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

days and the median was 3 days. The amount of blood lost (as reflected in number of sanitary protection products used in the prior 24 hours) rapidly and significantly declined. Reflecting that rapid cessation of blood loss, mean, and median hemoglobin levels drawn on the day of enrollment and on study day 3 were the same.

Forty-four women underwent endometrial biopsies during their initial visits prior to study enrollment. The most common histology was proliferative endometrium (21 of 44), followed by secretory endometrium (7 of 44), sloughing endometrium (7 of 44), chronic endometritis (3 of 44), and fragments of endometrial glands and stroma (3 of 44). Polyps were detected in 3 cases, alone in 1 case and in conjunction with previously mentioned proliferative endometrium in 2 more cases. Additionally, there were 2 cases of simple hyperplasia without atypia and 1 case of complex hyperplasia without atypia. Because all women stopped bleeding, no association was seen between histology and response to therapy. Thirty-two of the women had ultrasounds performed at the first visit; the presence, but not the specific size or location, of leiomyoma was documented in 13 of these women. All 13 women with leiomyoma stopped bleeding.

Women were asked at each contact whether they had experienced any side effects from the therapy. Table 4 displays the very few complaints that women reported. Many of the complaints (eg, fatigue, cramping, and dizziness) were more likely to have been attributable to their bleeding or to their anemia than to the use of the study medication.

At the end of the trial, women were asked to rate their satisfaction with the therapy using a scale of 1-3 (1, poor; 2, good; or 3, excellent). The median score was 3, and the mean was 2.75. No woman rated her satisfaction as poor. Perhaps more importantly, all 48 patients said they would recommend this treatment to a friend.

Concern about the use of DMPA may not relate to questions about its short-term efficacy but rather about the possibility that treatment with DMPA might make any subsequent bleeding more difficult to treat.[20] Because of this safety concern, several months after completion of the research project, we conducted a quality assurance chart review to assess any immediate-term problems that our subjects may have encountered. Entries were found for follow-up care for 39 of the subjects. All 3 women with endometrial hyperplasia received appropriate therapy and cleared that abnormality without experiencing additional excessive bleeding. Thirty-one subjects had adequate control of their bleeding for the 3 months following the initial injection; only 15% (6 women) returned within 12 weeks of their injections with complaints of subsequent spotting and/or bleeding. All of them responded promptly to additional medical therapies. No women required surgery to arrest the repeat bleeding in the 12 weeks following DMPA.

TABLE 2
Baseline subject characteristics and baseline and day 3 hemoglobin values

Characteristic	Mean (SD)	Median	Range
Age, y	40.7 (9.35)	42.0	19–53
BMI, kg/m^2	34.9 (8.09)	33.0	21.5–51.2
Hemoglobin, baseline, g/dL	10.9 (1.58)	11.1	6.9–14.5[a]
Hemoglobin, day 3, g/dL	10.9 (1.62)	11.2	6.9–14.2[a]

[a] Hemoglobin on CBC was lower than the value from the point-of-care test (hemocue) used to determine the patient's eligibility for study participation.

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Comment

Although this was a single-arm, noncomparative pilot clinical trial, it is the largest prospective study to date to measure the effectiveness of a proposed hormonal treatment of acute abnormal uterine bleeding. Subjects experienced excellent success with this relatively low-dose, progestogen-only therapy that potentially offers more longer-term (3 months) protection than prior therapies.

The earliest studies using hormonal therapies to stop excessive acute bleeding utilized very high hormonal doses. For example, in a retrospective report of 59

TABLE 3
Response to treatment by study day

Variable	Number of women (still) bleeding	Number of women who stopped bleeding in prior 24 h	Cumulative number of women who stopped bleeding	Percent of women who stopped bleeding	Mean number of sanitary protection products used in prior 24 h[a]
Baseline (day 0)	48	—	—	—	8.5
Day 1	36	12	12	25.0	2.0
Day 2	28	8	20	42.7	1.0
Day 3	14	14[b]	34	70.8	1.0
Day 4	9	5	39	81.3	1.0
Day 5	0	9[c]	48	100.0	0.0

[a] Number of products used by women who were still bleeding; [b] One woman was still spotting on day 3 but was lost to later follow-up; [c] Four women still had spotting but no longer required sanitary protection products.

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TABLE 4
Incidence of complaints on therapy

Complaint	n (%)
Bloating	7 (15)
Fatigue	6 (13)
Cramping	3 (6)
Mood changes	2 (4)
Nausea	1 (2)
Increased appetite	1 (2)
Bone pain	1 (2)

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patients, Claessens and Cowell[15] used 40 mg intravenous conjugated estrogen every 4 hours for up to 6 doses in conjunction with combination oral contraceptives with 5 mg progestogen (given 2 tablets for a loading dose followed by 1 tablet every 6 hours) with or without additional norethindrone acetate (NETA) 5 mg given every 6 hours.

