Plan B Agonistics

Doubt, Debate, and Denial

Rev. Deacon Thomas J. Davis Jr.

Abstract. Researches over many years have examined whether levonorgestrel emergency contraception (Plan B, Next Choice) has a postfertilization effect. In a recent article in the Catholic Health Association's journal *Health Progress*, Sandra Reznik, MD, asserts that "levonorgestrel acts to prevent pregnancy before, and only before, fertilization occurs." A companion article by Ron Hamel, PhD, argues for the moral certainty that Plan B is not an abortifacient. Reznik fails to address the principal model supporting a potential postfertilization mechanism of action, specifically, that preovulatory administration of levonorgestrel disrupts the delicate ratio of estrogen and progesterone essential to healthy endometrial development and induces the equivalent of luteal phase insufficiency, thereby jeopardizing implantation. Hamel's argument for moral certitude is similarly inadequate. This article critically reviews both articles and the sources on which they rely. *National Catholic Bioethics Quarterly* 10.4 (Winter 2010): 741–772.

Whether levonorgestrel emergency contraception (Plan B, Next Choice) prevents or compromises endometrial implantation of a fertilized ovum has been examined by various authors in the medical literature over many years.[1] In a recent article in the

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[1]Plan B (Duramed Pharmaceuticals) and Next Choice (a generic version marketed by Watson Laboratories) are the trade names of the two levonorgestrel-based emergency

Catholic Hospital Association's journal *Health Progress*, Sandra Reznik, MD, makes the categorical statement that "levonorgestrel acts to prevent pregnancy before, and only before, fertilization occurs."[2] Her claim fails to address significant literature that recognizes the potential for a postfertilization mechanism of action (MOA). Some of the studies she relies on are too small to have the power of extrapolation, contain flaws in methodology or reporting, or do not address the potential postfertilization action of levonorgestrel when it is administered in the preovulatory fertile phase (days -5 to -2).[3] These defects have been examined by Patrick Yeung, MD, Rev. Joseph

contraceptives available in the United States. Broad survey articles that assess most of the scientific literature include Vivian W. Y. Leung, Marc Levine, and Judith A. Soon, "Mechanisms of Action of Hormonal Emergency Contraceptives," *Pharmacotherapy* 30.2 (February 2010): 158–168, http://www.medscape.com/viewarticle/719473; and James Trussell and Elizabeth G. Raymond, "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy," September 2010, http://ec.princeton.edu/questions/ec-review.pdf. For a specifically Catholic perspective, essential reading includes the following chapters in the 2009 edition of *Catholic Health Care Ethics: A Manual for Practitioners*, ed. Edward J. Furton (Philadelphia: National Catholic Bioethics Center): Patrick Yeung, Erica Laethem, and Joseph Tham, "Argument Against the Use of Levonorgestrel in Cases of Sexual Assault," 143–150; Peter J. Cataldo, rebuttal to "Argument Against the Use of Levonorgestrel," 150–153; Cataldo, "Argument in Favor of the Use of Levonorgestrel in Cases of Sexual Assault," 134–141; Yeung et al., rebuttal to "Argument in Favor of the Use of Levonorgestrel," 141–143; and Marie T. Hilliard, "Moral Certitude and Emergency Contraception," 153–162. Essential reading also includes the following article and letters to the editor in the *NCBQ*: Nicanor P. G. Austriaco, "Is Plan B an Abortifacient? A Critical Look at the Scientific Evidence," 7.4 (Winter 2007): 703–707; Hilliard, letter, 8.1 (Spring 2008): 9–12; Austriaco, letter, 8.1 (Spring 2008): 12–13; Yeung et al., letter, 8.2 (Summer 2008): 217–219; Austriaco, letter, 8.2 (Summer 2008): 219–221; Yeung et al., letter, 8.3 (Autumn 2008): 418–420; and Austriaco, letter, 8.3 (Autumn 2008): 421–425.

[2] Sandra E. Reznik, "Plan B: How It Works," *Health Progress* 91.1 (January–February 2010): 59–61, www.chausa.org/2010_annual_index.aspx.

[3] An action, mechanism, or modality of a postovulatory intervention that prevents the implantation of an embryo in the endometrium is properly referred to as *interceptive*. Postimplantation disruption of pregnancy is properly referred to as *contragestive*. Both are clearly abortive and receive the same moral assessment. See Congregation for the Doctrine of the Faith, *Dignitas personae* (September 8, 2008), n. 23. Some molecules are capable of either function, with the realized action dependent on the timing of administration and the progress of the underlying reproductive biological processes. One well-known example is mifepristone, or RU-486, marketed under the trade name Mifeprex. Although commonly known as the abortion pill because of its contragestive properties, it may also operate as an interceptive: "Mifepristone is a first-generation progesterone receptor modulator that is approved for use in many countries for early first-trimester medication abortion. Mifepristone has been shown to be highly effective for use as emergency contraception, with few side effects (delayed menstruation following the administration of mifepristone is one notable side effect). However, the use of mifepristone as an abortion pill may limit its widespread acceptability for use for emergency contraception." Trussell and Raymond, "Emergency Contraception: A Last Chance," 2. Leung, Levine, and Soon also note that "mifepristone (RU486) is sometimes used for emergency contraception." "Mechanisms of Action," 158.

Tham, LC, MD, and Erica Laethem in past issues of the *NCBQ* and, more recently, in the new edition of The National Catholic Bioethics Center's *Catholic Health Care Ethics*.[4] Reznik fails to address the possible postfertilization MOA they propose as their central hypothesis: preovulatory administration of levonorgestrel disrupts the delicate ratio of estrogen to progesterone and the development of the corpus luteum, thereby impairing endometrial development and jeopardizing implantation at an alarming rate.

To fully appreciate the excess in Reznik's commentary, it is essential to understand the model advanced by Yeung et al. and the critical significance of levonorgestrel administered before ovulation:

> The time *before* ovulation that is within the fertile window comprises days -5 to -2 before ovulation and will be referred to as the "preovulatory" period. The administration of levonorgestrel during the preovulatory period will be called "preovulatory levonorgestrel."
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> Levonorgestrel given before the fertile window raises no moral issue, since the chance of pregnancy is near zero. Levonorgestrel given after ovulation (including the LH trigger) may not interfere with implantation, since levonorgestrel is a progestin, a synthetic derivative of progesterone. Progesterone is the dominant hormone produced in a woman's cycle *after* ovulation (during the luteal phase). This is why progestins are often used in artificial reproductive technology protocols to support a pregnancy, and why from a physiological standpoint, levonorgestrel is not expected to interfere with implantation when given after ovulation. By contrast, the dominant hormone produced *before* ovulation (during the follicular phase) is estrogen, not progesterone. Therefore, from a physiological standpoint, the *preovulatory* period is *precisely* the time in question, when levonorgestrel might have postfertilization effects *after* ovulation that interfere with implantation.
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> The ability of the endometrium (lining of the uterus) to receive an embryo at implantation depends on the function of the *corpus luteum*, which in turn depends on the function of the follicle. *Postfertilization effects of levonorgestrel that interfere with implantation could occur in the following way:* administration of levonorgestrel *before* ovulation does not prevent ovulation (that is, a "breakthrough" ovulation occurs) but interferes with the normal development and function of the *corpus luteum*; a dysfunctional *corpus luteum* then leads to an impaired endometrium that interferes with embryonic implantation. *Physiologically, postfertilization effects that interfere with implantation when levonorgestrel is given in the preovulatory period make sense*.[5]

Ignoring Yeung, Reznik interprets selective research data to support the claim that levonorgestrel's antifertility action is limited to the suppression of ovulation and the inhibition of sperm migration by thickening of cervical mucus. The anovulant property of levonorgestrel is universally agreed upon, although breakthrough

[4] Yeung et al., "Argument Against the Use of Levonorgestrel"; rebuttal to "Argument in Favor of the Use of Levonorgestrel"; and letters, *NCBQ* Summer and Autumn 2008.

[5] Ibid., 144, original emphases. The LH (luteinizing hormone) surge, or LH trigger, normally occurs twenty-four to forty-eight hours before ovulation, on day -2 or -1.

ovulation is a recognized phenomenon and constitutes the entire basis for the post-fertilization debate. But the claim that levonorgestrel retards sperm migration is based on decades-old research that has been seriously challenged by a recent study.

A 1974 study by E. Kesserü is frequently cited by levonorgestrel proponents as support for an alternative theory for prefertilization MOA.[6] However, a recent study designed to test that theory found that levonorgestrel does not inhibit sperm migration.[7] And while Reznik cites two sources published in the last decade to support her claim, both sources simply rely on the Kesserü study, and neither had the benefit of the subsequent research undermining the earlier findings.[8] All this is borne out by leading emergency contraception advocates James Trussell, PhD, and Elizabeth Raymond, MD, in their well-known online publication "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy": "In a study conducted more than 30 years ago, levonorgestrel was found to interfere with sperm migration and function at all levels of the genital tract; however, a study designed to assess this issue found that 1.5 mg levonorgestrel had no effect on the quality of cervical mucus or on the penetration of spermatozoa in the uterine cavity."[9]

What, then, of Reznik's unalloyed certainty that Plan B is not an abortifacient? She makes several claims that expose her failure to address, or perhaps grasp, the Yeung model.[10]

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[6] E. Kesserü et al., "The Hormonal and Peripheral Effects of d-Norgestrel in Postcoital Contraception," *Contraception* 10.4 (October 1974): 411–424.

[7] Josiane A. do Nascimento et al., "In Vivo Assessment of the Human Sperm Acrosome Reaction and the Expression of Glycodelin-A in Human Endometrium after Levonorgestrel Emergency Contraceptive Pill Administration," *Human Reproduction* 22.8 (August 2007): 2190–2195.

[8] The sources Reznik cites are Horacio B. Croxatto, "Emergency Contraception Pills: How Do They Work?" *IPPF Medical Bulletin* 36.6 (December 2002) and K. Gemzell-Danielsson and L. Marions, "Mechanisms of Action of Mifepristone and Levonorgestrel When Used for Emergency Contraception," *Human Reproduction Update* 10.4 (July–August 2004): 341–348.

[9] Trussell and Raymond, "Emergency Contraception," 10; see also Leung, Levine, and Soon, "Mechanisms of Action," 164.

[10] It is unclear whether Reznik evades Yeung or is simply uninformed. One striking factual error in her commentary suggests poor source research. In the second sentence of her article she claims that Plan B can now be obtained without prescription "for women 18 and older." On March 23, 2009, a federal court ordered the FDA to allow over-the-counter (OTC, without prescription) Plan B to be marketed to women seventeen years of age and older. On April 22, 2009, the FDA announced that it would not appeal that order. See FDA press release of April 22, 2009, at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149568.htm. On July 10, 2009, the FDA approved OTC Plan B One-Step for women seventeen years of age and older. See the approval letter at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/021998s000ltr.pdf. Reznik's ignorance of Plan B availability without prescription to seventeen-year-olds raises questions about her background research and may explain her failure to address Yeung et al.

First she asserts, "If Plan B worked by preventing implantation, then the most effective time to administer the contraceptive would be right around the time of implantation." But Yeung's model assumes that the use of levonorgestrel after ovulation or even during the LH surge does not have a postfertilization effect. It points to the preovulatory use of levonorgestrel from nine to twelve days prior to implantation (days -5 to -2), which may disrupt, before ovulation, the ratio of estrogen and progesterone appropriate for healthy endometrial development and further occasion a dysfunctional corpus luteum, thereby denying appropriate progesterone when it is needed after ovulation. Preovulatory use of levonorgestrel is long before what Reznik claims would be "the most effective time" if a postfertilization MOA were to be realized.

