Clinical, ethical, and medical legal considerations on emergency contraception

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Summary

Purpose of investigation: To evaluate how many women required the so-called "emergency contraception" at our outpatient service and what the actual role is of this kind of pharmacological administration in interfering with ovulation and pregnancy, paying particular attention to the ethical and medico-legal aspects of this subject.

Methods: During the period from 1 December 1998 to 30 November 2003, emergency contraception was prescribed to a total of 1,160 women. With regard to the contraceptives used, in most cases (1,132, 97.6%) a combined oral estrogen-progestogen pill (ethinyloestradiol 0.05 mg plus levonorgestrel 0.25 mg) was prescribed; in some cases (20 patients, 1.8%) danazol (400 mg), in four women (0.3%) a progestin-only pill (levonorgestrel 0.75 mg), and in four other women (0.3%) an intrauterine device.

Results: It does not come out that there were any pregnancies in our study patients since none of them, who were told to come back for follow-up, were seen at our termination of pregnancy service or delivery room.

Conclusion: The "Yuzpe regimen" of a combined oral estrogen-progestogen pill has been the most commonly used method for emergency contraception. A new method recently proposed, a progestin-only pill with levonorgestrel 0.75 mg, is having better results than the previous one, with a lower incidence of side-effects and higher efficacy. Moreover, the treatment with this method does not interfere in case of a pregnancy already being carried and cannot interrupt it.

Key words: Emergency contraception; Interception; Post-coital pill; Ethinyloestradiol; Levonorgestrel.

Introduction

In recent years the concept of "responsible motherhood" has taken on little by little an exact definition. In fact, with the more direct involvement of women in the work force and with a new organization of family structure, an adequate and modern answer has been given to the need of limiting the number of undesired pregnancies and consequently of voluntary abortions. Along side the development of techniques of assisted reproduction, in fact, we have acquired much more knowledge about the various moments that precede and follow ovulation and conception [1, 2].

Implantation of the conceptus is a key step in pregnancy and the word "pregnancy" itself, above all in humans, cannot be disjoined from a complete and deep synergy between a fertilized ovum and the maternal hosting uterus. This concept, which was already underlined in 1985 by the World Health Organization (WHO), has been addressed again by bulletin number 254 dated 1 November 2000 of our Ministry of Health [3].

Obviously, this concept is not considerable if we add ethical arguments or religious presuppositions to purely biological considerations. The foreboded program of contraception in adolescence started to be introduced when the reality of the social framework was changing (with the different engagement of women in the work force and consequently a new role for them), together with the consciousness of the problem, above all in some over-populated countries [4, 5].

The improper response to this topic was the termination of pregnancy and the attempt to regulate it with legislative instruments which has certainly not been the most adequate reaction. The so-called "morning-after pill" has been used at the same as oral contraceptives and the "Yuzpe regimen", which uses combined estrogen-progestogens and has been utilized as an emergency contraceptive [6, 7].

Levonorgestrel, a progestin widely used for regular hormonal contraception, is also used for emergency contraception to prevent pregnancy after unprotected intercourse. However, its mode of action in emergency contraception is only partially understood. One unresolved question is whether or not emergency contraception prevents pregnancy by interfering with post-fertilization events. In the rat, levonorgestrel inhibits ovulation totally or partially, depending on the time of treatment and/or total dose administered, whereas it has no effect on fertilization or implantation when it is administered shortly before or after mating, or before implantation. It is concluded that acute post-coital administration of levonorgestrel at doses several-fold higher than those used for emergency contraception in women, which are able to inhibit ovulation, has no post-fertilization effect that impairs fertility in the rat [8].

The objective of our study was to evaluate how many drugs for emergency contraception have been required at

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our ambulatory service and what the effective role is of this kind of pharmacological administration in the interference with ovulation and pregnancy.

Materials and Methods

In the period from December 1, 1998 to November 30, 2003, post-coital emergency contraception was prescribed to a total number of 1,160 women who are the subjects of our study. We should note, however, that the requests of women who came under our observation after unprotected sexual intercourse, has been high, but obviously they did not all result at risk for pregnancy. Moreover they did not all accept the emergency contraception pill after consulting with a physician.

