

COMMENT ON THE DECISION OF THE GERMAN BISHOPS REGARDING THE USE OF EMERGENCY CONTRACEPTION IN RAPE VICTIMS*

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Introduction

On 21st February this year, the media echoed a statement made public by the German Episcopal Conference on the approval of the use of hormonal contraception in women who had been raped, with the condition that the methods used would act only by preventing ovulation.

These are the facts. On 31st January 2013, Cardinal Joachim Meisner, archbishop of Cologne, told German newspaper *Kölner Stadt Anzeiger* that “if a medication that hinders conception is used after a rape with the purpose of avoiding fertilisation, then this is acceptable in my view”. This was stated by the Cardinal after, it seems, he had sought the opinion of various experts who told him that the drug did not have anti-implantation, i.e. abortive, action. He also added that this opinion had been issued in accordance with the Congregation for the Doctrine of the Faith and the Pontifical Academy for Life, after having consulted both institutions.

However, in a statement to the Catholic News Agency on 19 February 2013, president of the Pontifical Academy for Life, Monsignor Ignacio Carrasco de Paula, in a text signed by Dr. Gaetano Torlone, said that the Cardinal (referring to Monsignor Joachim Meisner) in his statement simply said that in the care of “women who have been raped, the process is complex and goes beyond the pharmacological aspect”. In this case, said Torlone, “it is licit to use contraceptive drugs, but never to use those that have abortive effects, because it is never licit to murder a human being”. “It appears”, continued Torlone, “the Cardinal was talking about any drug that prevents conception, but not the morning-after pill”.

However, last 21st February, after a three-day meeting of the German Episcopal Conference in Tréveris (Germany), their spokesperson stated that the morning-after pill could be used after a rape, “as long as the drug has a prophylactic (contraceptive) and not an abortive effect”, but that “medical and pharmaceutical methods that induce the death of an embryo may still not be used”. Furthermore, the Assembly of German Bishops reiterated that “at Catholic hospitals women who are victims of rape receive human, medical, psychological and pastoral help as a

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matter of course”, in response to a statement that a young 25-year-old woman had not been given such care in one of them.

Undoubtedly, the reason for the controversy we are discussing has its foundation in the fact that some media have stated that the “morning-after pill” can be used if it acts only by a contraceptive and not anti-implantation mechanism. However, after analysing the mechanisms of action of methods currently used for emergency contraception in the medical literature, it appears very risky to say that any of them can meet the requirements of the German bishops in order for their use to be morally licit in the aforementioned circumstances, since it cannot be assured that they always and exclusively act by a contraceptive mechanism.

Methods used in emergency contraception and their mechanisms of action

The only non-pharmacological method used in emergency contraception is the intrauterine device (IUD), which may or may not contain hormone medication. However, although not unanimous, there is scientific consensus on the principal mechanism of action of this device, which is specifically to alter the uterine lining, so that implantation of the embryo becomes extremely difficult^{1,2}. It can therefore be unreservedly ruled out that this method is purely anovulatory.

Mifepristone

The four pharmacological methods of hormonal emergency contraception currently used are: the Yuzpe method, levonorgestrel, ulipristal acetate and mifepristone (pill RU-486)³.

Mifepristone (or the abortion pill) is used, as well as as an emergency contraceptive, as an abortive method in consolidated pregnancies, i.e. when the embryo has already implanted in the mother’s endometrium. Its mechanism of action excludes it from exclusively anovulatory methods⁴.

Of the three remaining methods, the Yuzpe method is the more obsolete and least effective as a contraceptive. It uses a combination of oestrogens and progesterone in high doses which, depending on the time at which it is used, acts by an either anovulatory or post-fertilisation mechanism, as shown in various published studies^{5,6,7,8,9}.

The appearance some years ago of the so-called Plan B as a method of emergency contraception, based on high-dose levonorgestrel alone (a method known as the post-coital or “morning-after pill”) has almost completely displaced the use of the Yuzpe method, for two main reasons: its better efficacy as a contraceptive and the non-use of oestrogens.

