## Response to Rodes

*To the Editor:* I welcomed Professor Rodes's reflections "On Marriage and Metaphysics" in the *Quarterly* (Winter 2007). I should like to add the often overlooked fact that any suggestion of a woman living in a man's body (or vice versa) is a tacit yet forceful acknowledgment that the difference between men and women goes beyond the biological. Ironically, it is often the case that those most open to claims about inhabiting the wrong body are those who, in other contexts, find it useful to trivialize the difference between the sexes by reducing them to a matter of "plumbing."

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## Plan B's Abortifacient Effect

*To the Editor:* In the Winter 2007 issue of the *Quarterly*, Fr. Nicanor Austriaco asked, and answered in the negative, the question "Is Plan B an Abortifacient?"[1] Two recent studies are cited as challenging the claim that Plan B is an abortifacient (Novikova et al. and Lalitkumar et al.).[2] There are sufficient data to question the conclusion of these two papers, especially as developed by Austriaco.

Austriaco begins by critiquing two other papers that "purport to present scientific evidence that support an abortifacient effect for Plan B" (704).[3] His critique is based on the fact that both of these studies present what he terms theoretical evidence, not "demonstrative proof" of the abortifacient effect of levonorgestrel:

> It is important to acknowledge that neither of the studies summarized above demonstrate an abortifacient effect for levonorgestrel. They simply point out that statistically, Plan B taken after ovulation reduces the expected number of pregnancies in a manner that cannot be attributed to its anti-ovulatory effects alone, and that theoretically, Plan B could prevent implantation by adversely affecting the thickness of the endometrium. Together, these point to a possible abortifacient effect for Plan B. However, statistical and theoretical studies do not amount to demonstrative proof. (705, original emphasis)

This very same claim can be made of the basis for comparison used by Novikova et al. in estimating the probability of clinical pregnancy after unprotected intercourse if there were no intervention with levonorgestrel: "To determine the efficacy of the ECP [emergency contraceptive pill], we compared the number of observed pregnancies with the number of expected pregnancies."[4] Estimates of probability are based on observed data. It is an acceptable scientific method to draw inferences from observed data. Furthermore, Novikova et al. conclude about their research: "The small number of participants in our study does not enable us to make a definitive statement on the hypothetical postfertilization effect of the ECP."[5]

There are other concerns about the research methodologies in the Novikova study. Specifically, the subjects were women between fifteen and forty-three years of age. There is no control provided for the age of the women and the incidents of pregnancy. Maternal age beyond thirty-five years affects implantation rates, with a linear decrease in implantation rates of 2.77 percent per year.[6] Blastocyst implantation studies in animals are indicating that receptivity to implantation is largely maternally controlled.[7] There

was no reported attempt to control by age of subject in relationship to the probability of pregnancy rate used for comparison. In fact, the peak of female fertility occurs before age thirty.[8] There is no control for the wide age differences among subjects.

Austriaco also concludes that "the study by Lalitkumar et al. confirms the earlier findings of Durand et al., who had shown that the endometrial histology of surgically sterilized women taking [levonorgestrel] was indistinguishable from that of controls" (707).[9] The purpose of the Lalitkumar study was to investigate the effect of levonorgestrel and mifepristone on attachment of human embryos to an in vitro endometrial construct. The researchers concluded, "Levonorgestrel did not impair the attachment of human embryos to the in vitro endometrial construct."[10]

To interpret that the Lalitkumar research has resolved the question of the anti-implantation effect of levonorgestrel is simply unwarranted. There are a number of unanswered questions raised by this research. The small sample raises serious questions of interpretation of findings. Furthermore, this study demonstrated that more of the control (untreated) embryos successfully implanted (ten) than did not (seven), and fewer of the levonorgestrel-exposed embryos successfully implanted (six) than did not (eight). While the difference in rates of implantation is not statistically significant at this sample size, one should not conclude that this study has demonstrated that there is no anti-implantation effect with levonorgestrel.

