Menstrual dysfunction

Gail Busby

Abstract

Menstrual dysfunction is common, with approximately 9–30% of reproductive-aged women presenting with menstrual irregularities requiring medical evaluation. The causes are diverse and multiple treatment options are available. Appropriate management relies on relevant investigation and accurate diagnosis. This article reviews the most common causes of menstrual dysfunction using case histories for illustration. The conditions covered in this review include menstrual dysfunction around the time of menarche, ovulatory and anovulatory dysfunctional uterine bleeding, polycystic ovarian syndrome, uterine fibroids and dysfunctional bleeding around the perimenopause. Appropriate investigations and current management strategies are also discussed.

Keywords abnormal uterine bleeding; dysfunctional uterine bleeding; endometrial hyperplasia; menstrual dysfunction; perimenopausal bleeding; polycystic ovarian syndrome; uterine fibroids

Introduction

The majority of menstrual cycles are between 24 and 32 days and a normal cycle is considered to be 28 days. The menstrual cycle varies during the reproductive years, and is most regular between the ages of 20 and 40. The mean blood loss per cycle is between 37 and 43 ml, and the upper limit for menstrual loss is taken as 80 ml per menses. Menstrual dysfunction, or disruption in the flow or timing of this cycle is a very common cause for presentation to a gynaecologist. The causes are myriad, but several common causes are reviewed here and treatment options discussed.

The normal menstrual cycle

The first day of the menstrual cycle is the first day of menstruation, when oestrogen and progesterone are low. Ovulation occurs mid-cycle in response of high oestrogen and luteinizing hormone (LH) levels. The remaining granulosa cells then become the corpus luteum which produces progesterone. If fertilization does not occur, the corpus luteum degenerates and progesterone and oestrogen levels fall.

In the uterus, endometrial cells proliferate in response to rising oestrogen levels in the follicular (preovulatory) phase of the ovary, glands enlarge, and the endometrium becomes richly supplied with blood vessels. The secretory phase after ovulation is characterized by progesterone secretion by the corpus luteum, which makes the endometrium receptive to a fertilized embryo. In absence of pregnancy, the decrease in oestrogen and progesterone result in involution of the endometrium and menstrual loss.

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Menstrual dysfunction or abnormal uterine bleeding generally can be categorized as anovulatory or ovulatory abnormal uterine bleeding (AUB). Anovulatory AUB is caused by failure of the corpus luteum to sustain the developing endometrium. Ovulatory cycles are predictable and patients often have an imbalance of prostaglandin levels and increased fibrinolytic activity. Both ovulatory and anovulatory AUB may coexist with intracavitary lesions, including polyps or fibroids, which may cause heavy or erratic bleeding. In all cases of dysfunctional uterine bleeding, pregnancy, and the complications thereof should be ruled out as a cause.

Table 1 summarizes the differential diagnosis of menstrual dysfunction.

This review gives five scenarios which are common presentations of menstrual dysfunction.

Case 1: abnormal uterine bleeding around the menarche

A 15-year-old presents with a history of heavy, irregular periods. Her periods started nine months before and although initially average in flow, they increasingly became heavier and more frequent.

Anovulation looms large in the pathogenesis of heavy, irregular bleeding around menarche. Within the first 2 years after menarche, lack of ovulation is common due to the immaturity of the hypothalamic–pituitary–ovarian axis. The result of this is prolonged stimulation of the endometrium by oestrogen until the thickened endometrium is unable to be supported and sheds.

The adolescent with irregular and heavy periods should be investigated for clotting abnormalities as the reported prevalence of bleeding disorders in adolescents with menorrhagia varies between 10.4% and 48%. Specifically, von Willebrand's disease and platelet disorders may present for the first time at menarche. Pregnancy should not be forgotten as a possible cause of irregular bleeding in this age group. Appropriate investigations include a pregnancy test, full blood count with platelets, bleeding time, prothrombin time and partial thromboplastin time and von Willebrand's factor.

Women with clotting abnormalities should be co-managed with a haematologist. Successful medical options for treatment of von Willebrand's disease include the combined oral contraceptive pill (COCP), desmopressin acetate, antifibrinolytic agents and plasma-derived concentrates rich in the high-molecular-weight multimers of von Willbrand's factor (vWF).

