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EMERGENCY CONTRACEPTION: WHICH ARE THE AVAILABLE TOOLS?

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SUMMARY

The purpose of emergency contraception (EC) is to prevent unplanned pregnancy when there has been unprotected intercourse. It's a medical strategy that allows birth control, without being a regular method of family planning. Initially was called "morning-after pill", which was an inadequate definition because it's not always a pill, it should not be expected the next morning to use it and can be used several days after intercourse. To identify available tool for EC, a literature review was performed in the PubMed, ScienceDirect, EBSCOhost, OvidSP, Embase (English) and Scielo (Spanish) databases. The application of the intrauterine copper device, within the first five days after intercourse, is the most efficient way to perform EC. Similarly, ulipristal acetate is the best way for hormonal EC. The effectiveness rates of levonorgestrel-only pills and those of ethinyl estradiol combined with levonorgestrel (Yuzpe's method) are important, statistically significant and accepted for EC, remembering that dose and timing should be respected when administered. Mifepristone 10 mg, single dose, is approved in Russia, China, Vietnam and Armenia, as EC. Health professionals should advance high quality contraceptive counseling, to offer as plan B any of the above tools to administer EC. Governments should be concerned about the permanent availability of EC. The prescription of EC should be accompanied by sufficient instructions for women to initiate a regular method of birth control.

KEYWORDS: Contraception postcoital; Contraceptive agents; Intrauterine devices; Contraceptives oral hormonal; Contraceptives postcoital hormonal.

INTRODUCTION

Emergency contraception (EC) or postcoital contraception, which was previously erroneously referred to as the "morning after pill", only has valid foundations from the scientific point of view, when it is framed in preventing pregnancy when there have already been unprotected sexual intercourse but before implantation.[1] It is the second chance or plan B for family planning, without it being one of the regular methods.[2] The main reason for EC is the prevention; it is an effective strategy to prevent unwanted pregnancy, induced abortion, especially those performed under risk conditions, therefore, reduce maternal morbidity and mortality.[3]

EC is an effective family planning strategy that does not interrupt established gestation, if gestation is considered from the beginning of embryonic implantation, as defined by the American College of Obstetricians and Gynecologist (ACOG). ACOG also maintains in its bulletins that there is confusion between medications that induce abortions, which are used to terminate pregnancy, and EC. EC is done with preparations that are only effective if they are administered before embryo implantation is established.[4,5] EC is ineffective once the implantation of the fertilized egg has taken place. Although the mechanisms of action are increasingly clear and it is emphasized that its main effect is before implantation,[5] there are strong currents that consider it as an abortive strategy, which is why it is usually regarded with distrust or rejection.

In spite of the availability and knowledge of the diverse and effective regular contraceptive methods, the use of them is usually less than expected and some pregnancies, if not many, are not planned. These pregnancies may carry a higher risk of morbidity and mortality, especially

if they are resolved by resorting to abortion and if they are also practiced under risk conditions.[6] The World Health Organization has estimated that every year unplanned, unwanted or unintended pregnancies lead to more than twenty-two million induced abortions and cause the death of more than eighty thousand women.[6] Langer.[7] analyzed the adverse impact that unplanned pregnancy has on the health and society of Latin America and the Caribbean. Offering and facilitating the use of EC can help reduce those unwanted pregnancies, preventing unsafe abortion, which negatively affect the health in general and especially the sexual and reproductive health of women, especially those that are very young or old enough to carry out a pregnancy.[3] The objective of this narrative review, was to identify the available tools and their effectiveness in performing AE.

METHODOLOGY

Bibliographic research with review of clinical, epidemiological studies, systematic reviews, consensus, expert meetings, meta-analysis, books, guides and protocols, in English and Spanish. Type of participants: articles published on POP. Research strategy: electronic search was carried out in PubMed, ScienceDirect, EBSCOhost, OvidSP, Embase (English) and Scielo databases (Spanish), between 2000 and 2018. A total of 818 titles were identified, 313 (38.2%) were repeated, therefore they were chosen 505. The summaries of all of them were obtained and two rounds of reading were carried out, 143 (28.3%) had content that was subjectively considered not to fit the objective of the review and was discarded, for that reason 362 abstracts were taken into consideration. From them, the purchase of the articles in full text was made, obtaining 197 (54.4%). They were reviewed and without advancing qualification or measurement of the quality of the documents, 31 (15.7%) were discarded because they did not have enough information about AE, consequently 166 documents were selected. Over the snowball methodology, seven other complete articles were chosen and through the Google Scholar electronic alert system from January to December 2018, with the term "emergency contraception", another three were obtained. The review was carried out in 176 documents. The relevant contents were hosted in a data table specially created in Microsoft Excel. The most representative texts were included in the list of bibliographic references.

