Menorrhagia and the Levonorgestrel Intrauterine System

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1. Introduction
1.1 Menorrhagia

Heavy menstrual bleeding can be defined as excessive blood loss which interferes with a woman’s physical, emotional, social and material quality of life. It is a subjective complaint by a woman of heavy periods. Menorrhagia on the other hand is an objective diagnosis of blood loss over 80 millilitres over several consecutive cycles.

The average blood loss in a Caucasian female population is approximately 30-40 millilitres per menstrual flow (Cole et al. 1971; Hallberg et al. 1966), the majority of which is lost in the first forty eight hours. Menorrhagia is the commonest cause of iron deficiency anaemia in women in the developed world and occurs in sixty per cent of women with objective menorrhagia.

1.2 Significance

Only half of the women who present to clinicians with heavy menstrual loss have objective menorrhagia. However, it is the main reason for women requesting hysterectomy and 1 in 5 women have a hysterectomy in the United Kingdom for this reason by the age of fifty five. At histopathology, a vast majority of these uteri are found to be benign. With less invasive and effective alternatives to hysterectomy, women should be carefully counselled with regards to morbidity and mortality associated with this major operation.

Menstrual disorders are now more common than they were a century ago because modern career women are choosing to have smaller or no families and not breastfeeding. Menorrhagia affects about 1.5 million women in England and Wales and accounts for twenty per cent of all gynaecology referrals to the outpatient clinic (Census 2001.2002).

1.3 Pathophysiology

A majority of cases of menorrhagia have no identifiable cause and hence are described as ‘dysfunctional’. Dysfunctional uterine bleeding is associated with anovulation and occurs in a fifth of women at extremes of their reproductive life.

Menorrhagia is also associated with uterine fibroids, endometrial polyps, adenomyosis, pelvic infection, bleeding diathesis, and rarely malignancies like endometrial cancer. Over a half of women with blood loss over 200 millilitres will have underlying fibroids.
The exact mechanism of menorrhagia is poorly understood. It is thought to result from increased activity of prostaglandins or the endometrial fibrinolytic activity. There is an elevation of prostaglandins (PGE2 and PGF2α) in the endometrium of women with menorrhagia, suggesting that menorrhagia may result from an increase in vasodilator PGE2 as compared to vasoconstrictor PGF2α prostaglandins (Smith et al. 1981).

The endometrium also contains a fibrinolytic system whose activity is increased in women with menorrhagia compared to those with normal menstrual loss.

1.4 Causes of menorrhagia

Although no cause can be found in most cases, other causes of menorrhagia such as uterine pathology and medical disorders (Table 1) should be actively sought and excluded.

<table>
<thead>
<tr>
<th>Dysfunctional uterine bleeding (DUB)</th>
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<tr>
<td>Uterine pathology</td>
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<tr>
<td>Medical disorders including thyroid or bleeding disorders</td>
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Table 1. Causes of heavy periods

1.4.1 Dysfunctional uterine bleeding

Dysfunctional uterine bleeding is a diagnosis of exclusion, when no other cause of bleeding can be found. Some people further sub-classify it into ovulatory and anovulatory bleeding although this does not have much clinical relevance. Ovulatory or ‘idiopathic’ bleeding is where periods are regular while anovulatory bleeding tends to occur at the extremes of the reproductive age.

In ovulatory cycles, bleeding results from the withdrawal of progesterone. It is typically painful and characterized by a cramping sensation. Anovulatory bleeding is caused by excessive proliferation of endometrium due to unopposed oestrogen. The absence of prostaglandins in the endometrium, which is usually synthesized in response to progesterone, may explain the absence of pain/cramps.

1.4.2 Uterine abnormalities

Fibroids are benign whorls of smooth muscle and collagen. They usually present in multiples and can grow to enormous sizes. They occur in a fifth of women and are commoner in women of the Afro-Caribbean origin. They occur in the uterine body or cervix and can be submucosal, intramural or subserosal.

The clinical signs and symptoms depend on their site and size. Symptoms include heavy periods, infertility, miscarriage or dyspareunia. They may cause pain in pregnancy due to red degeneration. When large they can cause pressure effects on surrounding organs and may present with urinary frequency, hydronephrosis and recurrent urinary tract infections. Only less than 0.1% of fibroids undergo malignant change resulting in leiomyosarcoma.

Polyps are localized growths of the endometrium which comprise of fibrous tissue surrounded by columnar epithelium. It is thought that they arise from disordered apoptosis and regrowth of the endometrium. Malignant change is extremely rare.
1.4.3 Medical causes

In rare cases, menorrhagia can occur as a result of systemic diseases which result in hepatic and renal impairment although amenorrhea is common with end stage disease. Both hypo and hyperthyroidism can also cause heavy menstruation.