If there are no haematological abnormalities, irregular cycles can be regulated by the use of cyclical progestogens or the COCP. These should both make the periods regular and decrease menstrual flow. If flow remains a problem, the addition of Tranexamic acid and/or Mefenamic acid during withdrawal bleeds is frequently adequate.

This treatment can be continued indefinitely, or stopped after 1 year or so to determine if ovulatory cycles have commenced, which should result in regular cycles of normal flow.

Case 2: ovulatory abnormal uterine bleeding

A 28-year-old nullipara is referred to the gynaecology clinic due to heavy regular periods. She is in a stable relationship, but not wishing to conceive at the moment. She uses barrier contraception. Clinical examination and pelvic ultrasound scans are normal.

Differential diagnosis of abnormal uterine bleeding

Category	Differential diagnosis
Anovulatory	Adolescence
	Diabetes mellitus uncontrolled
	Eating disorder
	Hyper-/hypothyroidism
	Hyperprolactinaemia
	Anticonvulsants
	Antipsychotics
	Perimenopause
	Polycystic ovarian syndrome
Ovulatory	Bleeding disorders (Haemophilia carriers)
	Factor deficiency (FVII, FXI, FV + FVIII, FXIII, FV, FX, Fibrinogen deficiency)
	Leukaemia
	Platelet disorders (Bernard–Soulier syndrome, Dense granule deficiency, Glanzmann's thrombasthenia, Alpha granule deficiency)
	von Willebrand's disease
	Liver disease, advanced
	Structural lesions – fibroids, polyps

Table 1

The diagnosis here is AUB due to endometrial causes. This is defined as abnormal bleeding in the absence of intracavitary or uterine pathology. The history of regular periods suggests that this is a case of ovulatory AUB.

The need to preserve fertility in this case limits treatment options to non-surgical, hormonal and medical non-hormonal treatment modalities. The need for reliable contraception should be taken into consideration in deciding upon treatment options.

Antifibrinolytics

Antifibrinolytics such as Tranexamic acid may reduce menstrual loss by 29–58%. Tranexamic acid acts to reduce the breakdown of fibrin in pre-formed clot. Menstrual bleeding involves the liquefaction of clotted blood in spiral arteries within the endometrium, and tranexamic appears to work by retarding this process. Tranexamic acid is not contraceptive.

Non-steroidal anti-inflammatory agents

Non-steroidal anti-inflammatory agents (NSAIDS) such as Mefenamic acid and Naproxen have been shown to reduce menstrual loss by 20–49%. They work by decreasing prostaglandin synthesis by the inhibition of cyclooxygenase. Prostaglandins are implicated in uterine bleeding and uterine cramps. They also therefore have a positive effect on dysmenorrhoea. They should not be used in heavy menstrual bleeding associated with clotting abnormalities. NSAIDS are not contraceptive.

COCPs

COCPs contain oestrogen and progestogen in combination. They work on the hypothalamic–pituitary axis to inhibit ovulation and decrease fertility. They may reduce menstrual loss by 43%, and also provide reliable contraception in the compliant patient.

Progestogens

Oral progestogens taken solely in the luteal phase of the menstrual cycle have not been shown to be effective in reducing heavy menstrual bleeding. Cyclical progestogens taken for 21 days of the cycle (day 5–day 26) have been shown in a small study to reduce menstrual loss by 83%. The mechanism of action of oral progestogens in reducing menstrual loss is unclear.

Injected progestogens such as Depot Medroxyprogesterone Acetate (DMPA) provide reliable contraception and are injected every 12 weeks. Although this is not licenced for the treatment of heavy menstrual bleeding, it is associated with amenorrhoea rates of 12–47% after one year of use.

The levonorgestrel-releasing intrauterine system (Mirena) provides an effective treatment option for AUB in the patient who is also desirous of reliable contraception. This device produces a dramatic decline in menstrual blood loss (65–98%) within 12 months of use. The device, imbedded with 52 mg of levonorgestrel, releases 20 μg of levonorgestrel per day, causes pseudodecidualization of the endometrium with very little systemic absorption of progesterone. It is licenced for contraception, treatment of idiopathic menorrhagia, and as the progestogenic arm of HRT. Its contraceptive effect lasts for 5 years.

