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Abnormal uterine bleeding guidelines and clinical practice are based on poor quality evidence

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ABSTRACT A critical appraisal and clinical application of Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: A randomized controlled trial. *Obstet Gynecol.* 2006 Oct;108(4):924-929. doi:10.1097/01.AOG.0000238343.62063.22

Keywords: medroxyprogesterone acetate, combined oral contraceptives, acute abnormal uterine bleeding, AUB, dysfunctional uterine bleeding, American College of Obstetricians and Gynecologists, ACOG

Clinical Context

A.F. was a 42-year-old $G_3P_2A_1$ female with a four-year past medical history of uterine fibroids and anemia who presented to the emergency department (ED) with severe, intermittent pelvic cramping three times per hour and heavy menstrual flow for the last three days. Although typically heavy, this period was heavier than baseline, requiring her to change her pads seven times per day. The patient admitted to headaches, malaise, dizziness, and chest palpitations since the bleeding began. On arrival at the ED the patient's vital signs were within normal limits with a blood pressure of 113/61 mmHg. CBC revealed a hemoglobin of 5.6 g/dL and a hematocrit of 18.5%. Platelets were 40,000/mcL but consistent with a stable history of chronic thrombocytopenia. Blood pH was 7.42 and electrolytes were also within normal limits. Gynecology was consulted and performed a transvaginal ultrasound revealing a fundal fibroid that had grown since previous studies to a size of 7.5 x 5.4 x 6.4 cm. A.F. was diagnosed with symptomatic acute abnormal uterine bleeding (AUB) secondary to leiomyoma (AUB-L).[1] Due to her stable vital signs, Gynecology determined that she did not require emergent surgical intervention. Packed red blood cells (pRBCs) were administered and options for medical management of her acute AUB were considered until a hysterectomy could be performed.

Clinical Question

Which hormonal therapy is most effective at terminating structural AUB in hemodynamically stable, non-pregnant women?

Research Article

Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: A randomized controlled trial. *Obstet Gynecol.* 2006 Oct;108(4):924-929. doi:10.1097/01.AOG.0000238343.62063.22

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Literature Review

Many medical and surgical interventions to control acute AUB exist; however, there is limited randomized control trial (RCT) evidence to guide choice of treatment. The Committee Opinion, Number 557, from the American College of Obstetricians and Gynecologists (ACOG) somewhat addresses this issue stating that hormonal management constitutes the first line of medical therapy for hemodynamically stable cases of acute AUB, excluding AUB secondary to coagulopathies (AUB-C) such as von Willebrand disease.[2,3] According to these recommendations, accepted medical therapies include IV conjugated equine estrogen (CEE), combination oral contraceptives (OC), medroxyprogesterone acetate, or tranexamic acid. Each of these recommended therapies is based on a single RCT. For this literature review the search parameters were limited to those RCTs cited by ACOG and the significant studies referenced by these RCTs. Articles were found and accessed using PubMed.

IV CEE (Premarin®) is perhaps the most commonly used AUB therapy; however, this ACOG recommendation is based on a well-known randomized placebo-controlled study by De Vore et al. that is controversial because its purported intention-to-treat analysis was flawed, leading to doubt about the validity of this therapy.[4,5] Tranexamic acid, an antifibrinolytic, has not yet specifically been analyzed in a RCT for acute AUB.[3,6] In order to ensure best practice in the case of A.F., medroxyprogesterone acetate and combination OCs as studied in a RCT by Munro et al. and cited in ACOG recommendations was evaluated as an alternative treatment to Premarin® and forms the basis of this critical appraisal. Munro et al. compared the efficacy of medroxyprogesterone acetate (20 mg TID for 7 days then daily for 3 weeks) with a combination OC (1 mg norethindrone and 35 µg ethinyl E2 TID for 7 days then daily for 3 weeks) as a therapy for acute AUB in 40 patients. The results of this study demonstrated that cessation of life-threatening bleeding was achieved in 88% of patients receiving the combination OC and 76% of those receiving medroxyprogesterone acetate in a median of three days.[7] There was no significant baseline difference between the two groups. The authors performed an exhaustive literature review regarding the use of medroxyprogesterone acetate in AUB, finding only one inferior study by Aksu et al.[8], confirming that the best available evidence concerning this therapy is contained in the article under review. Similarly, no RCTs exist regarding the use of combination OCs in the treatment of AUB. Aksu et al. had previously showed that high-dose medroxyprogesterone acetate (60-120 mg for 1 day then 20 mg daily for an additional 10 days) effectively suppressed AUB to acceptable levels in all studied cases and terminated bleeding entirely in 25% of cases.[8] This critical appraisal examines the quality of evidence supporting medroxyprogesterone acetate and combination OCs as acute AUB treatments and their effectiveness in the case of A.F.

