

MEDICAL MANAGEMENT OF MENORRHAGIA

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Abstract : One-third of all women experience heavy menstrual bleeding or menorrhagia at some point in their life and about fifty to eighty per cent of these women have no detectable pathology, genital or extragenital. The aim of therapy in these cases is to reduce blood loss, reduce the risk of anemia and improve quality of life. Medical treatment is the mainstay of treatment in the younger age group and is the initial choice in older women with no demonstrable pathology. Medical management involves non- hormonal and hormonal agents and include non-steroidal antiinflammatory drugs (NSAIDS), antifibrinolytics, progestins, estrogens, combined oral contraceptives, androgens and GnRH analogues. Non hormonal treatment, mefenamic acid and tranexamic acid is generally tried first and are effective in reducing blood loss by about 20 to 50% respectively. Progestational agents are indicated in anovulatory menorrhagia and endometrial hyperplasia. Oral contraceptives reduce the blood loss by 50% and regularize the cycles as well. GnRH analogues are very effective in controlling menorrhagia but are not the first line treatment because of the hypoestrogenic side effects. In order to make drug therapy successful, it is important to individualize the approach to management and involve the patient in this process. More than the measures of bleeding, that is, the duration, frequency, and volume, the degree of patient satisfaction may be influenced by factors such as cost, inconvenience, and treatment side effects. Effective medical treatments are available and have the potential to reduce the need for surgical interventions to a large extent.

INTRODUCTION

Menorrhagia, also known as heavy menstrual bleeding (HMB), is defined as a menstrual blood loss greater than 80 ml per cycle. One-third of all women experience heavy menstrual bleeding at some point in their life especially during adolescence and before menopause. About fifty to eighty per cent of women presenting with HMB have no demonstrable pathology, genital or extragenital. Acute menorrhagia may present as an emergency requiring prompt medical or surgical intervention. Chronic menorrhagia can lead to anemia and affects a woman's quality of life in her work, family, and social interactions. The aims of therapy are to reduce blood loss, reduce the risk of anaemia and improve quality of life. Four types of treatments are available for menorrhagia - medical therapy, levonorgestrel-releasing intrauterine system (LNG-IUS), endometrial resection or ablation and hysterectomy. In every age group, medical treatment is the initial choice and is especially indicated when there is no obvious pelvic abnormality. It is the mainstay of treatment in younger women. In elderly women, surgical treatment by endometrial destruction or hysterectomy is sometimes required. Medical management involves non-hormonal and hormonal agents. Non-hormonal treatment is given during menstruation itself and should be the first line in these women. Non hormonal options include nonsteroidal antiinflammatory drugs (NSAIDS) and antifibrinolytics. Hormonal agents include progestins, estrogens, combined oral contraceptives, androgens and GnRH analogues. General measures including reassurance and hematinics have to be initiated with any form of therapy. In order to make drug therapy successful, it is as important to individualize the approach to management and involve the patient in this process. However, there is considerable variation in practice and lack of consensus regarding the most effective therapy. Also poor compliance and unpleasant side effects have limited the satisfaction rates associated with medical therapy. Increased use of effective medical therapies has the potential to reduce the number of surgical procedures, such as endometrial ablation and hysterectomy. This

part of the review focuses on which drug to use and when and recent studies and developments regarding the drug treatment of heavy menstrual bleeding.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Nonsteroidal anti-inflammatory drugs or cyclooxygenase inhibitors are the most thoroughly investigated agents for medical treatment of abnormal uterine bleeding and bring about a reduction in mean menstrual blood loss of about 20%.¹ They also improve dysmenorrhea in up to 70 percent of patients.² Furthermore, these are also effective in women with a copper or non-hormonal intrauterine contraceptive device. NSAIDS act through the inhibition of endometrial prostaglandins.³ Women with ovulatory HMB, have relatively high levels of vasodilating prostaglandins such as PGE2 and PGI2 and therefore, experience therapeutic benefit secondary to reductions in the local levels of these compounds.⁴ The demonstrated involvement of prostaglandins in the genesis of menorrhagia points to cyclooxygenase inhibitors as a potentially effective treatment. Cyclooxygenase inhibitors, commonly referred to as non-steroidal anti-inflammatory drugs (NSAIDs), can be chemically classified into two main groups - COX-1 inhibitors which include aspirin, indomethacin, naproxen, ibuprofen, mefenamic acid, flufenamic acid, and meclofenamic acid. COX-2 inhibitors include celecoxib. Mefenamic acid is most commonly prescribed and is started on the first day of menses and continued for 5 days or until the cessation of menstruation. Usual dose is 500 mg, 2 to 4 times daily. Common side effects of NSAIDs are gastrointestinal irritation and inhibition of platelet aggregation. These agents are the first line treatment for most of the cases and are often preferred to estrogen-progesterone preparations.

