Mechanism of action of levonorgestrel emergency contraception

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Therehas been much debate regarding levonorgestrel emergency contraception's (LNG–EC's) method of action since 1999 when the Food and Drug Administration first approved its use. Proponents of LNG–EC have argued that they have moral certitude that LNG–EC works via a non-abortifacient mechanism of action, and claim that all the major scientific and medical data consistently support this hypothesis. However, newer medical data serve to undermine the consistency of the non-abortifacient hypothesis and instead support the hypothesis that preovulatory administration of LNG–EC has significant potential to work via abortion. The implications of the newer data have important ramifications for medical personnel, patients, and both Catholic and non-Catholic emergency room protocols. In the future, technology such as the use of early pregnancy factor may have the potential to quantify how frequently preovulatory LNG–EC works via abortion.

Lay Summary: *How Plan B (levonorgestrel emergency contraception) works has been vigorously debated ever since the Food and Drug Administration approved it in 1999. Many doctors and researchers claim that it has either no—or at most—an extremely small chance of working via abortion. However, the latest scientific and medical evidence now demonstrates that levonorgestrel emergency contraception theoretically works via abortion quite often. The implications of the newer data have important ramifications for medical personnel, patients, and both Catholic and non-Catholic emergency room rape protocols.*

Keywords: Levonorgestrel emergency contraception, Abortion, Moral certitude, Early pregnancy factor

HISTORY

Emergency contraception (also known as postcoital contraception or the morning-after pill) refers to the use of drugs or devices as an emergency measure to prevent pregnancy (Zieman 2014). In 1966, researchers began to use synthetic estrogens such as diethylstilbestrol and ethinyl estradiol as emergency contraception (EC). These formulations had both low efficacy and numerous side effects. In the early 1970s, the Yuzpe regimen was invented. It was a combination birth control pill given within a twelve-hour interval within three days of sexual relations. In 1999, the Food and Drug Administration approved Plan B (levonorgestrel emergency contraception, LNG-EC) as the first progestin-only type of EC. Plan B had various advantages over the Yuzpe regimen, including higher efficacy and the absence of estrogen-related side effects. Plan B is often given

in both secular and Catholic hospitals (under certain conditions) in order to attempt to prevent pregnancy. Recently, other methods of EC have been introduced (e.g., ulipristal acetate, a selective progesterone receptor modulator), but levonorgestrel emergency contraception has garnered the most attention as it is the most widely used EC in the world (Trussell and Raymond 2013).

The controversy over LNG-EC focuses mainly on whether it is an abortifacient, that is, whether it causes the loss of life after fertilization. In order to answer this question, researchers have conducted numerous studies over the years. A critical element of such studies is the ability to accurately determine a woman's day of ovulation. Many earlier studies[1] (Arowojolu, Okewole, and Adekunle 2002; Creinin et al. 2006; Hamoda et al. 2004; He et al. 1991; Ho and Kwan 1993; Tirelli, Cagnacci, and Volpe 2008; Von Hertzen and Van Look 1998; von Hertzen et al. 2002) have relied on a woman's recall of the last day of her previous menstrual period as well as its length; this has been shown to be inaccurate (Espinós et al. 1999; Noé et al. 2011). Other studies have relied solely on hormone levels (Hapangama, Glasier, and Baird 2001; Novikova et al. 2007). To date, five studies have measured both recall and hormone levels (Croxatto et al. 2004; Durand et al. 2001, 2010; Massai et al. 2007; Noé et al. 2011); four of these studied primarily sterilized women (Croxatto et al. 2004; Durand et al. 2001, 2010; Massai et al. 2007).

New Developments

The Noé Study

In 2010, Noé et al. published the most sophisticated study to date on levonorgestrel emergency contraception (Noé et al. 2010), which they updated in 2011 (Noé et al. 2011). This is the largest study to date to employ serial transvaginal assessments of follicular size to determine ovulation. It contains some of the key data that support the claim that LNG-EC works at times via abortion. Noé et al. enrolled 450 women who requested LNG-EC at a Chilean family planning clinic; each received 1.5 mg of LNG-EC within 120 hours of unprotected sexual relations, and 99 percent received LNG-EC within 72 hours of relations. In their study, 103 were determined to have had relations within the five days prior to ovulation (e.g., days -5, -4, -3, -2, or -1), that is, the preovulatory group; 45 women had relations on the day of ovulation (day 0) or after, referred to as the postovulatory group. Noé et al. estimated the number of expected pregnancies for each group by calculating the likelihood of pregnancy based on the work of Wilcox, Weinberg, and Baird (1995), who in 1995 generated a predictive model to estimate the probability of pregnancy for each day of the menstrual cycle by measuring hormonal urine profiles in women who were trying to become pregnant. Noé et al. found that none of the women who took LNG-EC in the preovulatory period became clinically pregnant, while they predicted sixteen women should have become pregnant had they not received LNG-EC. They concluded that levonorgestrel EC was 100 percent effective in stopping clinical pregnancy if given prior to ovulation. In the postovulatory group, they found that eight women who received LNG-EC became pregnant, while the Wilcox model predicted that 8.7 pregnancies should have occurred. They concluded that levonorgestrel had no effect in stopping pregnancy if given on the day of ovulation or after ovulation.

