Published in final edited form as:

Obstet Gynecol Surv. 2008 June ; 63(6): 395–405. doi:10.1097/OGX.0b013e3181706620.

Therapeutic Amenorrhea in Patients at Risk for Thrombocytopenia

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Abstract

To examine the need for and evaluate the method of menses suppression in women at risk for thrombocytopenia. A systematic review of the published literature in MEDLINE using the search terms thrombocytopenia, menorrhagia, therapeutic amenorrhea, progestin intrauterine device, combination oral contraceptive—extended and cyclic, gonadotropin releasing hormone agonist, danazol, and progestins. There are an increased number of reproductive age women at risk for thrombocytopenia who would benefit from menses suppression. A number of effective medical regimens are available. In patients who fail medical therapy, endometrial ablation appears to be effective in women with thrombocytopenia. As a result of the increased number of women at risk for thrombocytopenia, there is a need for therapeutic amenorrhea. The type of regimen selected depends upon the patients need for contraception and the ability to tolerate estrogen-containing medications. For women who fail medical therapy, there are surgical options, which are associated with less morbidity than hysterectomy.

Dysfunctional uterine bleeding is one of the most common complaints in the field of obstetrics and gynecology (1). The incidence of menorrhagia and abnormal uterine bleeding is about 5% in the general population (2), and a cause is identified in only 50% of affected individuals (3). Patients with thrombocytopenia are at particular risk for gynecologic bleeding complications. Almost half of patients with thrombocytopenia caused by current disease or treatment also have menorrhagia (4). Some studies have indicated that the incidence of women presenting to a physician complaining of menorrhagia who have a

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The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

The authors have disclosed that GnRH agonists (Lupron) has not been approved by the U.S. Food and Drug Administration for use in the treatment of menses suppression in patients with thrombocytopenia. Please consult product labeling for the approved usage of this drug.

Lippincott Continuing Medical Education Institute, Inc. has identified and resolved all faculty conflicts of interest regarding this educational activity.

coexisting inherited coagulation disorder is 17% to 20% (5,6). Uterine bleeding in this population can cause significant morbidity and require inpatient treatment and transfusion.

Thrombocytopenia in reproductive age women can result from a number of causes: a decrease in platelet production, an increase in the destruction of platelets, and iatrogenic effects of medications. Patients with leukemia, myelodysplastic syndrome, aplastic anemia, liver failure, or hereditary syndromes may have thrombocytopenia secondary to decreased platelet production. Patients with systemic lupus erythematosus (SLE), idiopathic thrombopenic purpura (ITP), or thrombotic thrombocytopenic purpura may have increased platelet destruction causing thrombocytopenia. Chemotherapy, radiotherapy, and hematopoietic stem cell transplantation/bone marrow transplantation (BMT) patients may have medication-induced thrombocytopenia. All of these causes of thrombocytopenia can lead to gynecologic bleeding complications, most often menorrhagia.

Von Willebrand disease is one of the most common inherited bleeding disorders. Other rare disorders like Glanzmann thrombasthenia, Bernard-Soulier syndrome, and factor VIII, X, XI deficiencies can also cause menorrhagia. These diagnoses should be considered when patients present with significant menorrhagia at the time of menarche so that preventative measures can be implemented before the onset of significant bleeding (5,6).

Like patients with inherited blood dyscrasias, patients with increased platelet destruction are also at risk for menorrhagia. Fifty-three percent of Lupus patients, for example, have been reported to have menstrual irregularities. Women with poorly controlled disease were at the greatest risk for menstrual abnormalities (7). Consistent with these findings, Silva et al demonstrated about a 50% incidence of menstrual irregularities, which also correlated to disease activity and the use of corticosteroids (8).

Treatment-related causes of thrombocytopenia are multiple and include chemotherapy, radiotherapy, and BMT. There are an estimated 670,000 new cancer cases in female patients expected in the United States in 2007 (9) of which 8% are under 40 years old (10). It appears that there is an increase in the number of young adults developing malignant disease (11) and an increase in overall survival rates over the last 30 years secondary to more effective treatment options. A consequence of the increase in disease rates and iatrogenic thrombocytopenia is an increased incidence of abnormal bleeding and an increased need for therapeutic menses suppression (4).

