Contraception

The FDA Ought to Change Plan B's Label

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The FDA Ought to Change Plan B's Label

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Abstract: This commentary defends three arguments for changing the label of levonorgestrel-based emergency contraception (LNG EC) so that it no longer supports the possibility of a mechanism of action after fertilization. First, there is no direct scientific evidence confirming any post-fertilization mechanisms. Second, despite the weight of evidence, there is still widespread public misunderstanding over the mechanism of LNG EC. Third, this FDA label is not a value-free claim, but instead it has functioned like a political tool for reducing contraceptive access. The label is laden with anti-abortion values (even though EC is contraception, not abortion), and it imposes these values on potential users, resulting in barriers to access such as with *Burwell v. Hobby Lobby*. These three arguments together provide scientific, social, and ethical grounds for the FDA to take the initiate in changing Plan B's drug label.

Keywords: Emergency Contraception; Mechanism of Action; Levonorgestrel; US Food and Drug Administration (FDA); drug label; patient understanding;

Background

Fifteen years ago, when the US Food and Drug Administration (FDA) initially approved over-the-counter (OTC) sale of Plan B (albeit with an age restriction), it was a cause for celebration among advocates of contraceptive access. Since 2003, the Bush Administration had delayed the switch to OTC status of this levonorgestrel-based emergency contraceptive (LNG EC), exerting a top-down influence in an "unusual" decision process [1]. In addition to concerns about the use among young adolescents and increases in sexually transmitted infections, some of the members of the FDA Advisory Committee for Reproductive Health Drugs worried that the pill might act after fertilization [2–4]. Contrary to mainstream medicine [5,6], this small minority believed that "pregnancy" (and thus personhood and rights) begins at fertilization, so a drug with a mechanism of action after fertilization would be morally equivalent to abortion [7].

Accordingly, one compromise during the 2006 switch to OTC sale was the creation of a highly unusual drug label about the mechanism on the outer carton: "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)*" [8, emphasis added]. At this time, there was significant uncertainty about the mechanism because of the lack of research, so this description was very hypothetical and speculative [9,10]. As committee member Alastair J.J. Wood (then editor of the *New England Journal of Medicine*) admonished, "I would caution, however, against studding the outside of the packet like a Christmas tree with all sorts of issues. I'm particularly concerned about putting things on the outside of the package which are unsupported by data" (p. 341) [2]. It is exceedingly uncommon to describe a mechanism on the Drug Facts for lay users—especially with such hedged language couched in uncertainty—yet, this wording was suggested by those same anti-abortion advisers, allegedly to provide potential users with "informed consent" [9].

The actual effect of this drug label, however, has been to reduce contraceptive access for cisgender women as well as transgender and non-binary people who might need it. The most direct case involves the 2014 US Supreme Court case *Burwell v. Hobby Lobby*, in which several companies refused to provide federally mandated contraceptive coverage to their employees based on religious objections to abortion. The plaintiffs' scientific justification was that according to the FDA certain required services like Plan B acted as an abortifacient (meaning "after fertilization," rather than the standard medical definition of "after implantation"). The appeals court acknowledged the "ongoing medical debate" about Plan B's mechanism based on conflicting *amicus curiae* briefs, but it decided not to "wade into scientific waters" (p. 13) [11]. Then, the Supreme Court relied on the FDA's webpage about Plan B for its ruling in favor of the business owners to refuse covering alleged abortifacients for employees' insurance [12].

The FDA label continues to limit contraceptive access, as evidenced by a current court case in Peru. In 2009, following a lawsuit from a Catholic organization citing the FDA, the Constitutional Tribunal prohibited free distribution of LNG EC in public health facilities in Peru, based on constitutional protections for life beginning at fertilization. In part because the ban disproportionately affected poor women's access, reproductive rights advocates challenged this decision, with temporary success, and the Constitutional Tribunal is presently reassessing the scientific grounding of their decision (G. J. Oporto Patroni, personal communication, June 9, 2021). If the FDA does not change the label, it has the potential to continue to reduce access to EC globally and thus limit the range of choices needed to ensure reproductive autonomy and health.