Arguments Against an Abortifacient Effect and Rebuttals

Argument Number 1: Redefinition of Pregnancy

Some today advance the argument that LNG-EC is not abortifacient because they attempt to define pregnancy as beginning at implantation and argue that any loss of life prior to implantation is not abortion. This definition was first promoted by the American Congress of Obstetricians and Gynecologists (ACOG)[2] in 1965 (American College of Obstetricians and Gynecologists Terminology Bulletin 1965), who attempted to redefine life as beginning at implantation. If one accepts this definition, then one may conveniently forgo mentioning its abortifacient effect to patients, as any destruction of life prior to implantation would be defined as "prior to being pregnant." This argument justifies its conclusions by arbitrarily altering the definition of when life begins. We consider this argument devoid of biological accuracy. For clarity, the terms used in this paper accept the definition that any hormone or device that causes an artificial interruption of life after fertilization is an abortifacient.

Argument Number 2: LNG-EC Stops, Delays, or Alters Ovulation

Proponents of LNG-EC have argued that LNG-EC's dominant mechanism of action is inhibition or delay of ovulation. For example, in 2008, the International Consortium for Emergency Contraception and International Federation of Gynecology & Obstetrics stated that LNG-EC "inhibits or delays ovulation" and that "this should be its primary and possibly only mechanism of action" (International Consortium for Emergency Contraception (ICEC), International Federation of Gynecology & Obstetrics (FIGO) 2008). Furthermore, in August 2013, the American Congress of Obstetricians and Gynecologists noted that "Before ovulation, treatment with emergency contraception is believed to disrupt follicular maturation and consequently inhibit or delay ovulation."[3] Finally, in a recent review article, Gemzell-Danielsson, Berger, and Lalitkumar (2013) noted:

> Emergency contraception with a single dose of 1.5 mg LNG … acts through inhibition of or postponing ovulation.

This has also been one of the main arguments used by some bishops to justify the use of LNG-EC in rape protocols when given prior to ovulation.[4]

However, recent studies clearly demonstrate that LNG-EC does not consistently stop or delay ovulation. Noé et al. also noted that 80 percent of women in the pre-ovulatory group had evidence of follicular rupture[5] if LNG-EC was given on days -5 to -1; this increased to 92 percent (i.e., 22 out of 24) if it was given on day -2. In addition, they noted that if LNG-EC was given on day -2 or -1, about 93 percent (i.e., 26 of 28) of women had evidence of both follicular rupture (via ultrasound) and elevated progesterone levels (over 12 nmol/l) (Noé et al. 2010).[6] Three other studies that measured ovulation via both hormone levels and ultrasound corroborate Noé et al.'s findings. Massai et al. (2007) noted that 84 percent of women had evidence of follicular rupture if they were given LNG-EC when the follicular diameter was 18 mm or greater. Croxatto et al. (2004) noted that 74 percent (29/39) of women who received LNG-EC on or after day -4 and 88 percent (15/17) of women whose follicular diameter was over 18 mm (i.e., near day -2) had evidence of both follicular rupture and progesterone levels over 12 nmol/l. Durand et al. (2010) studied thirty women who took LNG-EC in the

preovulatory period. All of the women who took LNG-EC when the average follicular diameter was 18.4 mm (i.e., estimated to be day -2) had evidence of both follicular rupture and elevated progesterone levels. Thus, the studies to date that used both ultrasound and hormone levels to measure the day of ovulation found that when LNG-EC was given within 5 days prior to ovulation, it had limited effect upon ovulation (Croxatto et al. 2004; Massai et al. 2007; Noé et al. 2011) and even less so if given near day -2. Finally, Durand et al. (2001) noted that LNG-EC had no effect upon the day of ovulation when given on day -3, that is, it caused no delay in ovulation. Brache et al. (2013) also noted that if LNG-EC was given around day -2, it caused no delay in ovulation. We consider these points strong evidence against the claim that levonorgestrel EC stops or delays ovulation when given in the preovulatory period. A recent paper co-authored by Dr. Croxatto seems to partially concede this point:

> From previous studies, it has become clear that the ability of LNG to interfere with the ovulatory process decreases as ovulation nears. (Brache et al. 2013)

Noé et al. offer an alternative explanation as to why women in the preovulatory period who receive LNG-EC do not become pregnant. They claim that LNG-EC alters the normal ovulatory process and therefore makes it more difficult for fertilization to occur. The basis of this claim comes from Dr. Croxatto's 2004 paper (Croxatto et al. 2004) in which he defined the term "ovulatory dysfunction" as: "Follicular rupture not preceded by an LH peak or preceded by a blunted LH peak (<21 IU/l), or not followed by elevation of serum P over 12 nmol/l." However, there is scant support in the literature for the ovulatory dysfunction hypothesis for several reasons.

First, we noted above that the studies of both Noé et al. and Durand et al. found that preovulatory administration of LNG-EC resulted in both successful follicular rupture and progesterone levels over 12 nmol/l in about 93–100 percent of cases when given around day -2. In addition, Croxatto et al.'s own paper noted that all women who experienced "ovulatory dysfunction"—even those who received LNG-EC as early as 5 days prior to ovulation—experienced progesterone peak levels over 36 nmol/l. Therefore, the data in the medical literature are not consistent with the latter half of Dr. Croxatto's own definition of ovulatory dysfunction, which specifies progesterone levels under 12 nmol/l.

Second, in 2004, Croxatto et al. noted that

> Cohlen et al. reported that the probability of conception in spontaneous cycles was related to the pattern of LH surge. A low LH surge (25–42 IU/l) of short duration (1 day) was associated with a reduced pregnancy rate of 5.6%, whereas a 2-day surge exceeding 42 IU/L resulted in a pregnancy rate of 23%.

However, while Croxatto et al. emphasized the height of the LH surge, they failed to emphasize the duration of the surge. For example, Cohlen et al. (1993) noted in Table 2 of their paper that in women who had LH surges of shorter duration, the difference in pregnancy rates between low and high LH levels was only 5.6 percent versus 9.9 percent. In addition, in women who had LH surges of longer duration, the difference in pregnancy rates between low and high LH levels was only 20 percent versus 23.4 percent. Therefore, if one compares pregnancy rates for different LH surge levels, while keeping the duration of the LH surge constant, far less difference is observed.

In addition, Cohlen et al.'s study noted that cycles with lower LH surge levels of

longer duration (i.e., 25–42 IU/l) were at times associated with higher pregnancy rates than cycles with higher LH surge levels of short duration (e.g., 20% versus 11.6%). Cohlen et al. actually emphasized this point: "The data in Table 2 also suggest that the duration of the LH surge is more important than the height: in the rather exceptional cases in which high-short and low-long surges occur, the pregnancy rate in the cycles with the low-long surges is almost twice as high as the one with the high-short surges." Cohlen et al. concluded:

> Taking into account that the duration and height of the LH surge are correlated, it seems that duration is more important than height.

Lastly, Croxatto et al. cited Verpoest et al.'s in vitro fertilization study (Verpoest et al. 2000) in which Verpoest et al. noted that oocytes that had higher concentrations of LH in their follicular fluid demonstrated higher rates of fertilization. However, Verpoest et al.'s conclusions were based on in vitro measurements of follicular LH levels, which cannot even be measured in vivo. In addition, Verpoest et al.'s study results seem to conflict with those of Cohlen et al.; Verpoest et al. noted that the median serum LH level of the unfertilized oocyte group was 42.5 IU/l; however, the Cohlen et al. study noted high rates of fertilization when serum LH levels were above 42 IU/l. In light of the inconsistencies and medical data noted above, the "ovulatory dysfunction" argument does not provide convincing or consistent support in favor of a non-abortifacient action of LNG-EC.

Argument Number 3: Progestins Alter Sperm Flow and/or Function

Noé et al. cite this as a possible mechanism of action when LNG-EC was given in the preovulatory period. They note:

> Follicular rupture was detected in most women … nevertheless, they did not become pregnant. One possible explanation is the increase in cervical mucus viscosity produced by LNG, which interferes with sperm passage. (Noé et al. 2011)

In an earlier paper, Croxatto (2002) referenced an older study (Kesserü et al. 1974) as the basis of their claim:

> Administration of 400 mcg of LNG 3–10 hours after sexual intercourse affected sperm migration between 3 and 9 hours after treatment. It reduced the number of spermatozoa recovered from the uterine cavity, increased the pH of the uterine fluid (which immobilized the spermatozoa) and increased the viscosity of cervical mucus (which impeded further passage of sperm cells into the uterine cavity).