Iatrogenic thrombocytopenia can result in significant blood loss necessitating blood products, delaying chemotherapy, and decreasing the likelihood of an optimum treatment response (4). Menstrual suppression to prevent severe menorrhagia should be considered in these patients. It is most effective if it is initiated before chemotherapy, radiotherapy, and BMT treatment, and before the development of thrombocytopenia (12).

Symptomatic thrombocytopenia patients often require transfusion of platelets and other blood products. Multiple transfusions put the patient at risk for a number of complications, and compatible units can be increasingly hard to obtain (13,14). Complications of transfusions include febrile nonhemolytic reaction, viral and bacterial infection, acute hemolytic reaction, anaphylactic reaction, transfusion-associated acute lung injury, volume

and iron overload, and transfusion associated graft-versus-host disease. The most common adverse transfusion reaction is a febrile nonhemolytic reaction, which is clinically benign but problematic to the patient. Although the risk is small, the risk of hepatitis quoted in 1 European study is about 14 per million, human immunodeficiency virus (HIV) is 2 per million, and hepatitis C virus is 7 per million (15). The viral infection risk cited in U.S. studies is slightly lower with a risk of hepatitis B virus at 1 to 4 per million, and a risk of both HIV and hepatitis C virus at 0.5 to 2 per million (16,17). The rate of bacterial infection is higher and estimated at 1 per 50,000 risk with platelet transfusion and 1 per 500,000 risk with red blood cell transfusion (18). In patients that are expected to be thrombocytopenic, a method of medical prophylaxis—therapeutic amenorrhea—should be discussed with the patient before the initiation of therapy that is likely to result in thrombocytopenia.

METHODS OF MENSES SUPPRESSION

There are multiple medical and surgical options for the prevention of menorrhagia in patients with thrombocytopenia (Table 1). The choice of agents or surgical option is dependent upon the patient's need for contraception and her desire for future fertility. Some hormonal options that have been suggested for the treatment of menorrhagia in women with inherited bleeding disorders are combined oral contraceptives (OC), depo medroxyprogesterone (DMPA), levonorgesterol-releasing intrauterine device (IUD), danazol, and gonadotropin-releasing agonist (GnRH-a) (19). Many of the methods discussed in this review represent an unlabeled use of a Food and Drug Administration-approved commercial product and in some cases the product was used in the setting of a clinical investigation (Table 2).

Four prospective studies analyzed the treatment of menorrhagia or therapeutic suppression of menses in patients with hematologic disorders or undergoing treatment for malignant disease using levonorgestrel-releasing IUDs, GnRH-a, and GnRH-a with progestins. Kingman et al conducted a prospective study treating menorrhagia with the levonorgestrel-releasing IUD in 16 women with inherited bleeding disorders. After 9 months of follow-up, all women had lighter menses and hemoglobin concentrations increased significantly (20). Two studies analyzed the use of leuporelin acetate, or a GnRH-agonist, to prevent menstruation in women undergoing stem cell transplantation and myelosuppressive chemotherapy. One of the studies added progestin to the regimen to control heavy or breakthrough bleeding. Both studies concluded that the use of GnRH-a is a safe and effective way to prevent menstruation with minimal side effects (21,22).

Although the use of danazol has decreased as a result of its androgenic effects, there is evidence of its efficacy in treating thrombocytopenia. In a study of the use of danazol in refractory ITP patients, oral danazol was given to 25 adult females with metrorrhagia. All patients involved in the study had favorable results—48% attained platelet levels $>50 \times 10^9$ /Liter; 36% of patients had platelet levels $<50 \times 10^9$ /Liter, but no longer required the use of prednisone for abnormal bleeding. A total of 84% of the patients had amenorrhea or oligomenorrhea after 1 or 2 months of treatment. All patients had side effects of increases in body weight of 1 to 4 kg, acne, asthenia, myalgias, partial hair loss, and headaches. Although the authors suggest danazol as the first choice treatment in ITP affected females

who have menorrhagia, the androgenic side effects, and the availability of other options have limited its use (23).