By the time of the classic prospective study by deVore et al,[5] the estrogen had been reduced to a single dose of 25 mg administered intravenously and repeated once in 3 hours if bleeding persisted; only 17 women were treated with active therapy and 17 controls were given placebo. Foss[11] and Rao[12] each reported the results of 9 women, each given norgestrel 0.5 mg with 50 μg ethinyl estradiol up to 4 times a day with a very slow taper. Retrospective studies reporting the success of high-dose progestogens in limited numbers of women followed up, first with high-dose norgestrel[16] and later with MPA.[14] A progestogen-only therapy using 60-120 mg MPA for 1 day, followed by daily doses of 20 mg for 4 additional days was prospectively tested in 24 adolescent women.[11]

In the most recent and largest study to date, Munro et al[6] enrolled 40 women into a trial comparing the efficacy of multiple doses of oral contraceptives (ethinyl estradiol [EE] 35 mg/NETA 1 mg) given orally every 8 hours for 7 days and then once daily for 21 days to high-dose (20 mg) MPA therapy given every 8 hours for 7 days followed by 3 weeks of once-daily dosing; both arms were highly successful, with median time to bleeding cessation of 3 days and a 100% response rate among users of MPA.[6] These authors reported encountering barriers to patient recruitment similar to those that we had earlier experienced while trying to perform comparative trials with estrogen-containing treatments.

The most significant limitation of our pilot study is that it was not a comparative trial. A placebo arm was considered unethical, and estrogen-containing therapies had resulted in discouraging enrollment in past trials. Another limitation was that because women were enrolled into the study only after they had been deemed eligible for outpatient management, so not every patient underwent the identical pretreatment diagnostic evaluation. However, we were able to characterize the endometrium and to document fibroids in significant numbers of women to demonstrate the efficacy of this therapy in a wide range of clinical situations. Another limitation is that we studied only short term (5 day) response to therapy. Finally, the high patient satisfaction scores that the treatment received could have been influenced by the experimental design itself. Patients were provided the treatment on site and did not have to fill any prescriptions for hormonal therapy. They also appreciated the personal attention they received from one of the investigators (S.R.A.), who kept in close contact with the patients throughout the study.

The use of DMPA as part of a therapy for the treatment of acute excessive uterine bleeding has been highly controversial based mostly on theoretical concerns. In fact, its use has been proscribed in the most recent edition of a highly respected textbook.[20] However, given the challenges our patients have in obtaining medications, we wanted to determine whether in combination with oral MPA, DMPA might be effective. Our safety review failed to find any harm that resulted from use of this progestogen-only regimen.

This pilot study, which is the largest study of any hormonal method to be tested prospectively, suggests that an injection of DMPA 150 mg intramuscularly combined with MPA 20 mg given orally 3 times a day for 3 days is an effective outpatient treatment for acute abnormal uterine bleeding among hemodynamically stable women with a variety of pathologies. It has been shown to halt bleeding rapidly, while appropriate testing can identify underlying pathophysiology; as such, it provides a temporary bridge to long-term targeted therapies. This regimen has good compliance, few side effects, and high patient satisfaction. It is a particularly attractive treatment option for women with contraindications to estrogen, those who need more prolonged therapy, and those who may have difficulty with daily pill administration. Future research with more organized intermediate follow-up and larger numbers of subjects could help evaluate its full potential as an important immediate bridging therapy.

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REFERENCES

1. Munro MG, Critchley HO, Fraser IS; FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril 2011;95:2204-8.

2. Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Semin Reprod Med 2011; 29:383-90.

3. Munro MG, Critchley HO, Fraser IS. The flexible FIGO classification concept for underlying causes of abnormal uterine bleeding. Semin Reprod Med 2011;29:391-9.

4. Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3-13.

5. 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; 59:285-91.

6. 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;108:924-9.

7. Munro MG. Abnormal uterine bleeding. Cambridge, UK: Cambridge University Press; 2010.
8. Stafford RS. Regulating off-label drug use—rethinking the role of the FDA. N Engl J Med 2008;358:1427-9.
9. Sherman RB, Woodcock J, Norden J, Grandinetti C, Temple RJ. New FDA regulation to improve safety reporting in clinical trials. N Engl J Med 2011;365:3-5.
10. Gillick MR. Controlling off-label medication use. Ann Intern Med 2009;150:344-7.
11. Foss GL. A clinical trial of a new totally synthetic low dose progestagen. J Reprod Fertil 1969;18:59-66.
12. Rao KP. Treatment of menstrual disorders with a combination of norgestrel and ethynyl estradiol. Curr Med Pract 1971;15:586-9.
13. Aksu F, Madazli R, Budak E, Cepni I, Benian A. High-dose medroxyprogesterone acetate for the treatment of dysfunctional uterine bleeding in 24 adolescents. Aust N Z J Obstet Gynaecol 1997;37:228-31.
14. Falcone T, Desjardins C, Bourque J, Granger L, Hemmings R, Quiros E. Dysfunctional uterine bleeding in adolescents. J Reprod Med 1994;39:761-4.
15. Claessens EA, Cowell CA. Acute adolescent menorrhagia. Am J Obstet Gynecol 1981; 139:277-80.
16. Greenblatt RB, Junck EC. Gynecologic uses of new multifaceted progestogen. Clin Pharmacol Ther 1966;7:490.
17. Gidwani GP. Vaginal bleeding in adolescents. J Reprod Med 1984;29:417-20.
18. Katz VL. Comprehensive gynecology, 5th ed. Philadelphia: Mosby Elsevier; 2007:558.
19. Berek JS. Novak's gynecology, 13th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002:363.
20. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility, 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2010:606–7.
21. Women's health—what's new worldwide. BJOG 2010;119:1304.