In cases of ovulatory AUB where the patient has no further reproductive ambitions, surgical options can be entertained such as endometrial ablation and hysterectomy.

Endometrial ablation

Endometrial ablation refers to a host of techniques designed to destroy the endometrium, and thereby reduce menstrual bleeding. Initially, rollerball ablation, transcervical resection and laser ablation were the predominant endometrial destruction techniques performed under direct hysteroscopic vision. Over the past decade, a second generation of techniques, which do not require hysteroscopy have been developed which are safer, easier to perform, involve shorter hospital stays or are performed in the outpatient setting under local anaesthesia.

These techniques employ devices which are sited within the uterine cavity and are activated in order to produce global destruction of the endometrium. Various methods of destruction are used, including high-temperature fluids within a balloon (Thermachoice and Cavaterm), Microwave energy (Microsulis), and Bipolar radiofrequency electrical energy (Novasure). Less commonly used ablative techniques include free fluid at high temperature (Hydrothermablator), endometrial laser intrauterine thermotherapy (ELITT) and cryoablation (HerOption). Other than free fluid thermal ablation, these are blind techniques.

A recent network meta-analysis of second generation techniques produced the following results:

There was an increased rate of amenorrhoea with bipolar radio frequency ablation (48% at 5 years) compared with thermal balloon ablation (32% at 5 years). Free fluid ablation was associated with reduced rates of amenorrhoea and increased rates of heavy bleeding compared with bipolar radio frequency ablation. Microwave ablation was associated with an increased rate of amenorrhoea (84–87% at 5 years) compared with thermal balloon ablation and cryoablation, and some reduction in the rate of heavy bleeding compared with free fluid ablation.

With regard to patient satisfaction, there was some evidence of reduced rates of dissatisfaction with bipolar radio frequency

ablation compared with thermal balloon ablation. Increased dissatisfaction was seen with free fluid thermal ablation compared with bipolar radio frequency. Overall rates of dissatisfaction were low (such as 0–7% for bipolar radio frequency ablation).

The Endometrial laser intrauterine thermotherapy (ELITT) is no longer marketed, and the microwave endometrial ablation system from Microsulis has been withdrawn from the European market after Hologic acquired intellectual property for this device.

It is recommended that normal endometrial histology is confirmed prior to the ablation procedure.

Reliable contraception is essential after endometrial ablation performed by any technique, and women should be counselled about this is an appropriate procedure only in women with no future desire for fertility.

Hysterectomy

Hysterectomy is the only surgical technique which guarantees amenorrhoea. It however can be associated with serious complications such as pelvic haematomas (3.9%), urinary tract injury (1% for cystotomies and 0.1% for ureteric injuries), and bowel injuries (0.3%). Compared with all other treatment modalities, hysterectomy is favoured for elimination of bleeding symptoms and need for additional treatment. Hysterectomy is also favoured over ablation techniques for pelvic pain beyond the immediate post-operative period. However, these superior outcomes are achieved with the tradeoff of higher risks of adverse events, and should therefore be reserved for cases in which more conservative treatments have been unsuccessful.

Case 3: anovulatory abnormal uterine bleeding

A 30-year-old nullipara presents with a history of irregular and heavy periods over a period of 2 years. Her periods last for 9 days and occur every 2–3 months. Prior to this she had been on the combined oral contraceptive pill for 10 years and had regular periods on this. She is currently using barrier contraception as she stopped the COCP due to significant weight gain. On direct questioning she also reveals a history of unwanted hair growth on her face, chest and abdomen.

When ovulation does not occur, no corpus luteum forms to produce progesterone. The endometrium therefore undergoes prolonged oestrogenic stimulation, excessive proliferation, endometrial instability and erratic bleeding. Prolonged unopposed oestrogenic stimulation of the endometrium can lead to endometrial hyperplasia or carcinoma.

The most common cause of anovulation is polycystic ovarian syndrome (PCOS). There are however, numerous other causes, including thyroid disease, uncontrolled diabetes mellitus and hyperprolacinaemia. Anticonvulsants and antipsychotics can also cause anovulation.

