
Mechanism of Action of Levonorgestrel

To the Editor: Rev. Nicanor Austriaco's latest contribution to the dialogue about the mechanism of action (MOA) of levonorgestrel when used as an emergency contraceptive (LNG-EC) is a reply to Walter Rella, MD, who proposed a robust postfertilization MOA.¹ Rella correctly pointed out that raw data from a study by Gabriela Noé and colleagues establishes an extraordinarily high ovulation rate among women who took LNG-EC during the fertile window and, paradoxically, a total absence of expected pregnancies.² Rella hypothesized that at least 50 percent of the antifertility action is attributable to a postfertilization MOA, and proposed a significantly shortened luteal phase associated with impaired function of the corpus luteum as a candidate. Austriaco's reply, in which he claims that "damning" evidence undermines Rella's opinion, is deeply flawed.

Austriaco cites a recent opinion on luteal phase deficiency from the American Society of Reproductive Medicine.³ That opinion addresses the relationship, widely suspected but still debated, between natural infertility and spontaneously occurring luteal phase deficiency. Austriaco seizes on the following quote from the ASRM opinion: "While progesterone is important for the process of implantation and early embryonic development, [luteal phase deficiency], as an independent entity causing infertility, has not been proven."⁴ From this

he concludes, "If Rella's hypothesis were true—if shortened luteal phases do in fact lead to pregnancy loss—then one would expect women with shortened luteal phases to experience infertility. As the committee concludes, however, after decades of study (luteal phase deficiency was first described in 1949), there is still insufficient evidence to warrant this claim."⁵

Context is everything. The ASRM opinion addresses the possible linkage between infertility and luteal phase deficiency. Those terms of art must be properly understood if the ASRM opinion is to be properly evaluated. The Mayo Clinic states, "Infertility is defined as not being able to get pregnant despite having frequent, unprotected sex for at least a year for most people and six months in certain circumstances."⁶ ASRM itself clearly states that "infertility is the result of a disease."⁷ Infertility is not a onetime substance-induced failure to conceive or interruption of conception, which is the core issue in the Plan B debate. It is an underlying condition. When ASRM refers to "infertility" in relation to luteal phase deficiency, it is not referring to a single incident in which pregnancy is prevented or interrupted by a drug such as levonorgestrel. It addresses the relationship of a persistent, spontaneous condition and sustained absence of pregnancy over a certain defined time period. The ASRM was clear enough: "Although there appears to be an association with infertility, it has not been established that persistent [luteal phase deficiency] is a cause of infertility. Moreover, [luteal phase deficiency] is only clinically relevant if it is consistently present in most cycles."⁸

This has nothing to do with *induced* luteal phase deficiency, which considerable evidence points to as the consequence of the intentional introduction of LNG-EC. A recent paper by Rebecca Peck, MD, and Rev. Juan Vélez, MD (which appears in this issue of the Journal) examines some of this evidence and proposes that LNG-EC is likely to produce an *induced* one-time condition that mimics luteal phase deficiency.⁹ There is no question that *induced* significant shortening of the luteal phase has

been repeatedly observed in studies where LNG-EC was administered in the late follicular fertile phase.¹⁰ Several of these studies, systematically unpacked by Peck and Vélez, also show impaired luteal phase progesterone following LNG-EC intake in the late follicular phase, a significant indicator of corpus luteum dysfunction.¹¹ Austriaco also questions whether Rella correctly points to shortened luteal phase at all, debating the length of impairment sufficient to meet the criteria for that diagnosis. While Rella touches on data concerning shortened luteal phase associated with LNG-EC intake during the follicular phase, the body of data is more extensively presented by Peck and Vélez.

