The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 606 • August 2014

Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescent Patients Undergoing Cancer Treatment

ABSTRACT: Adolescents undergoing cancer treatment are at high risk of heavy menstrual bleeding, and gynecologists may be consulted either before the initiation of cancer treatment to request strategies for menstrual suppression or during an episode of severe heavy bleeding to stop the bleeding emergently. Therapy in both situations should be tailored to the patient, her cancer diagnosis and treatment plan, and her desires for contraception and fertility. Options for menstrual suppression include combined hormonal contraceptives, progestin-only therapy, and gonadotropin-releasing hormone agonists. Adolescents presenting emergently with severe uterine bleeding may benefit from hormonal therapy, antifibrinolytics or, as a last resort, surgical management. In choosing appropriate treatment, considerations such as current platelet count, course of treatment, time to expected nadir, risk of thromboembolism, and need for contraception should be considered. Because of the complex nature of cancer care, collaboration with the adolescent's oncologist is highly recommended.

The diagnosis of cancer in females between the ages of 15 years and 19 years is rare, with an incidence of 20 cases per 100,000 individuals per year (1). Adolescents undergoing cancer treatment are at high risk of heavy menstrual bleeding as a direct result of hematologic malignancies or as a secondary effect of chemotherapy, radiation therapy, or bone marrow transplantation that induces myelosuppression that leads to thrombocytopenia. Even normal menstrual blood loss may pose a threat to adolescents who are already anemic from hematologic malignancies or cancer treatment. Disruption of the hypothalamic–pituitary–gonadal axis during cancer treatment also may cause anovulatory uterine bleeding. Gynecologists may, therefore, be consulted either before the initiation of cancer treatment to request strategies for menstrual suppression or during an episode of severe heavy bleeding to stop the bleeding emergently. Therapy in both situations should be tailored to the patient, her cancer diagnosis and treatment plan, and her desires for contraception and fertility. Because of the complex nature of cancer care, collaboration with the adolescent's oncologist is highly recommended.

Although several therapies for prophylactic menstrual suppression and emergency treatment of bleeding have been reported in the literature, data comparing the therapies are limited. Options for menstrual suppression include combined hormonal contraceptives, progestin-only therapy, and gonadotropin-releasing hormone (GnRH) agonists. Adolescents presenting emergently with severe uterine bleeding may benefit from hormonal therapy, antifibrinolytics or, as a last resort, surgical management. In choosing appropriate treatment, considerations such as current platelet count, course of treatment, time to expected nadir, risk of thromboembolism, and need for contraception should be considered.

Prophylactic Menstrual Suppression

Combined Hormonal Contraceptives
The results of one study indicate that combined estrogen–progesterone containing oral contraceptives (OCs) are effective in producing amenorrhea when used in a continuous fashion. Women aged 18–45 years who took 20-microgram ethinyl estradiol/100-microgram

levonorgestrel pills experienced light bleeding or amenorrhea by 3 months (68%) and 12 months (88%) of use (2). However, there are no equivalent studies to support this data in the adolescent population. The *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010* notes that when OCs are primarily used as therapy, rather than to prevent pregnancy, even in women where contraceptive use might be cautioned or contraindicated, the benefits from therapeutic use might outweigh the risks (3). The decision to use estrogen should be tailored to the individual patient after careful, collaborative consideration of the risk–benefit ratio; thorough counseling; and a commitment to close monitoring for known adverse effects.

In a study of 33 premenopausal females (age range from 14 years to 51 years) undergoing bone marrow transplants who also were treated for heavy menstrual bleeding, 18 patients were given either high-dose (50-microgram ethinyl estradiol pills) or standard-dose combined OCs as first-line therapy, and all but one had resolution of their symptoms (4). Although this study used OCs for the treatment of heavy menstrual bleeding rather than menstrual suppression, most females continued taking OCs with good control of bleeding during their cancer treatment. No adverse effects were reported related to OC use. Other authors, however, have observed increases in hyperbilirubinemia and hepatic venoocclusive disease in patients treated with OCs during bone marrow or stem cell transplant and caution against their use when alternatives are available (5–7). Use of other combined hormonal contraceptives, such as the vaginal ring or the contraceptive patch, may not be appropriate because of mucositis or skin reactions during cancer treatment (8). Progestin-only therapy may be more appropriate for patients who are not candidates for combined hormonal therapy.