Next she claims that the rapid drop in the effectiveness of levonorgestrel when it is used more than two days after coitus demonstrates that it is not an abortifacient. This argument relies on a small study showing that levonorgestrel did not prevent pregnancy when administered after ovulation.[11] The same study reports that no pregnancies occurred when levonorgestrel was administered before ovulation, but that result is consistent with either an anovulant MOA or breakthrough ovulation and fertilization followed by interception or some other postfertilization action. Reznik attributes the result exclusively to a prefertilization MOA, a narrowed field given the dubious data supporting inhibition of sperm migration. In fact, the study she relies on does not rule out a postfertilization effect related to preovulatory use.[12]

An even smaller substudy examined eight women who received preovulatory levonorgestrel.[13] Seven experienced suppressed ovulation, but the small size of the study precludes reliable population-wide projection. The study also lacked the "methodological design to contradict a postfertilization effect."[14] Nonetheless, it did demonstrate that preovulatory levonorgestrel significantly shortens the luteal phase, thereby leading to "the equivalent of a luteal phase insufficiency"[15]—a finding supportive of a postfertilization MOA in the event of breakthrough ovulation and fertilization.

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[11] Natalia Novikova et al., "Effectiveness of Levonorgestrel Emergency Contraception Given Before or After Ovulation: A Pilot Study," *Contraception* 75.2 (February 2007): 112. That result suggests that Plan B does not meaningfully inhibit sperm migration or otherwise inhibit fertilization by any means other than suppression of ovulation.

[12] See Leung, Levine, and Soon, "Mechanisms of Action."

[13] Alessandra Tirelli, Angelo Cagnacci, Annibale Volpe, "Levonorgestrel Administration in Emergency Contraception: Bleeding Pattern and Pituitary-Ovarian Function," *Contraception* 77.5 (May 2008): 328–332.

[14] Yeung et al., rebuttal to "Argument in Favor of the Use of Levonorgestrel," 142; and Leung, Levine, and Soon, "Mechanisms of Action," 164, who also note that the results of this study "were limited by the sample size."

[15] Tirelli, Cagnacci, and Volpe, "Levonorgestrel Administration in Emergency Contraception," 329–331; the quoted words are from Yeung et al., rebuttal to "Argument in Favor of the Use of Levonorgestrel." 142.

More recently, a clinical study in Chile followed seventy-two women who used levonorgestrel during the preovulatory fertile phase following coitus.[16] None became pregnant (defined by confirmed implantation) despite follicular rupture detected in fifty-seven (79.16 percent)—a finding the authors themselves recognize as indicative of a mechanism other than suppression of ovulation. The authors suggest inhibited sperm migration, citing Kesserü, but that mechanism is doubtful, given the more recent study challenging the Kesserü findings.

Reznik also cites a study in which human embryos successfully attached to mature human endometrial tissue that was exposed to levonorgestrel.[17] But she fails to note that the study has nothing to say about the effect of preovulatory levonorgestrel on earlier endometrial development or the potentially causal relationship between preovulatory levonorgestrel and dysfunction of the corpus luteum.[18] The endometrial tissue in the study was never exposed to levonorgestrel in the preovulatory phase.

Reznik also dismisses the possibility that levonorgestrel is abortifacient because it is a progestin, similar in structure and function to the female hormone progesterone, and progestin "helps to make the uterus more receptive to implantation and helps maintain pregnancies." Given that biological background, she concludes that "the concept of a progestin rendering the endometrium less receptive to implantation is completely illogical." But her argument is selective. Yeung et al. make the same observation about the role of progesterone in supporting pregnancy but critically distinguish the timing of its role. Progesterone and estrogen secretion by the ovaries is relatively constant in the follicular phase until about seven or eight days before the LH surge, when estrogen, especially estradiol, begins a slow but accelerating increase.[19] Progesterone levels do

[16] Gabriela Noé et al., "Contraceptive Efficacy of Emergency Contraception with Levonorgestrel Given Before or After Ovulation," *Contraception* 81.5 (May 2010): 414–420. The best evidence to date is that levonorgestrel does not inhibit sperm migration, as discussed above. For further discussion of the Noé study, see the letter from Thomas J. Davis Jr. in the Colloquy section of this issue of the *NCBQ*.

[17] P. G. L. Lalitkumar et. al., "Mifepristone, But Not Levonorgestrel, Inhibits Human Blastocyst Attachment to an In Vitro Endometrial Three-Dimensional Cell Culture Model," *Human Reproduction* 22.11 (November 1, 2007): 3031–3037.

[18] See Yeung et al., "Argument Against the Use of Levonorgestrel," 147. The same distinction moots the application of two recent studies of endometrial receptivity markers to the Yeung model: C. X. Meng et al., "Effects of Oral and Vaginal Administration of Levonorgestrel Emergency Contraception on Markers of Endometrial Receptivity," *Human Reproduction* 25.4 (April 2010): 874–883; and Wilder Alberto Palomino, Paulina Kohen, and Luigi Devoto, "A Single Midcycle Dose of Levonorgestrel Similar to Emergency Contraceptive Does Not Alter the Expression of the L-Selectin Ligand or Molecular Markers of Endometrial Receptivity," *Fertility and Sterility* 94.5 (October 2010): 1589–1594. In these studies, levonorgestrel was administered between days LH +1 and LH +4 (Meng et al.) or on LH 0, the day of LH surge (Palomino et al.), but not during the preovulatory fertile phase. For additional discussion, see the letter from Thomas J. Davis Jr. in this issue of the *NCBQ*.

[19] Mark K. Beers and Robert Berkow, eds., *The Merck Manual of Diagnosis and Therapy*, 17th ed. (Rahway, NJ: Merck, 1999), 1929–1930.

not increase significantly until the day before the LH surge. They increase throughout the ovulatory phase and are critically associated with the corpus luteum in the luteal phase. Endometrial development in the late follicular phase is dependent on estradiol and is markedly affected by progesterone in the luteal phase.[20] This delicate balance of estrogen and progesterone is essential to healthy endometrial development. Excess progesterone in the late follicular phase may disrupt that balance and may, Yeung et al. suggest, lead to a dysfunctional corpus luteum. Accordingly, Reznik's dismissal of any postfertilization effect related to implantation as "completely illogical" fails to present a full picture, because it does not address the specific preovulatory fertile (late follicular) phase model offered by Yeung.[21]

The studies cited by Reznik simply do not rule out the Yeung model. An objective analysis must conclude that a postfertilization MOA may be real. That modest conclusion is actually supported by Trussell and Raymond. Recognizing the limits of the scientific literature, they caution that some draw excessive conclusions precluding postfertilization effects. On the contrary, they maintain that informed consent requires disclosure of the possibility that levonorgestrel is an interceptive:

> While some find the existing human and animal studies adequate to conclude that levonorgestrel-only ECPs [emergency contraceptive pills] have no post-fertilization effect, others may always feel that this question has not been unequivocally answered. … To make an informed choice, women must know that ECPs … prevent pregnancy primarily by delaying or inhibiting ovulation and inhibiting fertilization, *but may at times inhibit implantation of a fertilized egg in the endometrium*.[22]

In a recent survey article, "Mechanisms of Action of Hormonal Emergency Contraceptives," Vivian Leung, Marc Levine, and Judith Soon made a nearly comprehensive and generally even-handed review of pertinent English language literature

[20] Ibid., 1931.

[21] The relation of progestins to successful pregnancy raises another dilemma regarding the use of Plan B in treatment after sexual assault. In "Plan B and the Politics of Doubt," Frank Davidoff and James Trussell raise the possibility that Plan B may actually increase the likelihood of successful implantation: "Plan B used after ovulation might actually prevent the loss of at least some of the 40% of fertilized ova that ordinarily fail spontaneously to implant or to survive after implantation." *Journal of the American Medical Association* 296.14 (October 11, 2006): 1777. If Plan B promotes or sustains implantation when administered *after* the preovulatory fertile phase, it would hardly be what a rape victim wants. That suggests that informed consent may require related disclosure of that risk, a speculative insight to be sure, but one entirely consistent with the Yeung model and Reznik's biological analysis.

[22] Trussell and Raymond, "Emergency Contraception," 6, emphasis added. From time to time this online article has undergone edits. The most recent version deletes the following statement which, despite its redaction, highlights the potential postfertilization MOA of Plan B: "Based on their studies on humans and animals, some are tempted to conclude that there is definitely no post fertilization effect. It is unlikely that this question can ever be unequivocally answered, and we therefore cannot conclude that ECPs [emergency contraceptive pills] never prevent pregnancy after fertilization."

on the MOA of emergency contraception.[23] While they conclude that an interceptive MOA is "unlikely," they plainly recognize the unsettled science.

Their analysis of studies, including the principal ones relied on by Reznik, strongly suggests the likelihood of some level of breakthrough ovulation with preovulatory levonorgestrel: "In most studies, preovulatory administration of emergency contraceptives did not consistently disrupt ovulation." While presumed breakthrough ovulation in some studies may partly be explained by inaccurate assessment of the precise cycle stage, it may also be associated with "variability in ovarian sensitivity to the drugs" in some study participants. Leung, Levine, and Soon, in full accord with Yeung et al., continue, "Emergency contraceptives are not expected to prevent pregnancy every time they are used; if they act primarily by disrupting ovulation, there will be instances when ovulation proceeds despite treatment." Indeed, the nearer in time to ovulation that emergency contraception is used, "the less likely it is to interfere with ovulation."

Leung, Levine, and Soon also confirm that "physical and biochemical changes in the endometrium have been observed after treatment" with levonorgestrel-only emergency contraception, but they note that "the data are sparse," it is not known if the results "were spontaneous observations or persistent effects," "it is not clear whether the type and magnitude of changes observed in the studies would have prevented implantation," and "further investigation in this area is needed." They conclude,

> Although anovulation (or dysfunctional ovulation) can explain the effectiveness of emergency contraceptives, it does not preclude other effects. It is possible that multiple mechanisms account for the total effect … [but that] available data are insufficient to verify theoretical contributions of an alteration in … markers of endometrial receptivity. Even less information is available for other proposed mechanisms, such as disturbance of corpus luteum function. Further investigations are needed to clarify these questions. … For those who object to the use of emergency contraceptives because there is insufficient evidence to completely exclude the possibility of interference with implantation, emergency contraceptives are not acceptable contraceptives.[24]

It may eventually be demonstrated that Plan B has no interceptive MOA. But the data to date do not eliminate reasonable doubt. Reznik compounds her overstatements by flatly rejecting Plan B product literature, which advises that Plan B may prevent implantation. Her claim echoes others that similarly dismiss the product insert.[25] Reznik claims, "Some of the concerns about how Plan B works have been driven by the unfortunate and inaccurate description on the package insert, which includes a statement

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[23] Leung, Levine, and Soon, "Mechanisms of Action," 158–168. Unfortunately, Leung, Levine, and Soon do not consider the writings of Yeung et al. or the high incidence of detected follicular rupture reported by Noé et al.

[24] Ibid., 166.

