A new progestogen-only medical therapy for outpatient management of acute, abnormal uterine bleeding: a pilot study

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OBJECTIVE: The objective of this investigation was to study short-term efficacy and feasibility of a new progestogen-only treatment for outpatient management of acute abnormal uterine bleeding.

STUDY DESIGN: This was a prospective, single-arm, pilot clinical trial of a progestogen-only bridging treatment for acute abnormal uterine bleeding in nonpregnant, premenopausal women in the Gynecologic Urgent Care Clinic at Harbor-UCLA Medical Center. Subjects were administered a depo-medroxyprogesterone acetate 150 mg intramuscular injection and given medroxyprogesterone acetate 20 mg to be taken orally every 8 hours for 3 days. The primary outcome measures included a percentage of women who stopped bleeding in 5 days, time to bleeding cessation, reduction in numbers of pads used, side effects, and patient satisfaction.

RESULTS: All 48 women stopped bleeding within 5 days; 4 women had spotting only at the time of their last contact during the 5 day follow-up. Mean time to bleeding cessation was 2.6 days. Side effects were infrequent and patient satisfaction was high.

CONCLUSION: Injection of depo-medroxyprogesterone acetate 150 mg intramuscularly combined with 3 days of oral medroxyprogesterone acetate 20 mg every 8 hours for 9 doses is an effective outpatient therapy for acute abnormal uterine bleeding.

Key words: acute abnormal uterine bleeding, depo-medroxyprogesterone acetate, menorrhagia, progestogen-only treatments

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The classification of abnormal uterine bleeding (AUB) has recently been revised in the new PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia–coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) classification for causes of abnormal bleeding, developed by the International Federation of Gynecology and Obstetrics Menstrual Disorder Group.[1-4] Acute AUB is defined as an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient severity to require immediate intervention to prevent further blood loss.[5,6]

Acute AUB is a relatively common problem seen in both the office practice and in emergency rooms.[7] Typically at the time of presentation, tests are performed to determine the etiology of the excessive bleeding to design targeted, long-term therapies. The clinical challenge is that the woman's bleeding needs to be halted promptly, usually before the results of those tests are available.

Unfortunately, there are no Food and Drug Administration–approved products for short-term treatment of acute excessive bleeding. Despite calls for new scrutiny for off-label use of drugs,[8-10] there is very little in the literature to support claims of efficacy for any of the myriad of currently utilized therapies to halt acute abnormal uterine bleeding. Only 4 therapies cumulatively reporting the experience of 116 women have been studied in prospective trials published in peer-reviewed journals to control acute nonpuerperal excessive bleeding.[5,6,11-13] Retrospective reports of clinical experiences with a variety of different hormonal therapies add the experience of fewer than 200 more women to the literature.[14-16] These numbers become even more modest when we recognize that many of the therapies used in those reports would not be used today because of the safety concerns about the use of high doses of estrogen.[6,13,17-20]

The Gynecologic Urgent Care Clinic at Los Angeles County Harbor-UCLA Medical Center (Torrance, CA) serves indigent and uninsured patients who often face challenges filling their prescriptions and returning for follow-up care. Historically, hemodynamically stable women with acute abnormal uterine bleeding have been treated with a variety of different hormonal therapies, guided primarily by the attending physician. Prior attempts to conduct comparative randomized clinical trials utilizing more conventional interventions have failed because of provider bias against the use of estrogen in high-risk women and because the barriers patients have in returning for short-term follow-up.

Given that with high-dose oral medroxyprogesterone acetate (MPA), the median time to bleeding cessation in the most well-designed, randomized clinical trial was shown to be 3 days[6] and given that by 3 days, serum levels of depome-

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TABLE 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Premenopausal	Hemodynamically unstable
Acute excessive uterine bleeding documented by history and physical examination	Hemocue less than 8 g/dL Condition requiring immediate surgery Contraindications to progestogen therapy
Vital signs demonstrate hemodynamic stability	Pregnancy
No need for transfusion	Failure of prior outpatient management of this episode of bleeding
Ability to understand outpatient therapy	Known endometrial or cervical carcinoma
Ability to participate in all study follow-up activities	Inability or unwillingness to participate in all aspects of study

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droxyprogesterone acetate (DMPA) are therapeutic, we sought to study the ability of that combination of progestogen-only therapies to control acute abnormal uterine bleeding. The specific regimen studied was DMPA 150 mg given intramuscularly followed by MPA 20 mg orally every 8 hours for 9 doses.