This commentary builds on my existing historical and philosophical research about the political nature of Plan B's label, including its scientific and ethical deficiencies [9,13,14]. Here,

I defend three interrelated arguments for why the FDA ought to change the label of LNG EC so that it no longer mentions the possibility of a post-fertilization mechanism. First, there is no direct scientific evidence confirming a post-fertilization mechanism. Second, despite the weight of evidence, there is still widespread public misunderstanding over the mechanism of LNG EC. Third, this FDA label is not a value-free claim, but instead it has functioned like a political tool for reducing contraceptive access. The label is laden with anti-abortion values (even though EC is contraception, not abortion), and it imposes these values on potential users, resulting in barriers to access such as with *Burwell v. Hobby Lobby*. The drug sponsors have failed to counter the misleading claims made by the anti-abortion groups and conservative religious organizations (D. Davis, personal communication, July 28, 2021). Thus, these three arguments together provide scientific, social, and ethical grounds for the FDA to take the initiative in changing the drug label.

Argument 1: Lack of Scientific Support for Post-Fertilization Mechanisms

There are a variety of potential mechanisms of action for any post-coital form of contraception, including effects on ovulation, fertilization and sperm functioning, embryo development/transport, and endometrial receptivity and implantation. The only well confirmed mechanism for LNG EC is the suppression of ovulation within a very narrow window of effect [15–17]. When administered prior to ovulation, LNG EC delays development of the leading follicle (which releases the mature egg) by inhibiting or suppressing the luteinizing hormone peak. If taken after ovulation, LNG EC is ineffective at preventing pregnancy. While an early *in vitro* study from the 1970s suggested that levonorgestrel might affect sperm migration, more recent *in vivo* studies demonstrate that LNG EC affects neither quantity nor quality of sperm, nor

does it impair cervical mucous. Furthermore, LNG EC administration does not result in higher rates of ectopic pregnancy, so it is unlikely that the pill slows tubal transport of zygotes. Unlike mifepristone, LNG EC does not significantly reduce endometrial receptivity of blastocysts, nor does it interfere with processes after implantation (see Appendix for further reading).

Because post-fertilization mechanisms lack scientific support, they ought to be removed from the FDA drug label. The International Federation of Gynecology & Obstetrics has supported this change since 2008 [16]. Accordingly, the European Medicines Agency approved a label change for NorLevo (equivalent to Plan B) in 2015 [18]. Nevertheless, some opponents of abortion (publishing in Catholic journals and elsewhere) have contended that, while delaying ovulation is likely the primary mechanism, the ability of LNG EC to suppress ovulation is overstated; instead, it could *possibly* prevent implantation through pre-ovulatory induced effects that impair later luteal functioning [19–21]. Even some EC advocates have admitted that the science cannot completely prove the impossibility of post-fertilization effects [4,10].

Ultimately, the anti-abortion dissenters' alternative interpretations of existing studies depend on debatable value judgments about the proper standard of evidence needed for "moral certitude" in disproving an abortifacient mechanism [19]. Because they value zygotes as human persons with an inviolable "right to life" and want to reduce the risk of abortion, they utilize a much higher burden of proof than the usual scientific standards of evidence for disconfirming post-fertilization effects [9]. While acknowledging the ethical rationale for the anti-abortion standard, two members of the FDA advisory committee (Frank Davidoff and James Trussell, both advocates of EC) criticized it: "Beyond that lack of information [of knowing definitively whether Plan B prevents implantation] lies the more subtle logical difficulty—some would say the impossibility—of proving the lack of existence of any particular mechanism" (2006, p. 1777)