Of course, the length of the luteal phase is not the only biological datum critically associated with progesterone levels. In addition to its nexus with shortened luteal phase and inadequate endometrial development, deficient luteal progesterone points to vulnerability of the embryo to immunological attack. Adequate progesterone regulates maternal immune response to the embryo, thereby making successful pregnancy possible.¹²

To explain the absence of pregnancies despite a high ovulation rate among women who took LNG-EC during the follicular phase, Austriaco proposes that a blunted LH (luteinizing hormone) surge results in eggs that are “hard to fertilize.” This is the same theory he suggested in the Winter 2011 issue of the *NCBQ* after other proposed preferentialization MOAs collapsed under scrutiny.¹³ But the hard-to-fertilize egg theory is merely conjecture, and its reliance on findings by Willem Verpoest et al. is misplaced.¹⁴ The Verpoest group reported that eggs resisted fertilization in IVF procedures when they were conditioned by inadequate LH. However, their definition of fertilization required two pronuclei and continued cleavage for up to seventy-two hours.¹⁵ This means oocytes that were actually fertilized but failed to sustain cleavage for the specified duration were deemed “unfertilized.” The fact that “unfertilized” oocytes included actual embryos on a path to early demise is further evidenced by reported LH levels. Some of the “unfertilized” oocytes were from women whose peak serum

LH and follicular fluid LH concentrations fell within the ranges associated with oocytes that were fertilized and sustained cleavage (specifically, serum LH levels were 43–58 IU/L for fertilized oocytes and 36.5–47 IU/L for “unfertilized” oocytes, while follicular fluid concentrations of LH were 13.2–16.4 IU/L for fertilized oocytes and 7.9–13.9 IU/L for “unfertilized” oocytes).¹⁶

Assuming for the sake of argument that this MOA actually occurs in vivo, it would constitute something monstrous—the predestined, preprogrammed early demise of human beings. But whether such events occur is unclear. In a recent article by Vivian Brache et al., the authors search for a preferentialization MOA to explain the absence of expected pregnancies despite follicular rupture reported in the 2011 study by Noé and others and the 2007 study by Natalia Novikova et al.¹⁷ They plainly admit that whether “the abnormal blunted or absent LH peak preceding follicular rupture in the LNG-treated cycles in which rupture occurs contributes to the alteration of the ovulatory process and has any clinical consequence is unknown.” The most they can offer is that it is “biologically plausible.”¹⁸

That is a rather tepid assertion and one that does not reference the Verpoest findings. This is doubly significant. One of the authors of the Brache study is Horacio Croxatto, who previously cited the Verpoest study for the hard-to-fertilize-egg theory.¹⁹ Moreover, the authority cited by Brache et al. to support biological plausibility is a 1993 study that reports merely a higher successful pregnancy rate associated with normal LH.²⁰ Finally, additional research suggests that a synthetic progestin, such as levonorgestrel, administered before ovulation may actually trigger the resumption of egg maturation and meiosis in the presence of blunted LH.²¹ That is an area warranting further study, but the hard-to-fertilize-egg theory is an extraordinarily weak explanation for the absence of expected pregnancies in the 2011 Noé study and, even if true, would almost certainly entail a postfertilization MOA.

Good evidence also suggests that LNG may affect embryo transport through the

fallopian tube by inhibiting muscular contractions or reducing tubal epithelial ciliary beat frequency, essential mechanisms enabling timely zygote migration to the uterus.²² If slowed beyond the implantation window, the embryo would be unable to nest in the endometrium.²³ Delayed tubal transport is but one of several possible postfertilization MOAs requiring further inquiry.

The discussion about LNG-EC and its MOA is properly about moral certitude. And the burden of establishing moral certitude should properly rest on the proponents of LNG-EC.²⁴ Moral certitude that LNG-EC is not abortifacient requires resolution of reasonable doubts to the contrary. That is the standard long accepted in Catholic teaching on moral certitude.²⁵ It is clear that claims of that level of clarity by proponents of LNG-EC are and always have been unwarranted. Although several proponents claim that the data satisfy that standard, their representations do not withstand rigorous scrutiny.²⁶ Peck and Vélez show that the weight of the data, properly understood and freed from excessive opinion, conjecture, and bias, makes a considerably stronger case for a predominant postfertilization MOA than for an MOA that occurs principally before fertilization. Their analysis includes a powerful refutation of MOAs associated with impaired sperm migration, survivability, and capacitance, sperm–egg binding, suppression of ovulation, and ovulatory dysfunction. In 2011, Bruno Mozzanega and Erich Cosmi similarly demonstrated in a concise fashion the weakness of proponents' claims.²⁷ Peck and Vélez provide an evidence-based argument for the reasonableness of postfertilization MOAs, including impaired function of the corpus luteum as well as impaired endometrial receptivity and embryo implantation. Their superb work will be essential reading for all interested in this topic.