Critical Appraisal

The study by Munro et al. is described by the authors as a RCT comparing the efficacy of medroxyprogesterone acetate and combinations OCs regimens as medical management for AUB in hemodynamically stable, non-pregnant women. Forty AUB patients that met inclusion criteria were selected at two Kaiser Permanente Medical Centers in Los Angeles and randomized into two treatment groups via a sequential numbering system that distributed study participants in blocks of 10 using sealed opaque envelopes that were shuffled into a random order. Despite an appropriate system for randomization, mean duration of current bleeding episode differed between treatment groups (as described in Munro et al., Table 1) – 15.5 versus 8 days, favoring combination OCs – due to the small number of cases in this study. This RCT was performed as an open label study where study personnel, physicians, and patients were not blinded at any point, including outcome assessment. As a result, this study was subject to observer and reporting biases. In particular, secondary outcomes, which were subjective and assessed at the two-week follow-up appointment by the study coordinator who was not blinded, were most at risk of bias. Aside from the treatments administered, both groups were treated equally.

The primary outcome of this trial was the avoidance of unscheduled surgery within the 28-day follow-up period. The NCT registration (NCT00350480) confirms this outcome measure. This was a reasonable primary outcome but should be evaluated with common sense only. It lends the reader some practical knowledge of how to medically manage patients with acute AUB; however, both treatments are not based on high quality evidence. Since this study involved a population at risk of severe anemia and was conducted as a largely outpatient therapy, a placebo control group was not possible. Furthermore, as stated earlier, the authors' comprehensive literature review yielded only one previous study assessing the efficacy of medroxyprogesterone acetate as an AUB treatment. The Aksu et al. trial deemed medroxyprogesterone acetate effective but is severely limited by having not used a control group itself. Similarly, by the authors' own admission, evidence for the use of combination OCs in AUB is comprised of only "a combination of textbook recommendations and expert opinion." De Vore el al. investigated the use of estrogen as an AUB therapy

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but no RCTs have examined combination OCs specifically.[3,4] Currently, both medroxyprogesterone acetate and combination OC regimens have never individually been shown to significantly improve AUB outcomes over no treatment. Our ability to draw conclusions about the efficacies of these treatments is extremely limited because we are unable to determine with certainty if cessation of AUB was achieved by the administration of these hormonal therapies or because it would have stopped regardless.

The study found no difference in absolute risk reduction between the two treatment groups. In addition, no placebo group was used and neither treatment is an appropriate active control for the other. As a result, the number needed to treat cannot be calculated for either therapy.

All patients were analyzed in the group to which they were randomized. Unlike the De Vore et al. trial, intention-to-treat analysis was maintained over the four week study period despite several patients being lost to follow-up. The medroxyprogesterone acetate treatment group lost three patients to follow-up and the combination OC group lost four patients; however, the researchers were able to monitor for hospital admissions and operating room use by these patients at all 12 Southern California Kaiser Permanente Medical Centers.

Finally, the authors calculated that 200 participants would be required for this study to have adequate power. Only 40 participants were enrolled, so had a difference in efficacy existed between treatment groups it may not have been detected. Also in the power analysis, the authors claim, “number of subjects to demonstrate equivalence…”, however, the study design was not appropriate to justify this claim.

Munro et al. designed an underpowered study at risk for several types of bias, investigating treatments not supported by evidence-based medicine. Although participants were fairly appropriately randomized and intention-to-treat analysis was maintained, the study’s limitations suggest that the authors’ primary conclusion that medroxyprogesterone acetate and combination OCs may be effective at stopping AUB is premature. This is a low quality RCT that provides Level 2b evidence according to the Oxford Centre for Evidence-based Medicine.

Clinical Application

Due to the lack of evidence supporting the use of medroxyprogesterone acetate or combination OCs, Premarin® was ultimately used to treat A.F. Bleeding was controlled with a twenty-four hour course of IV Premarin® chosen because of the attending physician’s experience with this treatment. She was also transfused with a total of 8 units of pRBCs. Although not supported by RCT evidence,[3] after twenty-four hours she was switched to a course of oral Megace® as is generally done following Premarin® treatment until a hysterectomy could be performed. Hemoglobin stabilized at 11.0 g/dL after four days.

It should be noted that A.F. did not meet the inclusion criterion for hemoglobin level (>8 g/dL) of the Munro et al. study, or any other AUB hormonal management RCT, due to her severe anemia.[9] Also, the mean BMI of both groups in this study were 30.3 kg/m^2 and 29.0 kg/m^2 for medroxyprogesterone acetate and combination OCs, respectively. The authors infer from these relatively high BMIs that the primary cause of AUB in their study population was non-structural anovulatory AUB. In contrast, A.F. had a significantly lower BMI of 25.7 kg/m^2 and was diagnosed with fibroids, a structural cause of AUB. However, due to the general lack of high quality studies supporting ACOG recommendations it is justified in this case to apply a mismatched study. This highlights the role of clinical judgment in the everyday clinical practice of evidence-based medicine.

Take Home Points:

1.) Current treatment guidelines for AUB are not supported by evidence, and ultimately, the choice of medical treatment for acute AUB is at the discretion of physicians and their individual experiences with these therapies.
2.) Larger blinded RCTs with appropriate control groups are needed in order to draw any conclusions regarding the medical management guidelines for AUB.

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