

ABORTIFACIENT POTENTIAL OF EMERGENCY CONTRACEPTIVES

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Abstract

The debate over conscience rights and emergency contraceptive agents among pharmacists and other healthcare professionals centers on the potential abortifacient potential of such agents. Such an important ethical and scientific question should be guided by established facts. This paper reviews the available evidence for post-fertilization effects of the emergency contraception drug levonorgestrel, and demonstrates that such evidence is uniformly lacking. The authors then discuss the ethical implications of these findings. This lack of any substantial evidence for post-fertilization effects may significantly weaken conscience claims, and may militate against refusals to dispense or to refer.

Key Words: emergency contraception, conscience rights, professional ethics, informed consent, religious ethics, abortifacient

In November of 2005, John Menges, a pharmacist at a Walgreens pharmacy in Illinois, was dismissed for refusing to fill prescriptions for Plan B® (levonorgestrel), also known as the “morning-after pill” or “emergency contraception.” One of eleven Illinois pharmacists suspended for this reason, Menges claimed that Plan B is more than a contraceptive, in that it may cause an early abortion. Dispensing the drug to customers would violate his Roman Catholic beliefs on the sanctity of human life.¹ Yet the Illinois governor had already passed an emergency rule to compel pharmacies in the state to “accept and fill prescriptions for contraceptives without delay,”² and Menges was dismissed on this basis.

Menges and many others have a legitimate concern that may be lost if not examined closely. In 1988, the Food and Drug Administration (FDA) granted permission for marketing of pharmaceuticals aimed at preventing pregnancy up to three days after unprotected sexual intercourse. The treatment contains a hormone that, according to FDA approved labeling, may prevent ovulation or, if ovulation has already occurred, may interfere with successful implantation. The first mechanism is contraceptive and does not raise sanctity of life concerns. However, the second mechanism is interceptive and, thus, problematic for those who hold to the conception view of personhood,³ as such interception may destroy an early human life. What should a healthcare professional such as Menges do under these circumstances?

This is not just an ethical question; it is a scientific one as well. Determining the facts concerning pharmaceuticals such as Plan B will guide decision-making for Menges and others like him. At the heart of the dilemma that Menges’ situation poses is a long-standing concern about emergency contraception. It seems reasonable to probe the possibility that the most commonly used pharmaceutical formulations may interfere with implantation. The available evidence for such an effect, however, is either lacking or is shrouded in politicized rhetoric.

A scientific review by Austriaco appeared in 2007, in which the author presented “mounting evidence that levonorgestrel has little or no effect on post-fertilization events.”⁴ Since that time, the evidence has become even more persuasive, and a survey of the more recent data is in order.

This paper will review the available evidence for post-fertilization effects of the emergency contraception drug levonorgestrel, which may act directly to either inhibit implantation or indirectly to change the hormonal nourishment of the endometrium. The authors will then briefly discuss the ethical implications of these findings for healthcare professionals.

The Scientific Context

Prevention of ovulation, while the primary effect of COCs, is not their only possible mechanism of action. So-called “escape,” “on-pill,” or “breakthrough” ovulation may occur occasionally, where ovarian follicular development and rupture occur in spite of compliant pill usage.^{6,7} In such cases an additional effect, a change in composition of the cervical mucus, may act to prevent sperm from reaching the fallopian tubes for fertilization of the ovum.⁸

In addition to these first two mechanisms of action, of great interest in the moral debates over the use of COCs has been the possibility of a further effect, namely the inhibition of implantation. Such a post-fertilization effect could cause a conceptus to be lost that otherwise would safely implant into the inner layer of the endometrium approximately seven days after conception. For those holding the conception view of human personhood, this would truly represent an abortifacient effect of oral contraceptives. One of the authors of this report has reviewed this subject in some detail.⁹

So the moral and scientific debate over EC occurs against the backdrop of an already contentious discussion of oral contraceptives. Yet, the prevailing scientific conclusion about compliant COC use is that such agents do not have a measurable post-fertilization effect, and that moral concern over their abortifacient potential (even in light of the conception view of personhood) is unwarranted.⁸⁻¹¹ On the other hand, could such an effect nonetheless exist for emergency contraception?