The prescription for emergency contraceptives, in fact, always occurred after adequate information was given to the women about the choice of the most appropriate drug, the conditions of assumption, the possible contraindications and side-effects. Moreover, such prescription is only given after the patient's data is reported about her menstrual and obstetrical history, use of contraceptive methods, a remote pathological history and recent history (date and hour of the unprotected sexual intercourse, last menstruation) and an informed consent is signed [9]. With this last one, the woman states she has been informed that the recourse to post-coital hormonal contraception represents a method which does not necessarily prevent her from fertilization but can prevent implantation in the uterus with a chance of failure up to 25% and that in 10% of cases an ectopic pregnancy occurs. Moreover, that the treatment may cause undesired side-effects such as headache, mammary tension, spotting, nausea and vomiting and finally, that menstruation usually returns in a timely period and in case a pregnancy is already being carried the drug certainly would not provoke fetal malformations (the increase of the teratogen risk is < 0.1% vs a risk of 2% in the general population), since the drug administration occurs before organogenesis [10, 11].

Results

The average age of women who resorted to post-coital emergency contraception was 24 years (range: 15-51 years). Regarding obstetric history, 1,024 patients (88.3%) were nulliparous, 76 (6.5%) had undergone one or more terminations of pregnancy, while 36 (3.2%) had had one or more deliveries and 1% (6 women) had had one or more spontaneous abortions; in another six cases (1%) they had had both deliveries and spontaneous abortions or terminations of pregnancy.

The most utilized contraceptive method used by the 1,160 patients in the past was condoms, (748 cases, 64.4%), followed by oral contraceptives (576 cases, 49.6%), coitus interruptus (130 cases, 11.2%), intrauterine devices (28, 2.4%), and diaphragms (2, 0.3%); in 94 cases (8.1%) no methods were used. As for contraception at the moment of the unprotected sexual intercourse, 744 women (64.1%) stated they used condoms, 78 (6.7%) practiced coitus interruptus, and 50 (4.3%) had temporarily interrupted the assumption of oral contraceptives; 288 women (24.8%) did not use any contraceptive method.

Obviously, in the interpretation of these percentages it should be taken into account that some patients used more than one contraceptive method at the same time. Moreover, the datum according to which a quarter of the studied women did not use contraceptive methods while 6.7% only practiced coitus interruptus (which may seem incorrect), could be explained if we consider that many women who in reality use the so-called "natural methods", often claim not to use any contraceptive method.

In 204 cases (17.6%) the women had previously resorted to emergency contraception, while for most of them (956 cases, 82.4%) it was the first time.

Finally, regarding the drugs administered, in most of the cases (1,132, 97.6%) we prescribed an estrogen-progestogen pill (ethinyloestradiol 0.05 mg plus levonorgestrel 0.25 mg, 2 pills at a distance of 12 hours), in 1.8% of cases (20 patients) danazol (400 mg, one pill for three times at a distance of 12 hours), in two women (0.3%) a progestin-only pill (levonorgestrel 0.75 mg, not yet for sale in the emergency contraception confection) and in another four women (0.3%) an intrauterine device.

It does not come out that any pregnancies occurred in the patients of our study since none of them, who were told to come back for follow-up, were seen at our termination of pregnancy service or delivery room.

Discussion

Emergency contraception is a therapy for women who have had unprotected sexual intercourse, including sexual assault. It also has been called the "morning-after pill", interception, and post-coital contraception. Methods of emergency contraception include use of combination or progestin-only oral contraceptives, danazol, synthetic estrogens and conjugated estrogens, antiprogestins, and the insertion of an intrauterine device [12]. Combination and progestin-only oral contraceptives are the most frequently used methods. One particular combination of an oral-contraceptive regimen is the Yuzpe method [13].

The Yuzpe regimen of combined oral contraceptives, introduced in clinical practice in 1974 [14, 15], has been the most commonly used for emergency contraception and is based on the administration of ethinyloestradiol 0.05 mg plus levonorgestrel 0.25 mg, repeated after 12 hours and starting within 72 hours from the unprotected sexual intercourse. This treatment allows about 75% of undesired pregnancies to be avoided. However, one must take into account that, since it has been used for emergency contraception, it is not possible to estimate the Pearl index under the same conditions of a classic contraceptive [16, 17].

This protocol, nevertheless, is not free from side-effects. In fact, 50% of the treated patients reported nausea and more than 20% vomiting after the administration of these drugs at the indicated doses. On the other hand, this was without doubt the most effective and tolerated method. The two regimens, the older one and the one used today, have the same efficacy to prevent the occurrence of pregnancy when evaluated in terms of pregnancy rates, number of pregnancies prevented, and side-effects [18, 19].

As for the actual regimen with levonorgestrel, it is reaching better results than the previous regimen, with

reduced incidence of side-effects and higher efficacy. On the other hand, it decreases with time from the moment of the unprotected sexual intercourse (95% within 24 hours, 85% within 48 hours, 58% within 72 hours) [20].