Recent studies have analyzed the use of danazol to treat menorrhagia in women with myomas and have found it to be effective in inducing amenorrhea and improving bleeding symptoms (24,25). Danazol appears to be more effective than placebo, progestins, and combination OC, but causes more adverse effects in women with heavy menstrual bleeding (26). A double-blinded randomized study with danazol and DMPA showed that blood loss throughout treatment phases was significantly lower than baseline levels with either treatment option (27).

Another therapeutic treatment for menorrhagia mentioned previously is GnRH-a. The induced hypoestrogenism of GnRH-a may reduce episodes of menorrhagia. However, the main adverse effects associated with GnRH-a are severe bone loss and an unfavorable lipid profile. During a 3-month period, a bone loss of about 3% can be expected (28). Other side effects include menopausal symptoms such as vaginal dryness and hot flushes (29). Therefore, the main use of GnRH-a as a therapeutic agent in the management of menorrhagia is best suited for perimenopausal women or in preoperative patients who require menses suppression. If therapy for greater than a 6-month period is planned, add-back therapy with estrogen and progestins should be offered. The use of GnRH-a or GnRH-a and progestins has been evaluated in multiple retrospective studies. Meirou and colleagues compared the use of GnRH-a or DMPA to suppress menstruation in patients receiving myelosuppressive therapy with concurrent severe thrombocytopenia. Although GnRH-a was superior in reducing the occurrence of hypermenorrhea, both agents demonstrated a safe and effective method of preventing vaginal bleeding (4). These findings support the recommendations of other authors regarding the use of leuprolide to prevent hypermenorrhea. Ghalie et al recommend that the GnRH-a be initiated 2 weeks before the onset of thrombocytopenia in order to allow time for pituitary suppression and the induction of amenorrhea. Once thrombocytopenia occurs, the success rate is decreased (12).

An increasing number of women are candidates for menses suppression as a result of an increase in the indications for stem cell transplantation. The indications have been broadened to include treatment of some autoimmune diseases, such as refractory lupus nephritis and some malignancies (30). These patients are also at significant risk for thrombocytopenia, and are likely to benefit from therapeutic menses suppression. In a study of the management of uterine bleeding in hematopoietic stem cell transplantation, approximately 10% of patients suffered from menorrhagia, a mean of 12 days after stem cell infusion. Patients received high dose OC, standard dose OC, medroxyprogesterone + estrogen, medroxyprogesterone only, or transdermal estrogen. All but 1 patient had resolution of symptoms. Complications of the therapy must be considered in the choice of agents as oral preparations may be difficult to tolerate due to mucositis, nausea, emesis, or elevated bilirubin levels (31).

Like patients with iatrogenic thrombocytopenia, patients with hematologic disorders may require therapeutic amenorrhea. Kadir et al evaluated the use of combined OC in a review of the management of menorrhagia in women with blood dyscrasias. Combined OC were

shown to decrease menstrual blood loss by 43% similar to the effects of low-dose danazol. Cyclic progestins were less effective than progesterone IUD and danazol. GnRH-a, which appears to have the highest success rate, can be used with combination estrogen/progesterone (add-back therapy) for patients at risk for more severe blood loss that require prolonged treatment (32).

USE OF THE IUD IN MENSES SUPPRESSION

Although the effective use of the levonorgestrel IUD to treat menorrhagia has been documented in the gynecologic literature (33–38), this method is often not considered in neutropenic or immunosuppressed patients. Based on published reports, there is no evidence to suggest that immunosuppressed patients have an increased likelihood of febrile morbidity with IUD usage. Two prospective controlled clinical trials studied contraception and IUD used in SLE and HIV-1 patients. In a controlled clinical trial, 162 women with SLE were randomly assigned to combination OC, progestin only pills, or copper IUD contraceptive groups. There was no significant difference found among the treatment groups in global disease activity, incidence of flares, medication use, or severe infections. The study did not, however, provide laboratory documentation of the patient's immune status (39). In a controlled prospective clinical trial of HIV-1 infected women, complications of IUD usage were examined over a 4-month study period. Patients were stratified according to extent of disease. Overall, there was no difference between the groups, and severely infected individuals had a 0% co-infection rate; but the study was limited in selection bias and had inadequate power (40). One clinical commentary article considered IUDs a good contraceptive choice, especially when estrogen is contraindicated, and the authors did not find evidence that rates of infection were increased in immunosuppressed patients (41).

