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Levonorgestrel in cases of rape: How does it work?

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The Ethical and Religious Directives for Catholic Health Care Services allows the use of an emergency contraceptive for a woman who has been raped, as a defense against her attacker's sperm, provided the drug prevents fertilization and does not act against a conceived human life. Catholic emergency rooms around the country have been pressured to provide Plan B (LNG-EC) to patients seeking help after a sexual assault. Catholic bioethicists have supported the use of this drug based on their interpretation of the scientific literature regarding its mechanism of action. This paper presents a review of the mechanisms of action of LNG-EC when given during the fertile window, showing a high probability that it acts against human life rather than preventing fertilization, and proposes another class of drugs as a possible alternative.

Keywords: Emergency contraception, Rape, Levonorgestrel, Peoria protocol, Catholic hospitals, *Dignitas personae*, Meloxicam

Introduction

The sexual assault of a woman is a horrific crime that can carry with it long-term consequences to the woman such as sexually transmitted diseases, post-traumatic stress syndrome, or pregnancy. The *Ethical and Religious Directives for Health Care Services* in directive 36 shows the care that Catholic hospitals should take in protecting the victim of rape from possible consequences of the assault, including pregnancy, as long as the agent used is contraceptive:

> Compassionate and understanding care should be given to a person who is the victim of sexual assault. Healthcare providers should cooperate with law enforcement officials and offer the person psychological and spiritual support as well as accurate medical information. A female who has been raped should be able to defend herself against a potential conception from the sexual assault. If, after appropriate testing, there is no evidence that conception has occurred already, she may be treated with medications that would prevent ovulation, sperm capacitation, or fertilization, *all of which would be contraceptive actions. It is not permissible, however, to initiate or to recommend treatments that have as their purpose or direct effect the removal, destruction, or interference with the implantation of a fertilized ovum*. (USCCB 2009, emphasis added)

The standard emergency contraceptive used for this purpose is levonorgestrel (LNG-EC) 0.75 mg given within 120 hours of the sexual assault and then repeated 12 hours later, or 1.5 mg given in

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a single dose. The medical literature claims that the drug works primarily by preventing ovulation. Despite concerns that this drug might work after fertilization, the use of this drug in Catholic emergency rooms in cases of rape was mandated in some states (Davis 2007). Its use has been justified under the "three moral fonts" approach, described by Cataldo, as first, the moral object of the act is self-defense against the sperm of the attacker; second "the intention of the survivor must be to suppress ovulation in order to prevent the unjust circumstance of the gametes meeting, and not to cause the death of a newly conceived human being if fertilization has occurred." Lastly, "if the circumstances surrounding the act are not in due proportion, that is, they are morally defective, then the act is immoral" (Cataldo 2009). That is, tests must be done and a menstrual history obtained that would assure the patient and doctor that it is only remotely possible that the drug would be acting after fertilization. This paper will demonstrate that well-designed medical studies, studying various aspects of the mechanism of action of LNG-EC, have shown that this drug is probably acting after fertilization a significant amount of the time and therefore cannot be given in a Catholic emergency room because the second and third moral fonts are not met. The possibility of ever achieving the goal of a drug being used after a sexual assault acting only by a contraceptive effect will be discussed.

Sexual assault of females is predominantly a crime against the young and has reached epidemic proportions in the United States. There are approximately 683,000 adult women raped annually in the United States, with only 6 percent occurring past the age of thirty (Kilpatrick, Edmunds, and Seymour 1992). The majority of rapes (61%) occur in childhood and adolescence, and in 75 percent of cases the assailant is known to the victim, and is often a relative. Only 26 percent of rape victims seek medical help after a rape, usually because of physical injuries (McFarlane et al. 2005). The main concerns a woman has after a rape are the possibility of pregnancy, of having acquired a sexually transmitted disease, including HIV, and of public knowledge about the attack. The "rape trauma syndrome" is a common sequel with serious physical and psychological symptoms leading to disruption of existing relationships and the ability to work or go to school (Baram and Basson 2007). Any person who has been sexually assaulted should receive counseling for an extended period by someone skilled in treating post-traumatic stress syndrome. Approximately 5 percent of women of childbearing age who are fertile and not using contraception at the time of the attack will become pregnant as a result of the assault (Beckmann and Groetzinger 1989).