The final verdict on LNG-EC awaits its day, and perhaps further study will resolve all reasonable doubt. On the path to that day the burden of proof rests on proponents of the use of levonorgestrel as emergency con-

traception. The evidence plainly shows that the burden has not been met.

REV. DEACON THOMAS J. DAVIS JR.,
JD, LL.M., MA
Pope John Paul II Bioethics Center
Holy Apostles College and Seminary
Cromwell, Connecticut

SISTER HANNA KLAUS, MD
Natural Family Planning Center
of Washington, DC,
and Teen STAR Program
Bethesda, Maryland

JUDITH M. MASCOLO, MD
Connecticut Guild of the
Catholic Medical Association
West Hartford, Connecticut

BRUNO MOZZANEGA, MD
University of Padua
Padua, Italy

DOMINIC M. PEDULLA, MD
Oklahoma Vein and Endovascular Center
Oklahoma City

JULIO TUDELA, PhD
Life Sciences Institute
Catholic University of Valencia
Valencia, Spain

PATRICK YEUNG JR., MD
Saint Louis University School of Medicine
St. Louis, Missouri

¹ Walter Rella, letter, *National Catholic Bioethics Quarterly* 13.1 (Spring 2013): 7–10; and Nicanor Pier Giorgio Austriaco, letter, *National Catholic Bioethics Quarterly* 13.3 (Autumn 2013): 398–399.

² G. Noé et al., “Contraceptive Efficacy of Emergency Contraception with Levonorgestrel Given Before or After Ovulation,” *Contraception* 84.5 (November 2011): 491.

³ Practice Committee of the American Society for Reproductive Medicine, “The Clinical Relevance of Luteal Phase Deficiency: A Committee Opinion,” *Fertility and Sterility* 98.5 (November 2012): 1113.

⁴ ASRM Practice Committee, “Clinical Relevance,” 1115.

⁵ Austriaco, letter, 398.

⁶ Mayo Clinic staff, “Infertility: Definition,” Pa-

tient Care and Health Information, July 19, 2013, <http://www.mayoclinic.org/diseases-conditions/infertility/basics/definition/CON-20034770>.

⁷ ASRM, "Infertility," *ReproductiveFacts.org*, 2013, <http://www.reproductivefacts.org/topics/detail.aspx?id=36>.

⁸ ASRM Practice Committee, "Clinical Relevance," 1112.

⁹ Rebecca Peck and Juan Vélez, "The Post-ovulatory Mechanism of Action of Plan B: A Review of the Scientific Literature," *National Catholic Bioethics Quarterly* 13.4 (Winter 2013): 000–000.

¹⁰ Peck and Vélez point to findings of LNG-EC-induced shortened luteal phase in the following studies: D. Hapangama, A. F. Glasier, and D. T. Baird, "The Effects of Peri-ovulatory Administration of Levonorgestrel on the Menstrual Cycle," *Contraception* 63.3 (March 2001): 123–129; M. Durand et al., "On the Mechanisms of Action of Short-Term Levonorgestrel Administration in Emergency Contraception," *Contraception* 64.4 (October 2001): 227–234 (Durand 2001); M. Durand et al., "Late Follicular Phase Administration of Levonorgestrel as an Emergency Contraceptive Changes the Secretory Pattern of Glycodelin in Serum and Endometrium during the Luteal Phase of the Menstrual Cycle," *Contraception* 71.6 (June 2005): 451–457 (Durand 2005); M. Durand et al., "Hormonal Evaluation and Midcycle Detection of Intrauterine Glycodelin in Women Treated with Levonorgestrel as in Emergency Contraception," *Contraception* 82.6 (December 2010): 532; H. B. Croxatto et al., "Pituitary–Ovarian Function following the Standard Levonorgestrel Emergency Contraceptive Dose or a Single 0.75-mg Dose Given on the Days Preceding Ovulation," *Contraception* 70 (2004): 442–450 (Croxatto 2004); I. A. Okewole et al., "Effect of Single Administration of Levonorgestrel on the Menstrual Cycle," *Contraception* 75.5 (May 2007): 372–377 (Okewole 2007); and A. Tirelli, A. Cagnacci, and A. Volpe, "Levonorgestrel Administration in Emergency Contraception: Bleeding Pattern and Pituitary–Ovarian Function," *Contraception* 77.5 (May 2008): 328–332. See Peck and Vélez, "Post-ovulatory Mechanism," 12, 14–16, 18, 20, 23–24, and 28.