GENERALITIES

The basic indications of EC are: (a) incorrect use of a regular planning method or mishap during its application, (b) unprotected intercourse when pregnancy is not desired, (c) victim of sexual abuse or assault.[1]

In the general population, knowledge about EC is usually limited. According to the National Survey of Demography and Health of Colombia (ENDS-2015) [8], 73.1% of women of childbearing age, regardless of their social status, know about the existence of EC. In turn, the method is known by 69.9% of married or in union women, 88.3% of unmarried women with sexual experience and recent sexual activity; for 61.8% of women who have never had sexual relations and for 77.9% of those currently united who reside in urban areas, while only 45.6% of residents in rural areas know it. EC is known for 42.9% of young women aged 13-14 years and 75.2% of adolescent girls (15-19 years old).

In fact, since ancient times different communities have practiced EC; here are stories about the use of crocodile manure or rabbit fat plasters, mixtures of roots, herbs and vinegar, placed in the vagina to prevent pregnancy after intercourse. Dance, jumping and sneezing were also recommended to expel sperm after unprotected sex. In 1960, comments were made on the use of Coca-Cola in postcoital showers.[2] All these empirical actions are completely invalid in the light of current knowledge; today, various hormonal and non-hormonal measures are available to effectively perform contraception when it is desired to prevent pregnancy after unprotected intercourse.[9]

As noted, it is not appropriate to call the EC as the "morning after pill" or "the next day pill", as it moves away from the true concept and form of administration.[3] It is not for the next morning, because you do not necessarily, have to wait until the next day to start it. In fact, the right time to use it goes beyond the next morning, it can be administered in the first 72 or 120 hours after unprotected intercourse, depending on the scheme to be used.[10] In addition, it may not be a single pill, in some countries there are specific packages of EC that are composed of two or four tablets. In some circumstances it may still be valid to obtain a certain number of tablets from a traditional package of combined oral contraceptives or from only-progestin's ones. EC should not be framed in the concept of a contraceptive pill or tablet, since it may not be hormonal, e.g. the intrauterine copper device (IUD-Cu) applied in the first five days after an unprotected coital relationship offers high efficacy, with the advantage of immediately becoming a regular use planning method.[4,5,9]

The hormonal type EC began in the mid-1970s, when family planning pioneer Arie Haspels was the first to administer high doses of postcoital estrogens to a thirteen-year-old girl who was victim of sexual abuse in Germany. Thus emerged the first regimen of steroid hormone use to prevent an unwanted pregnancy.[9] In the early 1970s, diethylstilbestrol was recommended at high doses, 25 mg twice daily for 15 days, initiated in the first three days after unprotected intercourse. It was soon noted that this compound was related to vaginal adenosis and adenocarcinoma of the vagina in the daughters of women who had used it, which led to the search for other estrogens that had no teratogenic or oncogenic effect. Since then, diethylstilbestrol hasn't been used as a therapeutic tool.[11]

Ethyllestradiol Plus Levonorgestrel: In 1974, the Canadian physician Albert Yuzpe.[9,12,13,14] proposed the scheme that is now identified as the "Yuzpe method", in which two tablets of combined oral contraceptives of macrodosis are administered (50 µg ethinylestradiol plus 250 µg levonorgestrel) before the first 72 hours of unprotected intercourse, then the dose is repeated twelve hours later.[15] In 1994 the Yuzpe method was supported by the IPPF and in 1995 it was recommended by the World Health Organization.[9]

Since 1997 the FDA of the United States studied the administration of combined oral contraceptives according to the Yuzpe method for EC. In a 1998 press release the FDA announced that they approved the introduction of Yuzpe's method for EC.[9] The Gynétics Company launched the first presentation of oral contraceptives combined with four tablets under the name of Preven®, the first FDA-approved product to prevent pregnancy, administered within 72 hours after intercourse.[15] It was estimated that almost 50 percent of abortions and unwanted pregnancies could be avoided if women had access to EC. The pharmaceutical presentation was called Emergency Contraceptive Kit, consisting of four blue pills, each containing a fully synthetic progestin, levonorgestrel 0.25 mg (18,19-Dinorpregn-4-en-20-yn-3-one, 13-Ethyl -17-hydroxy -, (17a) - (-) plus 0.05 mg ethinyl estradiol (19-Nor-17a-pregna-1,3,5, (10) -trien-20-yne3,17-diol) and a Pregnancy Test to perform in urine before starting the intake of tablets, which used monoclonal antibodies and detected chorionic gonadotropin with sensitivity of 20-25 mIU / ml.[16]

Soon in many countries, especially in Western Europe, commercial presentations specific to EC with four pills began to be available, each with 50 µg of ethinyl estradiol plus 250 µg of levonorgestrel: two initial tablets and two at twelve o'clock. It is considered a safe, economical and accessible method.[15]

In those places where the specific presentation is not available, as in most Latin American countries, the necessary tablets for each dose can be taken from the conventional package of combined oral contraceptives containing ethinylestradiol plus levonorgestrel. If they are macrodosis (50 µg of ethinylestradiol plus 250 µg of levonorgestrel), two initial tablets will be administered and two at twelve hours. If they are microdosed (30 µg of ethinylestradiol plus 150 µg of levonorgestrel) four tablets and another four will be given at twelve hours. If they are low-dose oral contraceptives (20 µg of ethinyl estradiol plus 100 µg of levonorgestrel) it will be five initial tablets and another five at twelve hours. You should always start taking the tablets in the first 72 hours after intercourse.