[25] See Austriaco, "Is Plan B an Abortifacient?" 707. Austriaco dismissed the product labeling as unsupported by science and argued that, "given the limitations of scientific certitude," one must conclude that Plan B, when given once, is not an abortifaciant. In a subsequent letter in the Spring 2008 *NCBQ* (8.1), Austriaco repeated his claim of "scientific

that levonorgestrel acts by preventing implantation. There are absolutely no data to support this statement, while there are plenty of data, summarized above, to support the conclusion that levonorgestrel acts only before fertilization has occurred."[26]

That claim is misleading. The package insert is not an "inaccurate description" by any standard. It carefully and accurately states a well-documented theoretical possibility. It contains nothing like the categorical statement Reznik attributes to it ("levonorgestrel acts by preventing implantation"). Rather, it mentions the prevention of implantation as a *potential* MOA while correctly stating that the primary MOA is prevention of ovulation.

By misrepresenting what the product insert says, Reznik sets up the disingenuous claim that there are "absolutely no data to support" the claim that levonorgestrel acts by preventing implantation. However, there is evidence to support a different statement, one synonymous with the product insert: clinical data do not rule out an interceptive MOA that is physiologically consistent with the use of Plan B in the preovulatory fertile phase.

Regulatory History and Labeling of Plan B

The regulatory history of Plan B includes multidisciplinary reviews of drug safety and efficacy by the U.S. Food and Drug Administration (FDA), including product insert, label, and related consumer comprehension studies. The MOA statements in the product labels are essential for both scientific accuracy and informed consent.

Plan B was initially approved for prescription distribution by the FDA on July 28, 1999.[27] Although the clinical pharmacology and biopharmaceutics reviews referred to a theoretical interceptive MOA, the FDA-approved carton text language contained no mention of MOA.[28]

From June 18 to July 18, 2001, Family Health International, engaged by the sponsor of Plan B, conducted a label comprehension survey at various shopping malls and family planning clinics in the United States.[29] The survey was designed to

certitude." However, in a later letter he retreated from the claim of scientific certitude, stating that an interceptive MOA was "unlikely." *National Catholic Bioethics Quarterly* 8.3 (Autumn 2008): 424. Austriaco's scientific-certitude claim is discussed in more detail later in this paper.

[26] Reznik, "Plan B: How It Works."

[27] The FDA approval letter, dated July 28, 1999, is available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-045_Plan%20B_Approv.pdf.

[28] FDA, "Clinical Pharmacology and Biopharmaceuticals Review(s)," June 20, 1999, http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-045_Plan%20B_biopharmr.pdf. Women's Capitol Corporation, "Carton Text: Plan B (levonorgestrel) tablets, 0.75mg" (no date), http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21045lbl.pdf.

[29] The original sponsor was Women's Capitol Corporation, which subsequently sold its rights to market Plan B to Barr Pharmaceuticals. Barr Pharmaceuticals distributes Plan B through its subsidiary, Duramed. As used in this article, the term "sponsor" refers to any or all of these companies, as appropriate.

determine whether consumers understood the proposed packaging of OTC Plan B.[30] As with the then-existing carton label for prescription Plan B, the carton label used for the comprehension study did not include any mention of MOA.[31] However, MOA information did appear in the package insert and included the following statement: "Plan B may prevent a fertilized egg from attaching to the womb (*implantation*)."[32]

By April 2003, when the sponsor filed its application for OTC approval from the FDA, the carton label had undergone various modifications, but it still contained no information on MOA.[33] Shortly after, on December 16, 2003, two FDA advisory committees—the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD)—met jointly to consider the application, hear presentations by the sponsor, and receive public comments.[34] At the joint proceedings, the sponsor's representatives advocated a position only slightly less categorical than that taken by Reznik in her *Health Progress* article. In particular, the sponsor asserted that

> Plan B works like other progestin only oral contraceptives and prevents ovulation. Plan B is an oral contraceptive, not an abortion pill. The direct evidence is highly in favor of the fact that the primary mechanism of action, if not the sole mechanism of action, is prevention of ovulation. There are two hypothetical mechanisms that have been proposed: interference with fertilization and interference with implantation, but for levonorgestrel only contraceptives, levonorgestrel only emergency contraceptives, there is no data to suggest that either of these are impacted, either of these events are affected by Plan B. Again, I would reiterate Plan B works by preventing ovulation.[35]

Similarly, another member of the sponsor's presentation panel stated, "Clinical research data demonstrate that Plan B primarily prevents pregnancy by inhibiting

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[30] FDA Office of Drug Safety, "Study #9728: Plan B OTC Label Comprehension Study," 2001, http://www.fda.gov/ohrms/dockets/ac/03/briefing/4015B1_06_FDA-Tab%202-2-Label%20Conprehension%20Study.pdf. The appendix to the study document describes and illustrates the text and label for the actual package used in the comprehension study (18–20).

[31] Ibid.

[32] FDA Briefing Document, "Plan B (Levonorgestrel) for Emergency Contraception Rx to OTC Switch," Nonprescription Drugs and Reproductive Health Drugs Advisory Committee Meeting, December 16, 2003, appendix 7 (7-1), original emphasis, http://www.fda.gov/ohrms/dockets/ac/03/briefing/4015B1_01_WCC-Briefing Document.pdf.

[33] Ibid., 45–51. See also the sponsor's PowerPoint presentation: Carol S. Ben-Maimon, "Plan B (Levonorgestrel) for Emergency Contraception Rx-to-OTC Switch," December 16, 2003, slides 27, 30, 31, 32, and 33, http://www.fda.gov/ohrms/dockets/ac/03/slides/4015s1.htm.

[34] Advisory committees are composed of non-FDA member experts who assist the agency in scientific, technical, and policy matters. There are currently forty-nine such committees.

[35] FDA, "Transcript of Nonprescription Drugs Advisory Committee (NDAC) in Joint Session with the Advisory Committee for Reproductive Health Drugs (ACRHD)," December 16, 2003, comments of Carole Ben-Maimon, MD, president and chief operating officer of the proprietary research and development division of Barr Laboratories, 30–31, http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4015T1.pdf.

or preventing ovulation and secondarily perhaps by impairing the migration and function of sperm. In other words, it prevents pregnancy prior to fertilization."[36]

Later during the same proceedings, the sponsor sought to distinguish combination emergency contraception from levonorgestrel-only emergency contraception with respect to their potential effects on implantation:

> There have been some very early studies on combination therapy, and I think that's really important that there may be some changes in the endometrial lining, but again, that's combination, and when you give estrogen and progesterone, as you all know, the ratio is highly important in maintaining the integrity of the endometrial lining. And there are really no studies to date that have been published that show that levonorgestrel has any impact on the endometrial lining post ovulation. … As somebody said earlier, progestin traditionally is used to maintain the integrity of the endometrial lining, and is used in women with a luteal phase defect just for that purpose. In addition, anti-progestins, such as RU-486 or mifepristone, are detrimental to the endometrial lining. So, again, anti-progestins work to destroy the endometrial lining, not progestins. And so clearly, the only real evidence of how levonorgestrel works is that it prevents ovulation; it impacts sperm motility and sperm migration through changes in the cervical mucous and the pH, and there really is no data to suggest that there's any impact on implantation or fertilization.[37]

These comments, intended to dismiss any postfertilization MOA, were immediately followed by clarification from a member of the ACRHD, who pointed out that the sponsor's comments could have the effect of confusing the issue by introducing discussion of RU-486 and similar anti-progestins, which operate *inter alia* to disrupt established implantation. The true issue then under discussion was not interruption of established implantation, or contragestive action, but other effects on the endometrium that may inhibit implantation in the first place, i.e., interceptive action:

> Just a point of clarification. When one gives progesterone for luteal phase defect, you usually begin it around seven days after ovulation. You don't begin it in that immediate periovulatory period. I raise the issue because of obviously the issues of whether this is a contragestive or contraceptive. … So the issue becomes not does it necessarily create a hostile environment in the endometrium such that you would be able to affect advanced implantation because I agree with you. Progesterone is good, not bad to do that. But the issue becomes does it affect attachment, and does it act, in other words, like an IUD rather than an anti-fertilization agent. And it sounds like you're telling me no one has done the studies, and I couldn't find any that at least I could discern from a Medline search or from looking through your data.[38]

[36] Ibid., comments of Vivian Dickerson, MD, director of obstetrics and gynecology at the University of California–Irvine and president-elect of the American College of Obstetricians and Gynecologists, 36–37.

[37] Ibid., comments of Dr. Ben-Maimon, 266–268.

[38] Ibid., comments of Charles J. Lockwood, MD, chair of obstetrics and gynecology at Yale University School of Medicine, 268–269.

The reply from the sponsor was an enlightening admission that existing data did not rule out a postfertilization effect: "The studies are not available. The biggest issue here though is that Plan B or levonorgestrel only emergency contraceptions [sic] work like other oral contraceptives in that way, and so especially progestin only containing oral contraceptives, and so the data is clearly there's *no data that's definitive in either way*. But, again, I think logic precludes us from assuming that that's the mechanism of action."[39]

Of course, "no data that's definitive in either way" logically precludes an assumption *against* interception as well. It means that the issue is unresolved, which is precisely what Plan B labeling recognizes.

Shortly thereafter, another member of the ACRHD challenged the sponsor's presentation:

> I'd like to offer a little bit of a different opinion on that issue, and I think it is an important issue for women who want to have a clear idea of the best evidence of how this works and for their informed consent for use. *I don't think it's quite as clear-cut as has been presented that there's no data on one side and all data on the other side.* If you look through all of the studies we have got in our background book, there's data on both sides. … There's no way that -- you know, *there's certainly some epidemiologic evidence from there that suggests that it is working after fertilization some of the time, and I think it is misleading to say we have no suggestion of that happening.*[40]

Additional comments at the joint proceedings with respect to informed consent and the label comprehension study drove the point home. The sponsor's study included an analysis of consumer understanding of the use for which Plan B is intended. After reviewing the product carton, participants were asked, "Without looking at the label, tell me what Plan B is used for." Responses that included "abortion drug," "abortion pill," or "to kill the fertilized egg" were deemed "correct and acceptable."[41] The point, of course, is not that consumer response in a comprehension study constitutes a scientific basis for MOA analysis, but rather that the sponsor viewed those answers as accurately describing the action of Plan B.[42]

The joint proceedings resulted in a majority of the members agreeing that disclosure of a possible interceptive MOA was appropriate for informed consent,

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[39] Ibid., comments of Dr. Ben-Maimon, 269, emphasis added.

[40] Ibid., comments of Joseph Stanford, MD, Department of Family and Preventive Medicine at the University of Utah, 269–270, 271, emphasis added.

[41] FDA Briefing Document, appendix 6, pp. 6-1 and 6-4.

[42] Particularly noteworthy are the following comments from two ACRHD members in response to the comprehension study report: "I understand, again, that *the data that we have on mechanism of action for Plan B is imperfect, incomplete, but I think it's a critical issue for those women who want to understand how it works and have informed consent for use.* So along those lines I have a question … [about the study] -- after they showed the women the package, they said, 'Without looking at the label, tell me what Plan B is used for,' and then classified answers as either correct and acceptable or correct but not acceptable or not correct and not acceptable, and they list them verbatim. And among the ones that are listed as correct

with some division on whether that disclosure should be printed on the outside of the packaging or on the insert that accompanies the product.[43] One member expressed the view that disclosure on the outer packaging might be too emotionally taxing for some women.[44] Others favored disclosure of interceptive potential on the product insert rather than the outer packaging as a matter of practicality or reasonableness.[45] Still others favored disclosure on the outer packaging,[46] some strongly expressing the view that disclosure of a potential interceptive MOA was essential for informed consent and that it must be clearly disclosed on the outside of the package where it would more likely be encountered by the product user.[47]

What is overwhelmingly clear from the joint proceedings is that the sponsor wanted to market OTC Plan B with as little discussion of interceptive MOA as possible,

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and acceptable are a number of women who said that -- one of them is, for example, an abortion type thing for the day after. One was [sic] them was to kill a fertilized egg, and basically showing that some women had that understanding, and it was classified by the company as a correct and acceptable understanding of what the product is for." FDA transcript, comments of Dr. Stanford, 288–289, emphasis added. These comments were promptly followed by those of another committee member: "I think that one of the things that Dr. Stanford is getting to -- and you can tell me if I'm wrong -- is a matter of informed consent such that the patient is as fully informed as possible based on all of the information that we know about how this product works. … *I've reviewed the literature, there is some data out there that really does suggest at very high dosages that there may be the possibility that you're interfering with the implantation.* And so I guess my comfort level would definitely -- I would definitely be a lot more comfortable making sure that the patient or the woman who makes that decision is as informed as possible that there potentially is a possibility that still gives that woman enough information to make an informed decision and not dilute any of her rights in deciding to proceed with this medication." Ibid., comments of Valerie Montgomery Rice, MD, chair of the Department of Obstetrics and Gynecology at Meharry Medical College, 290–291, emphasis added.