There were 2 case reports on the use of IUD in renal transplant patients. One of the studies reported pregnancies in 2 renal transplant patients who conceived with an IUD in place suggesting that immunosuppression may alter the action of IUD, reducing the efficacy and allowing conception to take place (42). In the second case report, a 43-year-old woman who was a renal transplantation patient with menorrhagia and need for treatment was reported. A levonorgestrel-releasing IUD was successful in elevating her hemoglobin from 5 gm/dL to a normal level with no evidence of infection (43). Patients in both studies were also able to avoid surgical treatment with hysterectomy or other methods, and the patients did not develop febrile complications.

The literature on IUD usage in immunosuppressed women is extremely limited. The information on IUD-associated pelvic inflammatory disease among nonimmunosuppressed women may be useful in the identification of the patients and clinical settings that have the greatest risk of pelvic infection. In a review of 12 randomized studies in nonimmunosuppressed individuals, the risk of pelvic inflammatory disease was greatest at the time and near the time of insertion. Infection rates decreased as time progressed. Infection rates were greater in younger women and women with fewer live births (44). Given the paucity of evidence in this area, the levonorgestrel IUD might be a consideration in patients who cannot take combination OC, and have a need for effective long-term contraception.

PATIENTS WHO ARE NOT CANDIDATES FOR ESTROGEN

The association of exogenous estrogen with increased hepatic production of coagulation factors and overall risk of venous thromboembolism has been well established (45). Certain patients, (those with a malignant diagnosis or an inherited coagulopathy) are at increased risk for this complication. The incidence of venous thromboembolism in patients with malignant disease ranges from 2% to 60% (46–49). As a result of the increased risk for thromboembolic complications, some oncologists are concerned about the use of OC and estrogens in patients with a malignant diagnosis. Because there is an increased risk of thromboembolism in healthy users of combination contraception, women with a disease-related increased risk of thromboembolism should consider a nonestrogen-containing method of contraception for menses suppression.

The World Health Organization offers a contraceptive risk assessment which is useful in the selection of methods of contraception and menses suppression. Women with known thrombogenic mutations, history of venous thromboembolism, or current thromboembolism should not use estrogen containing oral, transdermal, and transvaginal methods of contraception. General use of progestin only-containing IUD, implants, oral forms, injections, and the copper IUD is acceptable where the advantage of use outweighs the theoretical or proven risk (50). The American College of Obstetricians and Gynecologists has stated that women with a documented unexplained history of venous thromboembolism or thromboembolism associated with either pregnancy or exogenous estrogen use should not use combination contraceptive agents containing estrogen unless they are taking anticoagulants (45). In patients at increased risk for venous thromboembolism, estrogen containing contraception should not be used. Progestin only OC, injectable progestins, IUD, or implants are better options for these patients.

PATIENTS WITH HEPATIC DISEASE OR ABNORMAL LIVER FUNCTION TESTS

Hepatotoxicity is a complication of multiple chemotherapeutic agents; therefore, there is a risk of abnormal liver function tests and hepatic disease in patients receiving these agents. One study documented a 9.4% incidence of acute hepatotoxicity, measured with an elevation in alanine transaminase, in patients receiving doxorubicin and cyclophosphamide (51). Because contraceptive steroids alter hepatocellular function and use hepatic metabolism for clearance, estrogen-containing contraception is contraindicated in patients experiencing acute liver disease. Liver function tests should be followed until normalization before starting an estrogen-containing contraceptive (52,53).