Yuzpe's method completely replaced the use of diethylstilbestrol to prevent pregnancies after intercourse.[9] It has not been proven whether other combined oral contraceptives that include other progestins can be used in EC.

Croxatto et al.[17] demonstrated that the estrogen / progestin EC combination can inhibit or delay ovulation, as it is the main mechanism of action to explain the high effectiveness when it is used in the first half of the cycle. It has also been noted that biochemical and histological alterations occur in the endometrium, which alter endometrial receptivity for implantation processes.[3,5] Potential mechanisms of action have been described as: the interference in the function of the corpus luteum, the thickening of the cervical mucus that prevents the sperm from rising, the alterations in the tubal transport of the gametes and the direct inhibition of fertilization. The high efficacy of the Yuzpe method suggests the presence of several mechanisms of action that act simultaneously.[3]

It is important to emphasize that, as is the case with all the methods that are part of hormonal contraception, it is essential that the administration be carried out correctly to preserve efficacy. If the woman has vomiting within three hours from the moment she took the first or second dose of the pills, metoclopramide should be prescribed and thirty minutes later, the patient should take a new intake.[18] To replace the oral route in cases of persistent vomiting, it was suggested to place all tablets vaginally in a single dose. Kives et al.[18] when looking at the relative bioavailability of estrogen and progestin present in the Yuzpe method administered vaginally, they indicated having observed that the maximum concentration was lower and the maximum concentration time was later than when using the oral route; they suggest that at least three times the recommended oral dose may be necessary when using the vaginal route. The alternative did not have enough echo and no other studies are known.

Menstrual bleeding usually occurs on the expected date or before, if menstrual delay occurs, the existence of pregnancy should be identified. When prescribing EC, counseling should be done to raise awareness and motivate women about the need to initiate a regular method of birth control. In all circumstances for the rest of the cycle a barrier method should be used when having new intercourse.[1]

Ho,[19] stated that Yuzpe's method can prevent more than 74% of possible pregnancies, but the presence of adverse effects, especially gastrointestinal, is high. 46% of women have nausea, 22% vomit, 23% vertigo, 20% breast tension and headache is common.[18] These effects generally do not take more than 24 hours. Trussell et al.[3] also noted that Yuzpe's method reduces the risk of pregnancy by 75%, they point out that if one hundred women have unprotected intercourse during the second or third week of the cycle, eight will remain in gestation. If they use the Yuzpe method, the pregnancies will be two, estimating 2% as the failure rate. Other authors.[1,20]

also share the decrease: 75.4% [95%CI: 65.5%-82.4%], which means that the risk of pregnancy is reduced four times.

It has been noted that effectiveness declines significantly with the increase in time between intercourse and the onset of EC. However, it does not seem biologically plausible that the efficacy reaches zero within 72 hours after intercourse, so it was proposed to consider the application up to 120 hours after being necessary.[20] This proposal has no presence in any of the prescription guidelines.[1]

The Yuzpe method is safe, even in women who cannot regularly take oral contraceptives. Although the concentration of estrogen and progestin is high, since the administration time is very short, it can be used without any fear even in women with active cardiovascular pathology. The World Health Organization asserts that the only contraindication to use pills in the emergency contraception scheme is the existence of pregnancy.[3,21] If the method fails, no deleterious effect on organogenesis or on neonatal considerations is demonstrated.[3] The Yuzpe method was the frontline strategy for many years. Since the beginning of the 21st century it has given way to other schemes that offer some advantages, however there are no reasons to abandon it completely. Its prescription should be among the options to recommend when the woman had unprotected intercourse and does not plan to become pregnant, especially if other tools are not available.[1]

Table 1: Hormonal Methods to Perform Emergency Anticonception.

Components	Method	Dose	Presentation	Prescription
Combined oral contraceptives: ethinylestradiol (EE) and levonorgestrel (LNG)	Yuzpe's method	EE 100 µg +LNG 500 µg	Boxes with four tablets EE 50 µg + LNG 250 µg	Two tablets every 12 hours
		EE 100 µg +LNG 500 µg	Macrodosis tablets EE 50 µg + LNG 250 µg	Two tablets every 12 hours
		EE 120 µg +LNG 600 µg	Macrodosis tablets EE30 µg +LNG 150 µg	Four tablets every 12 hours
		EE 100 µg + LNG 500 µg	Low dose tablets EE 20 µg + LNG 100 µg	Five tablets every 12 hours
Levonorgestrel (LNG)	Only Levonorgestrel	LNG 1.5 mg	Boxes with two tablets LNG 0.75 mg	Two tablet single dose
		LNG 1.5 mg		One tablets every 12 hours
		LNG 1.5 mg	Boxes with one tablets LNG 1.5 mg	One tablet single dose
Selective progesterone receptor modulators (SPRMs)	Ulipristal Acetate	Ulipristal 30 mg	Boxes with one tablets Ulipristal 30 mg	One tablet single dose
	Mifepristone	Mifepristone 10 mg	Boxes with one tablets Mifepristone 10 mg	One tablet single dose

Table 2: Risk of Pregnancy With Different Emergency Anticoncept Methods.