¹¹ Peck and Vélez describe these findings from the data reported in Durand 2001 (group D), Durand 2005, Croxatto 2004, and Okewole 2007 (groups A and B). *Ibid.*, 14–16, 18, and 28.

¹² Ralph P. Miech, "Immunopharmacology of Ulipristal as an Emergency Contraceptive," *International Journal of Women's Health* 3 (2011):

391–397. While this article addresses ulipristal acetate as emergency contraception, it shows the critical role of progesterone as a regulator of the mother's immune system in successful pregnancy: "For a pregnancy to be successful, one of the many vital actions of progesterone is its ability to induce selective immune tolerance of the [maternal innate immune system] toward the paternal allogeneic embryo, beginning with fertilization and extending through implantation" (392).

¹³ Nicanor Pier Giorgio Austriaco, letter, *National Catholic Bioethics Quarterly* 11.4 (Winter 2011): 623–627. The proposed MOAs included impairment of sperm migration or survival, suppression of ovulation, and inhibited sperm–egg binding secondary to elevated intrauterine glycodelin-A levels. Peck and Vélez convincingly dismantle those claims. See also Thomas J. Davis Jr., letter, *National Catholic Bioethics Quarterly* 13.1 (Spring 2013): 10–14, and the correspondence cited there.

¹⁴ W. M. Verpoest et al., "Relationship between Midcycle Luteinizing Hormone Surge Quality and Oocyte Fertilization," *Fertility and Sterility* 73.1 (January 2000): 75–77.

¹⁵ *Ibid.*, 76.

¹⁶ *Ibid.*, 76, table 1.

¹⁷ V. Brache et al., "Ulipristal Acetate Prevents Ovulation More Effectively than Levonorgestrel: Analysis of Pooled Data from Three Randomized Trials of Emergency Contraception Regimens," *Contraception* 88.5 (November 2013): 611–618. The authors report that levonorgestrel inhibited or delayed ovulation only 14 percent of the time when administered in the advanced follicular phase, the highly fertile two to three days preceding ovulation, a rate effectively no better than placebo. Significantly, Brache was one of the experts who produced a statement for the International Consortium for Emergency Contraception and International Federation of Gynecology and Obstetrics (ICEC/FIGO) in 2011 (prior and subsequent versions were issued in 2008 and 2012) that claimed inhibition or delay of ovulation as the principal and possibly only MOA of levonorgestrel. But that claim, on which Austriaco relied in a letter in 2011 (*NCBQ* 11.4, 623–627) and which was repeated in all the ICEC/FIGO statements on LNG-EC, never warranted moral certitude, as those critically examining the objective data had long maintained. In the 2013 study, Brache et al. implicitly acknowledge that suppression or delay of ovulation is probably an insignificant player in the LNG-EC mechanism related to prevention of clinical pregnancy.

¹⁸ *Ibid.*, 617.

¹⁹ H. B. Croxatto et al., "Pituitary–Ovarian Function following the Standard Levonorgestrel Emergency Contraceptive Dose or a Single 0.75-mg Dose Given on the Days Preceding Ovulation," *Contraception* 70 (2004): 442–450.

²⁰ B. J. Cohlen et al., "The Pattern of the Luteinizing Hormone Surge in Spontaneous Cycles Is Related to the Probability of Conception," *Fertility and Sterility* 60.3 (September 1993): 413–417.

