New forms of interception and contragestation: a biomedical review

articolo

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The instruction *Dignitas Personae*, between the various and current bioethics issues that takes into account, reserves adequate consideration to "*New forms of interception and contragestation*"[1]. Defines the classification according to their mechanisms of action («[…] methods are interceptive if they interfere with the embryo before implantation and contragestative if they cause the elimination of the embryo once implanted»)[2]; represents and justifies the immorality of abortion («Therefore, the use of means of interception and contragestation fall within the sin of abortion and are gravely immoral»)[3] and intention of abortion («[…] anyone who seeks to prevent the implantation of an embryo which may possibly have been conceived and who therefore either requests or prescribes such a pharmaceutical, generally intends abortion»)[4]. «As is known, abortion is the deliberate and direct killing, by whatever means it is carried out, of a human being in the initial phase of his or her existence, extending from conception to birth»[5].

Preliminary remark the recognition of the dignity of person to every human being, from conception («The dignity of a person must be recognized in every human being from conception to natural death»)[6].

The aim of this article is a biomedical review of the new forms of interception and contragestation (only hormonal methods), with arguments supported by specialized scientific literature. Moreover, another purpose is to show how there is always a strong link between contraception and abortion[7].

Oral hormonal interceptive methods

With reference to the timing of interceptive methods administration, they are also defined "emergency contraceptives" (EC)[8]. From WHO «emergency contraception refers to back-up methods for contraceptive emergencies which women can use within the first few days after unprotected intercourse to prevent an unwanted pregnancy. Emergency contraceptives are not suitable for regular use»[9]. This definition summarizes the various and similar reported in the literature[10].

The interceptive methods, generally and improperly, are classified as contraceptives. The motivation originates from the handle definition of the beginning of pregnancy. That is a current of thought[11] believes that pregnancy begins from implantation[12]. Thus only in 7th day, approximately, from conception. It follows that any method, making for use in this initial stage of the new human being, could not be classified as an abortifacient but purely contraceptive. One was pregnant, by definition, assumes that the conception occurred. Furthermore, since conception are occurring metabolic and hormonal changes as the development and dissemination of circulating molecules that allow a first and refined communication between embryo and maternal organism, or more correctly between son and mother[13].

According to the WHO, the reasons for the use of EC would be: a) when no contraceptive has been used; b) when there is a contraceptive failure or incorrect use, including condom breakage, slippage or incorrect use; three or more consecutive missed combined oral contraceptive pills; progestogen only pill (minipill) taken more than three hours late; more than two weeks late for a progestogen only contraceptive injection; more than seven days late for a combined estrogen-plus-progesterone monthly injection dislodgment, delay in placing; dislodgment, breakage, tearing or early removal of a diaphragm-patch or ring; failed coitus inter-

ruptus; miscalculation of the periodic abstinence method; failure to intercourse IUD expulsion; c) in case of sexual assault when the woman was not protected by an effective contraceptive method. Also economic and psychological reasons are given for the EC. Refer, in fact as justifications, social costs («not only would making emergency contraception more widely available save medical care dollars, but also additional social cost savings would result»), psychological costs («not only the monetary costs of unwanted pregnancies and births but also the considerable psychological costs of unintended pregnancy») and costs of medical care for unwanted births («[…] the average medical care of unintended births is likely to be greater than the average cost of all births»)[14]. Several options are available for EC. The oral hormonal methods available, with great and present interest, are: a) progestogen-only pills containing levonorgestrel (LNG-EC) and b) selective progesterone receptor modulator or antiprogestogen mifepristone. There are also the combined hormonal method containing two doses of oestrogen and progestogen (known as the Yuzpe regimen) and Danazol but these methods are falling into disuse.