Days from unprotected intercourse	<1	2	3	4	s	6	7
Method	**Pregnancy risk (%)**						
Yuzpe	3.2	3.2	3.2	>3.2	>3.2	NA	NA
Levonorgestrel	2.3	1.6	1.6	2.B	3.0	NA	NA
Ulipristal	0.9	2.2	2.2	0*	0*	NA	NA
Copper IUD (DJU-Cu)	0.01	0.(1) 1	0.01	0.01	0.01	0.01	0.01

Table 3: Effectiveness of Ulipristal Against Levonorgestrel.

Hours from intercourse without protection	Ulipristal	Levonorgestrel	OR (95%IC)	p
	Pregnancies, n/N (%)			
0-24 hours	5/584 (0.9)	15/600 (2.5)	0.35 [0.11-0.93)	0.035
0-72 hours	22/1617 (1.4)	35/1625 (2.2)	0.58 (0.33-0.99)	0.046
0-120 hours	22/1714 (1.3)	38/1731(2.2)	0.55 [0.32-0.93)	0.025

Table 4: Eligibility Criteria For Emergency Contraception.

Hormonal contraception					
Conditions		**Yuzpe**	**LNG**	**Ulipristal**	**Comment**
Pregnancy		NA	NA	NA	It should not be used in pregnancy evident or suspected because it is not effective. No risk to pregnancy if administered by accident
Lactation		1	1	2	Does not affect the quality or quantity of breast milk
Ectopic History		1	1	1	Does not increase the risk of ectopic
Obesity		1	1	1	May be less effective in women with BMI greater than30 kg / m^2. No conclusive data
History of cardiovascular pathology. Stroke \ vascular or other thrombotic or embolic disorders		2	2	2	They do not generate clinical impact on any of the alterations indicated
History of myocardial infarction		2	2	2	
Episodes of coronary angina		2	2	2	
Migraine		2	2	2	No clinical impact
Liver disease, even with jaundice		2	2	2	Does not change the course of the entity
Rheumatoid arthritis under immunosuppressive therapy		1	1	1	Does not affect the entity or medication
Rheumatoid arthritis without immunosuppressive therapy		1	1	1	Does not affect the entity or medication
Inflammatory bowel disease Ulcerative colitis or Crohn's disease		1	1	1	Does not impact the indicated entities
Solid organ transplant carrier, with or without acute or chronic complications (tissue rejection, vasculopathy)		1	1	1	Pregnancy may be associated with severe adverse events that may deteriorate health
Risk condition for HIV		1	1	1	Use latex condom for prevention
Use of drugs or inducers of CYP3A 4 (examples: rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, phosphenytoin, nervirapine, primidone, rifabutin)		1	1	1	Potentially strong inducers of) cYP3A 4 could reduce the effectiveness of emergency contraceptives. However, it can be administered
Repeated use of emergency contraception		1	1	1	It must be discouraged. Suggest contraceptive counseling. Prescribe regular method
Sexual abuse		1	1	1	
Installation of IUD Cu					
Pregnancy		NA	Do not place when pregnancy is suspected or demonstrated. Application in pregnant women can lead to serum pelvic infection or septic abortion.		
Sexual abuse	High risk of sexually transmitted disease	3	Accompany antibiotic therapy and appropriate counseling		
	low risk of sexually transmitted disease	1			

Only Levonorgestrel: Fundamentally to avoid the nausea and vomiting that occur with the combined oral contraceptives that are administered as EC, the administration of high doses of progestin was studied. Levonorgestrel, a levorotatory enantiomer of the norgestrel racemic mixture (a progestin derived from 19-nortestosterone), was chosen. 0.75 mg of levonorgestrel was evaluated in the first 72 hours after unprotected intercourse, with a second dose at twelve hours.[3] From its initial studies it was observed that it was more effective and better tolerated than the Yuzpe method.[15]

The levonorgestrel-only scheme was approved by the FDA in July 1999, and specific presentations of EC made of two tablets that contains 0.75 mg of levonorgestrel immediately appeared worldwide. Later and to ensure adequate adherence, 1.5 mg of levonorgestrel was included in a tablet to be administered in a single dose. It based on a multicenter study conducted by the World Health Organization,[22] in which it was observed that there is no significant difference in the efficacy of both presentations, one dose had a 82% prevention fraction (95%CI: 70.9-88.7) and two doses 77% (95%CI: 64.9-85.4), RR: 0.83 (95%CI: 0.46-1.50), therefore they recommended that a 1.5 mg tablet could replace the two doses of 0.75 mg. The two presentations are currently in force, are equivalent in terms of adverse effects, tolerance and are present in almost all countries. Also in another study, eleven pregnancies (1%) were reported in 1118 participating women, seven in the two-dose group and four in the single dose. The relative risk of pregnancy in the two groups was similar, the effectiveness for two doses was 86.8%, statistically lower than the single dose of 92.2%, $p<0.05$; the authors conclude that both administration schemes are effective and safe anyway.[23]