Though there are a number of possible agents used for EC, the most common (and the main focus of this report) is a high-dose progestin called levonorgestrel, now marketed as Plan B One-Step (a registered trademark of Barr Pharmaceuticals, given as a single 1.5 mg tablet), or Next Choice (Watson Pharmaceuticals; two 0.75 mg tablets). If administered during the follicular phase of the menstrual cycle just prior to ovulation, levonorgestrel inhibits the release of luteinizing hormone (LH) from the anterior pituitary gland. Such inhibition may prevent or delay ovulation.¹² EC is therefore intended as “emergency” contraception, to prevent pregnancy in women who have not been using other forms of birth control effectively or at all, or where barrier methods have failed (e.g., condom breakage).

In a number of studies, levonorgestrel has demonstrated efficacy rates in a range from 52% to 94%.¹³⁻¹⁸ The package insert for Plan B gives an efficacy rate of 89%. It is worth noting that efficacy decreases with increasing amounts of time between coitus and medication usage.¹⁹ All of this data assumes, of course, that EC methods were used only during the period of the woman’s cycle just prior to or immediately after ovulation;

otherwise all other considerations are moot (i.e., the woman was not at risk of becoming pregnant in the first place). These efficacy rates are well established, but the mechanism of action has been poorly characterized, opening the door for considerable speculation concerning a possible post-fertilization effect, wherein the uterine endometrium may be rendered too unreceptive for implantation.

Kahlenborn and colleagues, in their 2002 publication, summarize early studies regarding the post-fertilization effects of EC agents.²⁰ Based on a combination of theoretical and empirical arguments, the authors argue that the efficacy of EC agents cannot be explained by ovulatory inhibition or the inhibition of sperm transport alone. Thus, they surmise that endometrial effects must also be present.

This position is bolstered by the FDA-approved labeling of Plan B One-Step: “Plan B One-Step works primarily by: preventing ovulation, possibly preventing fertilization by altering tubal transport of sperm and/or egg, [or] *altering the endometrium, which may inhibit implantation*. Plan B One-Step is not effective once the process of implantation has begun” (italics added).²¹ It is worth noting that the FDA-approved labeling of Plan B One-Step may allow for the possibility of a post-fertilization effect, even in the absence of supportive data. Computer models intended to clarify the mechanism of action have fallen short, always confirming the effect of ovulatory inhibition, but failing to rule out the possibility of a post-fertilization effect.²²

The ability to accurately assess EC efficacy is dependent on an accurate assessment of the timing of coitus relative to ovulation; self-reporting of such data by patients has been found to be grossly inaccurate.²³⁻²⁵ In 2007 Novikova published a small (n=99) study designed to remove some limitations of earlier analyses (e.g., self-reporting of the timing of menstrual cycle-related events and EC agent administration) by measuring serum concentrations of key endogenous chemicals, such as luteinizing hormone, estradiol, and progesterone.²⁶ Unlike earlier studies in which the estimated rate of pregnancy in treatment groups (i.e., those taking EC agents) compared to control groups (i.e., the expected rate in the absence of EC agent administration) could not be fully explained by ovulatory inhibition, the Novikova study demonstrated full congruence between observed and expected pregnancy rates. Though small, the study represents some of the most objective evidence available to date regarding the mechanism of action of levonorgestrel.

An ethically controversial study conducted in Sweden in 2007 has also been reported. There is no question that mifepristone (RU-486), an abortifacient anti-progestin, disrupts the ability of a viable embryo to remain attached to the endometrium. Lalitkumar and colleagues tested the ability of living human embryos (in a laboratory environment) to implant in endometrial tissue that had been treated with mifepristone (study group) compared to tissue that had not been so treated (control group). As expected, none of the embryos from the study group successfully implanted.