After the evidence has been gathered, and the patient has received treatment to cover any sexually transmitted diseases she could have acquired from the assault, it is standard practice to do a pregnancy test to make sure the woman is not pregnant from an act of intercourse two weeks or more before the assault; and if she is within 120 hours of the sexual assault, then she is offered an "emergency contraceptive," which could include, by mouth, LNG-EC 0.75 mg, followed by a second dose twelve hours later; LNG-EC 1.5 mg in a single dose; the Yuzpe regimen of two Ovral oral contraceptives, repeated in twelve hours; mifepristone 10 mg in a single dose; ulipristal acetate 30 mg in a single dose; or insertion of a copper intrauterine device into the endometrial cavity. For the sake of this discussion, we will only be assessing the moral judgment in using LNG-EC as an emergency contraceptive based on its known mechanisms of action.

Protocol for Catholic Hospitals: Is This Feasible?

Saint Francis Medical Center in Peoria, Illinois, developed a rape protocol for Catholic hospitals to assure "that the effect of the intervention would be truly contraceptive, and not abortifacient" (McShane 2009, 131). The emergency room rape protocol allows the administration of LNG-EC if the woman's menstrual history indicates she is preovulatory, her physical exam is compatible with being in the preovulatory phase, she has a negative urinary luteinizing hormone (LH) test, and has a serum progesterone level less than 1.5 ng/ml, which is compatible with being preovulatory. If the LH surge is positive, indicating the woman will ovulate in the next 24–36 hours, or the serum progesterone level is between 1.5 and 5.9 ng/ml, then she is near ovulation and LNG-EC should not be given. If she is postovulatory with a serum progesterone level of 6 ng/ml or greater, the drug can be given because she is already postovulatory and there is no harm in giving the drug. In this case the patient is beyond her fertile window and possible conception, anyway. The Saint Francis Peoria Protocol is based on the moral argument that

> treatment provided under this protocol is intended to prevent ovulation, sperm capacitation, or fertilization. Excluded from this protocol are treatments that would have as their purpose or direct effect the removal, destruction, or interference with the implantation of a fertilized ovum. (McShane 2009, 133)

Let us review the details of this protocol and see if that purpose can be fulfilled.

How reliable is the woman's menstrual history in determining where she is in her cycle, namely that she is preovulatory? In a study by Novikova et al., they found the history of the first day of the last period to be unreliable 39 percent of the time (Novikova et al. 2007). In addition they found a wide range of cycle lengths with the first day of one period to the first day of the next to be 21 to 35 days. With a longer cycle the woman could be on day 17 of her cycle but still be preovulatory and with a shorter cycle she could be on day 13 of her cycle and be postovulatory. Although one may suspect the woman is approaching ovulation on pelvic exam with the presence of highly fertile mucus at the cervical os, it is impossible for a physician to determine whether the woman is preovulatory on a pelvic exam, in particular in a woman who has just been sexually assaulted.

How reliable are LH testing and progesterone levels done stat in the emergency room in determining where the woman is in her cycle? The LH surge goes on over a twenty-four-hour period, and is usually detected by testing a first-morning concentrated urine. A random urine specimen, particularly late at night, may not detect the LH surge. In addition, serum progesterone levels are not emergency tests, and the results *often* are not available for twenty-four hours, even in major metropolitan hospitals, and even longer in small community hospitals. Therefore, *this protocol may not have a timely progesterone level available* to help determine if a woman is preovulatory in the emergency room.

