

## Emergency contraception

(NOVEMBER 2012)

**TO THE EDITOR:** In her recent overview of emergency contraception (November 2012),<sup>1</sup> Dr. Batur wrote that emergency contraception with levonorgestrel (Plan B One-Step) or combined estrogen-progestin-based methods does not cause abortion, noting that it is “unlikely to affect the ability of the embryo to attach to the endometrium.”<sup>1</sup> We disagree. We consider any interruption of human development after fertilization to be abortion (ie, abortifacient).

Recently, Noé et al<sup>2</sup> found that levonorgestrel was 100% effective in stopping clinical pregnancy when given 1 or 2 days before ovulation. However, previously, Croxatto et al<sup>3</sup> noted (through ultrasonography) that levonorgestrel allowed ovulation 88% of the time when given 1 or 2 days before ovulation. Since levonorgestrel’s efficacy is significantly higher than its ability to inhibit ovulation on these days, another mechanism of action must be operant when ovulation does occur, that is, the other 88% of the time. A non-contraceptive action is the most likely explanation by default since the other main effect (ie, thickening of cervical mucus) likely plays little role if levonorgestrel is taken several hours after sexual activity.

Dr. Batur states that levonorgestrel is not an abortion pill because it serves “to enhance the progesterone effect”<sup>1</sup> on the endometrium; however, it causes menstrual bleeding in about 15% of women taking it within 7 days.<sup>4</sup> In addition, Kesserü et al<sup>5</sup> noted that the intrauterine pH rose to more than 9 when a low dose was given. This is a 10-fold increase in alkalinity above the normal uterine pH. The pH within the fallopian tubes was not measured, but if a similar rise in pH occurred, it could easily explain how early embryos might die from levonorgestrel.

The medical literature cited above is consistent with the manufacturer’s claim that levonorgestrel “may inhibit implantation,”<sup>6</sup> and with the American Congress of Obstetricians and Gynecologists’ statement that “prevention of implantation may be a

secondary mechanism of action.”<sup>7</sup> Physicians and patients should be aware of this important ethical and clinical point.

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**IN REPLY:** I thank Drs. Kahlenborn and Severs for their comments. Controversy surrounds emergency contraception; thus, it is important to use peer-reviewed, current medical literature to reference mechanism of action. The product label is an unreliable resource, as it was written before current studies that clarified how emergency contraception works. The Noé study concluded that “levonorgestrel emergency contraception does not prevent embryo implantation and therefore cannot be labeled as abortifacient.”<sup>1</sup> They monitored ovulation via ultrasonography and hormonal assays, so they knew in which women ovulation had occurred when emergency contraception was taken. Of those who took it before ovulation, 16 pregnancies were expected and none occurred. When it was taken the day of ovulation or after, 8.7 pregnancies were expected and 8

pregnancies occurred. Because emergency contraception was ineffective after ovulation, a postfertilization effect is unlikely.

Although Drs. Kahlenborn and Severs cited 2004 Croxatto data, they did not cite the 2007 study by Novikova et al,<sup>2</sup> which concluded that levonorgestrel emergency contraception “has little or no effect on post-ovulation events, but is highly effective when taken before ovulation.”<sup>2</sup> In this study, when levonorgestrel emergency contraception was taken pre-ovulation, 0 out of 4 expected pregnancies occurred. When it was taken post-ovulation, 3 out of the 3 to 4 expected pregnancies occurred.<sup>2</sup>

The Frequently Asked Question 114 that Drs. Kahlenborn and Severs cited from the American Congress of Obstetricians and Gynecologists was updated in August 2011 and no longer cites prevention of implantation as a potential mechanism of action. Instead, it reads, “Progestin-only pills are thought to prevent pregnancy mainly by preventing ovulation.”<sup>3</sup> Another ACOG committee opinion, from November 2012, states, “A common misconception is that emergency contraception causes an abortion. Inhibition or delay of ovulation is the principal mechanism of action. Review of evidence suggests that emergency contraception cannot prevent implantation of a fertilized egg. Emergency contraception is not effective after implantation; therefore, it is not an abortifacient.”<sup>4</sup>

The International Federation of Gynecology & Obstetrics and the International Consortium for Emergency Contraception have issued a joint statement on emergency contraception, including mechanism of action.<sup>5</sup> This is a good resource for providers and patients. We owe our patients an honest discussion about the current science, from current references and guidelines, so they can make educated decisions based on their own comfort level with emergency contraception.

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## Bilateral adrenal masses

(DECEMBER 2012)

**TO THE EDITOR:** In their article “The clinical picture: bilateral adrenal masses” in the December 2012 issue,<sup>1</sup> Drs. Saberi and Esfandiari provide excellent points about adrenal hemorrhage as a differential diagnosis for adrenal masses. However, there are two points worth emphasizing when mentioning this diagnosis, especially in the case they presented.

Drs. Saberi and Esfandiari cryptically mention this patient’s coagulopathy (with thrombocytopenia and a rise in creatinine) and anticoagulation as the probable causes of adrenal hemorrhage. We wonder if a diagnosis of antiphospholipid syndrome (APS) was overlooked. Even though overt Addison disease is reported in only 0.4% of patients with APS<sup>2</sup> and APS is diagnosed in fewer than 0.5% of all patients with Addison disease,<sup>3</sup> we think that in this case, since the patient initially presented with an arterial thrombus in the abdominal aorta, screening for APS would have been warranted.