ANTIFIBRINOLYTICS

The most commonly prescribed antifibrinolytic agent is the plasminogen activator inhibitor tranexamic acid. It is the mainstay

for the treatment of ovulatory HMB in most parts of the world. It is administered in a dose of 1 g every 6 hours for the first 4 or 5 days of the cycle and has been found to be associated with a reduction in bleeding volume from 40% to 60% in most women.⁵ Side effects include nausea and leg cramps. Most studies have demonstrated a favourable side-effect profile with no increased incidence of gastrointestinal effects or thrombogenic events.^{6,7} But there is a possibility of the potential to cause adverse effects on the cardiovascular system (myocardial infarction) which has been highlighted by a case report, especially when used along with combined oral contraceptive pill but it needs to be evaluated further.⁸

PROGESTINS

Oral progestogens have been the most commonly prescribed hormonal agents for menorrhagia. These are very effective in cases of anovulatory dysfunctional uterine bleeding. They halt the endometrial growth and allow for an organized sloughing of the endometrium. Progestins are able to induce a secretory transformation in otherwise estrogen-stimulated proliferative endometrium.⁹ They also increase the PGF₂-[alpha]/PGE ratio by stimulating arachidonic acid formation in the endometrium, which may also contribute to decreasing abnormal uterine bleeding.¹⁰ Progestagenic agents may be administered via a variety of routes and dose schedules, ranging from intermittent luteal phase or continuous oral administration, through intramuscular injection, or through continuous local administration via a levonorgestrel releasing intrauterine system¹¹.

These are specifically indicated in women with anovulatory bleeding.¹² and have been shown to reduce both the amount and duration of uterine bleeding.

For the **anovulatory type** of dysfunctional uterine bleeding presenting with acute haemorrhage high doses of progestogens are given. *Norethisterone acetate* which has a better hemostatic effect is administered in a dose of 10 mg two to three times per day depending upon the amount of bleeding and tapered down to 10 mg twice daily after about three days when the bleeding reduces and is continued in a dose of 10 mg daily for a total of 21 days. Withdrawal bleeding which is not excessive occurs after about 48 hours. Instead of norethisterone, *medroxyprogesterone acetate* (MPA) or *dydrogestrone* can be given in a similar fashion. For long term management in these women or for women presenting with not so severe bleeding, progestational agents mentioned above may be administered from 16th to 25th day of the cycle for 3 to 6 cycles. Withdrawal bleeding follows after cessation of treatment each month and approximately 50% of the women demonstrating improved cycle control.¹³

On the other hand for **ovulatory menorrhagia**, progestins given in the luteal phase of the menstrual cycle are not effective and need to be administered for 21 days from day 5 to day 25 for reducing menorrhagia in these women.¹⁴ Cyclic therapy is given for 3-6 cycles after which treatment is discontinued and the response is assessed.

In cases of menorrhagia progestins are administered continuously for about three to six cycles in women with endometrial hyperplasia on endometrial biopsy. A repeat biopsy is taken after completion of treatment to check for resolution of the pathology. Common *progestin side effects* include breast tenderness, weight gain, bloatedness and headaches.

The parenterally administered long-acting contraceptive agent depot medroxy progesterone acetate reduces menstrual blood loss. However, due to a high rate of adverse effects and concerns regarding the long-term effects on bone density¹⁵, they are a less favourable option for treatment of menorrhagia in women not requiring contraception.¹⁶

COMBINED ESTROGEN AND PROGESTERONE

Combined oral contraceptive pills (COC) can be used to reduce heavy menstrual bleeding in women with either anovulatory or ovulatory menorrhagia. COC's induce endometrial atrophy which results in reduction of blood loss.¹⁷ A randomized controlled trial of women taking an OC containing 30 µg ethinyl estradiol showed a 43 percent reduction in menstrual blood loss compared to baseline.¹⁸ Use of the COC pill has the additional advantage of reducing the symptoms of dysmenorrhea, providing contraception, cycle control with reduced withdrawal bleeding episodes, hormone replacement in the perimenopausal phase and protection from endometrial and ovarian cancer by about 50%.¹⁹ The presence of uterine myomas, which are estrogen-dependent, is not a contraindication for COC use.²⁰ Disadvantages of combination therapy include the need for strict daily use and systemic side effects.²¹ Combined oral contraceptives can be safely used in nonsmoking women over 35 who do not have risk factors for cardiovascular disease.²² Smoking, age above 35, a personal or family history of thromboembolic disease, and certain other medical conditions like uncontrolled diabetes and hypertension are contraindications to the use of oral contraceptives.