a) LNG-EC

The most widely known hormonal oral EC is that containing levonorgestrel (LNG-EC)[15]. In a randomized double-blind trial of 4071 women, a single dose of 1500 mg was found to be as effective as two 750-mg doses taken 12h apart without additional side effects[16]. The effectiveness of the EC is determined by comparing the number of pregnancies observed after treatment to the expected number of pregnancies in the absence of treatment. The World Health Organization conducted a randomized trial in 1001 women: the pregnancies prevented in the progestin-only regimen (LNG-EC) was 85%[17]. However, it must be noted that EC is still less effective in pregnancy prevention than consistent use of other contraceptive methods[18]. Ectopic pregnancy can occur after EC[19]. The mechanisms of action of LNG-EC regimen is still not entirely clear. It has been postulated that LNG-EC may interferes with stages of conception from follicular maturation through to implantation[20]. Before fertilization, LNG-EC interrupts follicular development and ovulation[21]. It has also been shown that LNG-EC interferes with the luteinizing hormone surge, particularly when is instigated at least 2 days before the pre-ovulatory hormone rise[22]. When LNG-EC is administered in the peri-ovulatory period, ovulation may occur but luteal phase dysfunction frequently ensues[23]. An important issue is whether or not LNG-EC can act to prevent implantation, because human life begins at the time of the fertilization[24]. The argument in favour of a postfertilization effect is based on several grounds[25]. The first is that LNG-EC may induces changes in the endometrium to alter its receptivity to embryo-implantation[26]. The other reasons put forward for a possible postfertilization effect is that the effectiveness of LNG-EC is possibly not fully explained by ovulatory dysfunction alone[27]. These are the grounds on which pharmacists and doctors raise a conscientious objection to the supply of the medication[28]. There is no evidence that EC pills act after implantation to disrupt an already established pregnancy[29]. It is possible that doubt around the mechanism of action of LNG-EC may never be fully resolved, but studies which accurately estimate the timing of ovulation with hormone assays and ultrasound tracking of follicular development and rupture may lead to a better understanding of the issues[30]. Despite many studies, the true effectiveness of LNG-EC remains uncertain[31]. «The effectiveness of emergency contraception merits special discussion. The chance that pregnancy would occur in the absence of emergency contraception is estimated indirectly using published data on the probability of pregnancy on each day of the menstrual cycle. This estimate is compared with the actual number of pregnancies observed after treatment in observational treatment trials. Effectiveness is calculated as 1-[O/E], where O and E are the observed and expected number of pregnancies, respectively. Calculation of effectiveness, and particularly the denominator of the fraction, involves many assumptions that are difficult to validate. Recent studies have demonstrated that inaccuracies in estimates of when ovulation occurs within a woman's menstrual cycle are common, and most likely lead to inflated estimates of pregnancy risk. As the risk of pregnancy for women requesting emergency contraceptive pills (ECPs) is most likely inflated, estimates of ECPs efficacy are consequently likely to be overestimates. A more important considera-

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tion for most ECPs clients may be the fact that data from both clinical trials and studies on the mechanism of action clearly show that at least the LNG regimen of ECPs is more effective than doing nothing»[32]. A recent analysis suggested that LNG-EC reduces pregnancy risk at least 49% after a single act of unprotected sexual intercourse[33], but exactly how much more efficacious it is unknown[34]. However the access to LNG-EC does not have a measurable impact on the rate of unplanned pregnancy[35].