There are also a number of questions related to the Lalitkumar research design. The endometrial tissue used as a cell culture was from eleven women between the ages of twenty-two and forty years, at luteinizing hormone [LH] days +4 and +5. Research has demonstrated that "even though the blastocyst can implant in different human tissues, surprisingly in the endometrium, this phenomenon can only occur during a self-limited period spanning between days 20 and 24 of a regular menstrual cycle (day LH+7 to LH+11)."[11] The question needs to be asked whether more of the control group embryos, untreated with any substance, would have implanted if they were in tissue taken from donors within this self-limited window. The ability to state whether or not there is a significant difference in implantation rates among untreated/treated groups must first be grounded in a research design that provides for accurate baseline data. Thus, there is a question concerning how closely this study replicated the in vivo conditions of implantation.

No information about the qualities of the embryos was provided beyond the fact that the embryos had been cryopreserved for five or more years.[12] Cryopreservation of embryos has a detrimental affect on embryo quality. However, if the embryos underwent high-quality cryopreservation, it does not have detrimental effects on their implantation or pregnancy potential.[13] No embryo gradation is provided, nor is there a report of any attempt to assign embryos to control or treated groups based on similar qualities, parental origins, or age of mother. Clearly such factors as age of the mother could have an effect on embryo quality. The embryo assignment to groups was random, but no control for these or other variables was reported. Researchers tell us that the embryo is responsible for one third of implantation failures,[14] and without information on the quality of the embryos in this study, no helpful determinations of causality can be concluded.

As noted earlier, maternal age beyond thirty-five years affects implantation rates, with a linear decrease in implantation rates of 2.77 percent per year.[15] There is no information on how the age of the endometrial donor affected assignment of tissue for the three endometrial cell culture sites, if at all. As stated earlier, blastocyst implantation studies in animals are indicating that receptivity to implantation is largely maternally controlled.[16] There was no reported attempt to control tissue used, by age of donor, so that each area of the endometrial construct used for implantation was formed by an equal amount of tissue representative of the total donor group. The study reports that the endometrial tissue was "minced."[17] This would indicate that tissue from forty-year-old donors was combined with all younger donors, but no age breakdown of the eleven donors used is provided. No information is

provided on the age of the mothers and no information is provided on endometrial tissue donor assignment, except that the age range of the donor was between twenty-two and forty years. The researchers of this study report, "there is very limited information about the concentration of mifepristone or levonorgestrel at the endometrial cellular level when given orally for fertility control."[18] However, they conclude that "the dosage of these drugs used in this study is sufficient enough to inhibit the action of progesterone as shown by earlier studies (Catalano et al., 2003)."[19] But Catalano et al. identified key pathways responsible for endometrial receptivity using RU-486.[20] Human endometrial biopsies were cultured in the presence of estradiol and progesterone with or without RU-486. The results indicated that two important endometrial signaling pathways controlling gene expression are altered by RU-486. Endometrial receptivity to the implanting embryo is affected by steroids, and the identified genes are likely to be involved in this mechanism. However, while the progestin levonorgestrel is a synthetic progesterone, RU-486 (mifepristone) contains no estrogen or progesterone. The Catalano study makes no reference to the progestin levonorgestrel. It is unclear what dosing parameters were used in the Lalitkumar study to simulate the in vivo action of levonorgestrel.

This Lalitkumar research has not resolved the debate on the actions of levonorgestrel. In fact, the research design raises more questions than it answers. One cannot determine that this in vitro study has replicated the in vivo environment. Dosage of levonorgestrel that mimics the in vivo state cannot be validated. The condition, grade, and quality of the embryos are not addressed. The age of the mother of the embryos is not addressed. The control of the age of the endometrial biopsy donors in relationship to each implantation site is not addressed. Most glaring is the small sample size. Despite the fact that the research demonstrated no statistical difference in implantation rates between the control group and the levonorgestrel group, more of the control group embryos implanted than did not implant. However, more of the levonorgestrel-treated embryos did not implant than did implant. It would be a gross oversimplification to determine that this study has resolved the question of the effects of levonorgestrel on the implantation of embryos. Yet Austriaco's answer to the question of whether levonorgestrel prevents implantation is "It does not" (707). In fact, however, the research which he provides to support this claim "does not."