A thorough history and examination is required to determine the most likely cause of anovulation. A detailed clinical history often reveals any systemic and medical conditions that cause menstrual dysfunction. The examination should note the presence of galactorrhoea, weight gain, acanthosis nigricans, evidence of hyper- or hypo-thyroidism, hirsutism, virilization or acne. A speculum and bimanual pelvic examination should be performed to exclude any anatomical pathology. Should positive findings be elicited in the history or examination, appropriate investigations should be performed (e.g. serum prolactin levels in the presence of galactorrhoea, thyroid function tests if there is evidence of thyroid disease and a pelvic ultrasound scan).

In this patient with irregular periods, weight gain and hirsutism, the most likely diagnosis is PCOS.

PCOS

PCOS affects 7–10% women worldwide, making it the most common endocrine disorder among reproductive-aged women.

Ascribing a diagnosis of PCOS has many implications including an increased risk of infertility, dysfunctional uterine bleeding, endometrial carcinoma, obesity, type 2 diabetes, dyslipidaemia, hypertension and possibly cardiovascular disease. Therefore, this diagnosis should not be undertaken lightly, and robust criteria used for diagnosis.

The first clinical definition of PCOS arose from the proceedings of a meeting of experts sponsored by the National Institute of Child Health and Human Disease of the NIH in 1990. They concluded that the major criteria for PCOS should include: (1) Hyperandrogenism and/or hyperandrogenaemia (2) menstrual dysfunction and the (3) exclusion of other known disorders.

An expert conference held in Rotterdam, The Netherlands in 2003 recommended that PCOS be defined when at least two of the following three features are present: (1) oligo and/or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism and (3) polycystic ovaries. These criteria also recognize that other androgen excess or related disorders should be excluded before assigning a diagnosis of PCOS.

More recently, in 2009, the Androgen excess and polycystic ovary syndrome society proposed new criteria for the diagnosis of PCOS: (1) hyperandrogenism: hirsutism and/or hyperandrogenaemia AND (2) Ovarian dysfunction: Oligo-anovulation and/or polycystic ovaries AND (3) Exclusion of other androgen excess or related disorders.

Weight loss and physical activity

Women with PCOS have an increased prevalence of obesity, estimated at between 40% and 60%. Obesity and insulin resistance (IR) are closely linked to the development of PCOS and its clinical features. Due to the potential significance of IR in the manifestation of PCOS, and as obesity promotes IR, lifestyle modifications focussing on dietary weight loss and increased physical activity is the preferred first-line treatment for PCOS.

Modest weight loss of 5–14% improves CVD risk factors, hormonal profile and reproductive function in overweight and obese women with PCOS. Improvements include reductions in abdominal fat, blood glucose, blood lipids and IR, improvements in menstrual cyclicity, ovulation and fertility, reductions in testosterone levels and free androgen index and increases in sex hormone binding globulin. There have also been demonstrated improvements in self-esteem, depression and anxiety.

COCPs

COCPs are among the primary treatment options for PCOS, particularly for those patients not wishing to become pregnant. They produce regular menstrual periods, lower the risk of endometrial hyperplasia and improve acne and hirsutism. COCPs improve symptoms by increasing the production of SHBG, resulting in a decrease in circulating free androgens, as well as their

bioavailability. They also suppress the production of FSH and LH which in turn decreases LH-driven ovarian androgen production. Progestogens protect the endometrium against hyperplasia induced by unopposed oestrogen stimulation. Some progestogens, such as drospirenone and cyproterone acetate have proven anti-androgenic effects and therefore are of added benefit in PCOS.

Despite their potential benefits in PCOS, COCPs fail to diminish insulin resistance in PCOS and may actually be associated with long-term metabolic derangements such as glucose intolerance, abnormal lipid profiles and cardiovascular disease. Further longitudinal studies in adult women with PCOS receiving COCPs are needed.

Insulin sensitizers and insulin lowering drugs

These medications reduce insulin levels (Metformin) and increase insulin sensitivity (metformin and thiazolidenediones), thus treating the metabolic effects associated with PCOS and obesity.

Metformin

Metformin increases insulin sensitivity in the liver by reducing gluconeogenic enzyme activities, inhibiting hepatic uptake of lactate and alanine, increasing the conversion of pyruvate to alanine and inhibiting glucose output. In addition, metformin increases peripheral glucose uptake, decreases fatty acid oxidation and decreases glucose absorption from the gut. It therefore has a positive effect on the metabolic derangements in PCOS.