115 [10]. Davidoff and Trussell claimed that in "the absence of absolute proof…women should
116 continue to be informed, as they are now in the Plan B labeling, that its use may affect
117 postfertilization events," yet they still maintained that alone was misleading: "all women should
118 be informed that the ability of Plan B to interfere with implantation remains speculative since
119 virtually no evidence supports that mechanism and some evidence contradicts it" (p. 1777) [10].
120 Since the early 2000s, the positive evidence against a post-fertilization effect has grown
121 substantially, making the label even more unsubstantiated (see Appendix). Therefore, the anti-
122 abortion standard of proof is arguably not falsifiable scientifically with empirical testing, so their
123 version of a post-fertilization hypothesis is a "politics of doubt" based on *mere* possibility rather
124 than empirically confirmed possibility (p. 1775) [10]. Additionally, there are increasingly more
125 (anti-abortion) Catholic bioethicists who support the scientific consensus and recognize the
126 moral importance of EC availability for survivors of sexual assault [22,23].
127
128 **Argument 2: Widespread Public Misunderstanding about EC Mechanisms**
129 Because of the lack of scientific support for a post-fertilization mechanism, the current Plan B
130 label spreads misinformation to potential users and the general public. According to a recent US-
131 based survey, while nearly half of respondents did correctly attribute pre-fertilization
132 mechanisms to EC, most participants (61%) incorrectly described post-fertilization/pre-
133 implantation mechanisms [24]. Furthermore, a substantial portion (9%) conflated preventative
134 EC with medication abortion, which does act after implantation to terminate pregnancy [24]. In
135 Brazil, France, Germany, Italy, Spain, Turkey, and the UK, there are even higher rates (24-48%)
136 of respondents who incorrectly believe that EC acts as an abortifacient [25–28]. It is likely that
137 the inaccuracy of the FDA label is preventing use unnecessarily because potential users' stated

acceptability is higher for EC that acts earlier, compounded by the continued stigma of abortion [29,30].

The drug label is the primary medium for informing potential users about OTC drugs, so updating it can stop the spread of more misinformation. Granted, few consumers read labels completely and, even if they do, the current OTC label format may hinder patient understanding [31]. Nevertheless, while a new more accurate label will not decisively correct misunderstanding, it would provide potential users with more scientifically defensible information. It would also prevent further legal misuse of the label, such as in the Peruvian courts. Furthermore, many healthcare professionals do not accurately understand the mechanism of EC [32,33], and these misconceptions among practitioners are correlated with refusals to provide EC to potential users [34]. Thus, a more accurate label could afford more access to women and other people who need EC.

Argument 3: Value-Laden Information Imposes Values & Burdens on Potential Users

The third reason for changing this label involves the relation of ethics and science. The original decision to add this description of the mechanism to Plan B's label was not value-free. Instead, as I have shown elsewhere, it was premised on the ethical values and political goals of anti-abortion appointees who aimed to protect zygotes from alleged harm, ultimately limiting women's agency and access (even in cases of sexual assault) [9]. Anti-abortion science advisers at the FDA advocated for this post-fertilization label because of their commitment to the "right to life" of zygotes and how it influenced their judgments about managing uncertainty, such as their standards of evidence, their interpretation of studies, and their definition of terms [9]. Furthermore, my historical work on the morning-after pill illustrates how scientific claims about

contraceptive mechanisms function like political tools: scientists have either advocated for increasing access by distancing EC from post-fertilization potential, or they have limited access by aligning EC with abortion [13]. Because the present label is laden with anti-abortion values, uptake or use of the label can impose those implicit values on potential users who may not share the same ethical and religious beliefs. Such imposition can disrespect users' agency to choose their own values and coerce them into anti-abortionists' conception of "good women" who protect zygotes by abstaining from EC [14].

Even more worryingly, the label provides anti-abortion pharmacists with a tool for "moral gatekeeping," in which they punish allegedly "bad women" who risk zygotic life by refusing to dispense EC [35]. For instance, in Catholic healthcare facilities, the bishops' rules limit the use of emergency contraception to only pre-fertilization and only after sexual assault, as they consider both contraception and abortion to be grave moral failings for women [9]. Anti-abortion providers refuse to cooperate in what they consider an immoral act, claiming the status of "conscientious objectors" (which falsely equates forcible military conscription with voluntary medical decisions [36]). These refusals are often hostile reactions to behavior perceived as "unbecoming of a mother," and they interfere with potential users' ability to continue seeking the drug and to maintain their moral identity and sense of security [37]. Additionally, the refusals enabled by this FDA label disproportionately harm poor women, women of color, and Indigenous women because of structural barriers to their access and state control over their healthcare [38].