While chronic administration of progestins tends to inhibit sperm via thickening of cervical mucus (Okewole et al. 2007), this does not appear to be true for short-term administration of LNG-EC. For example, do Nascimento et al. (2007), in a recent and more sophisticated study than that of Kesserü et al. (1974), found that if women were given LNG-EC 12 to 36 hours after relations, viable sperm were found in uterine flushings up to 60 hours after coitus and sperm acrosome reaction was not affected. In addition, they noted that 14.5 million and 17.3 million spermatozoa/ml were found respectively in women who took LNG-EC at 24 or 48 hours after sexual relations. Brito et al. (2005) found that LNG-EC had no capacity to affect sperm's acrosome reaction in either capacitated or non-capacitated sperm. Finally, when LNG was given

> in a similar dose to that observed in serum following oral intake for EC, LNG had no effect on the number of motile spermatozoa recovered from the human fallopian tubes in vitro, on their adhesion to the

tubal epithelium, distribution or AR rate. (Hermanny et al. 2012)

Therefore the argument that LNG-EC effectively inhibits sperm flow or function is clearly not supported by current medical data.[7]

Argument Number 4: Progestins Stabilize the Endometrium

Proponents of levonorgestrel EC often argue that levonorgestrel EC is a progestin, and because progesterone, the body's natural progestin, is often used to stabilize a pregnancy, levonorgestrel EC in turn should have a stabilizing effect upon the endometrium. This may be true under certain conditions. While it is true that levonorgestrel EC is a type of progestin, it is a synthetic hormone that is given in supraphysiological doses. For example, one dose of LNG-EC contains 1.5 mg of levonorgestrel, the equivalent of more than 75 percent of the entire month's supply of the amount of levonorgestrel found in certain oral contraceptives.[8]

The effect of levonorgestrel appears to depend upon when in the cycle it is given. For example, the accumulation of data from three major studies (Arowojolu and Okewole 2004; Gainer, Méry, and Ulmann 2001; von Hertzen et al. 2002) show that 1,034 of 3,496 women bled within 7 days of taking LNG-EC (i.e., 29.6% bleeding rate), and this bleeding appears to be most common when LNG-EC is given prior to ovulation (Gainer, Méry, and Ulmann 2001). Endometrial bleeding denotes major endometrial instability and could cause loss of the embryo that is about to be or has recently been implanted.

However, if levonorgestrel EC is given on the day of ovulation or after, it could actually stabilize the endometrium and might have the potential to increase a woman's likelihood of pregnancy, as would

be the case if the observed number of clinical pregnancies were higher than the estimated number. Noé et al. (2011) noted that in the postovulatory group, eight women who received levonorgestrel EC became pregnant while they predicted that 8.7 women should have become pregnant. However, it is likely that Noé et al. overestimated the number of women expected to become pregnant as they based their estimates on the Wilcox study (Wilcox, Weinberg, and Baird 1995). In that study, women were trying to become pregnant, and women who are trying to become pregnant appear to have far higher sperm counts than women who take LNG-EC. For example, Espinós-Gómez et al. (1999) noted in their 2007 study that spermatozoa were detected in 63.8 percent of women who took EC but were present in 100 percent of controls who did not take EC and were trying to get pregnant.[9] They also noted that the controls had 3 times higher sperm counts than those who took EC. Based on the work of Espinós-Gómez et al., it is very likely that the women who received LNG-EC in Noé et al.'s study had lower sperm counts than women in the Wilcox study who were trying to become pregnant. In addition, Noé et al. noted that 41 and 6 percent of the included women said they had problems with condom use or coitus interruptus, respectively; these women would theoretically have lower sperm counts or even no sperm. This has been noted in the medical literature: Croxatto noted in 2007 that

> a large proportion of cases requesting EC in those studies correspond to "condom failures," and up to 36 percent of those have no sperm in the vagina or cervical canal within 6 hours after coitus. Those cases are included in the "at-risk group" in the efficacy studies leading to an overestimation of the efficacy of EC. (Croxatto 2007)

In light of these data, it is highly likely that the women who received LNG-EC in Noé et al.'s study had lower sperm counts—and some may not have had any sperm at all—compared with women who were trying to become pregnant. Therefore, Noé et al. may have overestimated the number of expected pregnancies, a point that Dr. Noé freely acknowledges.[10] If this were true, that is, if the expected number of pregnancies in the postovulatory group had been less than 8, then LNG-EC could actually be stabilizing pregnancy if given on or after the day of ovulation. Other authors have acknowledged this possibility. Davidoff and Trussell note:

> It even raises the counter-intuitive but undocumented possibility that Plan B used after ovulation might actually prevent the loss of at least some of the 40 percent of fertilized ova that ordinarily fail spontaneously to implant or to survive after implantation. (Davidoff and Trussell 2006)

Argument Number 5: LNG-EC Does Not Affect the Endometrium

It is argued that if LNG-EC does not affect the endometrium it cannot be causing an abortion. There are three main reasons why the *stable endometrium theory* is weak.