[43] Ibid., 318–346.

[44] "I would actually not encourage to include mechanism of action in the label because when a distressed, young woman comes into the pharmacy very apprehensive about the possibility of an unwanted pregnancy, the last thing she wants is to read some scientific jargon on mechanism of action." Ibid., comments of Francis Lam, PharmD, University of Texas Health Science Center, 400.

[45] Ibid. See representative comments of Dr. Lockwood (330), Vivian Lewis, MD (340), and Dr. Rice (346).

[46] Ibid. See representative comments of W. David Hager, MD (320), Larry Lipshultz, MD (321), and George Macones, MD (322–323).

[47] "I agree with the issues raised about labeling and the truth in labeling mechanism of action. I think as a young woman in this country of childbearing age that truth in labeling is very important, and I think if you don't print on the label that this may affect a fertilized egg in an unfavorable way that you're removing my choice and my ability to make the decision about how I am affecting my body and my pregnancy. And so I would very strongly agree that that needs to be on the outside of the package." Ibid., comments of Susan Crockett, MD, director of maternity services for the Christus Santa Rosa Family Medicine Residency Program, 408. See also comments of Dr. Stanford, 326–327.

and its presentation was designed to suggest that no such MOA existed.[48] Additional review of the regulatory history of the OTC application process is enlightening.

Although a majority of advisory committee members supported the sponsor's application, the Center for Drug Evaluation and Research, a division of the FDA, issued a "not-approvable" letter on May 6, 2004. Although this article is not concerned with the political controversy associated with the approval process for OTC Plan B, a subsequent political development is relevant to the MOA discussion: In response to FDA non-approval, certain members of Congress requested that the U.S. Government Accountability Office investigate the circumstances leading up to it. That report, although superficial as a study of MOA, maintained that Plan B "impedes further passage of sperm cells into the uterine cavity," a doubtful MOA given the results of later study.[49] Moreover, the GAO report states that "researchers have concluded that the possibility of a postfertilization event cannot be ruled out" and in a footnote further states, "There is no direct evidence either for or against the hypothesis that [emergency contraceptive pills] prevent pregnancy by affecting postfertilization events."[50]

On July 21, 2004, the sponsor submitted an amended supplemental new drug application proposing dual marketing of Plan B as OTC to women sixteen years of age and older and by prescription to adolescents under age 16. On August 24, 2006, the FDA issued an approval letter for OTC Plan B for women eighteen years of age and older.[51]

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[48]The sponsor's prepared materials for the meeting strongly discounted the possibility of a postfertilization MOA and included as an appendix one literature review that also discounted it. See pages 28 to 31 and appendix 1 of the FDA briefing document.

[49]U.S. Government Accountability Office, "Food and Drug Administration: Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual," November 2005, 12, http://www.gao.gov/new.items/d06109.pdf. See Kesserü et al., "Hormonal and Peripheral Effects," 411–424, and do Nascimento et al., "In Vivo Assessment," 2190–2195, as discussed above.

[50]GAO, "Food and Drug Administration: Decision Process," 13, text and note 31. Similarly, in a report to Congress, the Congressional Research Service (CRS), like the GAO, relied on the since-disputed decades-old study suggesting that Plan B inhibits sperm migration and may thereby prevent fertilization. With respect to interceptive MOA, the CRS relied exclusively on the same author and data presented by the sponsor to the FDA advisory committees in 2003, and advocated that author's position that prevention of ovulation or fertilization was a more likely MOA than prevention of implantation. The CRS acknowledged, however, that it "is possible that Plan B may inhibit implantation of the fertilized egg within the uterus by altering the endometrium (the uterine lining)." See Judith A. Johnson, Erin D. Williams, Vanessa K. Burrows, "Emergency Contraception: Plan B," November 9, 2006, CRS-5, www.policyarchive.org/handle/10207/bitstreams/3017.pdf.

[51]FDA, Letter of Approval for OTC Status for Plan B, August 24, 2006, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021045s011ltr.pdf. The OTC approval has since been extended to women seventeen years of age and older. See Food and Drug Administration, "Updated FDA Action on Plan B (Levonorgestrel) Tablets," April 22, 2009, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149568.htm.

The FDA medical review leading up to approval is a collection of expert reviews and recommendations on various aspects of the OTC application in the form of memoranda, reports, and correspondence. Questions regarding the potential interceptive effect of Plan B are discussed in several medical review entries, including a memorandum from a medical reviewer in the Division of Reproductive and Urological Drug Products (DRUDP) dated January 12, 2005.[52]

In that memorandum the medical reviewer makes plain the debate that had been raging over labeling and the question of a postfertilization mechanism of action of Plan B:

> The proposed product labeling contains much new and accurate information on contraceptive choices and STDs, but no information on the possible mechanisms of action (MOA) of Plan B for emergency contraception. A primary concern of a few of the Advisory Committee members at the December 2003 meeting was the MOA of the product. This is also an issue for some potential users of the product because of the belief that any interference during or after the process of fertilization of the ovulated egg is not acceptable.[53]

The reference to the advisory committee meeting is to the joint proceedings of NDAC and ACRHD discussed above. Taking into account the comments of advisory committee members and the absence of MOA information in the product labeling, the DRUDP reviewer's comment reveals that "the DRUDP provided to the OTC Division recommendations for specific MOA language to be added to the label, package insert and carton box. The language lists all of the possible mechanisms of action, even though some are theoretical and not clearly proven."[54]

The medical review also contains the following discussion of Plan B's MOA from the director of the Center for Drug Evaluation and Research:

> There are three theoretical mechanisms by which progestin-only emergency contraceptive drug products (e.g., Plan B) may prevent pregnancy. These include (1) prevention of ovulation or … ovulatory dysfunction, (2) interference with the actual process of fertilization by impeding the migration of sperm … or disrupting the processes that sperm undergo prior to fertilization of an ovum, and (3) prevention of implantation by a direct effect on the endometrium of the uterus. … Available clinical data do not exclude the possibility that these drug products, in a small percentage of women, also may prevent pregnancy by impeding the fertilization of a released ovum or implantation.
>
> Because of the possibility that Plan B may, in some instances, prevent pregnancy by a mechanism other than prevention of ovulation or disruption of the normal peri-ovulatory events, proposed product labeling for Plan B contains the following wording in the section "How does Plan B work?"

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[52] See Center for Drug Evaluation and Research (CDER), *Application Number: 21-045/S011—Medical Review*, August, 22, 2006, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021045s011_Plan_B__MedR.pdf.

[53] Daniel Davis, "Medical Officer Review of Complete Response," January 12, 2005, in CDER, *Medical Review*, 36.

[54] Ibid.

> *"Plan B works like a birth control pill to prevent pregnancy mainly by stopping the release of an egg from the ovary. It is possible that Plan B may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually occurs beginning 7 days after release of an egg from the ovary. Plan B will not do anything to a fertilized egg already attached to the uterus. The pregnancy will continue."*
>
> This labeling adequately informs women that in some cases Plan B could prevent attachment of a fertilized egg to the uterus. Thus, women are provided appropriate information for making an informed choice about its use.[55]

In its 2006 approval letter, the FDA mandated that the sponsor strictly comply with the labeling and product language that had been arrived at through the preceding years of review and modification. The carton text, which was contained in another release from the FDA on the same date, included the following statements in bold type: "This product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation). See consumer information leaflet."[56] The leaflet contained this statement: "Plan B works like a birth control pill to prevent pregnancy mainly by stopping the release of an egg from the ovary. It is possible that Plan B may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually occurs beginning 7 days after release of an egg from the ovary."[57] The FDA also mandated that the product information insert contain the following statement under "Clinical Pharmacology": "Emergency contraceptives are not effective if the woman is already pregnant. Plan B is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun."[58]

Putting aside the definition of pregnancy, this passage, taken together with the transcript of the December 2003 joint meeting of NDAC and ACRHD and with the DRUDP memorandum of January 12, 2005, demonstrates the FDA's ongoing concern with adequate disclosure of accurate information concerning MOA of Plan B.[59] It is

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[55] Steven Galson, MD, MPH, Memorandum, August 26, 2005, in CDER, *Medical Review*, 9, italics in original. The reference to a direct effect on the endometrium may not be to the Yeung model, which posits effects related to the corpus luteum. Nonetheless, the reference demonstrates ongoing study in this area and the uncertain status of MOA knowledge.

[56] Food and Drug Administration, "Plan B Label Information," August 24, 2006, 1 and 2, http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021045s011lbl.pdf.

[57] Ibid., 3.

[58] Ibid., 23. Excluding the first sentence, identical language appears in CDER, *Application Number: 25-045/S011—Clinical Pharmacology and Biopharmaceutics Review*(*s*), no date, 6, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021045s011_Plan_B__ClinPharmR.pdf.

[59] The definition of pregnancy depends on the source cited. Some assert that "pregnancy" arises only after implantation in the endometrium, and "conception" is likewise admitted

plain that the labeling and consumer product information criticized by Dr. Reznik was strongly supported by the FDA and its advisory committees. It is equally clear that the original sponsor sought to downplay that information but was compelled to revise the labeling and provide greater disclosure. The mandate for greater disclosure arose out of a well-founded belief that informed consent required it.[60]