While not all influences of ethical values on science are necessarily bad, these anti-abortion values and the harmful burdens they impose on patients are illegitimate because they coerce patients' agency and reinforce women's subordinate status as "obligatory mothers" [14].

Nonetheless, might the current label still help those potential users who do believe that life begins at fertilization to make an informed choice about EC [7]? While all patients deserve the right to know, the current label's hedged description of the mechanism is too vague to provide even anti-abortion patients with guidance for how to use EC while still reducing the risk to zygotes [14]. Either it prompts them to look elsewhere, or it discourages using EC at all—a recommendation that is unnecessary and rash given that evidence confirms that Plan B only prevents ovulation (see Argument 1). Further, it is not clear why a secular agency is responsible for informing special interest groups on matters so closely aligned with sectarian religious concerns.

Concluding Remarks

The FDA label is just one threat among many to EC access and reproductive justice more broadly. Nonetheless, if we see the current FDA label as it truly is—scientifically outdated misinformation that can function as a political tool for reducing contraceptive access—then we ought to seriously consider the prospects of changing it. Evidenced by the US *Hobby Lobby* case and present proceedings in Peru, the potential for injustice based on this label is immense.

Acknowledgements

I thank Kelly Cleland and Lisa Lloyd for their detailed comments on this paper, as well as the helpful reports from three anonymous referees and the editors of the journal. I am also indebted to Cristina Puig Borràs and Gabriela J. Oporto Patroni for information about the legal barriers to access in Peru and to David Turok for information about IUD EC.

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix:

Further Reading on Mechanisms of LNG EC

1. LNG EC delays or suppresses ovarian functioning:

Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. Contraception 2004;69:373–7.

Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, et al. Pituitary–ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 2004;70:442–50.

Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. Contraception 2001;63:123–9.

Lira-Albarrán, S, Larrea-Schiavon MF, González L, Durand M, Rangel C, and Larrea F. The effects of levonorgestrel on FSH-stimulated primary rat granulosa cell cultures through gene expression profiling are associated to hormone and folliculogenesis processes. Molecular and Cellular Endocrinology 2017;43: 337–45.

2. LNG EC is ineffective after ovulation:

Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: A randomised non-inferiority trial and meta-analysis. The Lancet 2010;375:555–62.

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Müller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. Contraception 2003;67:415–9.

Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation — A pilot study. Contraception 2007;75:112–8.

3. LNG EC does not affect fertilization via sperm functioning or cervical mucous:

do Nascimento JAA, Seppala M, Perdigão A, Espejo-Arce X, Munuce MJ, Hautala L, 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 2007;22:2190–5.

Hermanny A, Bahamondes MV, Fazano F, Marchi NM, Ortiz ME, Genghini MHRR, Croxatto HB, and Bahamondes L. In vitro assessment of some sperm function following exposure to levonorgestrel in human fallopian tubes. Reproductive Biology and Endocrinology 2012;10: 8.

4. LNG EC does not have post-fertilization effects on transport or implantation:

Cleland K, Raymond E, Trussell J, Cheng L, Zhu H. Ectopic pregnancy and emergency contraceptive pills: A systematic review. Obstet Gynecol 2010;115:1263–6.

Lalitkumar PGL, Lalitkumar S, Meng CX, Stavreus-Evers A, Hambiliki F, Bentin-Ley U, et al. Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model. Human Reproduction 2007;22:3031–7.

Meng C-X, Marions L, Byström B, Gemzell-Danielsson K. Effects of oral and vaginal administration of levonorgestrel emergency contraception on markers of endometrial receptivity. Human Reproduction 2010;25:874–83.

Vargas MF, Tapia-Pizarro AA, Henríquez SP, Quezada M, Salvatierra AM, Noe G, et al. Effect of single post-ovulatory administration of levonorgestrel on gene expression profile during the receptive period of the human endometrium. J Mol Endocrinol 2012;48:25–36.