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[1]Nicanor Pier Giorgio Austriaco, "Is Plan B an Abortifacient? A Critical Look at the Scientific Evidence," *National Catholic Bioethics Quarterly* 7.4 (Winter 2007): 703–707.

[2]Plan B is an oral emergency contraceptive, approved by the U.S. Food and Drug Administration, produced by Barr Pharmaceuticals, Inc., containing levonorgestrel. The studies he cites are N. Novikova et al., "Effectiveness of Levonorgestrel Emergency Contraception Given Before or After Ovulation—A Pilot Study," *Contraception* 75.2 (February 2007): 112–118; and 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 2007): 3031–3037.

[3] The studies critiqued are C. Kahlenborn et al., "Postfertilization Effect of Hormonal Emergency Contraception," *Annals of Pharmacotherapy* 36.3 (March 2002): 465–470; and R. T. Mikolajczyk and J. B. Stanford, "Levonorgestrel Emergency Contraception: A Joint Analysis of Effectiveness and Mechanism of Action," *Fertility and Sterility* 88.3 (September 2007): 565–571.

[4]Novikova et al., "Effectiveness of Levonorgestrel," 115.

[5]Ibid., 117.

[6]S. D. Spandorfer et al., "An Analysis of the Effect of Age on Implantation Rates," *Journal of Assisted Reproduction and Genetics* 17.6 (July 2000): 303–306.

[7]J. D. Aplin and S. J. Kimber, "Trophoblast-Uterine Interactions at Implantation," *Reproductive Biology and Endocrinology* 2, published online July 5, 2004, http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=471567.

[8]Mark P. Trolice, "Diminishing Ovarian Reserve," http://www.infertilityspecialist.com/age_infertility-trolice.html.

[9]See M. Durand et al., "On the Mechanisms of Action of Short-Term Levonorgestrel Administration in Emergency Contraception," *Contraception* 64.4 (October 2001): 227–234.

[10]Lalitkumar et al., "Mifepristone," 3031.

[11]H. Achache and A. Revel, "Endometrial Receptivity Markers, the Journey to Successful Embryo Implantation," *Human Reproduction Update* 12.6 (November–December 2006): 731.

[12]Lalitkumar et al., "Mifepristone," 3032.

[13]C. E. Selick et al., "Fertilization and Early Embryology: Embryo Quality and Pregnancy Potential of Fresh Compared with Frozen Embryos—Is Freezing Detrimental to High Quality Embryos?" *Human Reproduction* 10.2 (1995): 392–395.

[14]C. Simón et al., "Cytokines and Embryo Implantation," *Journal of Reproductive Immunology* 39.1–2 (August 1998): 117–131.

[15]Spandorfer et al., "Analysis of the Effect of Age," 305.

[16]Aplin and Kimber, "Trophoblast-Uterine Interactions."

[17]Lalitkumar et al., "Mifepristone," 3032.

[18]Ibid., 3036.

[19]Ibid.

[20]R. D. Catalano et al., "The Effect of RU486 on the Gene Expression Profile in an Endometrial Explant Model," *Molecular Human Reproduction* 9.8 (August 2003): 465–473.

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*Rev. Austriaco replies:* I thank Dr. Marie Hilliard for her critique of my recent essay examining the scientific case for the alleged abortifacient effect of the contraceptive Plan B. In my analysis, I concluded that there is mounting evidence that suggests that this contraceptive is not an abortifacient.