As for considering this treatment as contraception or interception, we must underline that the process of implantation has never been directly observed in humans, and its timing remains uncertain. Some experiments have described human implantation as taking place by the seventh day after ovulation. More recent data, based on the detection of chorionic gonadotropin in the serum or urine of women undergoing treatment for infertility, have dated the implantation of a conceptus as late as 14 days after egg retrieval. However, fertility treatment may distort reproductive function, including the timing of implantation.

In laboratory animals there are three phases of endometrial development after ovulation: the uterine lining is initially neutral toward the implanting blastocyst, then receptive, and finally resistant. These three phases of uterine receptivity are also thought to occur in humans [21].

Throphoblast total ipotential, therefore, does not justify the use of the term "preimplantation embryo" because there is a definite biological sequence which does not cause reason for such terminology in human pregnancy. Thus, it is necessary to make the first distinction regarding the timing of fertilization and implantation: fertilization as a single moment cannot be absorbed as pregnancy, but has to be inserted in what will constitute the presupposition of an actual maternal-fetal symbiosis.

If it is true that the gene in itself contains the promoter of a future evolution, we must not forget that the moment of expression is determined and conditioned by the correct implantation in maternal tissue which is not simply the host but the determinant for its evolution [22, 23].

The best indirect marker of implantation, however, is chorionic gonadotropin. In a study published in 1999 by Wilcox *et al.* [21] in the majority of successful pregnancies (84%) the first hormonal evidence of implantation was detected eight to ten days after ovulation (range: 6-12 days). The authors found a strong increase in the risk of early pregnancy loss with late implantation, a finding in agreement with data from other studies. The receptivity of the endometrium decreases during the late luteal phase, and the corpus luteum is less responsive to chorionic gonadotropin by 11 or 12 days after ovulation. Unhealthy zygotes may develop more slowly, or implantation may be abnormal, resulting in later and weaker production of chorionic gonadotropin.

Thus, there may be opportunities to increase fertility by extending the time during which implantation can occur [21, 24].

Treatment with levonorgestrel (0.75 mg), following the indicated dosage and way of administration (within and not over 72 hours from unprotected sexual intercourse), does not interfere in case of a pregnancy already in progress and CANNOT interrupt it. Therefore, physicians should not invoke any conscience objection. Moreover, progestin does not have any kind of embryo-toxic action. On the basis of the previously discussed considerations, we can say that this drug does not necessarily act as an interceptive because if it is true that it is not possible to demonstrate the exact moment of implantation it is also true that pharmacological action can develop at any moment starting from ovulation until the union of the oocyte with spermatozoon. It is therefore more likely that the action is contraceptive, since progestin acts by modifying the reproductive ecosystem with the alteration of spermatozoa and fallopian tube motility, thus reducing oocyte migration inside the fallopian tube and consequently avoiding the union of the two gametes, and finally interfering with implantation [25, 26].

Moreover, the data we have presented demonstrate the non exiguity of the request and firm will of patients who required such service to avoid any occurrence of pregnancy. It is not rash to say that these patients have been shielded from the termination of a pregnancy (in France there has been an estimated reduction in voluntary abortions of 30%) and from much more severe ethical-psychological problems. Until it is possible to determine in an indisputable way that this kind of pharmacological administration produces abortion, and the present data categorically exclude it, it is not right to define its action as interceptive. The eventual loss of oocytes, if demonstrated, comes within natural spontaneous retrieval, even if with data comparable to clinical-pathological situations of infertility [27, 28].

For the future it would be desirable to create an emergency contraception register in order to significantly evaluate what the real risk is of failure of the used methods. Additionally, in accord with the recommendations proposed in Bellagio, Italy in 1995, in the *Consensus Statement on Emergency Contraception* generated by, among others, the World Health Organization [29], it would be beneficial to have more information for users and sanitary operators, the availability of more adequate services, and the realization of more and more specific, effective, safe, simple to use, and easy to find products. Too often, in fact, sanitary operators are still little inclined to speak about the possibilities and limitations of emergency contraception, and family doctors are little informed about dosage and therapeutic schemes. Thus, we think that even consulting rooms should be more accessible and directed toward this problem, with a longer opening of the service and the institution of a "green" telephone number. Finally, we should underline the fact that the World Health Organization has included the pharmacological regimens of emergency contraception in the fundamental drugs category, and that the Ministry of Health in Italy has introduced them into the national health regimen [30-32].

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