Mechanisms of Action of Emergency Contraceptives

Even if the time of ovulation can be determined with a reasonable degree of accuracy in the assault victim, what is the mechanism of action of LNG-EC when given during the fertile window? Several recent studies have provided valuable information. There is a six-day fertile window when a woman can conceive,

based on sperm survival of five days leading up to the day of ovulation and one day of oocyte survival (Wilcox, Weinberg, and Baird 1995). For the sake of this discussion, these days are described as days −5, −4, −3, −2, −1, and 0 with day −1 indicating the day of the LH surge and day 0 indicating the day of ovulation. The studies that accurately determined the timing of the drug relative to the day of ovulation by hormone studies and pelvic ultrasound showed that the drug had different effects depending on the day it was given in the fertile window and that some of the effects were immediate and some were delayed. Since the 1970s, drugs that interfere with the synthesis, secretion, or peripheral actions of progesterone have been tested as emergency contraceptives because progesterone and its effects on the endometrium are critical for the successful implantation and establishment of a pregnancy. Because of the variability in timing of the administration of the drug, if the emergency contraceptive worked only to prevent ovulation and interfere with fertilization, it would have limited success, so according to researchers,

> to achieve the highest possible efficacy, the ideal emergency contraceptive drug needs to act *interceptively*; that is, it should be capable of interfering with a physiological event that occurs after fertilization—during the period of early embryonic development prior to implantation. (Von Hertzen and Van Look 1996)

Any drug that interferes with ovulation and the process of fertilization would be *contraceptive*, but any drug that prevents normal development of the zygote and successful implantation of the blastocyst, would be preventing pregnancy by an *interceptive* or *contragestive* mechanism of action. Any drug which could disrupt a previously implanted embryo would be *abortifacient*. As a people who value all human life from conception to natural death, drugs are not acceptable which carry interceptive, contragestive, and/or abortifacient effects and thereby act against a human life at its earliest stages.

The process of fertilization, also known as conception, occurs within 24 hours of ovulation at the distal end of the fallopian tube. The newly created zygote travels down the fallopian tube until it reaches the uterine cavity 3.5 days after conception. It forms the blastocyst stage at this point by 4.5 days and implants in the endometrium at 7–9 days after conception. There is no test at this time that can determine that fertilization has taken place or that a conceptus is present until *∼12* days after *conception*, by a serum quantitative β-hCG level. In order for successful implantation to occur, the endometrium has to evolve from the prereceptive phase to the receptive phase. According to Johnson

> the uterus can be thought of as a primarily hostile environment able to carefully control a potentially dangerous invasive trophoblastic tissue. Clearly, for the conceptus to survive, its early development and transport must be coordinated precisely with the changing receptivity of the uterus. This coordination is achieved by the mediation of the steroid hormones. Progestagenic domination is required if the uterus and implanting blastocyst are to engage effectively. (Johnson 2007, 198)

There are still many details of that nine-day period leading up to implantation that are not known, but from the research done so far, it is extremely complex and the proper levels of progesterone at critical times are necessary for it to be successful.

In assessing whether a drug has had a purely contraceptive effect, the only parameter that can be observed is to determine whether ovulation has occurred by ultrasound. There is no way to

determine whether sperm have made their way up to the fallopian tube or have fertilized the ovum at the end of the tube. Studies that accurately assess when ovulation occurs normally in a particular woman's cycle and whether the drug interferes with ovulation in a subsequent cycle are the most reliable determinants of a contraceptive effect. Likewise, those investigators who claim there is no effect of LNG-EC on post-fertilization events, but fail to study the hormonal milieu throughout the luteal phase cannot make that claim accurately. In addition, the process that allows successful implantation of the human blastocyst is quite complex and is not entirely understood at the present time.

Mechanisms of Action of LNG-EC: Timing Is Everything!

Durand et al. studied the anovulatory effect of LNG-EC in forty-five women who had been sterilized (Durand et al. 2001). The first cycle was the control cycle, and the women themselves tested for urinary LH each day until it was detected and then underwent daily ultrasounds until ovulation occurred. Serum LH levels were assayed daily until the progesterone level reached 3 ng/ml. Daily serum estradiol and progesterone levels were measured until the onset of menses. Endometrial biopsies were also performed on day LH + 9, or eight days after ovulation. During the study cycle, LNG-EC was administered on day 10 of the cycle. The important aspect of this study, in contrast to others, was their ability to pinpoint the exact day of the cycle in which LNG-EC was administered, relative to the LH surge. As an aside, they found that urinary LH was falsely positive in 13.3 percent of cycles, and they concluded that serum detection of LH was more reliable.