Dr. Hilliard makes six major criticisms in her letter. I will respond to each in turn. First, in response to my comments on the study published by Novikova et al., Hilliard argues that conclusions based on statistical data can never amount to demonstrative proof. I agree. In fact, as I acknowledged in my original piece, the pilot study's small sample size precluded the research team from accomplishing precisely this. However, I did argue that it casts into serious doubt the statistical data that purports to demonstrate an abortifacient effect for the contraceptive. Hilliard's criticism does not undermine this conclusion.

Second, Hilliard criticizes the Novikova study because "there was no reported attempt to control by age of subject." This is a surprising charge, given that the Novikova study compared their own data with data taken from three well-known and well-established studies—the two studies by Wilcox et al. and the study by Trussel et al. cited by Novikova—which calculated the incidence of pregnancy in women of a wide-range of ages. These well-documented studies are excellent age controls for the Novikova study. What better control does Hilliard expect?

Third, Hilliard criticizes the Lalitkumar study because it is not clear if this study replicated the in vivo conditions of implantation. Here Hilliard raises a doubt that is applicable to all scientific experiments done in the laboratory: how do we know when any in vitro conditions exactly replicate in vivo conditions? As a biologist, I would argue that we can never really know if a laboratory experiment exactly replicates conditions in the human body. That is why experiments have internal controls that allow scientists to make conclusions limited by the experimental design itself. Therefore, as I acknowledged in my essay, all we can say about the Lalitkumar study is that it shows that human IVF embryos exposed to levonorgestrel can implant in laboratory-grown endometrial tissue in statistically comparable numbers as human embryos that were not exposed to any drugs. In contrast, none of the human embryos exposed to RU-486—a bona fide abortifacient—could implant at all. Again, I never claimed that this study had definitively proved that Plan B is not an abortifacient. However, it does raise serious doubt about Plan B's alleged anti-implantation effects. Finally, in light of the concerns raised by Hilliard, it is important to acknowledge the several studies cited in the Lalitkumar paper that demonstrate that the endometrial tissue grown in the laboratory has physiological properties that are comparable to endometrium found in vivo.

Fourth, Hilliard criticizes the Lalitkumar study because the study does not provide any quality controls for the human embryos used in the experiments. Some of them could have been damaged or sick or even dying. This is a legitimate criticism. However, it does not undermine the primary conclusion of the study. In fact, it strengthens it! The study suggests that human embryos, *even damaged or sick or dying ones*, can successfully implant in receptive endometrial tissue even when they and the tissue are exposed to levonorgestrel. This would be unlikely if levonorgestrel had even minor anti-implantation effects.

Fifth, Hilliard criticizes the Lalitkumar study because the study did not include any information on the age of the endometrial donors. She correctly notes that maternal age beyond thirty-five years affects implantation rates, with a linear decrease in implantation rates of 2.77 percent per year. She implies that the endometrial tissue used in the published experiment could have been too old for successful embryo implantation. However, she fails to acknowledge that Lalitkumar et al. had determined that their cultured endometrium had all the known biological markers—positive expression of estrogen receptors, progesterone receptors, androgen receptors, interleukin-1β, LIF, VEGF, MUC-1, and integrin $\alpha_v\beta_3$ on its epithelial cells—typically found on receptive endometrium from a wide age range of women. This is a good internal control for the endometrial tissue used in the experiment. Within the limits of scientific certitude, it suggests that the study's endometrial tissue was receptive to implantation.