First, while there are data, both in animals and humans, which show that LNG-EC has little effect upon the endometrium, other data do show an effect. For example, Ugocsai, Rózsa, and Ugocsai 2002) noted in 2002 that when higher doses of LNG-EC were given (i.e., about 2½ times the normal dose) they caused obvious loss of ciliated cells, and pinopodes disappeared. This could have implications for women who have low body weight and might experience higher peak concentrations of levonorgestrel.

Second, Durand et al. (2005) noted that LNG-EC changed endometrial glycodelin-A levels, which could affect implantation.

The third problem with the stable endometrium theory is that even though the endometrium appeared stable in some studies on a histological level, it appeared unstable on a clinical level. We noted earlier that women who take LNG-EC prior to ovulation are those who are most likely to bleed and that studies show that 29.6 percent of women who take LNG-EC develop menstrual bleeding within 7 days; thus, even if implantation did, or was about to occur, the embryo could easily be destroyed due to substantial sloughing.

Finally, even if LNG-EC had no effect on the endometrium, it could still cause abortion via alternative mechanisms as noted in the "Burden of Proof" section.

Argument Number 6: LNG-EC Does Not Increase the Ratio of Ectopic Pregnancies

Opponents of an abortifacient mechanism of LNG-EC argue that if it worked by preventing implantation it should decrease the number of intrauterine pregnancies but should have no effect on the number of ectopic pregnancies (Davidoff and Trussell 2006); therefore, the ratio of ectopic to intrauterine pregnancies should be on the high end of the expected ectopic pregnancy rate if LNG-EC worked via abortion and the low end if it did not. They cite Cleland et al.'s (2010) study, whose review paper concerning LNG-EC and ectopic pregnancy noted a 1 percent ectopic pregnancy rate (3/307) which falls on the lower end of their estimated normal rate of ectopic pregnancy (i.e., 1–1.9%). However, Cleland et al. did not include the results of two important studies, both of which obtained their data from retrospective chart reviews: the first, by Gainer, Méry, and Ulmann (2001) noted an ectopic pregnancy rate of 4.1 percent (3/73); the second, by Lo and Ho (2012) published after the Cleland

study, noted an ectopic pregnancy rate of 2.3 percent (3/128). If Cleland et al. had included these studies, the new ratio would have been 1.8 percent (9/508), a ratio more consistent with an abortifacient effect.

Argument Number 7: LNG-EC Does Not Work Efficiently

The American Congress of Obstetricians and Gynecologists claims that Plan B has an efficacy rate of 85 percent,[3] a statistic which is far higher than that of a more recent study (Noé et al. 2011). Researchers who have employed elaborate statistical models have noted that if LNG-EC were 85 percent effective, it would strongly imply that it worked via abortion a portion of the time and if LNG-EC were less efficacious, it would be less likely to be an abortifacient (Mikolajczyk and Stanford 2007; Valenzuela 2007). Recent trials such as that of Noé et al. (2011) noted an efficacy rate of 68 percent. However, even this estimate is likely too high, as we noted earlier, considering the lower sperm counts noted in women who receive LNG-EC. If the latter were a significant factor, then the efficacy of LNG-EC could actually be less than 50 percent. In addition, LNG-EC appears to have far less effect in obese women and almost no effect in women whose body mass index (BMI) is over 30 (Glasier et al. 2011).

We agree with many researchers that LNG-EC's efficacy is likely much lower than that promulgated by the American Congress of Obstetricians and Gynecologists and that the lower the efficacy rate, the less likely that LNG-EC will work by causing abortion. However, as noted in Noé et al.'s (2011) study, no women who took LNG-EC in the preovulatory period had clinical pregnancies, whereas sixteen pregnancies were expected (i.e., 0/16). If Noé et al. had had a more accurate method of estimating expected pregnancy (e.g., by

studying only women in whom sperm were present and excluding women who reported condom failure or coitus interruptus), they may have generated a lower expected pregnancy rate. However, even if Noé et al. had generated a lower estimate, the numerator would still have been zero, so that LNG-EC still would have been 100 percent effective in stopping clinical pregnancy in the preovulatory period while failing to stop ovulation and sperm flow and likely fertilization. Therefore, even if LNG-EC works less efficiently than national sources claim, the data still support an abortifacient method of action when given in the preovulatory period.