The use of Metformin in PCOS has been shown to increase menstrual cyclicity (in 50–60%), improve percentage of ovulatory cycles, and improve fertility.

Metformin use is associated with gastrointestinal side-effects, which can be minimized by titration to the desired dose over a one month period.

In adult women with PCOS, the addition of Metformin to a COCP decreases IR, as well as androgen levels. However, the anticipated correction of deranged lipid profiles and abdominal obesity through metformin use appears to be blunted.

Thiazolidenediones

Thiazolidenediones act as insulin sensitizers through their activation of the nuclear receptor PPAR-γ, leading to increased production of insulin-sensitive adipocytes and increased glucose uptake in these cells, increased secretion of adiponectin and decreased secretion of pro-inflammatory cytokines. Recent data suggests that in women with PCOS, thiazolidenediones exert additional benefit with respect to hyperandrogenism, IR, anovulation and inflammatory mediator levels, in both lean and obese women. The thiazolidenedione, pioglitazone, has been shown to ameliorate the signs and symptoms of PCOS in a cohort of women who failed a previous trial of metformin. There have been, however concerns regarding use of these drugs, including withdrawal from the market of the vanguard thiazolidenedione, troglitazone, and further concerns regarding potential adverse cardiovascular events in Type 2 diabetes patients taking thiazolidenediones. This reinforces the need for caution when considering use of this class of drugs.

Case 4: abnormal uterine bleeding secondary to uterine fibroids

A 35-year-old Para 4 attends the gynaecology clinic with a history of regular, heavy, painful periods over several years. This has been associated with gradually increasing fatigue. On examination she appears pale. Abdominal and bimanual examinations reveal a 16-week sized mass arising from the pelvis. A full blood count reveals that she is anaemic, and a pelvic ultrasound scan reveals uterine fibroids.

Uterine fibroids are the most common benign gynaecological tumours. Definitive management comprises a choice between surgical (hysterectomy, myomectomy) or radiological (uterine artery embolization) modalities. Medical therapies have been used but appear to be less effective in women with fibroids.

Uterine artery embolization

Uterine artery embolization (UAE) is a minimally invasive radiologic procedure in which transcutaneous insertion of a catheter through the femoral artery and subsequent occlusion of the uterine artery with Embospheres, polyvinyl alcohol beads, polyvinyl alcohol coils or Gelfoam causes cesstion of blood flow to the fibroid. Shortly thereafter, the fibroid necroses and shrinks. Menorrhagia symptoms resolve in 85–95% of patients treated in this way. Preprocedural investigations include Magnetic Resonance Imaging of the fibroids.

UAE is associated with an increased risk of minor complications versus myomectomy or hysterectomy, but the long term patient satisfaction is equivalent for the three procedures.

UAE is however associated with an increased risk of further surgical procedures for up to five years after the initial procedure. There are concerns regarding fertility after UAE due to the risk of premature ovarian failure and there have been reports of uterine rupture in labour with previous UAE.

Myomectomy

Myomectomy, the surgical excision of uterine fibroids, can be performed hysteroscopically, laparoscopically or via laparotomy depending on the number, size and position of fibroids. Submucous fibroids are amenable to hysteroscopic removal, whereas intramural and subserosal fibroids require an abdominal approach.

Pre-operative treatment with Gonadotrophin-releasing analogues or Ulipristal acetate, a selective progesterone-receptor modulator, decrease fibroid size and increase haemoglobin due to causing amenorrhoea in most patients. Due to the risk of osteoporosis, GnRH analogues should not be used for periods of longer than six months unless concomitant oestrogen replacement is prescribed. Ulipristal acetate is approved in the European Union for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is approved for treatment periods of three months duration or less, as the longer-term tolerability has not been established.

In two well-conducted trials, PEARL 1 and PEARL 2, Ulipristal acetate at a dose of 5 mg per day for 13 weeks was shown to control excessive uterine bleeding in $\geq$90% of women with uterine fibroids. Approximately half of the recipients were amenorrhoeic by day 10. Ulipristal acetate also resulted in a median reduction in fibroid volume of at least 21% following 13 weeks of treatment. These results were non-inferior to those of leuprolide acetate.