Overall, EC with levonorgestrel reduces the risk of pregnancy by 88%,[23] when one hundred women have unprotected intercourse and do not use EC, eight pregnancies can be expected. If one hundred women have unprotected intercourse and use EC with levonorgestrel, a pregnancy could be expected, that is, an eight-fold reduction in risk. Seven out of eight women who became pregnant would have avoided it if they had used EC with levonorgestrel. In addition, the incidence of nausea and vomiting was 50 and 70% lower than expected with the Yuzpe method.[15]

In cases of persistent vomiting, you can order the two tablets in a single dose. Kives et al.[18] studied the bioavailability of levonorgestrel administered vaginally and indicated that the maximum concentration is lower and the maximum concentration time is later, as observed with combined pills. They suggest that three times the recommended oral dose would be the vaginal dose. No pronouncements are known regarding this recommendation.

Administration as early as possible after intercourse, before 72 hours, can inhibit or delay ovulation or interfere with sperm migration.[3] Only levonorgestrel EC works by preventing ovulation by modifying the functioning of the hypothalamus-pituitary-ovarian axis. It is possible that it prevents the fertilization of the ovule by a deleterious effect on the cervical mucus, limiting the spermatic ascent through the cervical canal. It does not affect endometrial receptivity, implantation and is not abortive. The best available evidence suggests that its ability to prevent pregnancy is not related to post-fertilization events. It does not produce an alteration in pregnancy if the tablets are taken after implantation.[1] There are no studies with other progestins for EC purposes.

Recently, the FDA has spoken on the effectiveness of EC with levonorgestrel in women who weigh more than 165 pounds or have a body mass index greater than 25 kg / m2. He noted that the data is contradictory and limited to reach a definitive conclusion on whether effectiveness is reduced in this group and did not consider making modifications. All women, regardless of weight, can use EC with levonorgestrel to prevent an unplanned pregnancy after having unprotected sexual intercourse or failure to use a regular method. Additionally, it indicates that the most important factor that affects the efficacy of EC is the delay in its onset.[24] For more than ten years, levonorgestrel has been the first choice for AS, with equal or greater effectiveness than the Yuzpe method and lower incidence of nausea or vomiting.[3] While it is giving way to another molecule, it is not sufficient reason to stop considering its prescription.

Ulipristal Acetate: As with the initial investigations of EC with levonorgestrel, the World Health Organization was the pioneer in studying the Selective Modulators of Progesterone Receptor (SPRM) to develop EC.[1,15] Ulipristal acetate is product of these studies, which in doses of 30 mg has shown to be a good alternative and for the present is the first hormonal option to perform EC, due to its greater efficacy and similar safety to levonorgestrel. It can be administered up to 120 hours after unprotected intercourse, which provides an advantage over the method of Yuzpe and levonorgestrel.[15,25]

In 2009, its commercialization began in Europe, after approval by the European Medicines Agency [EMEA], the following year it was approved by the FDA of the United States and was gradually introduced in many countries.[26,27] It comes in cases with a 30 mg tablet. Ulipristal acetate is also called CBD-2914 or VA-2914, by its research codes. It corresponds to the chemical name 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione and formula: $C_{30}H_{37}NO_4$. It has progestogenic or antiprogestagenic action according to white tissue; its future is promising in long-term contraception, management of endometriosis,

uterine myomatosis, uterine hemorrhages secondary to myomas and in the prevention of breast cancer.[28]

Ulipristal acetate is derived from 19-norprogesterone with improved specificity for the progesterone receptor. Ulipristal acetate is derived from 19-norprogesterone, with improved specificity for the progesterone receptor. Studies indicate that it binds to the progesterone, glucocorticoid and androgen receptors, approximately six times more than the affinity of endogenous ligands. Ulipristal has important antiglucocorticoid and antiandrogenic activity in vivo. It exerts antiovulatory effect on the gonadotropic axis, without repression of gonadotropin secretion, when it is continuously administered at 5 and 10 mg / day. In animals the drug has rapid and almost complete absorption in the intestine, there is a delay in absorption when ingested with food although it is unknown if it is clinically relevant. It is metabolized in the liver, probably by CYP3A4, CYP1A2 and CYP2D6: its two main metabolites are pharmacologically active although to a lesser extent and are excreted in feces.[23,28,29,30,31,32]

Ulipristal as EC is administered in a single dose of 30 mg as soon as possible after unprotected intercourse or in the event of a failure to use the regular method. If vomiting occurs within the first three hours after taking the medication, another pill should be taken. Breastfeeding is not recommended within 36 hours after taking the drug since it is not known whether the drug or its metabolites are excreted in breast milk.[15,33] Common adverse effects include nausea, vomiting, abdominal pain, menstrual abnormalities and headache.[1,34,35]