Argument Number 8: Time-delay Argument

Two trials conducted via the World Health Organization have shown that the efficacy of LNG-EC decreases when the interval between intercourse and LNG-EC administration increases (Von Hertzen and Van Look 1998; von Hertzen et al. 2002). Noé et al. (2011) noted that if an endometrial effect were present, then theoretically the efficacy of LNG-EC should not decrease as the time period between administration of LNG-EC and unprotected intercourse lengthens as noted in the WHO trials. This argument appears weak mainly because in both of the World Health Organization trials the authors relied solely on recall to predict the expected day of ovulation. Noé et al.'s (2011) own study showed that this method is inaccurate and limits any firm conclusions from the trials. In addition, it is certainly possible that LNG-EC could be causing abortion via a non-endometrial (e.g., fallopian-based) effect. For example, there is evidence that LNG-EC may slow the transport of the newly fertilized ovum in the fallopian tube, which could cause it to arrive at the

endometrium outside of the implantation window and lead to a failure to implant. Mahmood et al. (1998) noted that higher progesterone concentrations inhibited ciliary beat frequency in the fallopian tube. It is conceivable that high-dose levonorgestrel levels could have a similar effect. In addition, Wånggren et al. noted that levonorgestrel markedly decreased muscular contractions in the fallopian tube in vitro (Wånggren et al. 2008). If LNG-EC slowed the kinetics of sperm/ova transport in the fallopian tube, it could explain why early administration might result in a higher efficacy than delayed administration, since the effects of LNG-EC on the fallopian tube could be time-sensitive.

THE BURDEN OF PROOF

Those who advocate a non-abortifacient action of LNG-EC must have moral certitude that it will not risk the loss of human life. We have noted significant weaknesses in all of the major arguments that have been used by those who claim that LNG-EC works via a non-abortifacient action. Two recent review papers have reached similar conclusions (Peck and Velez 2013; Raviele 2014). In light of the most recent scientific and medical data noted in this paper, the claim of moral certitude in regard to a non-abortifacient action of LNG-EC is not justifiable.

We noted earlier that the data support the hypothesis that functional sperm and ova are not inhibited from flowing freely to the fallopian tube and there is no obvious reason why fertilization could not occur.[11] However, Noé et al. (2011) found no evidence of clinical pregnancy when LNG-EC was given prior to ovulation. The absence of any evidence of clinical pregnancy in instances when fertilization occurs is, by definition, abortion. At this point, one cannot determine how frequently fertilization occurs when LNG-EC is given prior to ovulation, however, if future testing shows that fertilization occurs normally in the setting of preovulatory administration of LNG-EC, it would mean that prevovulatory LNG-EC's dominant method of action is via abortion.

Although the burden of proof lies on proponents who advocate a non-abortifacient action of LNG-EC, there are multiple theoretical explanations as to how LNG-EC could cause abortion when given prior to ovulation. First, as we noted earlier, LNG-EC has the potential to cause endometrial bleeding within 7 days of its consumption 29.6 percent of the time, especially when taken in the preovulatory period. This could cause abortion if fertilization had occurred via endometrial sloughing. Second, LNG-EC may cause a luteal phase defect phenomenon when given in the follicular phase. For example, Tirelli, Cagnacci, and Volpe (2008) noted that women who take LNG-EC in the preovulatory period experienced nearly an eleven-day shortening of their menstrual cycle, although this phenomenon occurred less frequently when LNG-EC was given closer to the day of ovulation. Third, we noted previously that LNG-EC may slow the transport of the newly fertilized ovum in the fallopian tube, which could cause it to arrive at the endometrium outside of the implantation window and lead to a failure to implant. Finally, it is possible that in the future LNG-EC might be found to cause changes in the fallopian tube or in the implantation process in ways that we are unaware of today. For example integrins and glycodelins, both discovered in the past 30 years, are critical to the implantation process; and it is likely that newer molecular proteins that could affect the fallopian tube and/or the implantation process will be discovered in the future. We conclude that based on

current scientific and medical data, there is significant potential that the clinical efficacy of preovulatory administration of LNG-EC is due to an abortifacient effect, with the death of the embryo in the fallopian tube, in utero, or after implantation.

