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# Intravenous estrogen is not proven effective for abnormal uterine bleeding: guidelines are based on flawed evidence

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**ABSTRACT** A clinical appraisal and clinical application of: DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. *Obstet Gynecol.* 1982 Mar;59(3):285-91.

This appraisal identifies significant statistical irregularities in the study. A reworking of the study's statistics leads to a conclusion different from that put forth by the authors of this paper: intravenous estrogen therapy is not, in fact, significantly more effective compared to placebo therapy for the cessation of acute abnormal uterine bleeding.

**Keywords:** intravenous Premarin, acute abnormal uterine bleeding, intravenous estrogen, conjugated estrogen

## Clinical Context

A 48-year-old female patient presented to the emergency department for acute abnormal uterine bleeding (AUB). She had been bleeding profusely from her vagina for six days. The blood had soaked through her pants, and she was experiencing lightheadedness, dizziness, and fatigue. Labs revealed a hemoglobin of 5.9 mg/dL. Attempts to stop the bleeding with megace (40 mg QID) were unsuccessful; the next day, IV estrogen (25 mg in 0.9% NaCl) was given, and the bleeding stopped.

The use of IV estrogen to control this patient's bleeding was surprising to me. Prior to this case, I had thought progesterone to be the preferred treatment; it was my understanding that progesterone would stabilize the endometrium by halting proliferation and promoting differentiation, allowing for withdrawal bleeding upon its removal.<sup>2</sup>

## Clinical Question

Is intravenous Premarin<sup>®</sup> (Conjugated Estrogen) effective in the cessation of acute abnormal uterine bleeding?

## Research Article

DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. *Obstet Gynecol.* 1982 Mar;59(3):285-91.

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## Literature Review

Readily available secondary sources, including an April 2013 Committee Opinion from the American College of Obstetricians and Gynecologists<sup>(3,4)</sup>, communicate that IV estrogen use is a mainstay medical treatment for acute AUB and reference the study by DeVore, et al. as sole evidence. Munro, et al. showed evidence for high dose medroxyprogesterone acetate, and Aksu, et al. compared the use of medroxyprogesterone acetate and combination oral contraceptive pills.<sup>(5,6)</sup> This latter study showed effectiveness for both modalities, but not a clinically significant difference between the two.<sup>6</sup> It is surprising that the DeVore, et al. article would be the only study to evaluate IV estrogen therapy for acute AUB; according to *Google Scholar*, DeVore, et al. is currently cited in 131 articles. This critical appraisal, therefore, looks at the quality of evidence supporting the use of this treatment modality and its effectiveness in this case scenario.

## Critical Appraisal

This is a randomized, placebo-controlled, double-blind study. It incorporates an open-label follow-up, demonstrating what should be Level 1b evidence according to the Oxford Centre for Evidence Based Medicine. The study was 'partially open' at the time it was conducted, meaning that if bleeding continued after two cycles of injections, IV estrogen was administered on an open-label basis regardless of which arm of the study the patient was assigned. This protocol was enacted due to the Human Investigation Committee's belief—based on common practice at the time—that IV estrogen was beneficial and should not be withheld from those patients in the control group.

The strengths of this study lie in its research methods: randomized, placebo-controlled, and double-blind. Considering the number of subjects used in this study, the investigators performed both a Chi-square test and a Fisher's exact test for statistical analysis. Although the authors claim to use an intention-to-treat analysis, the number of cases in each group is reported in an inconsistent manner throughout the paper, and statistical significance is only the result of the authors' failure to assess the data in accordance with the intent-to-treat standard. At the onset of the study, 16 patients were assigned to the placebo group; however, following the first injections, two of these patients withdrew from the study entirely with no follow-up assessment. The study calculates statistical significance by categorizing the two placebo patients as treatment failures. This is not in line with intent-to-treat protocols, which state that once a subject is randomized into a treatment group, they cannot be removed when analyzed even if they withdraw from the study or are lost to follow-up.<sup>7</sup>

The study also states that bleeding had stopped after two treatments in 72% of the IV estrogen group and 38% of the placebo group ( $p$ -value = 0.021). In order to obtain the 38% placebo response, the authors included the two dropout patients as treatment failures. However, assuming the two placebo group patients who withdrew had cessation of bleeding, eight out of the 16 patients in the placebo arm would have responded. If this were the case, 50% of subjects receiving placebo would have stopped bleeding versus 72% in the treatment group. Using these new values, a Chi-Square analysis shows that there is no statistical significance between the IV estrogen group and the placebo group ( $p$ -value = 0.183) in stopping AUB. This does not prove that IV estrogen is ineffective; in this study, the authors simply fail to demonstrate that IV estrogen stops AUB more effectively than placebo.

An appropriate critical analysis of this study should include a number needed to treat to determine the realistic value of this medication to a patient. However, in this case a number needed to treat cannot be calculated, because there is no absolute risk difference demonstrated between treatment and placebo groups.

Note: This study was funded by a grant by Ayerst Laboratories, the same laboratory that manufactures Premarin®.

### Clinical Application

The authors of this article skewed their results by assuming that two placebo patients who withdrew and were lost to follow-up would maintain their uterine bleeding. Three lessons can be learned from this critical appraisal: first, that even published authors misrepresent their own data; second, that current guidelines are based on poor quality evidence; and third, that following guidelines alone is not the same as evidence-based practice. Estrogen therapy is not without risks, most notably the increased chance of thrombotic events. For example, in one case report, a patient died due to a saddle embolus after six doses of 25 mg of IV estrogen.<sup>8</sup>



The patient I encountered in the emergency department had symptomatic AUB that was refractory to progesterone therapy. One potential explanation for the clinical course of this patient is that she received progesterone followed by estrogen, which the attending physician may have thought to be the clinical equivalent of combination oral contraceptives. Currently, combination oral contraceptives constitute the standard of care.

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