Bleeding disorders like von Willebrand’s disease or platelet defects are associated with menorrhagia.

1.5 Diagnosis

1.5.1 History

The diagnosis of menorrhagia is often made on history alone. This will take into account the severity of the complaint as judged by the presence of clots or how frequently a woman changes pads or sanitary towels, or if a woman uses both as ‘double protection’. Efforts should be made to find out the impact of the bleeding on the woman’s quality of life including time taken off work, avoidance of usual activities, embarrassment as well as the effect of anaemic symptoms and treatment.

A full obstetric and gynaecological history should include the woman’s general health, weight and height (body mass index), number of deliveries, pregnancy losses and cervical smears. The presence of other symptoms such as dyspareunia may point to a specific cause.

Drug history including tamoxifen use and a history of bleeding tendency are also important. Previous pelvic surgery and associated findings should be noted as well as past history of polycystic disease, hormonal usage, bowels or ovarian cancer.

1.5.2 Examination

This is aimed at assessing the general state, diagnosing anaemia and identifying possible causes of menorrhagia. It should therefore entail vital signs, inspection of mucous membranes, finger nails and abdominal palpation. A speculum assessment should be done to look for vaginal and cervical abnormalities. A bimanual pelvic examination will assess the size of the uterus, presence of adnexal mass and/or signs of a pelvic infection.

1.5.3 Investigations

A full blood count is useful to determine haemoglobin level and can be used to monitor treatment with haematinics. Thyroid function tests, coagulation defects, liver and kidney function tests should be done if clinically indicated.

An ultrasound scan of the pelvis and abdomen is a useful tool in diagnosis and for describing masses suspected or actually found on physical examination, especially in obese women where examination can be suboptimal. It is not usually required if uterine size is less than 10 weeks and there is no suspicion of other pathology. It is also justifiable after failure of medical treatment of heavy periods.

Cervical smear should be undertaken if screening is not up to date or where the cervix looks suspicious. Similarly an endometrial biopsy should be taken if a woman is over 40 or under 40 with particular risk factors like tamoxifen use, unopposed oestrogen or obesity.
1.6 Treatment of menorrhagia

1.6.1 Medical

Several medical options are available for treatment of women with heavy menstrual loss. Non-steroidal anti-inflammatory drugs act by inhibiting prostaglandin synthesis and reduce bleeding by about a quarter. The commonest used medication is mafenamic acid of which the main side effect is dyspepsia.

Tranexamic acid is an anti-fibrinolytic medication. It inhibits plasminogen activator and hence promotes clots formation in spiral arterioles and decreases bleeding by about a half. Side effects include nausea, vomiting, diarrhoea and rarely tinnitus and thromboembolic events. Hypotension may occur if given rapidly by the intravenous route.

The combined oral contraceptive pill makes periods regular and is associated with a fifty per cent reduction in blood loss. It is suitable for all age groups unless there are specific contraindications like family or personal thromboembolic disease, migraines with aura, hypertension, obesity and immobility.

Oral progesterones act by ovulation inhibition and directly suppressing the endometrium. Norethisterone 5mg three times a day from day 5 to 26 has been shown to reduce blood loss by eighty per cent. Depo-Provera may cause unpredictable bleeding initially but usually amenorrhea results. Common side effects include nausea, breast tenderness, bloatedness, weight gain, acne and voice changes.

<table>
<thead>
<tr>
<th>Non-steroidal anti-inflammatory drugs e.g. Mefenamic acid</th>
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<tr>
<td>Anti-fibrinolytic drugs e.g. tranexamic acid</td>
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<tr>
<td>Hormones</td>
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<td>Combined contraceptive pill</td>
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<tr>
<td>Synthetic progestogens (norethisterone, provera, medroxyprogesterone acetate)</td>
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<tr>
<td>Intrauterine progesterone (levornogetrel intrauterine system)</td>
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<td>Danazol and gestrinone</td>
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<td>Anti-oestrogen e.g. gestrinone</td>
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<td>Gonadotrophin releasing hormone agonists</td>
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Table 2. Medical treatment of menorrhagia

Gonadotrophin releasing hormone analogues act by down-regulating the pituitary hence inhibiting ovarian activity. Women become hypo-oestrogenised and may have distressing vasomotor symptoms of hot flushes and night sweats as well as vaginal dryness. They also cause demineralization of bones. Add-back hormone replacement therapy as well as bone mineral density scans should be considered if treatment goes beyond six months.