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to have occurred only after implantation, not at fertilization. This is the position adopted in the *Code of Federal Regulations* (45 CFR 46.202(f)) and applied by the FDA in its medical review. Consequently, since "abortion" is limited to disruption of a pregnancy, it can only refer to postimplantation actions—what *Dignitas personae* refers to as "contragestative." By this rationale, preventing the implantation of a fertilized ovum is not abortive but merely contraceptive. Some medical associations have accepted the new definitions; others have not. For example, the Merck Manuals Online Medical Library states, "Pregnancy begins when an egg is fertilized by a sperm," http://www.merck.com/mmhe/sec22/ch257/ch257a.html. One of the leading studies in human reproduction in the last decade is "Conception to Ongoing Pregnancy: The 'Black Box' of Early Pregnancy Loss," by N.S. Macklon, J.P.M. Geraedts, and B.C.J.M. Fauser, in *Human Reproduction Update* 8.4 (July–August 2002): 333–343. The authors make the following statements: "pregnancies may be lost at any time between fertilization and implantation, or up to term" (333); "published studies point to a rate of pregnancy loss prior to implantation of 30%" (335); and "it has become clear that from the moment of fertilization, there is a continuous reduction or 'selection' of conception products showing chromosome abnormalities. Starting from 38% at conception and ending at 0.6% at birth … selection against aneuploid embryos most probably starts at the morula/blastocyst transition" (339). Each of these statements presumes that conception occurs and pregnancy begins before implantation. See also Mark Beers and Robert Berkow, eds., *The Merck Manual of Diagnosis and Therapy*, 17th ed. (West Point, PA: Merck, 1999), 2014, which reads, "Conception (fertilization) occurs about 14 days before a menstrual period, just after ovulation." Medline's popular online medical dictionary adopts the Merriam-Webster definition of conception: "the process of becoming pregnant involving fertilization or implantation or both," http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=conception. *Dorland's Medical Dictionary,* 30th ed. (Philadelphia: Saunders, 2003), defines conception as "an imprecise term denoting the formation of a viable zygote" (404). It is more precise in defining *pregnancy* as "the condition of having a developing embryo or fetus in the body, after union of an ovum and spermatozoon. … In women, duration of pregnancy from conception to delivery is about 266 days (or 288 days from the last normal menstrual period to birth.)" This definition is also used in the online health care consumer's edition of *Dorland's*, available at http://www.mercksource.com/pp/us/cns/cns_hl_dorlands_split.jsp?pg=/ppdocs/us/common/dorlands/dorland/seven/000086088.htm. The debate is well summarized by Leung, Levine, and Soon in "Mechanisms of Action," 160: "Opinions differ regarding which specific event constitutes the beginning of life or pregnancy. In the scientific community, there are proponents for implantation and for the completion of fertilization to mark the beginning of pregnancy. The debate on whether emergency contraceptives affect established pregnancies therefore depends on when pregnancy is thought to begin." See also Christopher Gacek, "Conceiving Pregnancy: U.S. Medical Dictionaries and Their Definitions of *Conception* and *Pregnancy*," *National Catholic Bioethics Quarterly* 9.3 (Autumn 2009): 543–557.

[60]Failure to obtain informed consent may occasion liability. But liability concerns are mythical if the information withheld is not meaningful. Informed consent requires disclosure of "information which a reasonable patient would consider material to the decision whether or not to undergo treatment." See *Logan v. Greenwich Hospital Assn.,* 191 Conn. 288, 292–293

Developments after OTC Plan B Approval

Clinical, laboratory, and theoretical developments since the FDA approval of OTC Plan B have contributed to the debate Reznik unevenly presents. Most developments are well analyzed, criticized, and distinguished in an article by Rev. Nicanor Austriaco, OP; in letters from Marie Hilliard, Yeung et al., and Austriaco published in the *NCBQ* in 2007 and 2008; and in contributions to the most recent edition of the NCBC's *Catholic Health Care Ethics: A Manual for Practitioners* (2009), where Yeung et al. more thoroughly develop the interceptive MOA postulated in the *NCBQ* letters.[61] In their "Argument Against the Use of Levonorgestrel in Cases of Sexual Assault," Yeung et al. demonstrate that human subject clinical studies, including some on which Reznik relies, fail to adequately examine or test the preovulatory phase model they propose.[62] They also convincingly distinguish the in vitro study of human blastocyst attachment to levonorgestrel-exposed endometrial tissue on which Reznik relied in her commentary.[63] It would serve no useful purpose to rehash the various positions here, and the reader is directed to those sources for a thorough treatment.

Plan B is currently available in a two-dose package containing two 0.75-mg tablets that are taken twelve hours apart and in a one-dose form consisting of a single 1.5-mg tablet (Plan B One-Step). All the labeling, product inserts, and consumer information reviewed here apply to the two-dose 0.75-mg form of Plan B. In 2009, the FDA approved Plan B One-Step."[64] The FDA had by then the benefit of the studies that Dr. Reznik claims resolve the MOA issue. Nonetheless, the FDA mandated that

(1983). To lessen the subjectivity of the legal test, some courts recognize four elements of necessary disclosure: (1) the nature of the procedure, (2) the risks and hazards of the procedure, (3) the alternatives to the procedure, and (4) the anticipated benefits of the procedure. *Alswanger v. Smego*, 257 Conn. 58, 67–68 (2001). Only if a postfertilization MOA is within the "nature of the procedure" (or product) such that a reasonable patient would consider it material to her decision making could failure to disclose it expose a provider to liability. Given Trussell and Raymond's admonition concerning informed consent quoted above, a substantial case exists that adequate disclosure for Plan B treatment must include reference to its potential interceptive effect.

[61] See Austriaco, "Is Plan B an Abortifacient?"; Hilliard and Austriaco, letters, *NCBQ* Spring 2008; and Yeung et al. and Austriaco, letters, *NCBQ* Summer 2008 and *NCBQ* Autumn 2008. See also Yeung et al., "Argument Against the Use of Levonorgestrel" and their rebuttal to "Argument in Favor of the Use of Levonorgestrel."

[62] Yeung et al., "Argument Against the Use of Levonorgestrel," 146–148. See also their rebuttal to "Argument in Favor of the Use of Levonorgestrel" and letters, *NCBQ* Summer and Autumn 2008. Reznik relies most notably on Novikova, "Effectiveness of Levonorgestrel."

[63] Yeung et al., "Argument Against the Use of Levonorgestrel," 146–148, and letters, *NCBQ* Summer and Autumn 2008. The study Reznik cites is Lalitkumar, "Mifepristone, but Not Levonorgestrel."

[64] FDA, "New Drug Applications Approval: Plan B One-Step," July 7, 2009, emphasis added, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/021998s000ltr.pdf.

the prescribing information contain the following statement: "Plan B One-Step is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium)."[65] A less technical consumer information insert reads, "It is possible that Plan B One-Step may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb)."[66] In addition, the Drug Facts label on the One-Step package carries the following statement: "This product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation)."[67]

In 2009, the FDA approved Watson Laboratories' abbreviated new drug application for Next Choice, a generic equivalent of the two-dose 0.75-mg Plan B.[68] The product insert and the manufacturer's Web site contain disclosures similar to those accompanying Plan B. The consumer information insert contains the following statement:

> How does Next Choice work? Next Choice is two pills with levonorgestrel, a hormone that has been used in many birth control pills for over 35 years. Next Choice contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that Next Choice may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb).[69]

And the Next Choice Web site contains the following disclosure on its consumer question-and-answer page: "It is believed that Next Choice prevents the egg from being (1) released from the ovary (ovulation), (2) fertilized by the sperm (fertilization), or (3) attached to the uterus (implantation)."[70]

Watson Laboratories also maintains a specific "prescriber information" page on its Web site, which includes a section on the MOA of Next Choice that prescribers should review with their patients. It reads in part, "Next Choice works like a regular birth control pill to prevent pregnancy. It acts by stopping the release of an egg from

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[65] Duramed Pharmaceuticals, Plan B One-Step Prescribing Information, Consumer Information, and Package Information, July 2009, 4, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021998lbl.pdf.

[66] Ibid., 13.

[67] Ibid., 32.

[68] "FDA Approves Watson Pharmaceuticals ANDA for Levonorgestrel Tablets," August 29, 2009, http://www.news-medical.net/news/20090829/FDA-approves-Watson-Pharmaceuticals-ANDA-for-Levonorgestrel-tablets.aspx.

[69] Watson Pharmaceuticals, Next Choice Consumer Information, November 2009, http://pi.watson.com/data_stream.asp?product_group=1648&p=ppi&language=E.

[70] Next Choice, "Consumer Information Q&A: How Does Next Choice Work?" http://www.mynextchoice.com/Consumer/howtake_QA.asp.

the ovary, and may also prevent fertilization (by the sperm). Next Choice may also prevent the egg from attaching to the uterus (womb)."[71]

In summary, both levonorgestrel-only emergency contraceptives marketed in the United States contain the disclosures that Reznik describes as "unfortunate and inaccurate." Implicitly, she is claiming that the FDA either lacks competency or that the FDA and drug manufacturers are complicit in misrepresenting their products. Similar claims are becoming increasingly common among proponents of emergency contraception as well as among some Catholic ethicists.[72] In failing to recognize and address the postfertilization potential acknowledged by Trussell and Raymond, the FDA, and others, Reznik would deny women the truth essential for informed consent: that the MOA of levonorgestrel-only emergency contraception is not fully understood; that existing clinical, laboratory, and epidemiological data do not rule out a postfertilization potential; and that some of the data support it. There is ample support for the qualified statement in the product labeling, one that raises a legitimate debate about the morality of levonorgestrel-only emergency contraception in rape treatment protocols. And that is the real crux of the dilemma bedeviling Catholic health care facilities and practitioners who dispense Plan B.

Moral Certitude and Emergency Contraception

In a companion article to Reznik's "Plan B: How It Works," CHA senior ethicist Ron Hamel offers "Thinking Ethically about Emergency Contraception."[73] Hamel argues for the moral certainty that Plan B is not an abortifacient. His presentation suffers from omissions and inadequate analysis.

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[71] Next Choice, "Prescriber Information: What Should I Say to My Patients?" emphasis added, http://www.mynextchoice.com/Prescribers/Prescribers_WhatShouldSayPatDisc.asp. This is particularly significant for Catholic health care facilities because it expressly recommends individualized physician-to-patient disclosure of a possible interceptive MOA. How a Catholic facility may accomplish such disclosure, and thus obtain valid informed consent, is problematic at best. This author's personal interview of staff (physician and forensic nurse), health care ethicist, and administration at three of Connecticut's four Catholic hospitals revealed that women treated with emergency contraception are told either that it does not cause an abortion or that it prevents ovulation and pregnancy. None advise that it may have a postfertilization effect. See Thomas J. Davis Jr., "Emergency Contraceptive Mandates in Connecticut: A Case History," in *Christ or Caesar? When Compliance Violates Conscience: Proceedings of the Twenty-second Workshop for Bishops* (Philadelphia: NCBC, forthcoming). A version of the same article is available through the Pope John Paul II Bioethics Center at Holy Apostles College and Seminary, http://holyapostles.edu/bioethics/Deacon%20Davis%20EMERGENCY%20CONTRACEPTION%20MANDATES%20IN%20CONNECTICUT-%20A%20CASE%20HISTORY.pdf

[72] See Cataldo, rebuttal to "Argument Against the Use of Levonorgestrel"; and "Argument in Favor of the Use of Levonorgestrel." See also Austriaco, "Is Plan B an Abortifacient?" and letters, *NCBQ* Spring, Summer and Autumn 2008.

[73] Ron Hamel, "Thinking Ethically about Emergency Contraception," *Health Progress* 91.1 (January–February 2010): 62–67, www.chausa.org/2010_annual_index.aspx.

First, he asserts that a thorough review of scientific literature has been made by CHA[74] and that the association "obtained two independent analyses of the literature—one by an [obstetrician-gynecologist] and the other by a pharmacist," both of which concluded that "Plan B has little or no postfertilization effect." But such a claim merely begs the questions. Other physicians, as well as the FDA, dispute the claim that Plan B does not have the potential for a postfertilization MOA. Dr. Yeung, for example, is a board-certified obstetrician-gynecologist. His co-author Fr. Tham is also a medical doctor. Dr. Kathleen Raviele, who has also disputed the claim, is a board-certified obstetrician-gynecologist and past president of the Catholic Medical Association.[75] It is hard to imagine CHA's experts being more qualified than these. They have reviewed the same literature but reached a different conclusion. In trial practice, attorneys refer to this kind of dispute as a battle of experts. That is a fair description of the current scientific landscape on the question of the MOA of levonorgestrel.