²¹ S. M. Borman et al., "Progesterone Promotes Oocyte Maturation, but Not Ovulation, in Human Primate Follicles without a Gonadotropin Surge," *Biology of Reproduction* 71.1 (July 2004): 366–373.

²² K. Wånggren et al., "Regulation of Muscular Contractions in the Human Fallopian Tube through Prostaglandins and Progestagens," *Human Reproduction* 23.10 (October 2008): 2366. "Levonorgestrel markedly inhibited muscular contractions. This could be an additional contraceptive function of levonorgestrel as it may affect the transport of the pre-embryo through the Fallopian tube." T. Mahmood et al., "The Effect of Ovarian Steroids on Epithelial Ciliary Beat Frequency in the Human Fallopian Tube," *Human Reproduction* 13.11 (November 1998): 2991–2994: "Progesterone at concentrations of 10 umol/l and higher causes a significant reduction in [ciliary beat frequency] in all anatomical regions of the Fallopian tube."

²³ A good discussion of the MOA of LNG-EC, including reference to slowed tubal transport, is offered by Justo Aznar and Julio Tudela in "Comment on the Decision of the German Bishops Regarding the Use of Emergency Contraception in Rape Victims," *Civica*, website of the Asociación de Investigadores y Profesionales por la Vida, April 3, 2013, <http://www.investigadoresyprofesionales.org/drupal/content/comment-decision-german-bishops-regarding-use-emergency-contraception-rape-victims>.

²⁴ The question of who carries the burden of proof was muddled by a statement from the Connecticut Catholic bishops in September 2007, when they reversed ground from steadfastly opposing a legislative mandate to provide prescription emergency contraception to sexual assault victims. Their statement noted that provision of LNG-EC to rape victims "cannot

be judged to be the commission of an abortion because of... doubt about how Plan B pills and similar drugs work" and expressed "serious doubt about how Plan B pills work." Given those doubts, they opted for reluctant compliance with the law. However, they went further and stated, "If it becomes clear that Plan B pills would lead to an early chemical abortion in some instances, this matter would have to be reopened." By that statement they shifted the burden of proof to those raising serious doubts about the liceity of LNG-EC, and set a high bar: "if it becomes clear" that Plan B is an abortifacient. That burden shift and its standard are plainly erroneous and should be abandoned. The 2007 statement is available at <http://www.catholicculture.org/culture/library/view.cfm?recnum=7836>. For further discussion of the events in Connecticut in 2007, see Thomas J. Davis Jr., "Emergency Contraception Mandates in Connecticut: A Case History," presented at the 2009 NCBC Workshop for Bishops in Dallas, Texas, and available at http://www.holyapostles.edu/sites/default/files/bioethics/EMERGENCY_CONTRACEPTION_MANDATES_IN_CONNECTICUT.pdf.

²⁵ The standard is well formulated by Rev. Thomas Slater, SJ, in volume 1 of his *Manual of Moral Theology* (New York: Benzinger Brothers, 1925), a classic treatment of the morality of human acts: "We have to be content with what is called moral certainty. ... I may be conscious that mistake is possible but not probable, as when a man has been condemned on evidence which has satisfied a jury of intelligent men" (31). Even Ron Hamel, a LNG-EC proponent and ethicist for the Catholic Health Association, has acknowledged that moral certitude requires "that the agent has excluded all reasonable possibility of error." Hamel, "Thinking Ethically about Emergency Contraception," *Health Progress* 91.1 (January–February 2010): 65.

²⁶ For a discussion of the moral certitude standard and its application to LNG-EC, see Thomas J. Davis Jr., "Plan B Agonistics: Doubt, Debate and Denial," *National Catholic Bioethics Quarterly* 10.4 (Winter 2010): 760–770.

²⁷ B. Mozzanega and E. Cosmi, "How Do Levonorgestrel-Only Emergency Contraceptive Pills Prevent Pregnancy? Some Considerations," *Gynecological Endocrinology* 27.6 (June 2011): 439–442.