intercourse, observing that, if sexual intercourse takes place 5 days before ovulation and the drug is taken within the following 24 hours, the anovulatory effect, understanding as such the inhibition or delay of ovulation, would be 100%. The same happens if it is taken at 48 hours, but it decreases to 78.6% if taken at 72 hours and to 8.3% if taken at 96 hours. Therefore, the overall anovulatory effect, when sexual intercourse takes place 5 days before ovulation and the drug is taken between 0 and 96 hours afterwards, would be 57.4%. Following the same reasoning, the overall anovulatory effect when taken up to 48 hours after sexual intercourse would be 37.4%, if it is after 72 hours it is 17.4% and if taken after 96 hours is 1.7%, acting through an anti-implantation effect in all the other cases.

Note: The text of this table legend is identical to that of paragraph 2 on page 6.

### Table 1

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<thead>
<tr>
<th>DAY</th>
<th>UI*</th>
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</thead>
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</tr>
<tr>
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<tr>
<td>DAY +5</td>
<td>0 0</td>
</tr>
<tr>
<td>OVERALL ANOVULATORY EFFECT (%)</td>
<td>57.4 37.4 17.4 1.7 0 0 0</td>
</tr>
</tbody>
</table>

* (UI: Unprotected intercourse)
RIASSUNTO

Il forte aumento delle gravidanze e degli aborti negli adolescenti sembra giustificare l’adozione di misure per prevenirli. Sebbene la giusta soluzione al problema è senza dubbio l’educazione dei giovani ad un uso corretto della sessualità, e soprattutto in una considerazione di quest’ultima come parte fondamentale di qualcosa di molto più ampio come l’amore umano, alcuni intendono risolvere il problema implementando l’uso della contraccezione d’emergenza come unica misura contraccettiva.

Uno degli ultimi farmaci in commercio per questo scopo è Ulipristal acetato, che ha cominciato ad essere distribuito in alcuni paesi europei dal novembre del 2009.

Questo articolo fa riferimento alla composizione chimica di Ulipristal acetato, la sua efficacia contraccettiva, gli effetti collaterali, che non sono molto significativi, e in particolare al meccanismo d’azione con cui questo farmaco impedisce le gravidanze indesiderate, giungendo alla conclusione che per almeno il 60% del tempo esso agisce secondo un meccanismo anti-impianto, anche se ciò dipende in larga misura dal giorno in cui la donna lo assume entro il suo ciclo riproduttivo, e dal tempo trascorso dal rapporto sessuale.

SUMMARY

Ulipristal acetate. An emergency contraceptive?

The large increase in pregnancies and abortions in adolescents appears to justify taking measures to prevent them. Although the right solution to the problem is undoubtedly through educating young people in the proper use of sexuality, and especially in considering it as a fundamental part of something much wider like human love, certain classes advocate resolving it by implementing the use of emergency contraception as the only contraceptive measure.

One of the latest drugs marketed for this purpose is Ulipristal acetate, which began to be distributed in some European countries in November 2009.

This paper refers to the chemical composition of Ulipristal acetate, its contraceptive efficacy, the side effects, which are not very significant, and
especially to the mechanism of action by which this drug prevents unwanted pregnancies, concluding that at least 60% of the time it acts by an anti-implantation mechanism, although this depends to a large extent on the day on which the woman takes it, within her reproductive cycle, and on the time from sexual intercourse until she takes the drug.