Levonorgestrel

There is no consensus in scientific papers published to date on the mechanism of action of levonorgestrel. Numerous authors have stated that the only mechanism by which this drug prevents pregnancy is its ability to prevent or delay ovulation, although some clarify that this effect only occurs when it is administered early enough before ovulation, and that it is ineffective as an anovulatory agent if it is used immediately before or in the days after this process^{10,11,12,13,14,15,16,17,18,19,20}. Other authors do not hesitate to affirm that levonorgestrel can also have an effect other than anovulatory that may explain its contraceptive efficacy, even when administered at the time of the cycle in which its inability to act as a contraceptive has been demonstrated^{21,22,23,24,25,26,27,28,29,30,31,32,33}.

The indirect proof that its ability to prevent pregnancy by mechanisms other than anovulatory activity is that its contraceptive efficacy is greater than its anovulatory efficacy, which may be achieved by its effect on the endometrium or by altering transport of the zygote along the Fallopian tubes^{34,35,36,37}, making normal implantation of the embryo difficult. All this means that levonorgestrel cannot be considered as a simply anovulatory drug.

In relation to this, it is interesting to note that levonorgestrel, administered in the follicular (pre-ovulatory) phase, does not always seem to be able to prevent ovulation (measured as follicular rupture); although some authors report the total absence of ovulation on evaluating a small sample group³⁸, others have shown that, when administered one or more days beforehand, ovulation can occur in a variable percentage of cases, ranging from 23% in a study by Croxatto and Ortiz (2007)³⁹ to 66% in another more recent study (2010)⁴⁰, curiously by the same author. This requires us to search for a mechanism other than the anovulatory effect to justify the absence of pregnancy after unprotected intercourse. However, some authors refuse to accept that it is the anti-implantation effect that is ultimately responsible for its contraceptive efficacy, stating that it could be due to the interference of the drug in the migration of sperm through the cervical mucus. In this respect, there are several papers which report that levonorgestrel can make sperm migration difficult^{41,42}, although a more recent study refutes that claim⁴³. Even one of the two studies used to justify this possible interference⁴² warns that the effects observed *in vitro* using doses much higher than those used *in vivo* with the administration of levonorgestrel in emergency contraception would not be observable with the concentrations reached by the drug in this case.

There is also another argument that objectively casts doubt on the negative influence of levonorgestrel on sperm motility through the cervical mucus, the viscosity of which would

change, as a reason for its contraceptive efficacy. Indeed, as Wilcox describes in a recently cited study⁴⁴, the highest probability of pregnancy occurs when intercourse takes place on the day of ovulation or on the two preceding days. This means that if the ovum does not survive more than 24 hours after ovulation, this will be the time that the sperm have to fertilise it when intercourse takes place on the day of ovulation itself. Wilcox's data show that sperm, as is known, can reach the Fallopian tubes in effective quantities and fertilise the egg in less than 24 hours⁴⁵. In fact it is in this case, within only 24 hours, when the probability of pregnancy occurring is highest. Therefore, the question arises: how could levonorgestrel, which is always administered several hours after coitus (normally 24) have time to modify the viscosity of the cervical mucus and interfere in sperm transit, if by then they can be found in more than sufficient numbers in the tubes to produce fertilisation? Thus, it does not seem feasible that the effect of the drug on the cervical mucus, making sperm migration difficult, is the main reason for the contraceptive effect.

But does levonorgestrel have an anti-implantation effect only if it is administered in the post-ovulatory (luteal) phase?

Despite the convincing nature of the statements made in some of the studies cited with respect to the absence of anti-implantation activity of levonorgestrel, evidence of its contraceptive efficacy even when it does not inhibit ovulation means that other possibilities must be taken into account. In relation to this, it has been shown that the possible anti-implantation effect of levonorgestrel could occur precisely when it is administered in the follicular (pre-ovulatory) and not in the luteal phase^{46,47}, since when it is administered in the pre-ovulatory period, this would be exactly when the drug would exert the post-fertilisation effect responsible for its anti-implantation activity. Thus, when pre-ovulatory administration does not prevent ovulation, it may interfere in the development of the corpus luteum, and modify subsequent progesterone levels, which would alter the normal development of the complex mechanism that prepares the endometrium for implantation⁴⁸. Therefore, according to the studies discussed^{46,47}, the post-fertilisation effect that interferes with implantation would also be exerted by levonorgestrel when it is administered in the pre-ovulatory phase. Moreover, it is logical to think that the overdose of progesterone at a predominantly oestrogenic time in the cycle (follicular phase) must be much more disruptive to fertility than its administration in the luteal or post-ovulatory phase, when progesterone increases physiologically.