Danazol was originally produced for treatment of endometriosis but was found to cause amenorrhea. It is a synthetic androgen which has both oestrogenic and progestrogenic effects. It works by inhibiting the pituitary and also suppressing the endometrium directly. It has debilitating androgenic effects which restrict its use including acne, deep voice, hirsutism, breast tenderness and weight gain.
Gestrinone on the other hand, is a synthetic derivative of 19-nortestosterone which has both oestrogenic and progestogenic as well as androgenic effects. It is not commonly used for treatment of heavy periods. Its androgenic side effects are less than danazol but after cessation of use, bleeding can become heavy again.

The levonorgestrel intrauterine system is a medicated device that is inserted into the uterus and delivers progesterone which acts locally on the endometrium to cause thinning and amenorrhea. It is covered in more details in the second part of this chapter.

1.6.2 Surgical treatment

Endometrial destructive techniques can be divided into first and second generation. The former involve hysteroscopic destruction of the endometrium by rollerball, transcervical endometrial resection or laser ablation.

The cumulative hysterectomy rate after endometrial resection was found in one study to be 27.4 per cent after four years (Poorey et al., 1998).

Endometrial resection is associated with a long surgical learning curve and significant risks include uterine perforation and fluid overload resulting in hyponatremia. They have generally been superseded by second generation techniques which are quicker and safer.

| First generation       | Roller ball              |
|                       | Trans-cervical resection |
|                       | Laser ablation           |

| Second generation      | Thermal balloon ablation |
|                       | Microwave ablation       |
|                       | Novasure ablation        |

| Hysterectomy           | Total                    |
|                       | Subtotal                 |

Table 3. Different modalities of surgical treatment

Second generation endometrial ablation techniques aim to destroy the endometrium with resultant amenorrhea. They do not involve direct visualization of the endometrium. Techniques include thermal balloon, microwave or novasure endometrial ablation.

In practice, although patient satisfaction rates are over 70 per cent, the amenorrhea rate is less than 30 per cent (Lethaby et al., 2001). These are more successful in women over 45. The procedure can be repeated in women with persistent heavy menstrual bleeding after assessing the cavity hysteroscopically.

Rare complications include uterine perforation and accidental organ injury. Effective contraception is essential following endometrial ablation.

Hysterectomy remains the only method of ensuring complete amenorrhea and is generally offered to women where all other methods have been unsuccessful. It can be undertaken laparoscopically, vaginally or abdominally. The choice depends on the size of uterus, degree of uterine descent, previous surgery, whether ovaries are to be conserved, patient preference and surgeon's skills.
1.6.3 Specific treatment

Organic causes of heavy bleeding should be addressed. These include fibroids which can be resected hysteroscopically or by laparotomy or a laparoscopic approach if a patient wants to preserve fertility. In these cases, women should be warned of the risk of significant intra-operative bleeding necessitating blood transfusion and the possibility of an emergency hysterectomy.

Polyps can be removed at out patient hysteroscopy or in theatre under a general anaesthetic. Where malignancy is suspected, appropriate biopsies and referral should be made to the multidisciplinary team.

2. Medicated Intrauterine system

2.1 Background

The levonorgestrel intrauterine system is a reversible long acting contraceptive device that is aseptically fitted into the uterine cavity. It has a hormone cylinder that contains 52 mg of levonorgestrel that is released at the rate of twenty micrograms per day.

The term intrauterine system (IUS) is used to differentiate it from the intrauterine contraceptive device (IUCD) in the United Kingdom.

It was primarily produced as a contraceptive device but has other non-contraceptive benefits. It can be beneficial in the management of chronic pelvic pain, endometriosis, anaemia, dysmenorrhoea, and endometrial protection in women on oestrogen hormone replacement therapy.

Over one hundred and fifty million women worldwide use the intrauterine system for contraception. It is easy to insert and remove and does not require high level of technical skills. It is licensed for contraception use for up to 5 years following which a replacement can be made.

It can be inserted at any time of the cycle and during caesarean section (Lopez-Farfan, Maciel-Martinez, Velez-Machorro, & Vazquez-Estrada, 2010). It is useful in the peri and postmenopausal woman for bleeding, contraception and hormone replacement therapy (Kirk & McFall, 2009).

It is also widely used for menorrhagia. Its therapeutic effect is achieved by endometrial atrophy with a subsequent reduction in the heaviness of menstrual loss of eighty per cent in the first 6 months and up to 90 per cent in a year (Irvine et al., 1999, Hallberg et al., 1966, Stewart, et al., 2001).