Another contributor to the debate is the Catholic Medical Association, which maintains that the "scientific evidence supports the conclusion that all these formulations [including levonorgestrel-only emergency contraception] have some potential to prevent the implantation of a newly conceived human being."[76] Raviele's discussion of this precise topic at the 2009 NCBC Workshop for Bishops in Dallas, Texas, was a powerful example of the differing opinions held by highly qualified experts.[77]

Hamel presents CHA's literature reviews as authoritative, describing them as summaries of "the great majority of articles on emergency contraceptive medications' mechanisms of action." However, investigation of the summaries discloses that they do not include any of the letters by Yeung et al. in the *NCBQ* or the contributions by Yeung et al. to *Catholic Health Care Ethics: A Manual for Practitioners*, and several items the summaries do include support the view that a postfertilization MOA has not been ruled out and should be disclosed to product users. For example, a 2006 editorial by Trussell and Jordan in the journal *Contraception* is quoted as follows: "Treatment with ECPs [emergency contraceptive pills] containing only levonorg-

[74] Ibid. Hamel cites to two literature reviews: one of emergency contraception medications generally and another specific to levonorgestrel. The links he provides to Internet resources (in note 3 of his article) are no longer usable, but the reviews can still be found on the CHA Web site: Catholic Health Association, "Literature Review: Mechanisms of Action of EC Medications," July 2007, updated October 25, 2010, http://www.chausa.org/WorkArea/DownloadAsset.aspx?id=2147484406; and "Literature Review: The Mechanism of Action of Levonorgestrel (Plan B)—Summaries of the Scientific Literature," no date, http://www.chausa.org/WorkArea/DownloadAsset.aspx?id=2147484405.

[75] Kathleen M. Raviele, "State Intrusions into the Practice of Medicine," presentation at the Twenty-second NCBC Workshop for Bishops, Dallas, Texas, February 3, 2009.

[76] Catholic Medical Association, "CMA Responds to Connecticut Plan B Law," press release, November 5, 2007, http://www.cathmed.org/issues_resources/publications/press_releases/cma_responds_to_connecticut_plan_b_law/.

[77] Raviele, "State Intrusions into the Practice of Medicine."

estrel during the periovulatory phase may fail to inhibit ovulation but, nevertheless, reduce the length of the luteal phase LH concentrations; this observation suggests a postfertilization contraceptive effect."[78]

Another article summarized in the CHA literature reviews is the well-known "Plan B and the Politics of Doubt," by Davidoff and Trussell, a commentary in the *Journal of the American Medical Association* that is classified by CHA as a review article. The authors certainly argue that any postfertilization potential remains speculative and that all MOAs could be accounted for by prefertilization modalities. However, they frankly acknowledge that the jury is still out and that "women should continue to be informed, as they are now in the Plan B labeling, that its use may affect postfertilization events."[79] CHA deleted that sentence from the summaries in both literature reviews, thereby leaving any reader with a markedly different understanding of the authors' conclusion.[80] This is troubling, given Hamel's citation of the CHA reviews in note 3 of his article, a citation inviting readers to examine the selectively edited reviews. Unless intrepid readers were to independently locate the primary sources, they would be unaware that the authors of those documents actually endorse the disclosure of a possible postfertilization MOA on the Plan B label.

Moreover, the Davidoff and Trussell commentary points to another informed consent issue generated by the imperfect knowledge of levonorgestrel: that it is used therapeutically in assisted reproduction to increase the success rate of implantation and pregnancy and that "Plan B used *after* ovulation might actually prevent the loss" of pregnancy.[81] That would hardly be the result a victim of sexual assault would

[78] James Trussell and Beth Jordan, "Mechanism of Action of Emergency Contraceptive Pills," editorial, *Contraception* 74.2 (August 2006): 87, quoted in Catholic Health Association, "Literature Review: Levonorgestrel," 18, and "Literature Review: EC Medications," 55.

[79] Davidoff and Trussell, "Plan B and the Politics of Doubt," 1777.

[80] CHA, "Literature Review: Levonorgestrel," 38–39, and "Literature Review: EC Medications," 57–58.

[81] Davidoff and Trussell, "Plan B and the Politics of Doubt," 1777, emphasis added. The possibility that Plan B may actually secure implantation raises the issue of health care provider liability. Theories of liability include variants of so-called wrongful life or wrongful birth: "The terms 'wrongful birth' and 'wrongful life' are but shorthand phrases that describe the causes of action of parents and children when negligent medical treatment deprives parents of the option to terminate a pregnancy to avoid the birth of a defective child." *Procanik v. Cillo*, 97 N.J. 339, 347 (1984). Medical negligence in performance of sterilization procedures is also a basis of recovery for medical negligence, as in *Burke v. Rivo*, 406 Mass. 764 (1990), which recognized a right to recover for costs of raising a healthy child, expenses associated with the delivery of the child and damages for the emotional suffering incurred. It is a small conceptual step to extend such liability for the birth of a healthy child conceived through rape in the event that a health care provider failed to advise a woman that Plan B treatment may actually secure implantation. See *Burns v. Hanson*, 249 Conn. 809, 811, 734 A.2d 964 (1999): "The issues in this action for malpractice arise out of the birth of a healthy child to a severely disabled mother, who, in accordance with medical advice, had decided not to have another child." See also *Ochs v. Borrelli*, 187 Conn. 253, 258, 445 A.2d 883 (1982): "In our

expect, given the position taken by Hamel. Nonetheless, it too was edited out of the CHA summary, even though it obviously points out the uncertain science.

The remainder of Hamel's analysis of interceptive potential rests almost exclusively on the article and letters by Austriaco in the *NCBQ*.[82] Hamel represents Austriaco's original *NCBQ* article as a "thorough review of the scientific literature." In fact, that review was limited and was substantially expanded in a subsequent letter. The initial article relied heavily on a recently published clinical study and a recently published laboratory study, both of which were subsequently critiqued by Yeung et al.[83]

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view, the better rule is to allow parents to recover for the expenses of rearing an unplanned child to majority when the child's birth results from negligent medical care." This all the more strongly suggests that full informed consent is essential for the administration of levonorgestrel and requires disclosure not only of a potential postfertilization MOA, but also of the possibility that, depending on the timing of administration, it may actually increase the likelihood of successful implantation.

[82] Austriaco, "Is Plan B an Abortifacient?"; and letters, *NCBQ* Spring, Summer and Autumn 2008.

[83] The clinical study is Novikova et al., "Effectiveness of Levonorgestrel"; the laboratory study is Lalitkumar, "Mifepristone, but not Levonorgestrel." These studies are critiqued in Yeung et al., "Argument Against the Use of Levonorgestrel"; rebuttal to "Argument in Favor of the Use of Levonorgestrel"; and letters, *NCBQ* Summer and Autumn 2008. The study by Novikova et al., published in 2007, was central to Austriaco's initial claim that as a matter of "scientific certitude," Plan B has no postfertilization MOA. Austriaco, "Is Plan B an Abortifacient?" One of the study's conclusions was that previous articles and studies had exaggerated the rate of prevention of expected pregnancies. Since other studies suggested that suppression of ovulation could not account for the high rate of prevention of expected pregnancies, the inferential conclusion was that another MOA had to be at work, with interception being one possibility. Novikova et al. challenged that inference by their finding that women frequently erred in self-reporting their ovulation date, which resulted in overestimates of the postovulatory effectiveness of Plan B. However, if the effectiveness rate is much lower than previously believed, such that an alternative MOA is unnecessary to explain it, one would expect the FDA and the manufacturers and marketers of levonorgestrel-only emergency contraception to acknowledge the lower efficacy. However, current product labeling for Plan B One-Step, approved by the FDA in 2009, makes the following claims: "Among women receiving Plan B One-Step, 84% of expected pregnancies were prevented and among those women taking Plan B, 79% of expected pregnancies were prevented. The expected pregnancy rate of 8% (with no contraceptive use) was reduced to approximately 1% with Plan B One-Step" (6). The consumer product information included in the package also contains the following statement regarding the effectiveness of Plan B One-Step: "The sooner you take Plan B One-Step, the better it will work. Take Plan B One-Step as soon as possible after unprotected sex. If it is taken as soon as possible within 72 hours (3 days) after unprotected sex, it will significantly decrease the chance that you will get pregnant. Seven out of every 8 women who would have gotten pregnant will not become pregnant" (8). See http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021998lbl.pdf. Accordingly, Duramed and Barr Pharmaceuticals, along with the FDA, continue to maintain that levonorgestrel-only emergency contraception prevents pregnancy at a rate much higher than can be explained by suppression of ovulation.

In his article and first letter, a reply to Hilliard, Austriaco made a claim of "scientific certitude" for his conclusion that Plan B was not interceptive.[84] Hamel quotes that original passage at length without critical comment. He then quotes a subsequent *NCBQ* offering by Austriaco—written, we are told, in response to "critics"—which describes specific modes by which Plan B may theoretically act as an interceptive.[85] The second mode described by Austriaco is essentially the model proposed by Yeung et al. Hamel's entire analysis of that potential is limited to quoting Austriaco: Hamel says, "After reviewing the scientific literature, Austriaco concluded that 'together, these data suggest that the risk of a postfertilization effect from this mode of action for any particular individual woman, if it is real, would be vanishingly small.'"[86]

Several details are immediately apparent. First, Hamel provides no scientific assessment of the underlying data but merely relies on Austriaco's conclusion, citing his credentials as a "priest, theologian and scientist," the first two of which have no apparent significance for assessing the merits of clinical, laboratory, or epidemiological studies. Second, he fails to mention that Austriaco's "critics" include two medical doctors—Dr. Yeung and Fr. Tham, the latter also a "priest, theologian and scientist"—one of whom is a board-certified in obstetrics and gynecology and a Fellow of the American Congress of Obstetricians and Gynecologists. Third, Hamel makes no effort to present the scientific case advanced by those critics in support of the theoretical model of postfertilization MOA.[87] Fourth, and perhaps most tellingly, he fails to comment on the implicit admission by Austriaco that his "scientific certitude" claim could not be sustained in light of the existing literature and the critique by Yeung et al.

Austriaco's retreat acknowledged the possibility of a postfertilization effect but relegated it to a very uncommon occurrence "for any particular woman." By the end of his exchange of letters with Yeung et al., his defense of an exclusively prefertilization MOA rested on a different level of certainty than previously claimed: "I stand by my earlier conclusion: In light of the available scientific evidence and given the inherent limitations of the studies, it is *unlikely* that Plan B is an abortifacient."[88] Scientific certitude is entirely abandoned. In its place appears an assessment of likelihood. Hamel fails to acknowledge that shift.

Hamel proceeds to a presentation of moral certitude, which, given the unresolved science, is indeed the heart of the matter. "Moral certitude," Hamel states, "means that

[84] Austriaco, "Is Plan B an Abortifacient?"; and letter, *NCBQ* Spring 2008.

[85] Austriaco, letter, *NCBQ* Autumn 2008.

[86] Hamel quotes here from Austriaco, letter, *NCBQ* Autumn 2008, a reply to Yeung et al.

[87] Edward J. Furton, editor of the *NCBQ*, properly takes Hamel to task in an editorial titled "Selective Citations," which criticizes Hamel for cherry picking the relevant data and failing to provide a balanced presentation of the scientific data, particularly his failure to acknowledge the contribution of Yeung et al. to the debate. *National Catholic Bioethics Quarterly* 10.1 (Spring 2010): 39–41.

[88] Austriaco, letter, *NCBQ* Autumn 2008, 424, emphasis added.

the agent has excluded all reasonable possibility of error." Hamel then quotes from Rev. Thomas Slater's treatment of the morality of human acts in Slater's 1925 *Manual of Moral Theology*: "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."