Sixth, Hilliard criticizes the Lalitkumar study because the authors do not know if the dosage of levonorgestrel used in their laboratory experiments mimics in vivo levels. She is very critical of the authors of the study who defend their drug protocol because "the dosage of these drugs used in this study is sufficient enough to inhibit the action of progesterone as shown by earlier studies (Catalano et al., 2003)." She argues that this appeal to the Catalano study fails because the earlier study makes no reference to levonorgestrel, concentrating instead on RU-486, which contains no estrogen or progesterone. In response, I think that it is important to compare the concentrations of hormones used in both studies. In the Catalano paper, the research team used $1 \times 10^{-9}$ M of estradiol and $1 \times 10^{-7}$ M of progesterone to treat their endometrial tissue along with $1 \times 10^{-6}$ M of RU-486. As they point out, these concentrations of hormones had physiological effects on the endometrium. The Lalitkumar study, on the other hand, used $1 \times 10^{-5}$ M of RU-486 and $1 \times 10^{-5}$ M of levonorgestrel for their study. Notice that this concentration is ten times more concentrated than the amount of RU-486 and ten thousand times more concentrated than the amount of estradiol—an amount known to have physiological effects on the endometrium—used by Catalano et al. Although we do not know the in vivo concentrations of levonorgestrel, I believe that it is not unreasonable to expect that this high concentration of hormone—ten thousand times more concentrated than a physiologically effective concentration for another, similar hormone—would have been enough to affect the endometrium in vitro.

In sum, Hilliard's criticisms, though good ones, do not substantially undermine the two studies described in my essay. Therefore, I stand by the conclusion made at the end of my analysis: given the limitations of scientific certitude, the scientific evidence suggests that Plan B, when administered once, is not an abortifacient.

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## Hardt and O'Rourke Err in Minimizing the Scope of the CDF Response

Bioethicist Dr. John Hardt and canonist Rev. Kevin O'Rourke, O.P., are trying to use canon law against a Congregation for the Doctrine of the Faith (CDF) *Responsum* that upholds the basic right of patients in a "persistent vegetative state" to nutrition and hydration. I think their arguments are flawed. Here I summarize the events leading up to the CDF response and then assess Hardt and O'Rourke's attempt to minimize its impact.

On March 20, 2004, Pope John Paul II told an international medical-moral congress on "Life-Sustaining Treatments and Vegetative State" that "the administration of water and food, even when provided by artificial means, always represents a natural means of preserving life, not a medical act. Its use, furthermore, should be considered, in principle, ordinary and proportionate, and as such morally obligatory" (n. 4). The qualifications included in the Pope's remarks and his citations to various Church documents show that his statement is basically an application of well-established Catholic moral principles to more specific types of medical situations.

On July 11, 2005, the U.S. bishops send two follow-up questions to the Congregation for the Doctrine of the Faith. The bishops asked (1) "Is the administration of food and water (whether by natural or artificial means) to a patient in a 'vegetative state' morally obligatory except when they cannot be assimilated by the patient's body or cannot be administered to the patient without causing significant physical discomfort?" *and* (2) "When nutrition and hydration are being supplied by artificial means to a patient in a 'permanent vegetative state,' may they be discontinued when competent physicians judge with moral certainty that the patient will never recover consciousness?"

On September 16, 2007, to the surprise of almost no one, the CDF, with appropriate qualifications and explanations, published its answers to the bishops' questions.[1] Specifically, the CDF replied yes to the first question, meaning basically that nutrition and hydration may not be withheld from patients who can still make use of them, and no to the second, meaning that even a very poor prognosis for recovery of consciousness does not justify withholding nourishment and water from a patient.[2]

Claiming to be putting this CDF response "in perspective" in the November–December 2007 issue of *Health Progress*, Hardt and O'Rourke assert that it "limits the free exercise of rights [and thus] will only apply to a restricted number of cases, specifically to patients with a firm diagnosis of PVS" (45), and add that the response applies only in the United States. They further assert that had the CDF wanted to make its response more widely applicable, it would have used "another form of communication, for example, an Apostolic Instruction" (46). Hardt and O'Rourke claim their conclusions are based on Pope Boniface VIII's *Regulae iuris* (Rules of Law), which they say are applicable in "interpreting and applying the documents of the Holy See," and on Canons 18 and 52 of the 1983 Code of Canon Law. I think these claims are wrong in several respects.

