Menstrual dysfunction

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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.

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.

According to FIGO, AUB could be classified according to its causes-polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified (PALM-COEIN). In all cases of abnormal uterine bleeding, pregnancy, and the complications thereof should always 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.

Differential diagnosis of abnormal uterine bleeding

Category	Differential diagnosis
Anovulatory	Adolescence
	Diabetes mellitus uncontrolled
	Eating disorder
	Hypothyroidism
	Hyperprolactinaemia
	Anticonvulsants
	Antipsychotics
	Perimenopause
	Polycystic ovarian syndrome
Ovulatory	Hypothyroidism
	Hyperthyroidism Downs Syndrome
	Bleeding disorders (Haemophilia carriers)
	Leukaemia
	Factor deficiency (FVII, FXI, FV+FVIII, FXIII, FV, FX, Fibrinogen deficiency)
	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

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 were monthly with average flow, they increasingly became heavier, and more than once a month.

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

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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 Willebrand's factor (vWF).

If there are no haematological abnormalities, irregular cycles can be regulated by the use of cyclical progestogens or the COCP. The treatment is commenced after checking suitability of the hormonal preparation as per United Kingdom Medical Eligibility Criteria guideline (UKMEC).

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 (for painful periods) 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. She is medically fit and well and her smear test done a month ago was normal. Clinical examination and pelvic ultrasound scans are normal.

The diagnosis here is AUB due to endometrial causes. This is defined as abnormal bleeding in the absence of intracavitary or uterine pathology, such as endometrial polyps or uterine fibroids. 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.

The levonorgestrel-releasing intrauterine system (Mirena) is considered as the first line treatment in these cases. It 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, embedded 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 licensed for contraception, treatment of idiopathic menorrhagia, and as the progestogenic arm of HRT. Its contraceptive effect lasts for 5 years.

If hormonal IUS is not acceptable or suitable, the other choices are antifibrinolytics, NSAIDS or oral hormones. Copper coils are not suitable due to increased possibility of pain and is category two in medical eligibility criteria in patients with increased bleeding.

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 acid appears to work by retarding this process. Tranexamic acid is not contraceptive. The contraindications are thromboembolic disease, fibrinolytic conditions following disseminated intravascular coagulation and a history of convulsions.

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%. Though not as effective as tranexamic acid, they can be taken with tranexamic acid for better effect. 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 ethinylestradiol 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 to 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.

The progesterone only pill (POP) can be used to provide reliable contraception, but has a varied effect on menstrual flow. 20% patients will be amenorrhoeic, 40% bleed regularly and 40% have erratic bleeding. Due to inconsistent effect on menstruation this is not generally first-line treatment. Indeed, altered bleeding patterns are the most common reason given by women for stopping POPs. Injected progestogens such as depot medroxyprogesterone acetate (DMPA) provide reliable contraception and are injected every 12 weeks. Although this is not licensed for the treatment of heavy menstrual bleeding, it is associated with amenorrhoea rates of 12–47% after one year of use.

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

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Endometrial ablation

Endometrial ablation refers to a host of techniques designed to destroy the endometrial glands up to depth of 5 mm of endomyometrial junction (in uterus up to size of 12 weeks' gestation) 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. Various methods 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), 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 (40–50% in 12 months) compared with thermal balloon ablation (37–60% in 12 months). Free fluid ablation was associated with 24–32% of amenorrhoea in 12 months and increased rates of heavy bleeding compared with bipolar radio frequency ablation.

With regard to patient satisfaction, there was some evidence of increased satisfaction with bipolar radio frequency ablation (87–92%) compared with thermal balloon ablation (77%). Lesser satisfaction was seen with free fluid thermal ablation compared with bipolar radio frequency. Further treatment is required in 20–27% of patients having the procedure and 14–20% needing hysterectomy, majority being within 2 years.

Minitouch is a flexible ablation device which does not require cervical dilatation, can be used in outpatient setting with analgesia and thus requires minimum resources. According to a study in UK with 69 patients, the success rate was 81% and satisfaction rate was high.

In another study of 70 patients over 5 years, successful outcome was noted in 93% patients with majority reporting amenorrhoea. 93% patients were satisfied with the outpatient ablation procedure by Minitouch.

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. Hysterectomy can be either total or subtotal with preservation of cervix and can be done by various methods-abdominal, laparoscopic, and vaginal or by robotic surgery. However, every procedure has its own risks and the overall risk of serious complication in abdominal hysterectomy is 4% with pelvic haematomas (3.9%), urinary tract injury (1% for bladder and 0.1% for ureteric injuries), and bowel injuries (0.3%). Compared with all other treatment modalities, hysterectomy is favoured for elimination of bleeding and associated symptoms and need for subsequent 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 nulliparous woman 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 hyperprolactinaemia. 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 hypothyroidism, 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 10–18% 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)

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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.

Polycystic ovaries are present in general population in 20−33% and with improving ultrasound resolution it has been suggested that the threshold for PCO would be >25 follicles. It has also been currently suggested that measure of AMH (>35 pmol/L) would be a better estimate of PCO than ultrasound.