Studies show that it is highly acceptable with 40 % women choosing to have a second device inserted after five years (Lete et al., 2011).

2.2 Comparison with other treatments of menorrhagia

Its effect on heavy menstrual loss has been compared to alternatives in clinical practice. It has been found to be more successful than cyclical norethisterone (given from day 5-26 of
the menstrual cycle) in treating women with dysfunctional uterine bleeding although it was associated with more side effects such as breast tenderness and intermenstrual bleeding (Lethaby et al., 2010).

In comparison with tranexamic acid and non-steroidal anti-inflammatory drugs, it has been found to be superior in reducing menstrual loss (Stewart et al., 2001).

The intrauterine system has been proved to be effective in over 85% of patients with simple endometrial hyperplasia although the authors recommend long term follow up with periodic biopsies for up to 2 years (Scarselli et al., 2011).

When compared with thermal balloon endometrial ablation, no difference was noted in the quality of life, number of women requesting alternative treatment, or satisfaction between the two groups (Busfield et al., 2006). Both groups however showed an improvement in quality of life although patients with the intrauterine system recorded lower PBAC (Pictorial Blood loss Assessment Chart) scores at 12 and 24 months.

Compared to trans-cervical resection of endometrial (TCRE), satisfaction rates were both 80% in one study (Gupta, 2006) although intrauterine system requires less skill with no operative hazards. Continuation rates at five years were high with reasons sited in one study being bleeding, pain and infection (Backman et al., 2001).

It can be used successfully in selected women with coexisting morbidities. These include leiomyomas, obesity and those on anticoagulation therapies. There has not been any deleterious difference in endothelial or vascular function in thromboembolic high risk women on intrauterine system (Brito et al., 2010) and it is therefore can be considered after assessing the risks and benefits.

In a prospective comparative trial of 132 perimenopausal patients who smoked, IUS was found to be superior in preventing anaemia to both medroxyprogesterone acetate and continuous oral progesterone (Kucuk et al., 2008).

Like all hormonal contraception, the World Health Organization recommends avoidance among women with present or past history of breast cancer although there has not been any known increase in risk compared to the copper intrauterine contraceptive device (Gemzell-Danielsson, 2010). It is safe and effective in Human Immunodeficiency Virus positive women and like in the healthy equivalent, causes a reduction in bleeding. It has no effect on ovarian function and is not associated with increased viral secretion from the cervical mucus (Heikinheimo, 2010).

Compared to hysterectomy, the intrauterine system was found to be more cost effective (Hurskainen et al., 2004). However, a recent study (Roberts et al., 2011) has shown that although hysterectomy is initially costly, it produces more quality assured life years compared to the other treatment modalities for menorrhagia and therefore more cost effective in the long run. It is therefore a reasonable option of initial primary treatment.

The use of the intrauterine system has reduced the rate of hysterectomy among women with adenomyosis by 70% by decreasing dysmenorrhoea and bleeding episodes (Kulshrestha, et al, 2011).
2.3 Contraindications

Intrauterine system is contraindicated in pregnancy, local or systemic infection, suspected malignancy of the cervix or uterus, weight gain and unexplained vaginal bleeding among others.

2.4 Complications

During fitting there is a risk of perforation of the uterus with potential damage to surrounding organs. There is also a risk of infection which can spread to the pelvis and rarely systemically.

The expulsion rate is 4 per cent and is most common in the first year after insertion. Risk factors include young age, nulliparity and immediately postpartum. The rate of expulsion is not related to the uterine cavity length (Bahamondes, et al, 2011)

2.5 Side effects

It has been associated with a change in pattern of bleeding, spotting, amenorrhea or irregular bleeding. Rarely it may cause abdominal/pelvic pain, breast tenderness, acne, bloatedness, weight gain, headaches, hair loss, migraines, ovarian cysts, mood changes, nausea and low sex drive.

3. Conclusion

The levonorgestrel intrauterine system is an acceptable and cost effective treatment of heavy menstrual loss. It has additional benefits that make it a preferred choice for management of a number of other gynaecologic conditions at the same time. More research is required in long term outcome and cost analysis taking into account clinician preferences of choice.

4. Acknowledgment

I am grateful to Dr David Rae and Dr Wael Agur for their substantial input.

5. References


Menorrhagia and the Levonorgestrel Intrauterine System


Lethaby, A, Cook I, Rees, M: Progesterone or progesterone-releasing systems for heavy menstrual bleeding. Cochrane Database of systematic reviews. 11,2010


This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.

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