b) RU486

The antiprogestogen mifepristone (RU486), used in some places for chemical abortion, is another effective EC agent. RU486 can be used as a single dose up to 120h after a single act of unprotected sexual intercourse[36]. A Cochrane review examining interventions for EC reported that efficacy of mid-dose (25–50 mg) mifepristone is better than LNG-EC[37]. At lower doses (<25 mg), mifepristone appears to be as effective as LNG-EC, but more commonly results in delay in onset of the next menses.
The effects of mifepristone on the development of the follicle are dose-dependent and related to the timing of administration. The assumption during preovulatory period induces the destruction of the follicle, inhibition or delay of the ovulation. A reduced dose of mifepristone (<50 mg) hampers the maturation of the follicle that, upon completion of the action of mifepristone, continues until the ovulation. Otherwise is recruited another follicle[38]. The follicle, then, could also be blocked in the maturation process until the end of the cycle[39]. In light of the data reported in literature, mifepristone delays ovulation by a direct action on the mature follicle and / or by inhibition of LH peak, preferably by interfering with the peak of the progesterone level of the axis hypothalamus-pituitary[40]. The mifepristone also acts on the tubal function: acceleration in transporting the embryo by inhibition of embryo maturation and implantation[41], slowed development of the embryo from the stage of morula to blastocyst[42]. The mifepristone acts on particular substances (cytokines) that act as mediators between tuba and embryo, leading to adverse action in the development of embryo in early so preventing the next implantation[43]. The mifepristone alters endometrial receptivity by acting at multiple levels[44], thus inhibiting the embryo implantation. Particularly mifepristone is anti-implantation by the regulation of uterine natural killer cells during implantation phase[45].

Hormonal contragestative methods

Hormonal contragestative methods are chemicals that, occurred after implantation, induce the abortion by alteration of the endometrium and death of the embryo. To better understand the action of contragestative methods, we must define the chemical abortion: early pregnancy termination, generally before 9 weeks' gestation resulting from abortion-inducing medications and without primary surgical intervention. In studies of chemical abortion, success is defined as the expulsion of all products of pregnancy, with no need for surgical intervention (uterine aspiration)[46]. Currently, the available chemical abortion regimens are: a) mifepristone and a prostaglandin analogue (in the majority of the world, the analogue misoprostol is used); b) methotrexate and misoprostol; c) misoprostol alone.

a) RU486

The antiprogestogen mifepristone (RU486), used in some places for chemical abortion, is another effective EC agent

Mifepristone in association with misoprostol has a high efficacy (92%–99% of complete abortions)[47]. The criticalities related to the administration of RU486 in chemical abortion are summarized in the following: severe adverse events; methods of administration as risk cofactors; privatization of abortion.
Severe adverse events. Various studies point out risks and severe adverse events: a) the risk of maternal mortality after chemical abortion is 10 times greater than surgical[48]; b) adverse events[49] are numerous and extremely dangerous: massive hemorrhage[50]; sepsis; deaths for ruptured ectopic pregnancy and toxic shock syndrome; documented fetal malformations after misoprostol[51]. The deaths after administration of RU486/misoprostol were classified primarily as results of septic shock from Clostridium Sordellii[52].
The pathogenesis is still being researched. Different mechanisms are assumed. The mifepristone would reduce the immune system providing to lethal infection by C. Sordellii and other pathogens[53]. Also the misoprostol would play an immunosoppressive action, as recent research[54]. Cofactor for the onset of infection is the necrotic tissue inside the endometrium, pabulum for the develop-

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ment and multiplication of C. Sordellii[55]. Then, still in dispute: the doses, routes of administration of misoprostol (vaginal *vs.* oral), the prophylactic use of antibiotics[56], timing and techniques of follow-up to the development of protocols to encourage even more recourse to chemical abortion[57].

Methods of administration as risk cofactors. Are significantly increased by the methodologies and protocols of administration which include mainly the recruitment of misoprostol and accomplishment of abortion at home[58]. This means that: a) the woman alone, although informed and having signed the consent, must be able to recognize the symptoms of abortion in act differentiated from those related most dangerous severe adverse events[59], very subtle and difficult to interpret[60]; b) the remote controls programmed days after the administration can be rejected by the woman with serious risks; c) simplification of procedures - due to the administration and simplifying the first medical abortion visit, eliminating the second medical abortion visit, simplifying the third, or follow-up, medical abortion visit - led to minimizing the possibility of severe adverse events. In fact, I think it is really paradoxical that «simplifying the medical abortion regimen by reducing the number of visits required and by avoiding the routine use of ultrasound imaging has the potential to increase the availability, affordability and acceptability of the treatment and to help it meet its promise as a real alternative to surgical abortion in the first trimester».[61]