Hysterectomy

Patients who have symptomatic uterine fibroids and have completed their family may opt for hysterectomy, however this is associated with increased frequency of complications compared to hysterectomy with a normal-sized uterus.

Case 5: abnormal uterine bleeding in the perimenopause

A 48-year-old attends the clinic with a 6 month history of continuous bleeding. Her periods were previously fairly regular lasting 5 days every 26 days. The bleeding is not excessive, but she is getting frustrated by having to wear sanitary protection every day. Clinical examination is normal, and speculum examination reveals a small amount of bleeding coming through the os of a healthy-looking cervix.

A transvaginal ultrasound scan revealed an endometrial polyp. She underwent outpatient hysteroscopy which confirmed the presence of a large endometrial polyp filling the uterine cavity. She subsequently underwent an urgent hysteroscopy and endometrial polypectomy and biopsy under general anaesthetic. The histology revealed complex endometrial hyperplasia with atypia. She was appropriately counselled and underwent a hysterectomy and bilateral salpingo-oophorectomy.

Patients presenting with a recent onset of abnormal uterine bleeding around the menopause should be fully investigated to rule out cervical and endometrial pathology. Appropriate investigation includes a cervical smear, pelvic ultrasound scan (ideally transvaginal) and hysteroscopy with endometrial biopsy (this is often performed as an outpatient procedure).

Endometrial biopsy alone has a sensitivity and specificity of diagnosing endometrial cancer of 91% and 98% respectively. It is also a good test to diagnose atypical endometrial hyperplasia with a sensitivity of 82.3% and a specificity of 98%. It however is very poor at diagnosing intracavitary lesions such as endometrial polyps or submucous fibroids. Saline infusion sonography can be used as an adjunct to transvaginal ultrasonography in order to improve the pick up rate of intracavitary abnormalities and has a sensitivity of 88–99% and specificity of 72–95%. This is an improvement on TVS alone which has a sensitivity and specificity of 60–92% and 62–93% respectively. TVS also has the advantage over hysteroscopy alone of assessing for myometrial lesions and ovarian pathology. OPH itself has a sensitivity and specificity of 94% and 89% of diagnosing intracavitary abnormalities, with the added benefit of allowing directed biopsy of suspicious areas within the endometrium or excision of polyps depending on their size and number.

Management options

The finding of atypical endometrial hyperplasia conveys a risk of progression to endometrial carcinoma of 8.2% in 4 years, 12.4% in 9 years and 27.5% in 19 years. In addition, other studies have shown the presence of concurrent endometrial carcinoma in hysterectomy specimens removed for atypical hyperplasia in 43% patients. For this reason, it is recommended that hysterectomy be performed within 3 months of the diagnosis of atypical endometrial hyperplasia.

In contrast, the finding of endometrial hyperplasia without atypia has a very low risk of malignant transformation of 1.2% in 4 years, 1.9% in 9 years and 4.6% in 19 years. This abnormality can be treated with cyclical progestogens with re-biopsy to confirm regression of the hyperplasia.

In patients who have no further reproductive ambitions, total hysterectomy is the treatment of choice for endometrial hyperplasia with atypia. In patients who wish to retain their uterus for childbearing, treatment with high dose progestogens with re-biopsy can be employed after careful counselling.

Conclusion

Abnormal uterine bleeding is common and can have a substantial impact on women's quality of life. Cases need to be assessed on an individual basis by a thorough history, clinical examination and investigations relevant to the particular case. Pregnancy should always be ruled out in cases of menstrual dysfunction. Other investigations vary depending on issues such as age of presentation, co-morbidities and degree of menstrual loss.

There are a large range of available treatment options, including medical and surgical options, and these should be tailored to the specific case depending on the working diagnosis, and future reproductive ambitions of the patient. ◆

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Practice points

- Pregnancy should be ruled out in all cases of abnormal uterine bleeding
- Appropriate management will vary with age, co-morbidities and reproductive ambitions
- There are many treatment options now available, making hysterectomy a last resort due to higher risks of complications
- Menstrual dysfunction in the perimenopause should be investigated urgently due to the risk of a precancerous or cancerous cause