Progestin-Only Therapy

Progestin-Only Pills

Suppression of menses by daily administration of oral progestins allows for decreased endometrial proliferation and prevention of menses. Breakthrough bleeding may occur because endometrial atrophy and estrogen supplementation may be needed. Progestin-only pills should be taken every day, with no hormone-free days. Options for progestin-only therapies are norethindrone acetate (5–15 mg/d), norethindrone (0.35 mg/d), and norgestrel (0.075 mg/d) (9).

Depot Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate (DMPA) is a long-acting, progestin-only contraceptive that inhibits ovulation and decreases endometrial proliferation. Use of DMPA results in relatively high rates of amenorrhea, approximately 50% by 1 year of treatment (10, 11). However, initial irregular bleeding with DMPA makes it less reliable for rapid therapeutic menstrual sup-

pression (12, 13). Although data on progestin-only methods used by women with cancer are limited, DMPA is classified as category 2, even among women with a history of venous thromboembolism and active cancer according to the *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010* (3); that is, the advantages of using the method generally outweigh the theoretic or proven risks.

Long-Acting, Reversible, Progestin-Only Therapies

Currently, there are no published data to support the use of the levonorgestrel-releasing intrauterine system (levonogestrel intrauterine device [IUD]) in adolescents undergoing cancer treatment; however, its efficacy in women with heavy menstrual bleeding who are immunocompromised has been well documented (14). Amenorrhea rates after 3 months of use in women aged 18–45 years with heavy menstrual bleeding were 32% in one series (15), although initial irregular bleeding may limit the use of the device for menstrual suppression. Insertion of the device for emergent treatment of excessive menstrual bleeding is not appropriate because expulsion rates are higher in women when experiencing heavy bleeding than in women when they are not menstruating (16). The etonogestrel single-rod contraceptive implant also has not been studied in this patient population. In an integrated analysis of 11 clinical trials, more than one half of 942 women aged 18–40 years using the etonogestrel implant reported infrequent bleeding or amenorrhea (17). Despite this, irregular bleeding was the most frequently cited reason for etonogestrel implant discontinuation (17). The inability to predict bleeding patterns limits insertion of the device for prophylactic menstrual suppression or treatment of heavy bleeding.

If an adolescent has had the levonorgestrel IUD or the etonogestrel single-rod implant inserted for contraception before her cancer diagnosis and has infrequent bleeding or amenorrhea, a reasonable strategy would be to continue the method for menstrual suppression.

Gonadotropin-Releasing Hormone Agonists

Leuprolide acetate is a synthetic GnRH agonist that acts as a potent inhibitor of gonadotropin release when given in therapeutic doses. After an initial flare-up that causes a transient increase in circulating gonadotropins and sex steroids, leuprolide acetate reliably causes a hypoestrogenic state in 2 weeks (18). According to a systematic review, leuprolide acetate given to women undergoing cancer treatment, results in an increased rate of amenorrhea from 73% to 96% (13). In a retrospective review of 101 females of reproductive age (12–51 years) undergoing myelosuppressive chemotherapy that compared pretreatment with leuprolide acetate (3.75-mg intramuscularly [IM], monthly), DMPA (150-mg IM, every 3 months), or placebo, no females who received leuprolide acetate had episodes of moderate to severe bleeding compared with 21.4% of females who used DMPA and 40% of untreated females (12).

The dose and timing of leuprolide acetate for menstrual suppression during cancer treatment is not well established but different regimens have been reported in the literature. Ideally, leuprolide acetate should be started before induction of myelosuppressive therapy and at least 4 weeks before the expected onset of thrombocytopenia because of the possibility of a subsequent bleeding episode. Bleeding may be expected for 2–3 weeks after the injection until hormone levels decrease and endometrial proliferation ceases (13, 19). Leuprolide acetate may be given in doses of 3.75-mg to 7.5-mg IM, monthly, or 11.25-mg to 22.5-mg IM, every 3 months (20, 21). The 3-month formulation decreases the risk of more frequent monthly injections that may be due at a time of treatment-induced thrombocytopenia. For adolescents who are already thrombocytopenic and for whom intramuscular injections are contraindicated, leuprolide acetate may be given as a subcutaneous injection of 3.75 mg/mo or the subcutaneous formulation may be given intravenously at a dose of 1 mg/d until platelet counts increase or administration of platelets allow for injection (19, 22, 23).