Several studies.[33,34,36] have shown that the main mechanism of action of ulipristal acetate as EC is to inhibit ovulation.[15] When administered in the follicular phase of the menstrual cycle, and the follicles are between 14-16 mm, it causes delayed dose-dependent follicular rupture.[36] If the size of the follicle is equal to or greater than 18 mm, the follicular rupture fails in 59% of the cycles. Ovulation blockage or delay occurs in one hundred percent of women with very low levels of LH and in 79% of women with adequate levels of LH for the follicular growth phase. Ovulation blockage never occurs when the LH peak has been reached.[33]

Compared with levonorgestrel there are significant differences. Croxatto et al.,[35] since 2004, showed that when the follicle is between 18-20 mm, ovulation is prevented by levonorgestrel in 12%, similar what the placebo offers, which is 13%.Brache et al.[34] noted that if the surge in LH is on the rise, is prevented 79% of ovulation with ulipristal, 14% with levonorgestrel and 10% with placebo. This corroborates what has been pointed out by other authors,[37] who point out that ulipristal is effective even if it is administered in a short time before ovulation when LH is rising, at which point levonorgestrel is not effective. The ability to inhibit ovulation at that late follicular stage, prior to ovulation, is interesting, since the probability of conception is high. Ulipristal has particular properties: when progesterone levels are low it acts as an agonist, but when they are high it behaves as an antagonist, blocking the rise of LH and therefore the ovulatory peak. It is considered that in the prevention of ovulation it possibly acts by repressing the expression of genes dependent on the progesterone receptor, which are critical for ovulation.[15] A possible direct inhibitory effect on follicular rupture has also been indicated, so it is effective even when administered shortly before ovulation. When the LH reaches its peak, the follicle becomes insensitive to the action of the ulipristal, therefore, its main action occurs in the first half of the menstrual cycle. However, effects on other tissues of the reproductive system have been reported.[1,15,38,39]

Two recent studies have evaluated the action of ulipristal on the fallopian tubes.[38,39] In one of them it is pointed out that the ulipristal inhibits the frequency of cilia movement and the contraction of the musculature of the tube, affecting tubal function, without an increase in the ectopic pregnancy rate.[15,38] In the other, it is indicated that ulipristal downregulates the expression of the estrogen and progesterone receptor in the tube, unlike what progesterone does.[39] The posovulatory effects of ulipristal in relation to endometrial tissue have been studied, and mechanisms that contribute to explain the high efficacy have been determined. Stratton et al.[32] and Mozzanega et al.[31] demonstrated that dose-dependent reduction of endometrial thickness is caused and significant delay in maturation when administered in the early luteal phase.

The effects on sperm are also favorable. Suppression of the acrosomic reaction induced by progesterone, hyperactivation and calcium concentration in the sperm has been observed, for this reason it is an antagonist of the sperm functions that progesterone activates; unlike what was observed in vivo and in vitro with levonorgestrel, which does not affect sperm function in doses of EC.[15] No adverse effect was found in embryo implantation. Berger et al.[30] in 2015, studied human implantation in an in vitro endometrial model and pointed out that there is no significant difference in embryo fixation when administering ulipristal compared to controls, nor degenerative changes. This suggests that the level of genes of several factors that are considered important for embryonic implantation remained unchanged under exposure to ulipristal. In the study by Levy et al.,[40] which had more than one million women, 376 gestations were observed, in 232 of them the evolution of pregnancy was known: 28 normal infants, 34 spontaneous abortions, 151 induced abortions, 4 ectopics and 15 were still ongoing. The abortion and ectopic pregnancy rate did not increase, it was similar to that observed in the general population.

Mifepristone (RU-486): In addition to the three hormonal methods already indicated that are widely

available worldwide, mifepristone, a fourth hormonal compound, is approved only in Russia, China, Vietnam and Armenia, to administer as EC, in medium / low dose, usually of 10 mg.[15.41] While ulipristal acetate and levonorgestrel (formerly Yuzpe's method) are the EC to be referenced in America and Western Europe, mifepristone is in China and Russia.

This substance is a synthetic steroidal compound with antiprogestagenic and antiglucocorticoid properties, a progesterone receptor antagonist, also known as RU486 for its research code. Its chemical structure is 11β- [p-(Dimethylamino) phenyl] -17β-hydroxy-17- (1-propynyl) estra-4,9-dien-3-one and the formula: C29H35NO2. It was developed in 1980 by Jean Georges Teutsch, Germain Costerousse, Daniel Philibert, Roger Deraedt and Etienne-Emile Baulieu in France and patented a year later, it is registered in the United States (1983) and in Europe (1985).[41] It has been used in high doses as an abortifacient because of its antiprogestagenic effect. In several countries its administration is approved until the ninth week of gestation, in combination with misoprostol for the voluntary termination of pregnancy. The presentation includes tablets with 200 mg of mifepristone or the kit with the doses established in the protocol to interrupt pregnancy. The dose used as an abortifacient is up to sixty times that indicated for EC, according to the World Health Organization, which has it included in its list of essential medicines.[42]

In EC, the single dose of mifepristone is 10 mg; administered in follicular phase causes inhibition of follicular growth and retards ovulation three or four days.[22,43,44] Mifepristone is as effective as 1.5 mg of levonorgestrel, given in one or two doses. Altering endometrial maturity and receptivity and / or tubal functioning should contribute to the contraceptive efficacy of mifepristone,[43] although other authors,[44] noted that it does not affect endometrial markers such as cyclooxygenase (COX-1 and COX-2), the progesterone receptor, the integrins α4 and β3 and neither the levels of estrone and pregnandiol. With mifepristone there is a significant reduction in progesterone production, simulating the unbroken luteinized follicle situation. It is not clear how extent previous statement can modify the implementation process.