Either way, it seems reasonable to assume that it is together with other mechanisms that levonorgestrel may also have an effect on the endometrium, which has led to this effect being highlighted in the Summary of Product Characteristics (SPC) approved by the Spanish Agency for Medicines and Medical Devices (AEMPS), and to the Food and Drug Administration (FDA), which regulates drug approval in the United States, to also refer to an anti-implantation effect⁵⁰.

Regardless of the above, some authors state that levonorgestrel, in addition to the anovulatory effect, may also act by delaying ovulation^{18,49}. In our opinion, both mechanisms should be separated, since if it delays ovulation, this action could have a negative effect on implantation. Indeed the endometrium undergoes drastic changes during the menstrual cycle and is only prepared for implantation of the embryo for a short period of time^{50,51,53}, a few days after ovulation, so that if ovulation is delayed, it could happen that even if fertilisation occurs, the embryo will fail to reach the uterus at the proper time for implantation, so that the mechanism by which it would make it difficult to achieve an unwanted pregnancy would not be contraceptive, but anti-implantation.

The same interference in the implantation process would occur if we consider that it may alter transport of the zygote through the Fallopian tubes, as this would cause a delay in its arrival in the uterus and subsequent difficulty in implanting properly.

Regardless of the above however, it could be concluded that whether levonorgestrel acts by a contraceptive or anti-implantation mechanism depends to a large degree on the time at which unprotected intercourse takes place and the time of pill ingestion. In our opinion, and as an interpretive summary, we believe that if levonorgestrel is administered from five to three days before ovulation, its action would be preferentially contraceptive, although without excluding the anti-implantation effect; if administered between three days and one day before, its effect would be both contraceptive and anti-implantation, and if administered one day before ovulation to three days afterwards, its effect would be practically anti-implantation. In other words, it can be stated that levonorgestrel, depending on the day on which it is administered after unprotected intercourse, could act as a contraceptive or anti-implantation agent.

Finally, we would like to refer to the claims of some, in the sense that, if transvaginal ultrasound can reliably detect that ovulation has not occurred in a woman about to take levonorgestrel, the drug could be administered to prevent the unwanted pregnancy, since in this case we would have the security that the drug effect would be exclusively anovulatory; however, as specified above, there is no scientific evidence that this is so, since administering

levonorgestrel prior to ovulation may also, when it cannot prevent it, act by an anti-implantation mechanism.

In summary, the use of levonorgestrel as one of the acceptable drugs for the case of rape, based on the fact that it always acts by a contraceptive mechanism, does not have sufficient scientific support for its use to remain free of any ethical objection.

Ulipristal acetate

Finally, the most recently approved molecule for use in emergency contraception is ulipristal acetate, a drug that has advantages over levonorgestrel with respect to its greater contraceptive efficacy and longer period of use after unprotected sexual intercourse, which in this case extends up to 120 hours, unlike levonorgestrel, the efficacy of which falls notably 72 hours after intercourse.

This molecule has chemical similarities with mifepristone, mentioned above, and belongs to the same family of drugs, known as “selective progesterone receptor modulators”. Its mechanism of action consists of blocking these receptors, making it difficult for progesterone to act, both in the pre- and post-ovulatory phase. Unlike mifepristone, it has not yet been demonstrated that ulipristal might interfere with the development of an already implanted embryo.