Ovulation was suppressed in 80 percent of women receiving the drug on day 10 of the cycle, when that day was four days or more before the LH surge (day −5 or earlier), or on the first day of the fertile window. However, participants who received LNG-EC within 3 days of the onset of the LH surge (days −4 to −2) all ovulated. Progesterone production after ovulation was found to be deficient in those who ovulated, and there was a shorter luteal phase, which would interfere with successful implantation. Women who received the drug at the time of the serum LH surge (day −1) or 48 hours later (day +1) all ovulated. The administration of the drug on days −1 to +1 did not affect the production of progesterone or length of the luteal phase, indicating that there would likely be no harmful effect on survival of the zygote or successful implantation. Durand et al. also could not find any histological change in the endometrium in those women who received the drug in the fertile window and who ovulated, which casts doubt on an alteration in the histology of the endometrium as a mechanism of action, which has been frequently cited for EC in the past. In conclusion, they demonstrated in this study that ovulation was not prevented by LNG-EC when given in five of the six days of the fertile window and therefore, prevention of ovulation is not its main mechanism of action.

In a later study, Durand et al. specifically looked at three groups of women in this study group who were given LNG-EC in divided doses on day −4 and day −3 (Group 1), on day −1 or the day of the LH surge (Group 2), and day +1 or two days after the LH surge (Group 3) (Durand et al. 2005). They studied the long-term effect of a premature rise in progesterone from the administration of LNG-EC given during the fertile window at a time when progesterone levels are

normally low, by measuring daily progesterone and glycodelin levels in the luteal phase. An endometrial biopsy was performed on day +8 with staining for glycodelin-A. Glycodelin-A is an important progesterone-regulated glycoprotein, normally present in low amounts in the endometrium, except in the late luteal phase, around the time of implantation. Glycodelin-A is a potent inhibitor of sperm-zona binding, and therefore may interfere with fertilization, but it also plays a role in the feto-maternal defense mechanisms, preventing maternal rejection of the blastocyst. They found that "levonorgestrel taken for emergency contraception prior to the LH surge alters the luteal phase secretory pattern of glycodelin in serum and endometrium" (Durand et al. 2005, 451). The normally high levels of glycodelin-A in the late luteal phase, triggered by the rise in progesterone after ovulation, inhibits the natural killer cells of the mother that would reject the blastocyst as a foreign body; however, LNG-EC, a high dose synthetic progestogen, administered prior to ovulation, triggers an early surge of glycodelin-A, so that by the time the blastocyst is ready to implant, the glycodelin levels have decreased, and that inhibition of the natural killer cells would no longer be present, resulting in maternal rejection of the new life. This provides strong evidence that LNG-EC has an interceptive or contragestive effect in preventing a clinically detectable pregnancy.

In another study of thirty sterilized women, designed similarly to their previous two studies, Durand et al. administered LNG-EC on cycle day –3 and found that twenty out of the thirty women ovulated, but the luteal phase was significantly shortened (Durand et al. 2010). They assayed serum levels of LH, estrone and estradiol in the periovulatory period. Glycodelin levels in serum and uterine flushings were obtained on days 0 and +11. They found elevated levels of glycodelin around the time of ovulation and proposed that another mechanism of action of LNG-EC might be its effect on sperm to make them incapable of binding to the zona pellucida of the oocyte, thus preventing fertilization. However, a study published in 2007 by do Nascimento et al. looked at the effect on sperm recovered from the uterus twenty-four and forty-eight hours after LNG-EC was given in a single dose of 1.5 mg (do Nascimento et al. 2007). They found no difference in the acrosome reaction of the sperm and no difference in the glycodelin-A levels, making it unlikely that sperm function was affected by LNG-EC. In addition there was no effect on cervical mucus by the high dose progestogen as viable sperm were found in the uterus 36–60 hours after intercourse and 24–48 hours after LNG-EC.