EARLY PREGNANCY FACTOR AND LNG-EC

Studies to determine the frequency of abortion due to preovulatory LNG-EC might benefit if early pregnancy factor (EPF) technology was utilized. EPF is an immunosuppressive protein secreted by the ovary shortly after fertilization. It was discovered in 1974 by Morton, Hegh, and Clunie (1974) and has been described as the "most sensitive parameter for the surveillance of early pregnancy" (Straube et al. 1989). Since EPFs discovery, almost every study has corroborated its sensitivity and specificity except two (Cooper and Aitken 1981; Thomson et al. 1980). Both of these studies, however, deviated from Morton's original method of measuring EPF (Smart et al. 1982b). EPF has been described in detail in multiple papers from the 1970s through early 2000. We believe it could be a tool for settling the controversy regarding LNG-EC's mechanism of action for several reasons.[12]

First, both animals (e.g., mice, rats, pigs, sheep, and cattle) and humans exhibit EPF early in pregnancy (Fan and Zheng 1997; Shahani and Moniz 1992). It is detectable within 48 hours after fertilization (Rolfe 1982; Smart et al. 1981).

Second, EPF levels fall to normal within 2–5 days after induced abortion (Cheng et al. 2000; Hübel et al. 1989). This supports EPF's role as a marker for pregnancy as well as non-pregnancy.

Third, EPF levels correlate well with B hcg (Gerhard, Katzer, and Runnebaum 1991).

Fourth, historically, EPF has been cited as strong evidence to show that the intrauterine device (IUD) works by causing early abortions (Smart et al. 1982a); this finding was later corroborated by research that measured early pregnancy in IUD users via B hcg (Landesman, Coutinho, and Saxena 1976).

Fifth, EPF has been cited as giving evidence in favor of Clomid's potential abortifacient effect. Shahani et al. (1995) noted that Clomid resulted in an 80 percent loss of embryonic life, higher than the standard calculated rate of about 48 percent[13] (Mesrogli, Maas, and Schneider 1988).

Sixth, a review of the studies regarding very early pregnancy (i.e., within seven days after fertilization) showed that EPF was positive 93.6 percent of the time (i.e., 44/47) (Chen 1985; Fan and Zheng 1997; Koh and Jones 1982). A review of the studies of women who were pregnant in their first trimester showed that EPF was 91 percent accurate (i.e., 172/189) (Mehta et al. 1987; Morton, Rolfe, and Clunie 1977; Shu-Xin and Zhen-Qun 1993; Wang and Zheng 1990). Therefore, EPF has a good ability to detect early pregnancy (i.e., true positives), that is, it has high sensitivity.

Seventh, EPF has good specificity (the ability to measure true negatives). Two studies (Koh and Jones 1982; Qin and Zheng 1987) showed that EPF was negative in the serum of ninety of ninety-four (i.e., 95.7%) non-pregnant women or men.[14]

Given the fairly strong data about EPF and early pregnancy, the question should be asked: can EPF be used to confirm or deny the presence of human life when LNG-EC is given prior to ovulation? We noted earlier that EPF was found to be positive in six of 23 cases in which an IUD was present, which historically, has been cited as strong evidence in favor an abortifacient effect (Smart et al. 1982a).

However, using EPF to measure abortion rates with LNG-EC would be technically challenging. One would have to follow Morton's original protocol, which would require time and a sophisticated laboratory. One would have to confirm EPF's sensitivity and specificity for that particular study by simultaneously studying a side-control group containing early pregnancy and non-pregnancy cohorts. One would have to measure EPF several times at one-day intervals starting with the second day after fertilization to avoid missing very early pregnancies that might expire before having the opportunity to test for them. Finally, one would have to measure EPF when LNG-EC is given both prior to ovulation and after ovulation.

Would detection of EPF under these conditions prove the case? It would seem that even a low rate of detection (e.g., 3–4%) would be very strong evidence of an early abortion effect, because the rate of fertilization in women who seek LNG-EC is likely far lower than women who are trying to conceive, as previously noted.

CONCLUSIONS AND IMPLICATIONS

The arguments used to justify use of LNG-EC as a non-abortifacient drug carry substantial weaknesses; in addition, the preovulatory administration of LNG-EC does not consistently alter sperm or ova flow and function, yet there is absence of clinical pregnancy in cases where fertilization is likely, which suggests that abortion is a likely mechanism of action. Therefore, the claim that moral certitude exists via LNG-EC's non-abortifacient action is currently indefensible.

LNG-EC is not as efficacious as is currently being promoted by national organizations such as the American Congress of Obstetricians and Gynecologists.

In addition, LNG-EC does not appear to prevent pregnancy in women with high BMIs.