Estrogen-containing contraceptives have also been discouraged in liver disease in the past to prevent the enhancement or the provocation of cholestasis (54). Although some have recommended the use of trans-dermal estrogen with or without the use of medroxyprogesterone in patients with abnormal liver function tests (31), the World Health Organization has recommended that estrogen use be contraindicated in active hepatitis, cirrhosis, and liver tumor patients. Exogenous estrogen can be used in hepatitis carriers. Progestin only contraception is also not recommended in patients with a liver tumor, severe

cirrhosis, or active hepatitis (50). American College of Obstetricians and Gynecologists has not made a statement on the use of contraception in women with hepatic disease or elevated liver function tests. Caution should be used when considering a hormonal contraceptive in hepatic disease—benefits should outweigh the risks.

PATIENTS PRESENTING WITH MENORRHAGIA

If patients do not receive treatment to suppress menses or fail initial therapy, there are multiple options for the treatment of menorrhagia. Continuous combination OC have been observed to be a well tolerated option to induce amenorrhea. Infrequent bleeding was decreased in 88% of individuals during a 1-year period. When the continuous regimen was initiated, there was an initial increase in irregular spotting which decreased as the year progressed (55). Using extended combination OC with 4 scheduled menses per year showed similar findings (56). A systematic review of the literature indicated that there is a significantly poorer control of menstrual bleeding with extension of tricyclic OC formulations. Overall, extended OC use reduces the amount of scheduled withdrawal bleeding, but increases the amount of unexpected breakthrough bleeding (57). Menorrhagia can also be treated with a monophasic pill using 1 pill twice daily for at least 5 to 7 days. In patients who have no contraindications to estrogen use, this is a safe and effective option for menses suppression. For emergent bleeding intervention, intravenous estrogen given at a dose of 25 mg every 4 to 6 hours for 24 hours or until bleeding stops has been shown to be effective (58).

NONMEDICAL OPTIONS FOR MENSES SUPPRESSION

There are a number of studies discussing the effectiveness of the levonorgestrel IUD in the treatment of menorrhagia. Hubacher et al conducted a review of the noncontraceptive health benefits of the IUD and found that idiopathic menorrhagia responded positively to treatment with the levonorgestrel IUD (59). After 3 to 12 months of treatment with the levonorgestrel IUD, Stewart et al found that there was a significant reduction in menorrhagia in all studies with the majority of investigations showing an increase in iron levels (60). Lahteenmaki et al found that with IUD treatment the amount of bleeding days decreased by more than 50% after 12 months—from 7 days to 2 days (61). Several studies found that IUD use reduces the amount of blood loss in menorrhagic women by 67% to 94% (62–64), and there was a significant increase in hemoglobin, serum iron, and ferritin levels (65). Some authors have argued that the levonorgestrel IUD is 1 of the most cost effective methods in the management of menorrhagia, both minimizing morbidity and preserving fertility (66). Hurskainen et al claim that 60% of women with heavy menstrual bleeding will avoid hysterectomy secondary to the IUD treatment modality (67). Thus, the levonorgestrel IUD is safe, cost effective, and efficient in reducing bleeding symptoms in women with menorrhagia.

FAILED MEDICAL THERAPY

When medical management fails, there are surgical options available to treat menorrhagia in women with thrombocytopenia. Historically, the main treatment option for menorrhagia was hysterectomy (68). Nearly 600,000 women undergo hysterectomy in the United States every

year (69). Patients with thrombocytopenia are at greater risk for the complications associated with surgical blood loss, and are not always reasonable candidates for hysterectomy. In a study of clinical outcomes and costs at 5 years post-treatment, the cost of the levonorgesterel-releasing intrauterine system was less than hysterectomy. Hurskainen et al found that although 42% of the patients receiving the levonorgesterel treatment ultimately had a hysterectomy, the costs in the levonorgesterel group were substantially lower and satisfaction was similar among both groups (33).

As 1 case report illustrates, some patients will require hysterectomy when medical therapy fails. One adolescent with Fechtner syndrome and 1 adolescent with factor VII deficiency with menorrhagia underwent hysterectomy after discontinuation of successful hormonal therapies (70). In patients without thrombocytopenia, hysterectomy has been associated with better general health, it is a more definitive treatment, and has fewer unwanted symptoms (71). However, hysterectomy may not be an option in women with thrombocytopenia who are at increased risk of intraoperative and postoperative bleeding and the associated complications.