Palomino et al. studied the effect of administration of LNG-EC on the day of the LH surge and found, as Durand did, that giving this drug on that day of the cycle does not prevent ovulation nor does it disrupt progesterone receptors, plasma levels of glycodelin-A, or L-selectin ligand and integrin which are other factors necessary for implantation (Palomino, Kohen, and Devoto 2010). Their conclusion was that LNG-EC has no postfertilization effect, which led to premature excitement by Catholic bioethicists that this proved LNG-EC did not act against life. *However, that can be said only when the drug is given on the day of the LH surge, not the other days of the fertile window.* Studies such as this confuse some readers because generalizations are then made that LNG-EC has no postfertilization effect on *the conceptus or its successful implantation*.

An additional study reported by Noé et al. in 2010, evaluated women who sought LNG after "unprotected"

intercourse (Noé et al. 2010). A history of the last menstrual period and time of intercourse was obtained and blood work was done the day LNG-EC was given and daily for the next five days. Measurements of serum LH, estradiol, and progesterone levels as well as daily pelvic ultrasounds to measure the diameter of the follicle were performed. Of the 337 women who participated in the study, 215 women had relations during the infertile time of the cycle as determined by lab work and thus 63.7 percent of the women received the drug unnecessarily. A total of 87 women were preovulatory in days −5 to −1, and 35 women were on day 0 or later. Of the 87 women treated before ovulation, 62 women ovulated as determined by ultrasound, for an ovulation rate of 71 percent in patients given the drug on days −5 to −1, yet no pregnancies occurred in these women. The paper stated that 15 women did not attend the follow-ups so it could not be determined whether they ovulated, but they were included in the analysis. Excluding them would have raised the percent that ovulated despite LNG-EC to 86 percent. According to the paper, pregnancy would have been expected to occur in 13 out of the 87 women, but despite ovulation occurring, no pregnancies were clinically evident after LNG-EC. This is additional strong evidence that LNG-EC has a post-fertilization effect.

Of the 35 women who took LNG-EC on the day of ovulation or after, all ovulated and there were the usual number of pregnancies, indicating that LNG-EC does not interfere with the establishment of a pregnancy if it is given the day of ovulation or later. They stated in their conclusion:

> in the current study, FR (follicular rupture or ovulation) occurred in some two-thirds of women taking LNG-EC preovulatory; this suggests that other mechanisms than suppression of ovulation prevents pregnancy in these women. (Noé et al. 2010, 419)

In an article published in *Health Progress* for the Catholic Health Association in 2010, Sandra Reznik, a physician and researcher in reproductive pharmacology, stated "It is virtually undisputed that levonorgestrel prevents ovulation" (Reznik 2010, 59). She argued that the other mechanisms of action listed by the manufacturer on the package insert were incorrect when they stated it could prevent implantation, stating that there was "absolutely no data to support this statement" (Reznik 2010, 61); however, she made these statements without reviewing the studies described above that showed that this drug is not effective at preventing ovulation and thus prevention of ovulation should not be considered its main mechanism of action.

Reznik's incomplete review of the research literature on LNG-EC was followed by an article by Ron Hamel, who is the senior ethicist for the Catholic Health Association. He stated that criticism of the use of LNG-EC in Catholic hospitals in cases of rape was based on

> prevailing beliefs or assumptions about mechanisms of action that may be based on drug manufacturer labeling, or on *outdated* scientific literature, or on mere supposition. (Hamel 2010, 62, emphasis added)

He confidently stated that the literature shows that the drug prevents ovulation and that all other mechanisms of action are mere possibilities. He reminded his readers:

> One of the well-known truisms in ethics is that good moral judgments depend in part on good facts. Absent adequate and accurate information, there is an increased possibility of a faulty analysis and, therefore an erroneous judgment. (Hamel 2010, 62)

Based on a faulty understanding of the literature on LNG-EC and a failure to accept that better studies showed that it is a poor anovulant, I propose that the initial judgment that LNG-EC works to prevent ovulation and has little postfertilization effect should be reevaluated. Hamel went on to criticize Bishop Elio Sgreccia of the Pontifical Academy for Life who reaffirmed in 2007, that emergency contraception acted against life and that Catholic physicians and Catholic hospitals should not administer it in cases of rape. Hamel pointed to an article by Austriaco in 2007, in which he interpreted the medical literature as saying a postfertilization effect would be extremely small (Austriaco 2007). However, Austriaco did not have the three studies by Durand et al. and the article by Noé cited above to aid in his review.