In a study of 1359 women who received 10 mg of mifepristone, 21 pregnancies (1.5%) occurred for a prevention fraction of 81% (95%CI: 69.2-87.8). They were compared with 2712 women who received 1.5 mg of levonorgestrel, one or two doses, in which 44 pregnancies (1.6%) were presented for an 80% prevention fraction (95%CI: 71.2-85.6), RR: 1.05 (95%CI: 0.63-1.76), non-significant difference,[22] therefore it is accepted that mifepristone and levonorgestrel, in the indicated doses, do not differ in their preventive efficacy when used in EC. In a meta-analysis of twelve clinical trials in which mifepristone 10 mg was used in 10,989 women, the pregnancy rate was 1.7% (95%CI: 1.3%-2.2%), for a pregnancy prevention estimate of 83.4%.[45] Mifepristone increases the options of hormonal EC and can be administered in low doses with few adverse effects.[43]

Gemzell-Danielsson and Marions,[46] who agree with the above, presented a comprehensive evaluation of the mechanism of action of mifepristone and levonorgestrel in terms of effect on transport and sperm function, follicular development, oocyte maturation and fertilization, environment and function tubal, endometrial development and corpus luteum. Both medicines are considered in the doses announced as effective, convenient and safe, which act mainly in the inhibition or delay of ovulation without acting after implantation. However, in 2016, Boggavarapu et al.[47] studied embryo implantation processes in a three-dimensional in vitro model under the effect of low doses of mifepristone and concluded that during the endometrial receptive period the drug prevents implantation of human embryos and the effect is dose dependent.

Apparently the commercial presentation of 10 mg mifepristone is not available in the Western Hemisphere. Aspects referring to its use as abortion, other obstetric indications (softening and dilation of the cervix before cervical dilation, termination of pregnancy between 13-24 weeks of gestation or induction of labor due to fetal death) or in fetal death or treatment schemes for brain tumors, fibroids or endometriosis will not be considered in this chapter.[41]

The table 1 presents practical aspects for the prescription of hormonal methods of EC. As noted, the Yuzpe method is less effective and has more adverse effects than levonorgestrel and ulipristal, it is for this reason that the Canadian Contraception Guidelines indicate that it is recommended only when the other hormonal methods of EC are not available.[1]

Intrauterine Copper Device: The application of the intrauterine copper device (IUD-Cu) is a non-hormonal strategy to perform EC. It can be placed in the first five days after an unprotected intercourse and grants more than 90% efficiency; it is the most effective form of EC.[23] It was a proposal pointed out since 1976 and has the advantage of leaving a regular method for family planning that can continue for ten years, so it offers contraception for a long time and very low cost.[1] However, its usefulness may be limited in the following situations: nulliparous, very young women, high risk for sexually transmitted diseases or with factors for pelvic inflammatory disease.[3] Currently the levonorgestrel releasing intrauterine device is not recommended or approved for use as EC.[1]

In a systematic review of 35 years of experience with IUD-Cu conducted in 42 studies in six countries, between 1979 and 2011, using eight different models in 7034 women. It was observed that the overall pregnancy

rate was 0.09% (95%CI: 0.04%-0.19%), with an interval between unprotected intercourse and insertion from two to ten days, but most before five days.[48] An analysis in only women to whom T-380A was applied, the presence of pregnancy was not observed, regardless of whether there were less or more than five days between the estimated date of ovulation and the day of insertion.[49] The effectiveness of DIU-Cu is not yet confirmed if it is inserted beyond five days from the date of unprotected intercourse or from ovulation, so it is not recommended.[1] When the IUD-Cu is inserted in term of EC, the woman should have menstrual bleeding within the next 21 days and should be evaluated four to six weeks later to see that it has not been expelled.