Physicians who dispense LNG-EC to rape victims in the preovulatory period—especially if given within two days of projected ovulation—are giving LNG-EC at a time in a woman's menstrual cycle when it has significant potential to work via the death of the embryo. Physicians who dispense LNG-EC in the postovulatory period may be increasing a woman's risk of becoming clinically pregnant. Physicians who give LNG-EC in either of these periods who fail to inform their patient of these effects are not allowing their patients to receive fully informed consent.

Catholic hospitals that allow the dispensing of LNG-EC prior to ovulation—especially when given within 48 hours of ovulation—are permitting the use of a drug which has a significant potential of working via abortion.

In light of this, current Catholic rape protocols that allow for the dispensation of LNG-EC if the woman is determined to be in the preovulatory period, appear to be faulty and should be revised. Since the most recent medical data clearly note that LNG-EC does not effectively stop ovulation and has high potential to work via abortion when given prior to ovulation, these protocols would no longer be in compliance with Catholic teaching.

Given that the updated information presented in the Noé et al. paper strongly affirms LNG-EC's failure to inhibit ovulation and sperm flow, it is not accurate to label LNG-EC as simply a contraceptive. The nomenclature regarding LNG-EC should be updated. *If given prior to ovulation, LNG-EC should be labeled as emergency abortion/contraception.*

EPF may have the potential to more clearly define and quantify LNG-EC's mechanism of action. If and until such a trial is done, unless proven otherwise, the

medical literature supports the assertion that LNG-EC has significant potential to cause an abortion, especially when given within 48 hours of projected ovulation.

ENDNOTES

1. Tirelli, Cagnacci, and Volpe (2008) did use ultrasound and hormonal evaluation in a small subset analysis in eight women.
2. ACOG was formerly the American College of Obstetricians and Gynecologists. This is still their official position today. http://www.acog.org/About_ACOG/ News_Room/News_Releases/2012/April_ 20_Letter_to_the_ Editor.
3. http://www.acog.org/About_ACOG/ ACOG_Departments/Health_Care_for_ Underserved_Women/Frequently_Asked_ Questions_about_Hormonal_Approaches_ to_Emergency_Contraception.
4. The most common protocol, called the ovulation approach, based on the Peoria Protocol is described in detail by Hamel and Panicola (2012). This protocol allows dispensing emergency contraception if a woman's progesterone level is under 1.5 ng/ml and her urine LH (Luteinizing Hormone) test is negative, that is, if she is determined to be in the preovulatory period. This method is based upon the assumption that emergency contraception efficiently inhibits ovulation when given in the preovulatory phase and therefore theoretically should not work via abortion.
5. Follicular rupture is the abrupt disappearance or a reduction in size of at least 50 percent of the echo-image of a leading follicle that had at least attained 15 mm in diameter (Massai et al. 2007).
6. Email correspondence with Dr. Gabriela Noé, January 19, 2013.
7. To the best of this author's knowledge, no one has adequately studied the effect of LNG-EC when given 0–12 hours after sexual relations. Kesserü et al. used older technology and employed a dose of LNG that was 27 percent of today's LNG-EC dose. Extrapolating retrospectively via do Nascimento et al.'s study might lead one to hypothesize that LNG-EC would have little effect upon sperm migration if given within 12 hours of sexual relations.

8. The following contraceptives contain a total of 1.925 mg of levonorgestrel in each month's supply: Tri-levlen 21, Tri-levlen 28 and Trivora.
9. Email correspondence with Dr. Espinós: January 18, 2013.
10. Email correspondence with Dr. Gabriele Noé: April 25, 2013.
11. One could argue that LNG-EC has an *independent direct* effect upon sperm or ova which might be expected to be present in both the pre- and postovulatory phases and would theoretically inhibit fertilization in both phases. Since this clearly does not occur, this hypothesis does not appear to be valid.
12. EPF might also be used to test whether oral contraceptives work at times by causing the destruction of the embryo, as is implied by several papers (Larimore and Stanford 2000; Pierson et al. 2003).
13. The rate of pregnancy loss in women who have newly conceived has been debated at length with markedly different estimates. In their overview, Mesrogli, Maas, and Schneider (1988) quoted four studies. One of them (Hertig, Rock, and Adams 1956) simply measured congenital abnormalities in fertilized ovum taken from women's uteri during hysterectomy; the second study (Roberts and Lowe 1975), based the estimate on multiple assumptions and admitted that this amounted to "speculative arithmetic." The only two studies that had concrete ways of measuring early pregnancy loss were those of Miller et al. (1980) and Rolfe (1982). If we sum their findings, we note that from 170 conceptions they found 81 losses, for a total pregnancy loss rate of 48 percent.
14. Note: Men were used as controls because they cannot become pregnant.

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