The other factors that could account for a contraceptive effect of LNG-EC would be an inhibition of sperm transport, capacitation, and prevention of fertilization. Studies on various aspects of sperm function after LNG have not supported this as a mechanism of action.

With regard to sperm function, Yeung et al. looked at sperm motility, acrosome reaction, zona binding capacity, and oocyte fusion capacity of sperm treated with 1, 10, and 100 ng/ml of LNG for three hours. They showed that LNG-EC affected sperm function only at high concentrations and therefore was unlikely to play a role in the effectiveness of this drug to prevent pregnancy (Yeung et al. 2002). A study by Brito et al. also found no effect on the acrosomal reaction in sperm in the uterus 36–60 hours after coitus and 24–48 hours after LNG-EC administration, or on the number of sperm in the uterus (Brito et al. 2005). Their conclusion was that a single dose of 1.5 mg LNG does not impair the quality of cervical mucus or sperm penetration of the cervix or the ability of sperm to fertilize an oocyte. Therefore, it appears that the circumstances necessary to achieve fertilization of an ovum are not affected by LNG-EC unless it is given at the beginning of the fertile window. It also appears that the one parameter that could be *easily* assessed in the emergency setting, the LH surge, instead of being a criterion for not giving it, would be a day the drug could be given as it would not prevent ovulation anyway and would not have an adverse effect on the conceptus or on implantation. The period of time in which we have to be concerned about the effect of LNG-EC on survival of the conceptus and successful implantation is when the drug is given on cycle days −4 to −2. As has been demonstrated here, there is no way of knowing if the woman is in that part of her cycle when she presents to the emergency room after a rape, *and as the drug does not prevent ovulation or fertilization on those days, but is still highly effective in preventing a pregnancy, it has to be acting after fertilization has taken place*.

Bioethical Principles in the Use of an Emergency Contraceptive in Rape

According to Cataldo the principle of double effect should not be applied to the use of LNG-EC in cases of rape because he views the possible interceptive or contragestive effects of the drug to be improbable and therefore

> the inability to foresee reasonably that an abortifacient effect will occur as a result of receiving an anovulatory hormonal medication disqualifies this possibility as a trigger for the application of the principle of double effect. (Cataldo 2009, 136)

Therefore, he feels the traditional sources of a moral act: the object, the intention, and the circumstances should be

considered and are fulfilled in this case. We would all agree that the object of giving an EC in the case of rape is to protect the woman from the sperm of her attacker. However, if you ask either the woman or the doctor giving her LNG-EC what they are intending in taking the drug, their intention is *to prevent a pregnancy*, not to prevent ovulation. In fact, 50 percent of women who conceive from a rape will obtain an abortion. Obstetrician-gynecologists will say that they understand that one of the mechanisms of action of LNG-EC is to prevent successful implantation of a conceptus. The manufacturer states that this is a mechanism of action of LNG-EC in the accompanying drug information, and from the research presented above that is certainly probable. If the stated intention is to prevent ovulation, then that eliminates all synthetic hormones and progesterone antagonists as treatments, as they are poor anovulants.

Lastly, the circumstances for licit use of LNG-EC in cases of rape presented by the Peoria protocol—which assumed the drug worked primarily to prevent conception—including a history, medical exam, a urinary LH, an emergency progesterone level, and a pregnancy test would not accurately reassure the physician that this is a time in the woman's cycle when the drug will not affect survival and implantation of a conceptus. There is no way to determine where she is in the fertile window in an emergency room setting, and there is already a misunderstanding that she should not get the drug during the LH surge when that is in fact the time it is least likely to cause subsequent harm to a conceptus, *as compared with taking it on days −4 to −2 of the fertile window, when it will not prevent ovulation, but will prevent survival of the conceptus.*

The immoral conditions of giving EC *after a rape* are discussed in *Dignitas personae* which states:

> Alongside methods of preventing pregnancy which are, properly speaking, contraceptive, that is, which prevent conception following from a sexual act, there are other technical means which act after fertilization, when the embryo is already constituted, either before or after implantation in the uterine wall. Such methods are *interceptive* if they interfere with the embryo before implantation and *contragestative* if they cause the elimination of the embryo once implanted.
>
> *In order to promote wider use of the interceptive methods* (emphasis added), it is sometimes stated that the way in which they function is not sufficiently understood. It is true there is not always complete knowledge of the way that different pharmaceuticals operate, but scientific studies indicate that *the effect of inhibiting implantation is certainly present*, even if this does not mean that such interceptives cause an abortion every time they are used, also because conception does not occur after every act of sexual intercourse. It must be noted, however, that 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 an abortion* (emphasis added). (CDF 2008, n. 23, original emphasis except where indicated otherwise)

A recognized moral authority, the Congregation for the Doctrine of the Faith, states that this is an immoral act if the drugs given act in any way other than as a contraceptive. Because of the intrinsic value of every human life, no matter the circumstances of conception, we have to err on the side of protecting an innocent life.

What is the probability that human lives are lost as a direct effect of LNG-EC? Yeung, Laethem, and Tham calculated that three to thirteen percent of the time, a post-fertilization effect from LNG-EC would prevent successful

implantation (Yeung, Laethem, and Tham 2009). If there are at least 683,000 women in the U.S. of childbearing age raped each year, with a probability of pregnancy of 5 percent, this would result in 34,150 children conceived as a result of rape. If given LNG-EC, by Yeung and Tham's calculations, this would mean the deaths of 1,024 to 4,439 children from the use of LNG-EC in cases of rape in this country annually.

When looking at the problem of pregnancy after rape, is the distress for the mother from the pregnancy more significant than the possibility, which is not remote, of causing the death of a child? With good obstetrical care and emotional support, the woman's life is not in immediate danger because of the pregnancy. She is not obligated to raise the child after birth, but could place the child, who is after all, biologically hers, up for adoption. The poor anovulant *effect of LNG-EC, and likely interceptive or contragestive effects of the drug* poses a significant risk of interrupting a conception, and thus the good effect for the woman of not going through a clinical pregnancy is outweighed by the bad effect on the embryo.

Sulmasy argues that giving EC is moral from the principle of double effect, *that is, it is an action that is good in itself but there are two effects–an intended and otherwise not reasonably attainable good effect (prevention of a pregnancy as a result of a sexual assault), and an unintended yet foreseen evil effect (remote chance of ending the life of the conceptus); and this is licit as there is a due proportion between the intended good and the permitted evil* (Sulmasy 2006). He claims that giving EC has two effects: preventing conception and possibly preventing implantation of a very early embryo. *Certainly we do not have to have 100 percent certainty that LNG-EC can never act against a new human life, but we have shown with this review of studies on the mechanism of action of LNG-EC that this is not a remote possibility as many have led us to believe. This drug does not work consistently to prevent ovulation and fertilization.* Secondly, he proposes *that the administration of emergency contraceptive hormones is not intrinsically evil* because they are given for other disorders in women. That is an incorrect conclusion as the dosage of LNG-EC is equivalent to fifty "mini-pills" of a progesterone-only oral contraceptive and is not physiologic. He also states that a Catholic physician can prescribe these drugs as long as the intention is to prevent ovulation and fertilization. However, as shown above we know that this drug is a poor anovulant and does not appear to have an effect on sperm motility or capacitation, making this drug's mechanism of action more than a contraceptive and contrary to the principles of *Dignitas personae* quoted earlier. Lastly, he states

> it is not the case that the prevention of implantation of a conceptus is a necessary cause of the morally permissible good effect of preventing conception from taking place. (Sulmasy 2006, 316)

Noé et al. showed that despite at least 71 percent of the women ovulating when they were given LNG-EC during the fertile window, there were no pregnancies when at least 13 would have been expected, therefore it was having an effect post-fertilization. And so the use of LNG-EC in cases of rape is not justified by the principle of double effect, because the harmful effect on the conceptus is not a remote possibility.