Treatment with leuprolide acetate may have advantages over other hormonal agents in patients with cancer because of a lower risk of thromboembolism. In addition, although there is some evidence that treatment with leuprolide acetate may preserve ovarian function after cancer treatment, the data are inconclusive (24); therefore, more research is required before leuprolide acetate can be recommended for fertility preservation (25).

Disadvantages of leuprolide acetate are expected adverse effects related to a low-estrogen state, including vasomotor symptoms and bone density loss. When leuprolide acetate is used to treat endometriosis in adolescents, hormonal add-back therapy with a progestin (such as norethindrone acetate, 5 mg), which has estrogenic properties, once daily, has been shown to preserve bone mass and significantly reduces vasomotor symptoms without increasing the rate of bleeding (26, 27). Given the safety of progestins in women with complex disease, add-back therapy is a rational strategy for mitigating the adverse effects of leuprolide acetate without reducing its efficacy (21, 23).

Emergent Treatment of Acute Uterine Bleeding

Some adolescents may present with life-threatening bleeding in the setting of a new cancer diagnosis, whereas others who are undergoing myelosuppressive treatment may not have the time to benefit from prophylactic menstrual suppression and need more urgent therapy once bleeding occurs. The optimal therapy for treatment of acute bleeding has not been established (28, 29). However, hormonal therapy has shown good results, including treatment with high (50 or more micrograms of ethinyl estradiol plus progestin) or standard-dose OCs, or transdermal or intravenous estrogen (see Fig. 1) (28). As in the case of menstrual suppression, estrogen therapy for acute bleeding should be balanced against the elevated risk of thromboembolism. For adolescents who have been given estrogen, therapy should continue with standard-dose OCs until platelet counts have recovered and withdrawal bleeding can occur. If there is a risk of recurrent bleeding due to the course of therapy, menstrual suppression with another agent, such as a GnRH agonist, should be strongly considered along with the treatment of acute bleeding.

Other hormonal therapies that might be used for menstrual suppression, such as leuprolide acetate, DMPA, the levonorgestrel IUD, and the etonogestrel implant are not appropriate for managing acute bleeding because the onset of action is delayed and, in some cases, the bleeding pattern is unpredictable. These therapies may be used in conjunction with therapy for acute bleeding in order to prevent future episodes of acute uterine bleeding.

Antifibrinolytics prevent fibrin degradation and decrease production of tissue plasminogen activator by endometrial cells or increase the rate of clearance. Oral tranexamic acid is approved by the U.S. Food and Drug Administration for the treatment of cyclic heavy menstrual bleeding. It is contraindicated in patients with active thromboembolic disease, a history of thrombosis or thromboembolism, or an intrinsic risk of thrombosis or thromboembolism (30). Some hematologists have experience using antifibrinolytic therapy for patients with bleeding disorders (eg, von Willebrand disease). Data regarding oncology patients are limited and contradictory. More information on the use of antifibrinolytics as adjuvant therapy for adolescents and oncology patients is needed.

There are insufficient data to provide recommendations on the appropriate management of acute uterine bleeding in adolescents with contraindications to estrogen use. In one series of 24 adolescents with acute uterine bleeding and anemia, oral medroxyprogesterone acetate at a dose of 60–120 mg (5 mg every 1–2 hours) for the first day and 20 mg daily thereafter for 10 days successfully controlled bleeding. Complete cessation of bleeding was noted in 25% of patients within the first 24 hours and in all patients by the fourth day of therapy (31). A similar regimen noted to be effective in adult women is a dose of 20 mg of medroxyprogesterone acetate three times a day for 7 days and 20 mg daily thereafter for 3 weeks (32, 33).