The group then conducted the same study using levonorgestrel-treated endometrial tissue, (with levonorgestrel tissue concentrations equivalent to supra-normal doses). In complete contrast to the mifepristone study, there was no difference between the study and control groups in terms of implantation effectiveness. In other words, there was no observed endometrial effect of levonorgestrel. They also observed no gross cellular changes in the levonorgestrel-treated tissue.²⁷

In early 2010, Leung and colleagues published a review of the evidence available through July, 2009 regarding the mechanisms of action of levonorgestrel. The authors

concluded that the evidence “strongly supports disruption of ovulation” and that the drug is “unlikely to act by interfering with implantation, although the possibility has not been completely excluded.”²⁸ Another review by Langston reached similar conclusions.²⁹ Clinical and laboratory evidence published since July 2009 strengthens these findings.^{30,31} Austriaco, commenting a year after his original scientific review on levonorgestrel, has this to say: “In light of the available scientific evidence and given the inherent limitations of the studies, it is unlikely that Plan B is an abortifacient.”³² This still appears to be a reasonable summary of what we know about the mechanism of action of this agent.

For the past two decades the scientific community seems to have been burdened with the impetus to prove, in contrast with the typical protocol by which the mechanism of action for a drug is determined, the manner by which a drug *doesn't* act by proving “beyond a shadow of a doubt” the manner by which it *does* act. The authors of this manuscript would be foolish to believe that such a shadow will ever be completely removed from the inquiry at hand, at least until such a time as we have access to a test that might identify the moment of fertilization, as suggested by some writers.^{9,33,34} However, present evidence provides sufficient motivation to believe that levonorgestrel, used as EC, possesses no clinically relevant effect during the post-fertilization period.

The Ethical Context

A full discussion of the ethical issues informing healthcare conscience rights is beyond the scope of this review, but a few comments are in order. With regard to ethically controversial medical procedures, the contrarian approach revolves around three different types of refusals: 1) refusal to provide a legal, requested service (e.g., abortion or contraception), 2) refusal to refer to other professionals on the basis of moral complicity, and 3) refusal to fully disclose all medically relevant information because of moral concerns. In the first arena, the right of physicians, nurses, and medical and nursing students to decline participation or any involvement in certain procedures is well established in federal law.³⁵ Less clear, however, is the idea that these rights are shared by pharmacists and certain other health-care professionals. In the words of one legal scholar:

Conscientious objection laws provide *some* protection to *some* providers who conscientiously object to *some* procedures under *some* circumstances. Exactly what grounds for refusal qualify for conscientious objection is often unclear.³⁶

For pharmacists, the legal landscape is confusing. A total of thirteen states have provisions for health care workers to decline to dispense contraceptives, with six specifically mentioning pharmacists. Georgia's statute expressly grants pharmacists the right to refuse to dispense EC drugs.³⁷ However, Illinois and New Jersey have laws mandating the dispensing of contraceptives, and in California pharmacists can only refuse to dispense with their employer's approval.³⁸ In addition, the California approach has been recommended as a model for states such as Washington.³⁹

The central question at stake in all this is whether pharmacists can be considered “professionals” in the same sense as physicians and nurses are considered so. If we answer in the affirmative, the Hippocratic duties of beneficence and non-maleficence apply to pharmacists as well as doctors and nurses. A recent law journal review gives some insight, endorsing a balanced approach to patient autonomy versus pharmacist conscience:

[I]f pharmacists are considered professionals, then they should have the same right as doctors and other healthcare providers to refuse to participate in procedures they find morally or religiously objectionable. This view is apparently endorsed by the American Pharmaceutical Association, which envisions a system of care where “pharmacists work with patients as well as with physicians and other healthcare providers to promote drug therapy that contributes to a patient’s well-being.” As professionals, pharmacists enjoy more discretion in their decision making; they are part of a team, rather than an ancillary link between the doctor and the patient. Because courts have traditionally protected physicians’ moral autonomy on the basis that they exercise discretion in their practices, pharmacists’ ethical decisions should deserve similar protection, according to this view.⁴⁰