### *Preliminary Criticisms*

Hardt and O'Rouke state that the *Liber sextus* of Boniface VIII, wherein most of the Rules of Law are found, was published in 1300. Actually it was promulgated in 1298. An error of two years might be minor, but imagine one's discomfort if a lecturer on American political theory claimed that the Declaration of Independence was signed in 1778. Moreover, Hardt and O'Rouke's suggestion that the CDF could use a document known as an "apostolic instruction" is perplexing. Amid the myriad of document styles employed (sometimes inconsistently) by the Holy See, I have never encountered one called an "apostolic instruction," nor is it a genre listed in Francis Morrisey, *Papal and Curial Pronouncements*, 2nd ed (Ottawa: St. Paul University, 1995), or J. Huels, "A Theory of Juridical Documents based on Canons 29–34," *Studia Canonica* 32.2 (1998): 337–370. Again, Hardt and O'Rouke's claim that "many of the [Rules of Law] are repeated in one way or another in the present

Code of Canon Law" (45) seems excessively broad. (See E. Roelker, "An Introduction to the Rules of Law," *The Jurist* 10 (1950): 271–303, 417–436, an article replete with narrations of the pitfalls awaiting those who invoke the *Regulae iuris* without adequately understanding them.) In short, almost every assertion by Hardt and O'Rouke on the *Regulae iuris* is contestable or wrong.

But a much more fundamental objection lies against Hardt and O'Rouke's claim that canon law dictates a narrow reading of the CDF response.

*Primary Criticism*

Canons 18 and 52 and the Rules of Law upon which they draw are, by their plain terms, meant to inform one's interpretation of *laws* and *legal* directives. In issuing its response on nutrition and hydration, however, the CDF was *not* issuing a law, or an authentic interpretation of a law (can. 16), or indeed any other kind of juridic decree (administrative or otherwise). Instead, the dicastery was setting forth *moral* criteria for personal decision making, a point reinforced by the posting of the CDF response among the dicastery's doctrinal statements, not its disciplinary ones. In other words, by subjecting the CDF's enunciation of *moral* principles to interpretive techniques that were developed for assessing *legal* norms, Hardt and O'Rouke are basically criticizing the CDF response for not being something it never claimed to be.

Even at that, Hardt and O'Rouke's critique seems poorly done. For example, their claim that the response is applicable only in the United States is easy to refute. One need simply observe that the CDF published its response in French, German, Italian, Polish, Portuguese, Spanish, and Latin to show how implausible the assertion is that it was intended only for America. Likewise, their claim that the CDF response protects only patients in a "persistent vegetative state," and not necessarily those suffering from such conditions as Alzheimer's, is untenable. Logic dictates that persons similarly situated should be treated similarly and, obviously, both Alzheimer's patients and persons in a "persistent vegetative state" need food and water to survive. I cannot imagine the grounds upon which Hardt and O'Rouke think that the CDF might discriminate between these two groups.

The moral principles set out in the CDF response are meant to be applied regardless of the fact pattern that led to an individual's plight and regardless of where his or her suffering is taking place. I urge persons striving to understand and apply Catholic medico-moral principles in difficult nutrition and hydration situations to consult directly the statements on this matter offered by the organs of the Holy See, and not to be put off that inquiry because of the canonical objections that Hardt and O'Rouke have tried to allege against this important statement from the CDF.

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[1]Congregation for the Doctrine of the Faith, "Responses to Certain Questions of the United States Conference of Catholic Bishops concerning Artificial Nutrition and Hydration" (August 1, 2007), reprinted in this issue of the *Quarterly* on pp. 125–126.

[2]See the CDF commentary, also reprinted here on pp. 126–129.

*Dr. Peters' comments first appeared on his blog, "In the Light of the Law," http://www.canonlaw.info/2007/12/hardt-orourke-err-in-minimizing-scope.html, on December 16, 2007, and are used here with permission. They have been edited lightly for consistency of style.*