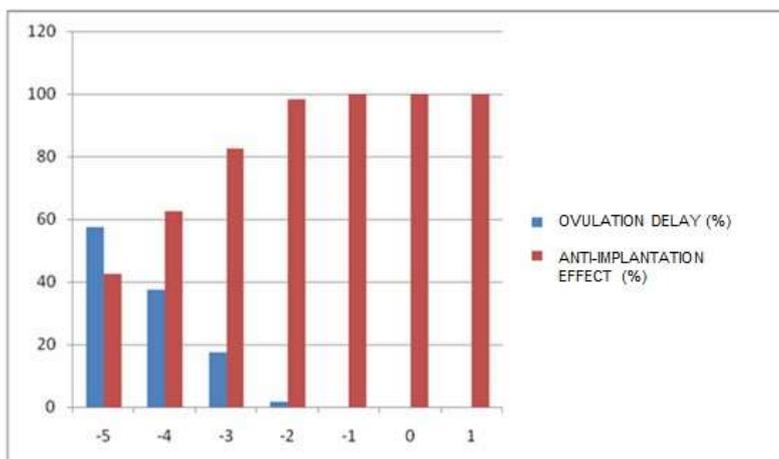
There is sufficient scientific evidence, both today, and at the time of its approval in 2009, about the interference of ulipristal with endometrial development and, therefore, with the implantation process^{52,53}. In fact, when the European Medicines Agency (EMA) approved this drug, among its mechanisms of action it included its ability to interfere with the implantation process of the zygote, as well as its anovulatory action. Surprisingly though, and for reasons that have not been well clarified, in 2011 the EMA amended the aforementioned SPC, deleting all references to its anti-implantation activity, based on some studies that did not change in any way the existing evidence of its undeniable effect on endometrial maturation, its ability to alter the secretory function of the endometrium, the modification of plasma levels of certain hormones and other effects, which would explain that the efficacy of ulipristal as a contraceptive is due to mechanisms of action other than anovulatory effects. Consequently, the anti-implantation mechanism must potentially be the main mechanism of action if all the circumstances in which the drug can be administered are considered, both with respect to the time of ovulation and the time between sexual intercourse and its intake^{54,55}. This activity on

the endometrium explains the drug's high clinical efficacy, even when administered after the luteinising hormone (LH) peak, when it naturally cannot have anovulatory activity.

To support the above, we analysed clinical efficacy data obtained from various trials on ulipristal as a contraceptive (Creinin et al. 2006⁵⁶, Anna F. Glasier et al, 2010⁵⁷, Fine et al. 2010⁵⁸). We were able to relate the data with its proven anovulatory activity, depending on the time at which the drug is taken with respect to ovulation (according to data presented by Brach V. et al.⁵⁹), considering all the possibilities that could occur depending on the day of the sexual cycle on which unprotected intercourse takes place, since as we know, it can be administered up to 120 hours afterwards. In our opinion, this was the first time that the day of the female cycle on which coitus took place and the time since the drug was ingested were analysed together⁶⁰. From this study, we can extract the number of times that ulipristal acetate acts by an anovulatory mechanism, by a mechanism that delays ovulation or by an anti-implantation mechanism (Fig. 2), showing that it can act by both a contraceptive and post-fertilisation mechanism.

Figure 1

The x-axis shows the day of the sexual cycle on which coitus took place; the y-axis shows the percentage efficacy attributable to each of these mechanisms.



Depot gestagens

Some have suggested that certain long-acting injectable contraceptive drugs (depot gestagens), such as Depo-Progevera (which contains 150 milligrams of medroxyprogesterone acetate) and other similar drugs, administered as skin patches, would have an exclusively contraceptive (anovulatory) effect. Thus they could be used to prevent fertilisation without

any moral difficulties when circumstances arise in which there is presumed to be a serious risk of rape of defenceless women, to thus try to prevent the dreaded pregnancy secondary to these brutal acts, since according to the SPC of the AEMPS (Ministry of Health), revised in 2007, Depo-Progevera 150 mg/ml in suspension for injection, when administered at the usual dose, inhibits the secretion of pituitary gonadotropin in the long-term, with subsequent inhibition of follicular maturation and ovulation.

However, if Depo-Progevera were used in emergency contraception for rape cases, the required conditions would not occur for the anovulatory effect to be the only one exerted by the drug, since administered after unprotected intercourse, it has not been shown to always be able to prevent ovulation⁶¹. Therefore, as in the case of other contraceptives analysed in this paper, there would still be the possibility that it could interfere in the implantation process when ovulation occurs, so the same ethical objections would have to be raised as in the previous cases.

Conclusions

The statements by the president of the German Episcopal Conference, Robert Zollitsch, Archbishop of Freiburg, saying that medical advances permit pills to be used that do not cause abortion but that only prevent fertilisation to prevent unwanted pregnancy after having unprotected intercourse, which is what the “morning-after pill” (levonorgestrel) and the “five days after pill” (ulipristal acetate) are used for, do not open the possibility of their use, since according to the scientific evidence to date, there are no drugs that always act by a contraceptive mechanism. That is to say, there will always be some occasion on which their effect is obtained by an anti-implantation, i.e. abortive mechanism, which would morally invalidate its use.

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