Assuming therefore, that a right of conscience is reasonable in the pharmacy profession, we come to the second arena of possible refusals, the idea of referral. If conscientious objections to dispensing certain agents are justified, the usual recommendation for pharmacists is that they refer the prescription to another nearby pharmacy. In some cases, larger employers have made allowances for conscience beliefs by stipulating that contrarians only practice during the hours when other colleagues are on duty who can fill EC drug prescriptions, thus obviating any potential conflict with clients. Such referrals or alternative provider ideas seem logical, and have been recommended by a number of authors.⁴¹⁻⁴⁴

Yet the referral option is not without its problems. For some objectors to the use of EC agents, even referring to another practitioner to fill a prescription is wrong (based on the idea of moral complicity).^{44,45} In one survey of physicians, a significant minority did not feel obligated to refer patients to other clinicians more willing to perform certain ethically controversial procedures.⁴⁶ Perhaps the concept of referral is more acceptable among pharmacists than among physicians, but this is by no means certain.

The third and final possible arena for contrarian refusals has been in the full disclosure of information to patients. However, according to the physician survey by Curlin and colleagues, a strong majority (83%) of physicians who objected to EC agents nonetheless felt obligated to disclose full information about that option.⁴⁶ The principle of informed consent dictates such complete provision of information, and does not seem as controversial overall. In the words of May and Aulisio, “The basic idea that informed consent must include full disclosure of options should be agreeable to all sides in the debate.”^{44, 36} Of course, such full disclosure must be based on accurate medical facts.

Note that none of the earlier cited state regulations specifies a basis for conscientious refusal other than for “moral or religious belief.”³⁸ But the medical evidence (or the lack thereof) for a claimed mechanism of action of EC agents is surely relevant to any moral objections to their use, and should be subject to possible scientific refutation. *Wicclair* has put it succinctly:

Although it may be inappropriate to require reasons for conscience-based objections to be “reasonable or justified,” it is warranted to reject claims of conscience if they are based on demonstrably false beliefs.^{47, 22}

It would be an overstatement to claim that the abortifacient claim for EC is a “demonstrably false belief.” After all, a possible post-fertilization effect for EC is still included in the FDA-approved package labeling for levonorgestrel. Yet, the paucity of supportive evidence challenges the warrant for such a claim, and may call for a reconsideration of

such labeling. It is the considered opinion of the authors of this present report that the evidence for a post-fertilization effect of EC agents has been sufficiently disputed in recent studies as to constitute, at the very least, a strong indictment against clinicians who would fail to disclose this information to their patients.

Furthermore, this dearth of evidence may actually invalidate such conscience claims entirely, and may militate against refusals to dispense or to refer. Of course, our conclusion only refers to claims for an abortifacient effect, and does not apply to other possible moral judgments about such agents, such as natural law objections to oral contraceptives generally.

Conclusion

How does all this affect pharmacists such as John Menges, as well as other healthcare professionals? On the one hand, Menges should be commended for taking a costly stand based on his personal convictions. In a highly publicized interview on CNN, former Illinois Governor Rod Blagojevich said, “The right of conscience does not apply to pharmacists.”⁴⁸ Predictably, this evoked a storm of protests across the country, leading to greater judicial protections for conscience rights, not only for pharmacists, but for other healthcare professionals as well.

Healthcare conscience rights remain a hotly debated matter in our society. At the very least, pharmacists, physicians, nurses, and other professionals should carefully and continually examine the scientific evidence that informs an ethical stance. It might be prudent for Menges and others like him to reexamine the evidence related to the EC issue in an unbiased manner. Certain established positions on the appropriate use of EC agents may need modification.

It is imperative that we healthcare professionals diligently maintain our knowledge of the risks, side effects, and ethical concerns related to all medications or treatments for which patients seek our assistance. Furthermore, failure to reconsider ethical positions in the light of ongoing evidence would itself be unethical.⁴⁹

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