The primary outcome measures of this pilot study included the following: (1) efficacy of the therapy in halting uterine bleeding (measured by the percentage of women who stopped bleeding, mean time to bleeding cessation, and drop in hemoglobin); (2) treatment feasibility (measured by patient utilization of the study drugs as directed); and (3) tolerability (measured by side effect reports and patient satisfaction).

Materials and Methods

Permission to conduct this pilot clinical trial was obtained from both the John R. Wolfe Human Subjects Committee (project no. 13530, approved Dec. 8, 2009) and the Research Committee of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. The study was registered with national clinical trials directory (CNCT01148420) and featured in the *British Journal of Obstetrics and Gynecology* under the title, "Women's health—what's new worldwide."[21] Additional local permissions were obtained from the Harbor-UCLA Director of Pharmacy and from the Department of Nursing.

Premenopausal, nonpregnant women who presented with complaints of acute heavy and/or prolonged uterine bleeding were evaluated by a resident physician working under the supervision of a faculty member from the Department of Obstetrics and Gynecology. This evaluation usually included a pelvic examination, laboratory testing (eg, pregnancy testing, hemoglobin assessment, and/or thyroid function tests), endometrial sampling, and pelvic ultrasound studies.

Women were excluded if they were hemodynamically unstable, required immediate surgery, had hemoglobin less than 8, or had failed an earlier hormonal treatment for the current episode of bleeding (Table 1). If the patient was judged to be a candidate for outpatient care, she was invited to participate in the study, and her informed consent was obtained. Baseline data included demographic data, information about the current bleeding episode, recent bleeding patterns, and medical problems as well as the findings from her examination and testing.

Each woman received DMPA 150 mg intramuscularly and a vial containing 18 tablets of MPA 10 mg from which she was instructed to take 2 tablets orally every 8 hours for 3 days. A formal complete blood count (CBC) was ordered before the patient left the clinic. A prescription for iron supplements was provided if the woman was anemic. She was also given an instruction sheet and told to note the time she took her pills, the numbers of sanitary protection products (pads or vaginal tampons) she used each day, and any side effects she experienced.

Each patient was called by 1 author (S.R.A.) on day 1 and on day 2 to collect the data for each of those 2 24 hour intervals. Each subject returned to the Urgent Care Clinic on day 3 and provided interval data about her bleeding, pill use, and side effects. A repeat CBC was obtained. If a woman had not stopped bleeding by that day 3 Urgent Care Clinic visit (ie, she was still using sanitary protection at the time of the visit), she was called again on day 5 to provide the data for days 4 and 5.

As a small single-arm pilot study, only the numbers and percentage of women who responded to therapy and the percentage of women who experienced side effects are reported. No power analysis or sample size calculations were performed and no comparative statistics or tests of significance are applicable.

Results

Fifty women were enrolled in the study. Data on 2 subjects were censored because their consents had been obtained using expired consent forms. Patient characteristics of the remaining 48 subjects are shown in Table 2. All 48 women were premenopausal (age, 19-53 years) and most were obese (mean body mass index [BMI], 34.9 kg/m^2; range, 21.5−51.2 kg/m^2). Women reported that the mean number of months they had experienced episodes of heavy bleeding (excessive bleeding) was 5.2 months. The mean duration of bleeding during their current episode was 30.6 days. In the 24 hours prior to presentation, women reported use of a mean of 8.5 sanitary protection products.

All 48 patients reported taking their medication as directed. None was lost to follow-up until after her bleeding had stopped. No patient required either surgical intervention or additional medical treatments during the 5 day study period (Table 3). The numbers of women who ceased bleeding by the time of contact on each day are displayed in that table. The mean time to bleeding cessation was 2.6