Privatization of abortion. In Italy, the advocates of L.194/78 have always said that the legalization of voluntary abortion "socializes" the phenomenon, or collectively the society assumes the responsibility to prevent illegal abortion, favoring direct action to protect the health of women and the prevention. With the chemical abortion there is, however, the "privatization" of the abortifacient action. The woman alone recourses to abortion by a method improperly presented as reliable, simple and rapid.

b) Methotrexate

Methotrexate (MTX) deprives cells of tetrahydrofolic acid, which is essential for DNA synthesis in rapidly dividing cells[62]. In obstetrics it has been used in single or short-term administration as an alternative treatment for ectopic pregnancy[63]. MTX is formulated for oral and intramuscular administration. Most of the regimens used a MTX dose of 50 mg/m^2 intramuscularly followed by 800 mcg of vaginal misoprostol 3-7 days later. In women with a pregnancy duration less than 49 days, the reported success rate after administration of 50/m^2 mg of oral MTX followed by 800 mcg of vaginal misoprostol was between 90% and 91%[64]. When 50 mg/m^2 of intramuscular MTX was followed by 800 mcg of vaginal misoprostol in women with a pregnancy duration less than 49 days, however, the observed success ranged between 75% and 95%[65]. Most clinicians used a second dose of misoprostol if abortion had not occurred after the first. Surgical interventions for true method failure (continuing pregnancy) ranged from 0.4% to 8% for excessive bleeding, incomplete abortion and infection ranged from 0.3% to 5.0%[66].

c) Misoprostol

Misoprostol is a synthetic prostaglandin E1 analogue approved worldwide for the prevention of gastric ulcers and is effective in labor induction, the treatment of postpartum hemorrhage and early pregnancy failure, and induction of second-trimester abortion. It is also used for cervical priming prior to hysteroscopy and surgical abortion during the first and second trimesters[67]. However, its use for gynecologic and obstetric indications is off-label in most countries. Misoprostol has been associated with teratogenicity in high doses, and a maximum safe dose has not been established[68]. It is almost always labeled for oral use but may be also intravaginally. The median time for the completion of a misoprostol induced abortion ranges from 6 to 9 h after the first dose and the overall success from 84% to 96%. Self-medication with misoprostol to induce an abortion has been documented in both legal and illegal contexts. Indeed, a further consideration is appropriate. The misoprostol, which is distributed in pharmacies with nominal non-repeatable recipe and to preserve for 6 months, requires very specific indications to prescribe[69]. However misoprostol is used to induce – clandestinely - abortion[70]. It requires, therefore, a review for the arrangements of the prescription and dispensing of the of products containing misoprostol.