The IUD-Cu induces an inflammatory reaction in the uterine cavity. Copper ions and inflammation products are toxic to sperm and oocytes, and increase the muscular activity of the fallopian tubes and myometrium. Copper can alter cytokines and integrins of the endometrial bed by inhibiting implantation in the event of the arrival of the blastocyst into the uterine cavity. Studies rarely shows elevated levels of chorionic gonadotropin or other early pregnancy factors in users of IUD-Cu.[1,50]

ELIGIBILITY CRITERIA AND OTHER CONSIDERATIONS

The table 2 presents the percentage pregnancy risks of the different EC methods according to the number of days since unprotected intercourse. It is observed that the method with the lowest failure rate is the IUD-Cu, followed by the ulipristal. The table 3 compares the effectiveness of ulipristal with levonorgestrel and it is observed that the former is significantly superior to the latter in all time intervals from unprotected intercourse to administration. The lower pregnancy rate with the ulipristal would be related to its ability to alter ovulation when LH is rising, while levonorgestrel is ineffective when LH elevation has begun.[1,25] The greater knowledge of the mechanism of action contributes to increasing the acceptability and, therefore, the availability of different products that have the intention of preventing unwanted pregnancies and the number of abortions.[50] Polis et al.[51] in 2013, in a Cochrane review, evaluated the possibilities of reducing unwanted pregnancy rates according to the anticipated provision of EC or the search when needed. With all the methods they found OR: 0.98 [95%CI: 0.76-1.25], Yuzpe's method OR: 0.90 [95%CI: 0.47-1.74], levonorgestrel OR: 0.82 [95%CI: 0.64-1.05] and mifepristone OR: 1.20 [CI95%: 0.74-1.93]. They point out the importance of women having contraceptive methods available when they need them, also they call out that remember that women have the right to receive information and easy access to EC because it is accepted that it decreases the chances of pregnancy. However, they report that current data indicate that the anticipated provision of EC is not able to reduce overall unwanted pregnancy rates.

One of the concerns in recent years has been regarding the negative impact of obesity on the effectiveness of hormonal methods used in EC. The publications are contradictory, although they seem to indicate that the adverse impact on obese women compared to women of normal weight is greater with levonorgestrel than with ulipristal. Despite this, the European Medicines Agency [EMEA] regulator concludes that the available data is limited and there are no robust figures to assert that the contraceptive effect is reduced with the increase in body weight, therefore the EC should continue to be offered to women after unprotected intercourse or contraceptive failure, regardless of their body weight.[52] Although it is noted in the Canadian consensus that after considering accessibility and costs, it may be more reasonable to offer EC with ulipristal to women with BMI> at 25 kg / m2 for better effectiveness.[1] It is not recommended to offer higher doses of levonorgestrel or ulipristal. Taking more tablets than indicated is not more effective and increases the adverse effects.

The next period after taking the EC may be earlier, on time or delayed. The presence of such bleeding within seven days of the expected happened in 75% of those who received ulipristal and in 71% of those who took levonorgestrel.[25] If there has been no menstrual bleeding within 21 days after applying any of the EC methods, a pregnancy test should be performed.[1]

It has not been observed increase in the risk of ectopic pregnancy with EC with levonorgestrel, ulipristal or mifepristone compared to the general population.[53] It has not been observed that EC could be dangerous for adolescent girls, so its use cannot be limited at some ages.[1] EC does not increase the rate of alterations in fetal growth, mental development or birth defects in newborns exposed in the uterus to hormonal components.[54]

The repeated use of EC is a call to counseling by professionals, since the expectation is that upon receiving a prescription from EC, women adopt a regular method of planning. Repeated uses within the same cycle are not recommended and the failure rate has been estimated as high when the woman has subsequent unprotected intercourse.[1]

There are no absolute contraindications to EC, except pregnancy or hypersensitivity to the ingredients of the formulations.[1] Although the method should not be used in obvious or suspected pregnancy, it is not known to be risky for pregnancy if it is administered accidentally, since the dose is reduced and the effect time is short.[55] It is possible that in cases of venous thromboembolism, previous or current history of breast cancer and intermittent acute porphyria, EC offers advantages over the theoretical or proven risks of administering estrogens to patients with these entities or when becoming pregnant.

The World Health Organization in its fifth edition of the Eligibility Criteria for contraceptive methods, has established a categorization with respect to EC. Table 4.[21] In the same document it is considered that hormonal EC can be prescribed without restriction to women taking medications that have pharmacological interactions with estrogens or progestins. There is no evidence to demonstrate the need to administer higher doses of EC.[1]

Education institutions and scientific associations must design and carry out continuing medical education actions, both training and awareness raising about the benefits offered by the EC and meet the goals suggested by the Emergency Contraception Consortium to generate global access to the population.[4,56] In the last decade, in many countries, EC is offered as an over-the-counter (OTC) free sale for adults. In 2011, the FDA reduced the age for the acquisition of EC in the United States to 17 years of age and in 2013 to 15 years, keeping the free sale.

EC is a valid strategy that, immersed in its true and real dimension, favorably influences the sociodemographic, biological and economic repercussions unplanned pregnancies generates. The society must contribute to the availability and accessibility of emergency contraception.[3,4]

CONCLUSION

The copper intrauterine device, the ulipristal, levonorgestrel or mifepristone pills and the Yuzpe method, properly used in terms of dose and hours of administration, are the tools available for emergency contraception. This intervention has an important place in preventive medicine, to facilitate the prevention of pregnancy, although it is not a regular method for birth planning. Once the emergency contraception is prescribed, the woman should receive sufficient guidance, counseling and motivation to choose between the different methods to regulate reproduction.

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