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 also leads to development of metabolic syndrome in 33% cases. Due to the potential significance of IR in the manifestation of PCOS, and as obesity promotes IR, lifestyle modifications focusing 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. Moreover, oestrogen-progesterone induces a moderate reduction of adrenal androgens, probably through a direct interaction with adrenal steroid synthesis.

Some progestogens also have antiandrogenic properties, due to their antagonizing effects on the androgen receptor and to the inhibition of 5α−reductase activity. This class of compounds includes cyproterone acetate, drospirenone and dienogest and 'third-generation' progestins (desogestrel, gestodene, norgestimate). Drospirenone per se has little antiandrogenic effect but its combination with contraceptive doses of estrogens confers an antiandrogen effect via inhibition of gonadotropin secretion.

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.

COCPs and progestogens including Mirena primarily should be used for inducing withdrawal bleeds after long periods of amenorrhoea (>3 months) in order to avoid future risks of endometrial hyperplasia.

Insulin sensitizers and insulin lowering drugs

These medications reduce insulin levels (Metformin) and increase insulin sensitivity (metformin and thiazolidinediones), 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. It has some role in reducing fasting blood glucose in women with impaired glucose tolerance but should not be used to treat IR with PCOS in normoglycaemic women.

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.

Thiazolidinediones

Thiazolidinediones (TZDs) act as insulin sensitizers through their activation of the nuclear receptor PPAR-g, 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. There has been several studies which demonstrated the therapeutic benefits of one or another TZD on insulin resistance, ovulatory dysfunction and hyperandrogenism in PCOS in both lean and obese women but the first meta-analysis to evaluate the role TZDs plays in the treatment of PCOS compared with placebo showed that TZDs can effectively reduce insulin and fasting blood glucose levels in patients with PCOS, but TZDs may not effectively reduce the Ferriman-Gallwey score or androgen levels and may increase body weight. Pioglitazone and rosiglitazone should be considered a second-line treatment alternative to metformin for management of women with PCOS who are resistant to insulin or who are obese. Troglitazone though has been withdrawn from market due to concerns of hepatotoxicity.

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Orlistat

Orlistat is an irreversible gastric lipase inhibitor could be used in obesity related to PCOS with similar effectiveness as metformin. It could be used in doses of 60–360 mg but has issues with compliance due to several gastrointestinal symptoms like steatorrhea and abdominal pain.

Case 4: abnormal uterine bleeding secondary to uterine fibroids

> A 35-year-old multiparous woman 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 has pale mucous membranes. 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 depends on the subtype of the fibroid (i.e. submucosal, intramural or subserosal) and comprises a choice between surgical (TCRF, hysterectomy, myomectomy) or radiological (uterine artery embolization) modalities. Medical therapies, such as those discussed above (tranexamic acid, COCP, progestogens) 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 cessation 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. A meta-analysis also suggested that the risk of major complications is lower than that of surgery.

UAE is however associated with an increased risk of further surgical procedures for up to five years after the initial procedure (23% needed further intervention according to HOPEFUL study). 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 by 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. According to a Cochrane review, preoperative use of GnRh led to 36% reduction in fibroid size in 12 weeks.

Endometrial biopsies have not shown any increased risk of endometrial atypia or carcinoma.

In two well-conducted trials, PEARL 1 and PEARL 2, Ulipristal acetate at a dose of both 5 mg and 10 mg per day for 13 weeks was shown to control excessive uterine bleeding in 90% of women with uterine fibroids. Approximately three-quarter recipients were amenorrhoeic by day 10. Ulipristal acetate also resulted in a median reduction in fibroid volume of at least 41% following 13 weeks of treatment and retained the change up until 6 months of stopping treatment. These results were non-inferior to those of leuprolide acetate.

However, on Feb 2018, a safety alert was circulated by MHRA (Medicines and Healthcare products Regulatory Agency) regarding Ulipristal acetate (Esmya) due to cases of severe liver injury worldwide, out of which some women needed liver transplant. Subsequently an EU review was done which finalized some measures to minimize this risk (MHRA August 2018). These have also been incorporated by NICE in its guidance on management of heavy menstrual bleeding. Esmya is contraindicated in women with underlying liver disorders. Liver function tests are done before initiation of treatment and if baseline ALT or AST is more thantwo times the upper normal limit, Esmya is withheld. The current indications for Esmya are as below—

- intermittent treatment (up to four courses of 5 mg Esmya) in moderate to severe symptoms of uterine fibroids for women of reproductive age who are not eligible for surgery
- one course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age

If ulipristal acetate is the preferred treatment option, the relative benefits and risks of ulipristal acetate should be discussed with women, including recognizing the signs and symptoms of liver injury, to enable an informed decision. Close monitoring of ALT/AST is performed during the course of treatment and treatment is discontinued if levels are more than three times the upper limit of normal levels.

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

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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 pickup 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% 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 with or without bilateral salpingo-oophorectomy depending on the age group 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 the most common cause of anaemia in the pre-menopausal woman 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 is 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

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