Note

[1] Congregation for the Doctrine of the Faith. «Instruction Dignitas Personae on certain bioethical questions». Roma, 08.09.2009; n. 23.
[2] Ibid.
[3] Ibid.
[4] Ibid.
[5] Ibid.
[6] Ibid., n. 1.
[7] L. Romano, M.L. Di Pietro, M.P. Faggioni, M. Casini, *RU-486. Dall'aborto chimico alla contraccezione di emergenza. Riflessioni biomediche, etiche e giuridiche*, Art, Roma 2008.
[8] In scientific literature, also: morning-after pill; postcoital contraception; after sex pill; birth control-emergency. «The use of alternative terms such as 'postcoital contraception' or 'the morning-after pill' is discouraged, as these terms may engender confusion either by implying a short time frame for use, or by suggesting that a pill is the only treatment option», in K.I. Black, «Developments and challenges in emergency contraception», in *Best Practice & Research Clinical Obstetrics and Gynaecology* 23 (2009), 221–231.
[9] WHO, «Emergency contraception»., in *Fact sheet* 244 (2005).
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[15] Formulations available of levonorgestrel for use as EC: a) common brand names: Escapelle, Norlevo 1.5, Levonelle one step; formulation per pill: LNG 1.5 mg ; number of pills: 1; b) common brand names: Levonelle-2, NorLevo, Plan B, Postinor-2, Vikela; formulation per pill: LNG 0.75 mg; number of pills: 2; c) common brand names: Microlut, Microval, Norgeston; formulation per pill: LNG 0.03 mg; number of pills: 50; d) common brand names: Ovrette; formulation per pill: LNG 0.0375 mg; number of pills: 40.
[16] H. von Hertzen, G. Piaggia, J. Ding, et al., «Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial», in *Lancet* 360 (2002), 1803–1810.
[17] WHO, «Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation», in *Lancet* 352 (1998), 428–433.
[18] American Society for Reproductive Medicine, «Hormonal contraception: recent advances and controversies», in *Fertil Steril*. 90 (2008), S103–113.
[19] C.L. Nielsen, L. Miller, «Ectopic gestation following emergency contraceptive pill administration», in *Contraception* 62 (2000), 275–276.
[20] J. Trussell, B. Jordan, «Mechanism of action of emergency contraceptive pills», in *Contraception* 74 (2006), 87–89.
[21] N. Novikova, E. Weisberg, F. Stanczyk, et al., «Effectiveness of levonorgestrel emergency contraception given before or after ovulation – a pilot study», in *Contraception* 75 (2007), 112–118; I. Okewole, A. Arowojolu, O. Odusoga, et al., «Effect of single administration of levonorgestrel on the menstrual cycle», in *Contraception* 75 (2007), 372–377.
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[33] The calculating conception rates based on the estimated day of ovulation by counting backwards from the subsequent period is less accurate than estimating fertility from the day of the last period (cycle day). In part, this is because EC treatments may delay the onset of the next menstrual period, and calculations of the ovulation day may therefore be imprecise. In using a new set of probabilities based on likelihood of conception by cycle day of intercourse, the effectiveness of EC pills has been overestimated by approximately 10%. Cfr: J. Trussell, C. Ellertson, H. von Hertzen, et al., «Estimating the effectiveness of emergency contraceptive pills», in *Contraception* 67 (2003), 259–265.

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[52] Clostridium sordelli is a bacteria that is anaerobic (it can live without oxygen) and in very rare cases produces toxins that are rapidly fatal. Clostridium sordellii exists in low numbers in the reproductive tracts of many women. Toxigenic strains of C. sordellii produce multiple exotoxins: the two principal agents are aptly named "lethal" and "hemorrhagic" toxins. These two molecules account for the dramatic lethality of C. sordellii infection. Rare infections with Clostridium sordelli can occur following childbirth (vaginal delivery and caesarian section), as well as following medical abortions. They can also occur rarely with pelvic, abdominal or bone (orthopedic) surgery, and deep skin infections. The bacteria may also be present in women's intestinal and rectal areas and cause no symptoms whatsoever, not producing any toxins. This is called "colonization" and is not known to be a health problem.

[53] «We suggest that mifepristone use impairs hosts re-

sponses and may predispose to lethal infection caused by toxigenic C. sordellii and other pathogens. RU-486 is a potent competitive inhibitor of both progesterone and glucocorticoid receptors. Mifepristone powerfully interferes with glucocorticoid receptor-mediated stress responses. In animal models of sepsis, mifepristone blocks endocrine stress responses and increases lethality», in J. A. McGregor, O. Equiles, «Risks of mifepristone abortion in context», in *Contraception* 72 (2005), 393.

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[60] The symptoms of septic shock from C. Sordellii is often atypical. Initially may be confused with the side effects of mifepristone / misoprostol: abdominal cramps, vaginal bleeding, headache, nausea, vomiting, diarrhea. Characteristic can be the absence of fever, tachycardia, hypotension, increased hematocrit, leukocytosis and neutropenia.

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Il vincolo tra contraccezione e aborto, dimostrato dagli studi scientifici, è anzitutto un vincolo strutturale, antropologico