Second, though it is rare, bilateral adrenal hemorrhage with normal imaging on initial presentation has been described,<sup>2,4</sup> which raises this additional question: Should screening for adrenal insufficiency in a patient with possible APS or other coagulopathy be done early while waiting for repeat computed tomography to reveal hemorrhage? Occasion-

ally, intraparenchymal microhemorrhages may not be recognized by sectional imaging but can nonetheless compromise adrenal function.<sup>4</sup>

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## Sex, statins, and diabetes

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**TO THE EDITOR:** The review article “Statins and diabetes: fact, fiction, and clinical implications”<sup>1</sup> left out one major fact: there are sex-based differences in the statin research results, particularly a higher risk for diabetes in postmenopausal women on statins, with an adjusted hazard ratio of 1.48.<sup>2</sup> The article promulgated the fiction that statins should be used for primary prevention in women. The first study the author reviewed when discussing the risk of diabetes in “patients” was WOSCOPS—which was an *all male* study.<sup>3</sup>

While statin therapy is an effective intervention for secondary prevention of cardiovascular disease in both sexes, it is important to note there is no benefit in rates of all-cause mortality or stroke in women.<sup>4</sup> The use of statins for primary prevention in women rightly remains controversial.

Any review article on statins or any condition or drug used in both sexes should include some discussion about sex-based differences. While it might be advanced that

the increased risk for diabetes, depression, cognitive impairment, and musculoskeletal pain can be justified in secondary prevention in both sexes, that argument is much, much weaker for primary prevention in women, especially since we have evidence showing a reduction in all-cause mortality and primary cardiovascular reduction in women given early postmenopausal hormone therapy.<sup>5</sup>

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**IN REPLY:** As Dr. Thacker notes, women are underrepresented in statin clinical trials. This, in addition to the fact that the meta-analyses reviewed did not generally stratify results by sex, makes a detailed discussion of sex-based differences on diabetes incidence and comparative outcomes difficult.

In terms of outcomes, some meta-analyses have found similar reductions of cardiovascular events with statin treatment in men and women, particularly in secondary-prevention populations.<sup>1–3</sup> Even though the cited report from Gutierrez et al<sup>4</sup> may not have been as inclusive as some other studies, it also demonstrated similar reductions in myocardial infarction, need for intervention, and coronary mortality rates compared with men. The lack of significant reduction in rates of cerebrovascular accidents and all-cause mortality in this study may be a function of the low percentage

of women in the analysis (20.6%), the low number of events, and the lack of power. However, the results did trend in a positive direction.

It is true that outcome benefits are harder to demonstrate in primary-prevention populations. However, a meta-analysis by Brugts et al<sup>5</sup> in 2009 examined 10 placebo-controlled statin trials, including at least 80% of individuals without cardiovascular disease or whose data were reported from a sole primary prevention group. Thirty-four percent of the participants were women. Overall, there was a 12% reduction in mortality, 30% reduction in coronary events, and 19% reduction in cerebrovascular events. Although sex-specific analysis did not show significant reductions in women alone, the directional trends were similar to those in men, and subgroup analysis revealed no heterogeneity in treatment effect by sex, age, or diabetes status.

The meta-analysis from the Cholesterol Treatment Trialists cited in this review included 27 controlled trials and stratified patients by estimated 5-year major vascular event risk<sup>6</sup>; 29% of the patients were women. As expected, annual event rates increased with increasing estimate of risk. Rates of major vascular and major coronary events were reduced by 21% and 30%, respectively. Similar significant proportional reductions were noted in all risk groups, including the lowest two risk groups (< 5% and 5 to < 10%). Although analysis was not stratified by sex, there was a proportionately higher percentage of women (54%) represented in the lowest-risk group, which had a similar relative risk reduction. In the primary-prevention trial JUPITER<sup>7</sup> in patients with elevated C-reactive protein and low low-density lipoprotein cholesterol levels, rosuvastatin significantly reduced the primary composite end point in women (38% of the study group) by 46%, which was similar to that in the men.<sup>7,8</sup> In the same paper, an additional meta-analysis of exclusively primary prevention trials reported a significant 37% reduction in cardiovascular events.

As for comparable diabetes incidence on statins, it is not accurate to imply that women have a higher risk of developing diabetes than men based only on the Women's Health Initiative observational analysis—an all-female study with no male comparison arm, without randomization to statins, and in which only 7% of participants at entry were taking the drug in question.

The use of statins in low-risk individuals and in women in particular does remain controversial, partially because of the lack of controlled data and sufficiently powered studies with women. It was not my intent to “promulgate a fiction” that statins should be used in primary prevention in all women, but rather to recommend the use of statins appropriately in at-risk patients after weighing the treatment risks. All therapies, including statin therapy, should be directed toward those who would have the best benefit-risk ratio. To lump together all primary-prevention women, however, is overly simplistic and may result in denying therapy to a patient who may benefit from the intervention. In women as in men, the available data (although imperfect) support statin use with an acceptable risk profile in those at moderate to high risk of subsequent cardiovascular events. Some of these patients would be in the primary prevention classification. Every decision to treat needs to factor in the patient's overall cardiovascular risk, the likelihood of adverse effects including diabetes, and the patient's sex.

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