If medical treatment fails and the adolescent is faced with life-threatening hemorrhage, surgical management options may be considered, including dilation and curettage, uterine packing, tamponade with a Foley balloon, or uterine artery embolization. However, there is no evidence to support surgical intervention for acute uterine bleeding in adolescents, and consideration of these treatments is based on extrapolation from the literature on adult patients. Uterine artery embolization is not suitable as a first-line therapy given the effect on fertility, but may be a safe surgical alternative to hysterectomy in an acutely ill patient (34).
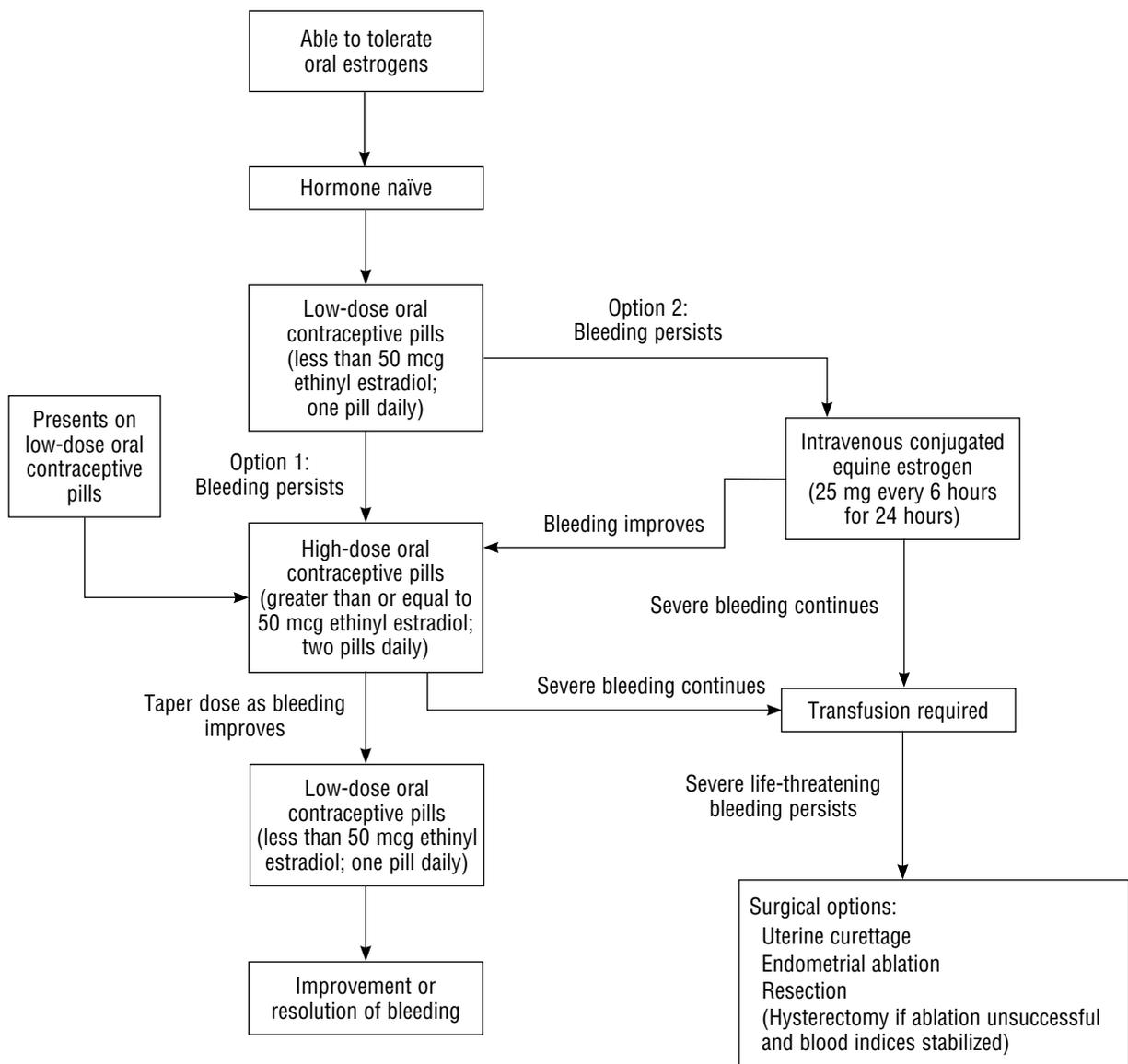
Fig. 1. Potential treatment algorithm for heavy menstrual bleeding in thrombocytopenia or myelosuppression for adolescents without contraindications to estrogen therapy. (Modified from Levens ED, Scheinberg P, DeCherney AH. Severe menorrhagia associated with thrombocytopenia. Obstet Gynecol 2007;110:913–7.) ⇐

Conclusion

Increased success in the management of oncology patients has led to increased survival rates and decreased morbidity. Addressing menstrual issues for adolescent patients undergoing cancer treatment is an important part of long-term management and will require collaborative involvement of obstetrician–gynecologists in the care of such patients.

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