A surgical option that should be considered in patients who are not candidates for hysterectomy is endometrial ablation. Global endometrial ablation was shown to be an effective method of treatment in 41 women with type I von Willebrand disease, acquired thrombocytopenia, and those receiving anti-coagulation treatment for thrombogenic disorders in 1 retrospective study. There was no difference found between the coagulopathy group and the control group in failed surgical therapy, time to treatment failure, or complications from therapy. The ferritin and hemoglobin levels were higher in both groups after treatment. Overall, endometrial ablation has minimal risk, and is a safe and effective treatment for menorrhagia in women with a coagulopathy (72). Ablation therapy may not be completely effective in all patients, and there are complications to therapy. The Aberdeen Endometrial Ablation Trials Group observed treatment outcomes 4 years after endometrial ablation, and found that 40% of women had some degree of treatment failure, thus needing further treatment (71). Pelvic pain is a complication of both ablation and hysterectomy with an incidence rate of 18% to 20% of individuals receiving ablation treatment and 15% of those receiving hysterectomy (71,73,74).

CONCLUSION

There are a number of reproductive age patients with underlying hematologic disorders and iatrogenic thrombocytopenia who would benefit from therapeutic menses suppression. The choice of agents is influenced by the patients need for contraception, desire for future fertility, and ability to tolerate estrogen containing medications. Patients who are at risk for thrombocytopenia should be assumed to be at risk for menorrhagia and options for menses suppression should be discussed with them before the onset of thrombocytopenia.

Acknowledgments

Supported, in part, by the intramural research program of the Reproductive Biology and Medicine Branch of NICHD, NIH.

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Learning Objectives

After completion of this article, the reader should be able to identify the causes of menorrhagia due to illness or iatrogenic cause of thrombocytopenia or platelet dysfunction, describe several options for managing menorrhagia in these women, and list the side effects of these various treatment options.

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TABLE 1

Treatment of thrombocytopenic women at risk for menorrhagia

Article*	Design	Population	N	Agent	Most Effective
Ambriz et al	Prospective	ITP	25	Danazol	Danazol
Amsterdam et al	Retrospective	Stem cell transplantation	33	High dose OC or standard dose OC or medroxyprogesterone + estrogen or transdermal estrogen	High dose OC 1st line Tx and prophyllactic standard dose OC
Chiusolo et al	Prospective	Stem cell transplantation	30	Leuporelin	Leuporelin
Ghalie et al	Retrospective	Bone marrow transplantation	34	Leuprolide	Leuprolide
Kingman et al	Prospective pilot	Inherited bleeding disorders	16	Levonorgestrel-releasing IUD	Levonorgestrel-releasing IUD
Lhomme et al	Prospective	Chemotherapy or radiotherapy treatment	20	Leuporelin	Leuporelin
Meirow et al	Retrospective	Oncology patients with treatment induced thrombocytopenia	101	Luteinizing hormone-releasing Hormone agonist or DMPA	Both effective Luteinizing hormone-releasing Hormone agonist more effective
Kadir et al	Review	Von Willenbrands disease and Menorrhagia patients	131	Combination OC	All effective in non-VWD
			988	Cyclic progestogens Danazol GnRH-a Levonorgestrel IUDz	OC and IUD effective in VWD Danazol, GnRH-a, cyclic progestogen not studied

* List of articles that discuss the treatment of thrombocytopenic women who are at risk for menorrhagia.

TABLE 2

Methods of menses suppression

Treatment Options	Menses Suppression	Effective Contraception
Combination estrogen + progesterone	Combination OC	Yes
Progestin IUD	Levonorgestrel IUD	Yes
Progestin-only pills	Progesterone only pill	Yes
Injectables	DMPA	Yes
GnRH-a *	Leuprorelin	Yes
Androgen therapy *	Danazol	Yes

* Not FDA approved for the indication of contraception.