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October 18, 2021

To the Editors:

I thank the editors for their kind words and helpful suggestions, which I have used to improve the accuracy of the final paper. All changes be found in red colored font in this second revision of the manuscript.

I should mention that I mistakenly thought that the Constitutional Tribunal in Peru had ruled in the favor of EC access this fall. This was wishful thinking of my part, I guess, as it turns out the case is still under consideration. I apologize for any confusion caused by my correspondence with the editorial staff; the manuscript remains unchanged in regards to the political stakes of the FDA label for EC access in Peru.

I look forward to hearing the editors' decision for next steps.

Graciously,

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Ms. Ref. No.: CONTRACEPTION-D-21-00311R1
Title: The FDA Ought to Change Plan B's Label
Contraception

<Editor Comments for article Contraception-D-21-00311R1> with responses from author:

<Editor's comments: Your revisions were highly responsive to the reviewer suggestions - thank you. Just a few additional minor suggestions:>

-Author: Thank you. I have made all four changes as suggested. You can find the changes described below.

<Editor: L57 is the word 'risk' correct here? do you mean 'limit' or 'reduce'?>

-Author: I have changed the text on page 3 (line 57) from "risk" to "limit":

--Old text: "The FDA label continues to risk contraceptive access, as evidenced by a current court case in Peru."

---New text: "The FDA label continues to limit contraceptive access, as evidenced by a current court case in Peru."

<Editor: L71-72 - I find the phrase about IUDs to be misleading, and I do not think that what you stated agrees with ref [15]. The Cu-IUD acts on sperm and on the tube and the uterus..... These effects are not themselves pre- nor post-ovulation. Our general understanding is that sperm in the tubes await ovulation. Thus, even Cu-IUDs as EC may be acting before ovulation and may prevent fertilization. I would prefer you to delete the explanation of why you are dropping the Cu-IUD from your discussion. Since the Cu-IUD has a different label (and is not labeled for EC), this is just irrelevant and may serve to reinforce an unfortunate notion about the Cu-IUD (and of course now we are also beginning to use the hormonal IUD as EC).>

-Author: I have deleted the following line from page 4 (formerly lines 70-72):

--Old text: "(Note that I am arguing only about EC with LNG, as other EC methods like copper intrauterine devices are more likely to act after ovulation [15].)"

<Editor: L112-113 - can you add the year 2006 here so readers don't have to look at the reference list for that. Trussell died several years ago, and was very much a part of this journal's community. Since you cite him repeatedly, better to be clear that you are (of course) citing work from when he was alive.>

-Author: I have added the year 2006 to parenthetical in-line citation on the bottom of page 5 (line 114):

--Old text: "While acknowledging the ethical rationale for the anti-abortion standard, two members of the FDA advisory committee (Frank Davidoff and James Trussell, both advocates of EC) criticized it:

“Beyond that lack of information [of knowing definitively whether Plan B prevents implantation] lies the more subtle logical difficulty—some would say the impossibility—of proving the lack of existence of any particular mechanism” (p. 1777) [10].”

---New text: “While acknowledging the ethical rationale for the anti-abortion standard, two members of the FDA advisory committee (Frank Davidoff and James Trussell, both advocates of EC) criticized it: “Beyond that lack of information [of knowing definitively whether Plan B prevents implantation] lies the more subtle logical difficulty—some would say the impossibility—of proving the lack of existence of any particular mechanism” (2006, p. 1777) [10].” (pp. 5-6, lines 110-115)

<Editor: L171 - perhaps delete 'their'.>

-Author: I have deleted “their” from page 8 (line 170):

--Old text: “Even more worryingly, the label provides anti-abortion pharmacists with a tool for “moral gatekeeping,” in which they punish allegedly “bad women” who risk zygotic life by refusing to dispense their EC [35].”

---New text: “Even more worryingly, the label provides anti-abortion pharmacists with a tool for “moral gatekeeping,” in which they punish allegedly “bad women” who risk zygotic life by refusing to dispense EC [35].” (page 8, lines 168-170).

<Thank you.>