These are well-phrased and accepted formulations describing the level of confidence necessary to reach moral certainty for decisions affecting life and death. It restates the standard of proof known in American criminal jurisprudence as "beyond a reasonable doubt." It does not require exclusion of every possible doubt but does mandate that no reasonable doubt exist with respect to a particular proposition of fact.

Other formulations that discount the abortifacient potential of Plan B are sometimes offered as a basis for moral certainty permitting its use. With reference to a possible postfertilization effect of emergency contraceptive drugs, however, words and phrases like "unlikely," "not probable," "more probable than not," "the preponderance of evidence," and "the weight of the evidence" are inadequate. Even the term "solid probability," frequently employed in various moral systems, may set the bar too low if it is used to express moral certainty that levonorgestrel does not have an abortifacient MOA. It is generally recognized that the greater the good, the greater also must be the reason for jeopardizing it. Certainly, the obligation to resolve doubt that a particularly grave evil will occur is greater in the face of greater goods. Judgments of moral certainty properly encounter a higher threshold where human life is at risk than when the good at stake is of lesser value, such as a property or even reputational interest.

Essentially, Hamel claims that no reasonable doubt exists, given the "mounting evidence from the scientific literature that Plan B does not prevent implantation."[89] But what "mounting evidence" overcomes the doubt raised by the thesis of Yeung et al.? Findings from studies relevant to that model are indeterminate, and the FDA continues to recognize the unresolved science by mandating risk disclosure. The few findings that do address the model are neither mounting nor substantial.[90] Yet Hamel dismisses any doubt as patently unreasonable: "It is, of course, theoretically possible that all of the studies that have been done could be mistaken, but this is not likely." But it is simply untrue that *all* the studies support his conclusion. Most do not address the observations by Yeung et al., none rule it out, and several provide strongly supportive data. Hamel's suggestion otherwise recalls Reznik's misrepresentation of the Plan B product labeling language and the Plan B sponsor's presentation during the December 16, 2003, joint proceedings of the NDAC and ACRHD.

Much of Hamel's moral-certitude claim for the uprightness of levonorgestrel-only emergency contraception in rape treatment echoes Austriaco's claim that any postfertilization effect would be "vanishing small." That is a debatable point. Daniel

[89]Hamel, "Thinking Ethically about Emergency Contraception," 65.

[90]The relevant findings can be found in Leung, Levine, and Soon, "Mechanisms of Action of Hormonal Emergency Contraceptives," as discussed above.

Sulmasy, OFM, MD, applies statistical probability analysis and concludes that the likely incidence of postfertilization MOA is strikingly low.[91] While acknowledging emergency contraception as a potential interceptive, he judges the risk to be minute, describing it as "very rare," if it exists at all.[92] Contrasting his understanding of the expected statistical incidence of rape-related pregnancy, pre-existing pregnancy, efficacy of drugs, and other factors, he maintains that "if EC [emergency contraception] drugs do cause indirect abortions, the proportion of cases in which these events occur if one uses the ovulation approach instead of the pregnancy approach will be on the order of 0.004 percent instead of 0.04 percent of cases."[93] Sulmasy's assumptions,

[91] Daniel Sulmasy, "Emergency Contraception for Women Who Have Been Raped: Must Catholics Test for Ovulation, or Is Testing for Pregnancy Morally Sufficient?" *Kennedy Institute of Ethics Journal* 16.4 (December 2006): 305–331.

[92] Ibid., 310. Sulmasy attributes his conclusion to "new data about emergency contraception's mechanism of action," asserting that "most medical scientists working in the field are prepared to say that the weight of the evidence suggests that EC drugs never work by preventing implantation." (309). He describes his small doubt as "residual scientific uncertainty."

[93] Ibid., 317. The ovulation approach requires a negative result on LH surge testing, typically referred to as ovulation testing, either by urine or blood analysis. The pregnancy approach accepts a negative pregnancy test result as sufficient prior to the administration of emergency contraception. Sulmasy's description of emergency contraceptive interception as "indirect abortion" is questionable. It calls to mind his earlier double-effect analysis in a comment accompanying Hamel and Panicola's earlier defense of emergency contraception in rape cases. See Daniel P. Sulmasy, "A Reasonable, Realistic, and Ethical Protocol," in Ron Hamel and Michael Panicola, "Emergency Contraception and Sexual Assault," *Health Progress* 83.5 (September– October 2002): 15, http://www.chausa.org/2002_Annual_Index .aspx. In that comment, Sulmasy defends the pregnancy approach because, he holds, it maintains "absolutely strict adherence to our deeply held conviction that it is never morally permissible to destroy directly any innocent human life from the moment of conception to natural death." But since postovulatory Plan B has no contragestive effect, it is unclear how the pregnancy approach is relevant in the manner suggested. Moreover, in order to apply the term "indirect" and avoid the prohibition on direct abortion, Sulmasy argues (in "Emergency Contraception for Women Who Have Been Raped") that the rule of double effect does not require binary outcomes, and thereby rejects the traditional formulation of double effect, which requires at least two effects be realized from a given act (313–314). Classical double-effect analysis "governs situations in which one action is followed by two effects, one good (and intended), the other evil (foreseen but not intended)." Furton and Moraczewski, "Double Effect," in *Health Care Ethics: A Manual for Practitioners,* 23. See also Germain Grisez, *The Way of the Lord Jesus,* vol. 1, *Christian Moral Principles* (Quincy, IL: Franciscan Press, 1983), 307, where Grisez describes the traditional analysis as requiring that the good and evil effects be realized "simultaneously." But one cannot posit the two effects under consideration (prefertilization and postfertilization) as concurrent or simultaneous, one good and one evil. An anovulant MOA precludes a postfertilization MOA and vice versa. Where only one effect is realized, traditional double-effect analysis has no place. See Thomas J. O'Donnell, SJ, *Medicine and Christian Morality*, 3rd rev. ed. (Staten Island, NY: Alba House, 1997), 196–197. Accordingly, if interception were to occur, it would not be "indirect" as envisioned in traditional double-effect analysis, such as when a cancerous uterus is surgically removed

and thus his conclusion, have been seriously challenged by Marie Hilliard, who has shown that his analysis relies on flawed estimates of rape-related pregnancy and invalid presumptions about pre-existing pregnancy.[94] She also shows that rape victims presenting at hospital emergency rooms tend to be among the younger women on the full fertile-age spectrum, include those most likely to be raped, and are in the age group at which fertility is the greatest. Finally, she challenges estimates predicting that 11 percent of women seeking emergency contraception in Catholic hospital emergency rooms are actually in their fertile period, and suggests that the rate may be as high as 32 percent. All these factors undermine Sulmasy's calculations by suggesting significantly higher rape-related fertilization than he assumed and thus higher rates of abortifacient action.

The analysis by Yeung et al. strikes directly at the notion that use of levonorgestrel in the preovulatory fertile phase poses only a rare abortifacient risk:

> An estimation of the percentage of time that levonorgestrel effectiveness can be explained by postfertilization effects when levonorgestrel is taken in the *preovulatory* period can now be made on the basis of these updated estimates—based on well-designed models—of clinical and theoretical effectiveness. Even if the estimate for clinical effectiveness is adjusted downward by another 10 percent, an estimate of postfertilization effects of preovulatory levonorgestrel is clinical effectiveness minus overestimation minus maximum theoretical effectiveness, that is, 72 percent minus 10 percent minus 49 to 59 percent, equaling 3 to 13

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from a pregnant woman. In that case two effects are actually realized, one good, one evil: the removal of the cancer and the death of the child. As tragic and difficult as rape-related pregnancy must be, it cannot be an "evil" in a traditional double-effect analysis that presumes an abortifacient effect: the "evil" effect would be the postfertilization MOA. In addition to anticipating dual effects, one intended, one not, the traditional formulation contains two additional elements: first, that "the good effect is not produced by means of the evil effect" and, second, that "there is a proportionate reason for permitting the foreseen evil effect to occur." Edwin Healy, *Moral Guidance* (Baltimore: Loyola University Press, 1942), 20, quoted by Daniel Cronin in his doctoral dissertation, "The Moral Law in regard to the Ordinary and Extraordinary Means of Conserving Life," republished in *Conserving Human Life*, ed. Russell E. Shaw (St. Louis: Pope John Paul XXIII Medical-Moral Research and Education Center, 1989), 26. One could posit a dual effect with emergency contraception: interception (evil and unintended) and freedom from carrying a rapist's child (good and intended). But that would clearly be a good effect achieved by means of an evil one. And what reason may be offered for acceptance of interception that is proportionate to the death of a human being? Traditional double-effect analysis is not without its difficulties, nor is it "a normative principle but a somewhat cumbersome attempt at clarifying what one is morally responsible for in freely accepting side effects which it would be wrong to choose." Grisez, *Christian Moral Principles*, 299. Sulmasy's approach is an attempt to wrestle with the concept. However, rather than twist traditional formulations to fit a difficult case, it might be better to respect the traditional formulation and set double-effect analysis aside, focusing instead on the issue of moral certainty with respect to the object chosen, which is discussed in more detail below. If the potential evil effect can be excluded to a moral certainty, then the better argument would be that the object chosen excludes it as well.

[94]Hilliard, "Moral Certitude and Emergency Contraception," 156–157.

> percent postfertilization effects that interfere with implantation. In other words, levonorgestrel is estimated to act as an abortifacient 3 to 13 percent of the time when it is administered in the preovulatory period.[95]

May an abortifacient rate of 3 to 13 percent of the subgroup be properly categorized as "rare"? A 1998 survey by the National Institute of Justice (NIJ) and Centers for Disease Control and Prevention (CDC) estimated that 876,100 women were raped in the United States during the twelve months preceding the study.[96] Assuming that rape occurs evenly across victims' menstrual cycles, approximately 14 percent of rapes would take place during the victims' preovulatory fertile phase. Given the estimates of the NIJ/CDC survey, if all rape victims in a preovulatory fertile phase were treated with Plan B, the Yeung model would predict a postfertilization MOA occurring in as many as sixteen thousand women annually in the United States alone. The mathematical analysis by Yeung et al. further challenges Hamel's moral certitude argument and demonstrates that the actual incidence of an abortifacient MOA could be significant.

Finally, Hamel attempts to distinguish the classic example of the hunter in the woods who, faced with the prospect that movement in the brush may be another hunter rather than a deer, must take the safer course and withhold fire until he positively resolves the doubt.[97] Hamel asks whether this example suggests that Catholic health care providers take the safer course and test for LH surge before administering Plan B to a rape victim. He rejects that view, asserting that it is unlikely that Plan B is interceptive and highly improbable that a fertilized egg is present following rape. With no real doubt to resolve, he concludes that ovulation testing is unnecessary. But Yeung et al. have already dismissed the need for such testing, since a positive ovulation test result would mean that levonorgestrel "will neither prevent ovulation nor have a negative effect on luteal function; that is it will not work to prevent pregnancy at all."[98] And a negative result would not distinguish the luteal phase from the follicular phase, including the preovulatory fertile period.

Accordingly, Yeung et al. hold that an "ovulation test is not a helpful guide since, whatever the result, levonorgestrel emergency contraception either will not prevent pregnancy or will be potentially abortifacient."[99] The model would simply preclude resort to Plan B, since the only effective use of Plan B would be during the preovulatory fertile window with its concurrent abortifacient risk. Until research rules

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[95] Yeung et al., "Argument Against the Use of Levonorgestrel in Cases of Sexual Assault," 146.