Use of high dose oral contraceptives may be considered in patients having heavy menstrual flow and becoming anemic. In these cases four pills containing 30-35 mcg ethinyl estradiol for 4 days are given followed by 3 pills for 3 days followed by 2 pills for 3 days and then one pill a day thereafter. effects This dose is then continued for 3 weeks which is followed by withdrawal bleeding on stoppage. At this point COC's may be stopped or continued for cycle control for 3 to 6 cycles

High dose OCPs give rise to nausea and vomiting and prior anti emetic reduces these unpleasant side effects.

ESTROGENS

High-dose estrogen therapy in the intravenous (IV) or oral form is useful in controlling acute bleeding episodes when the endometrium is thin, because it promotes rapid endometrial growth to cover denuded endometrial surfaces. Conjugated equine estrogen is used in the dose of 25 mg IV every 4 hours for up to 3 doses. Once bleeding has decreased it can be changed to oral estrogens 2.5 mg conjugated estrogen or 2 mg of micronized estadiol every 4 hours for 24 hours followed by a single dose daily for 14 to 21 days. In last 7 to 10 days medroxy progesterone acetate 10 mg once a day is added. Bleeding following withdrawal of estrogen and progesterone mimics normal menstruation.

ANDROGENS

Danazol is an isooxazole derivative of 17[alpha]-ethinyltestosterone. It suppresses ovulation and reduces ovarian production of 17-[beta]-estradiol. It also has direct effects on estrogen receptors in the endometrium and causes endometrial atrophy. Although in a Cochrane systematic review on the use

of danazol in the treatment of DUB, the authors concluded that danazol appears to be more effective than placebo, progestins, NSAIDs, and COCs in reducing heavy menstrual blood loss²³ it is generally not used because of its androgenic side effects. Reduction of menstrual blood loss by up to 80 percent^{24,24} Lamb MP. Danazol in menorrhagia: A double blind placebo controlled is reported. Following danazol therapy, 20 percent of patients reported amenorrhea and 70 percent reported oligomenorrhea. The recommended treatment is 100 to 200 mg daily for three months.²⁵ Danazol was also noted to have more adverse events like weight gain, oily skin, and acne compared to NSAIDs (odds ratio [OR] 7.0; 95% confidence interval [CI] 1.7-28.2) and progestins (OR 4.05; 95% CI 1.6-10.2); however, adherence to treatment was not affected. Thus danazol is effective for reducing heavy menstrual bleeding, but significant side effects limit its clinical use to short-term management of patient in whom estrogen progestin and anti-fibrinolytics are contraindicated or not effective.

GnRH AGONISTS

Gonadotropin-releasing hormone (GnRH) agonists are very effective in controlling menorrhagia but are not the first line treatment because of its hypoestrogenic side effects. It is specially useful in intractable menorrhagia and in severely anemic women as it gives time to build her up.

GnRH analogues are administered intramuscularly, subcutaneously, or by intranasal route. The common agents used include goserelin 3.6 mg subcutaneous every 28 days, leuprorelin acetate 3.75 mg every 28 days subcutaneous or intramuscular and triptorelin 3 mg every 28 days intramuscular. When administered continuously, GnRH agonists reversibly suppress pituitary secretion of gonadotropins and create a hypoestrogenic state leading to endometrial atrophy and amenorrhea. They may be helpful for short term use in inducing amenorrhea and allowing women to rebuild their red cell mass prior to surgery as bleeding recurs once treatment is stopped. These drugs have mainly been used in fibroid associated bleeding to bring about a reduction in the size of the fibroid. Their use has also been described for women with heavy menstrual bleeding, leading to a significant decrease in bleeding volume and length of menstruation.²⁶ However, there are some significant disadvantages to the use of GnRH analogs which include rapid bone demineralization associated with estrogen suppression, hot flashes and vaginal dryness after 6 months of use.²⁷ Add back therapy with conjugated estrogen 0.625 mg and medroxyprogesterone 2.5 mg daily is effective in preventing the hypoestrogenic symptoms. Thus though GnRH agonists are effective in reducing mean blood loss associated with DUB, it is limited to short-term use because of significant side effects and cost.

DESMOPRESSIN (DDAVP)

DDAVP is a vasopressin analogue and it has a role in the management of small subset of patients with type 1 von-Willebrand disease and hemophilia A presenting with menorrhagia. It is available as intravenous, subcutaneous injection and intranasal spray. It causes an increase in plasma concentration of factor VIII and von-Willebrand factor. Side effects include mild tachycardia, headache, flushing, hyponatremia and water intoxication. Patients need to be advised strict fluid restriction

and electrolyte monitoring for those who require several doses. It is usually given in the first 2 to 3 days of the periods but the dose and duration can be tailored according to the menstrual pattern of the patients. It can be used along with antifibrinolytics.

CONCLUSION

Effective medical treatment is available for the management of menorrhagia. Depending on the underlying abnormality and the needs of patient the most appropriate medical management can be chosen for the woman with reasonably good response

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