Is There a Possible Alternative?

No progesterone agonist or antagonist can be used as an emergency contraceptive because of the likely effects on survival of

the conceptus and the receptivity of the endometrium which could interrupt the normal development of this early human life. Is there any other class of drugs that are more in keeping with the intention of preventing ovulation?

Jesam et al. studied a partially selective cyclooxygenase (COX)-2 inhibitor, meloxicam, as an emergency contraceptive. COX-2 is an enzyme that regulates the formation of prostacyclins, prostaglandins and thromboxane (Jesam et al. 2010). It serves an important function in vasodilation and platelet aggregation. Disruption of COX-2 production causes reproductive failure in mice, including preventing ovulation, fertilization, implantation, and decidualization (Lim et al. 1997). Jesam et al. found that at doses of 30 mg/day taken for five days during the late follicular phase and the day of the LH surge, 90.9 percent of women failed to ovulate or had dysfunctional ovulation with no effect on LH, progesterone, estradiol levels, or cycle length. A non-hormonal drug which targets only ovulation would be a licit emergency contraceptive in cases of rape if the intention is to prevent ovulation. However, although this drug effectively targets ovulation when given during the fertile window, it can have other effects on the conceptus.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in pregnancy, particularly in the two weeks after ovulation before the woman knows she is pregnant with as many as 23 percent of pregnant women in the United States reporting taking them during the first trimester (Correa et al. 2012). They may be taken for headache, cramping, pain, and respiratory infections. The National Birth Defects Prevention Study is an ongoing case–control surveillance study to identify risk factors for birth defects. A total of 3,173 women in the study, who would deliver from October 1, 1997 to December 2004, were exposed to NSAIDs in the first trimester. They did not find NSAID exposure to be a major risk factor for birth defects, but they did find a moderate association with anophthalmia/microphthalmia, amniotic bands/limb body wall defects, pulmonary valve stenosis and neural tube defects, which had not been reported before, as well as oral clefts, which had been reported with naproxen use. A retrospective review of 14,915 women exposed to these drugs in the first trimester versus 5,546 controls showed that NSAIDS were not a major cause of birth defects, but there was a small statistically significant increased incidence of rare birth defects. Nielsen et al. also found no significant association with congenital malformation, low birth weight or preterm birth, but did find an increased risk of miscarriage (Nielsen et al. 2001). The authors could not be sure that the drugs were prescribed in some instances to control cramping from a miscarriage, however. In an infertility work-up, a history of NSAID use is taken and women are advised to stop using these medications as they could be interfering with ovulation.

Meloxicam has been shown to be a highly effective anovulant, throughout the five pre-ovulatory days of the fertile window and including the day of the LH surge, but one should avoid its use after ovulation, *as it can disrupt survival of the conceptus and implantation*. If we return to the Peoria protocol presented earlier, along with the other testing discussed, *if the progesterone level is less than or equal to 2.0 ng/ml* or if an LH surge is detected, *meloxicam* could be started in the emergency room. *Even if an emergency progesterone level cannot be obtained*, it could be followed up the next day and if the level is less than or equal to 2.0 ng/ml, the victim could start meloxicam at that time, and the physician could feel comfortable that

the drug will act primarily as an anovulant. *Further discussion on drugs such as this in cases of rape needs to be carried out to assist Catholic physicians and Catholic hospitals to "first do no harm."*

In summary, the literature on LNG-EC contradicts the commonly held belief, and subsequent bioethical conclusions, that this drug primarily works to prevent ovulation and fertilization and could be used licitly by physicians in Catholic hospitals in cases of rape. *Often it appears that the literature on LNG-EC is contradictory, but as each study is reviewed, it can be seen that it looks at a different part of the elephant, as it were. The timing of its administration relative to the day of ovulation shows a different effect of the high dose of this progestagen both immediately and days later in the woman's cycle, resulting in several mechanisms of action to prevent pregnancy. We can conclude from these studies that LNG-EC is a poor contraceptive*. Alternatives need to be sought that are in keeping with the intention of preventing ovulation and fertilization in cases of rape.

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