[96] Patricia Tjaden and Nancy Thoennes, "Prevalence, Incidence, and Consequences of Violence against Women: Findings from the National Violence against Women Survey, *Research in Brief*, National Institute of Justice and Centers for Disease Control and Prevention, November 1998, 4, http://www.ncjrs.gov/pdffiles/172837.pdf.

[97] Hamel, "Thinking Ethically about Emergency Contraception," 66.

[98] Yeung et al., "Argument Against the Use of Levonorgestrel in Cases of Sexual Assault," 148.

[99] Ibid.

out the model proposed by Yeung et al. or until their mathematical calculations are debunked, Hamel's justification for Plan B seems more akin to a selectively informed educated guess than to a morally certain judgment precluding reasonable doubt.

As for Hamel's assertion that it is "improbable" that an embryo is present following rape, it is simply impossible to know the answer in a given case. It has been well established that pregnancy resulting from rape is more common than was once thought.[100] One reliable study estimates that the national rape-related pregnancy rate is 5.0 percent per rape among victims of reproductive age (twelve to forty-five years) and that an estimated 32,101 pregnancies among adult women result from rape each year.[101] And since many embryos fail to implant in the normal course, the frequency of fertilization following rape must be considerably higher.[102] More fundamentally, Hamel cites as his authority a passage in the first edition of *Catholic Health Care Ethics* (NCBC, 2001) in which it is assumed that emergency contraception is administered "*only* during an infertile phase of the ovulation cycle" and "under the restricted conditions of the Saint Francis Medical Center protocol."[103] But the Yeung model is specific to administration during the preovulatory fertile phase and presumes that the Saint Francis protocol is irrelevant, even erroneous, as it permits treatment with anovulant emergency contraception during the preovulatory phase. In addition to relying on dated and low estimates of rape-related pregnancy, Hamel's "improbable" judgment simply cannot provide adequate assurance (beyond a reasonable doubt) that an embryo is not present in a particular case. His assessment is not a here-and-now conclusion based on relevant medical data but a statistical generalization that lacks conclusive power, a point relevant to much of statistical probability methodology, as Hilliard demonstrates.[104]

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[100] The Saint Francis Medical Center Protocol for Sexual Assault (also known as the Peoria protocol) holds that "conception rarely (0 to 4 percent …) results from the violence of rape." See *Catholic Health Care Ethics: A Manual for Practitioners*, 132). While 0 percent is, by definition, rare, a 4 percent rate is significant. Later studies suggest rates near 5 percent. Some pro-life advocates have understated the incidence of rape-related pregnancy in an effort to downplay the urgency of the issue. But bad facts make for bad analysis. One estimate that has recently been repeated, if not verified—that four hundred rape-related pregnancies occur annually in the United States—vastly underestimates reality and should be dismissed out of hand. See J. Daniel Mindling, "Breakfast Talk," Diocesan White Mass for Catholic Health Care Professionals, February 24, 2008, http://www.bridgeportdiocese.com/talk.2.24.08.shtml**.**

[101] Holmes et al., "Rape-Related Pregnancy: Estimates and Descriptive Characteristics from a National Sample of Women," *American Journal of Obstetrics and Gynecology* 175.2 (August 1996): 320–325. Other recognized experts estimate that at least twenty-five thousand pregnancies result from rape in the United States annually. See Felicia Stewart and James Trussell, "Prevention of Pregnancy Resulting from Rape: A Neglected Preventative Health Measure," *American Journal of Preventive Medicine* 19.4 (November 2000): 228–229.

[102] See Macklon, Geraedts, and Fauser, "Conception to Ongoing Pregnancy," 335.

[103] Cataldo and Moraczewski, eds., *Catholic Health Care Ethics: A Manual for Ethics Committee,* 1st ed. (Philadelphia: NCBC, 2001), 11/16–11/17, emphasis added.

[104] Hilliard, "Moral Certitude and Emergency Contraception," 157–158.

Behind Hamel's dismissal of the hunter analogy may lurk his own questionable analysis in an earlier *Health Progress* article addressing the same topic.[105] There, Hamel and Panicola hold that the hunter is faced with a real object, either an animal or another hunter, and must therefore follow the safer course. But in the case of anovulant hormonal treatment, there is doubt whether there is any object at all (i.e., an embryonic human). Hamel and Panicola emphasize the hunter's direct intention to kill something, whatever it may be. Given those distinctions, Hamel and Panicola argue, the analogy collapses. But the distinction is ephemeral. One may posit movement in the brush caused by wind or the hunter's overactive imagination as the source of the hunter's belief that a man or a deer is present when, in fact, nothing at all is there. Nonetheless, the classical analysis dictating the safer course would apply. Confronted with his own belief that another hunter *may* be present, the hunter is obliged to resolve the doubt. To believe that there is a significant risk that one's choice could cause the death of an innocent human being and to choose that action in the absence of a proportionate reason is gravely immoral. The hunter would be morally culpable if he fired at a "non-object" while internally doubtful whether he was shooting at a human being or an animal. Hamel's suggestion otherwise fails to adequately recognize the moral obligation to resolve doubt. In the case of levonorgestrel, the moral object that is chosen includes the decision to take (or provide) a medication that risks a postfertilization effect at a significant rate:

> In order for an object that endangers human life to be pursued in the absence of life-threatening circumstances, the risk of such an effect must be truly minimal. … To administer levonorgestrel in the preovulatory phase knowing that the best evidence available suggests that it acts as an abortifacient in a significant portion of cases is to *accept this effect as an aspect of the means chosen*. One must remember that the intention of the moral agent does not pertain only to the end or reason for which one acts, but also the moral object, including the means one chooses.[106]

The circumstance calls to mind Grisez' suggestion that unrestricted use of emergency contraception when postfertilization effects cannot be substantially ruled out leaves open the question of conditional acceptance of abortion.[107]

The Rise of Ulipristal

Given the Yeung model and the current state of research, it is difficult to conclude that a postfertilization MOA is precluded to a moral certainty. Reasonable doubt exists. In this respect it may be useful to examine the comments of Pope Benedict XVI in another context:

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[105]Hamel and Panicola, "Emergency Contraception and Sexual Assault." A similarly questionable analysis of the hunter example is offered by Peter Cataldo in both the 2001 and 2009 editions of the *Catholic Health Care Ethics*. See, for example, his "Argument in Favor of the Use of Levonorgestrel" (2009), 138.

[106]Yeung et al., rebuttal to "Argument in Favor of the Use of Levonorgestrel," 141, 143, original emphasis.

[107]Grisez, *Difficult Moral Questions*, 296–298.

> In these years science has accomplished further progress in certifying the death of the patient. It is good, therefore, that the results attained receive the consent of the entire scientific community in order to further research for solutions that give certainty to all. In an area such as this, in fact, there cannot be the slightest suspicion of arbitration and where certainty has not been attained the principle of precaution must prevail.[108]

Certainly most Catholic ethicists would agree that caution should govern medical interventions by which human life may be placed at risk. The question becomes how high a threshold to establish. While the circumstances differ, an analogous application of the Holy Father's comments to levonorgestrel-only emergency contraception suggests that the principle of precaution may preclude its use in rape protocols at Catholic health care facilities.

One final note of caution should be appreciated by all Catholic health care providers, ethicists, and legislators regardless of their assessment of levonorgestrel-only emergency contraception. Plan B is not the only emergency contraceptive on the market. RU-486 (mifepristone) has both anovulant and interceptive MOAs when used as emergency contraception, in addition to its contragestive MOA.[109] Ulipristal acetate (marketed under the trade name ellaOne in Europe and ella in the United States) is another emergency contraceptive, which was approved by regulatory authorities in Europe in March 2009 and, in August 2010, by the FDA as a prescription-only emergency contraceptive in the United States.[110] Because it effectiveness in preventing pregnancy (defined as implantation) extends the time for effective use from seventy-two hours after sexual intercourse to one hundred twenty hours, it is being promoted as an emergency contraceptive that is superior to Plan B. However, ulipristal acetate is a selective progesterone receptor modulator, which means that it attaches to the receptors to which progesterone normally attaches, preventing the hormone from having its effect. The 2009 medical evaluation of ulipristal acetate by the European Medicines Agency, while recognizing an anovulant MOA, strongly documents the drug's potential postfertilization MOA:

> Ulipristal acetate prevents progesterone from occupying its receptor; thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized. …
>
> Mid-luteal administration of ulipristal acetate resulted in early endometrial bleeding, indicating a direct action on the endometrium. …
>
> At mid-follicular phase, doses of 10–100 mg ulipristal acetate … inhibited luteal phase endometrial maturation similarly at all doses. …
>
> At early-luteal phase, … significant delay in endometrial maturation occurred in the 50 and 100 mg groups. …

[108] Benedict XVI, Address to Participants at an International Congress Organized by the Pontifical Academy for Life (November 7, 2008).

[109] See footnote 3 above.

[110] "FDA Approves ella Tablets for Prescription Emergency Contraception," FDA news release, August 13, 2010, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm222428.htm.

> In conclusion, the mechanism of action, as claimed in 5.1 of the SPC [supplementary protection certificate], "The primary mechanism of action is thought to be inhibition or delay of ovulation, but alterations to the endometrium may also contribute to the efficacy of the product," is sufficiently documented.[111]

The FDA review reached similar conclusions:

> Mid-follicular phase: … Inhibition of luteal phase endometrial maturation was observed at all dose groups. …
>
> Early luteal phase: … Ulipristal delayed endometrial maturation at all doses tested. …
>
> Administration of ulipristal in the luteal phase also alters the endometrium. Based on the findings of the pharmacodynamic studies, *ulipristal appears to exert an anti-progesterone contraceptive effect on both the ovary and endometrium*, depending on the dose and time of drug administration during the menstrual cycle.[112]

The FDA review also noted that ulipristal terminated late-gestation pregnancies in guinea pigs and early pregnancies in monkeys, and caused embryo-fetal lethality in rats and rabbits at drug exposures comparable to human exposure.[113]

The European Medicines Agency and FDA findings make plain the danger that ulipristal represents. Catholic hospitals, especially those that permit the use of levonorgestrel in rape treatment, must be vigilant lest ulipristal be introduced in their facilities with attendant culpability. Some states mandate that prescription emergency contraception be provided to rape victims upon request as part of standard protocol.[114] Once Plan B is approved as fully OTC, a likely development in the near future, it will no longer satisfy that statutory mandate. Only prescription products, like ella or RU-486, will meet that standard. Advocacy groups will lobby for the prescription drugs, citing evidence of greater efficacy at preventing pregnancy (defined as implantation). Attempts to amend statutory language to allow a fully OTC Plan B in lieu of the prescription drugs will be vigorously opposed.[115] We are approaching a critical trip wire.

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[111] European Medicines Agency, "Evaluation of Medicines for Human Use: CHMP Assessment Report for Ellaone" (2009), 8, 22–23, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001027/WC500023673.pdf.

[112] FDA, "Background Document for Meeting of Advisory Committee for Reproductive Health Drugs (June 17, 2010)," May 20, 2010, 11–12, emphasis added, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM215425.pdf.

[113] Ibid., 10.

[114] See, for example, Connecticut General Statute, sec. 19a-112e, (a)(1) and (b)(3), http://www.cga.ct.gov/2009/pub/chap368a.htm#Sec19a-112e.htm.

[115] For more on the risk posed by statutory rape-treatment mandates, see Thomas J. Davis Jr., "Plan B and the Rout of Religious Liberty: Reflections on the Status of the Law," *Ethics & Medics* 32.12 (December 2007).