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Progesterone and abnormal uterine bleeding/ menstrual disorders

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A B S T R A C T

This chapter explores the role of progesterone and progestogens in the management of abnormal uterine bleeding (AUB). Progestogens are used to regulate intermenstrual bleeding and decrease heavy menstrual bleeding (HMB) in women of reproductive age or who are perimenopausal. In menopausal women, progesterones and progestogens prevent endometrial hyperplasia and aim to reduce the development of endometrial cancer. We hope to make clear current best practice including preparation, specific benefits and risks. Progesterone also acts in concert with other hormones to affect breast, cardiovascular system, lipid profile and bone. We hope to explain how its unintended side effects may be used beneficially or may cause intended side effects.

Introduction

Use of progesterone and synthetic analogues, the progestogens, in abnormal uterine bleeding (AUB) and menstrual disorders including menopausal hormone replacement is well established [1–3]. AUB is defined as the menstrual bleeding of abnormal amount, duration or schedule. It is common and accounts for one in three gynaecology clinic attendances [2,4]. Medical management is largely by intrauterine systems or systemically with high-dose oral progestogens. AUB is exceedingly

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common at the extremes of reproductive years, puberty and perimenopausal, and accounts for 70% of gynaecology clinic attendances in the perimenopausal and menopausal period [5]. Perimenopause is defined as 'the period around onset of menopause, often marked by physical signs such as hot flushes and menstrual irregularities [2]. Timing and duration of perimenopause varies and AUB may last for several years before menopause [2]. As such, the management of AUB is a core gynaecological skill. Menopausal symptoms are another frequent clinical presentation. Hormone replacement therapy (HRT) is important in the management of these symptoms, which include, vasomotor symptoms, lower genitourinary symptoms, mood changes, sleep disturbances and musculoskeletal symptoms [5]. Menopause is defined as amenorrhoea for 12 months in the absence of biological or physiological causes. We will discuss preparations and routes of administration of progestogens and how this affects safety, acceptability and efficacy.

History of progestins and their classification

Progesterone was first isolated in 1934 by groups investigating the endocrine function of the corpus luteum [6].Progesterone deficiency inhibits the endometrium changing to its secretory state. A secretory endometrium is more vascular and glandular [7], which helps to allow the implantation and support of the newly fertilised ovum.

From 1942 to the mid-1970s, unopposed oestrogen was used in HRT. Studies from 1975 onwards showed that unopposed oestrogen increased the risk of endometrial cancer [4]. Research in the early 80s showed that the addition of progestogen had a protective effect against endometrial cancer. Medroxyprogesterone acetate (MPA) was most commonly used in the USA and norethisterone acetate in the UK and Europe [5].

There is confusion over the terminology, making some of the literature more difficult to compare. Progesterone should refer to the natural hormone or when micronized, and progestogen is the umbrella term to include progesterone and synthetic progestogens. Vaginal administration was developed followed by micronized progesterone as the absorption of the hormone through the skin is difficult, unlike oestradiol. Synthetic derivatives like norethisterone are more stable and absorb readily through the skin. Oral progesterone is poorly absorbed and until relatively recently, no micronized preparation was available.

Progestins also combine with other receptors such as glucocorticoid, mineralocorticoid and androgen, which results in different effects [8]. However, they all decidualise the endometrium, and their potency is judged by their ability to achieve this.

Progestin selection can be challenging, but should be determined by the mechanisms of action, bioavailability, drug interactions and safety profile. Their bioavailability depends on multiple factors [9], including the administration route, metabolism, protein binding and affinity to other steroid receptors (android, glucocorticoid and mineralocorticoid).

The structural and differential physiological effects of individual progestogens are of clinical and academic interest, as it affects their pharmacodynamics [10]. Receptor-binding properties can help decide on the treatment agent, e.g. cyproterone acetate is anti-androgen and useful in hirsutism, whereas drospirenone has anti-mineralocorticoid effects and may lower blood pressure (BP). Progestogens may also have different safety profiles depending on structure and binding [9].

As discussed earlier, women's age is thought to be an important consideration in prescribing the safety profile. Aging changes pharmacokinetics through various mechanisms [9] including declining hepatic and renal function. Cytochrome P450 metabolism of progestins declines with age and the ability of the liver to conjugate steroid hormones reduces, which can result in altered metabolism and clearance of progestins [9].

Abnormal uterine bleeding (AUB) and its management

To understand AUB, it is important to understand the normal menstrual cycle. The menstrual cycle is a result of hormonal interactions in the hypothalamic-pituitary-ovarian (HPO) axis [1]. The anterior pituitary releases follicle-stimulating hormone (FSH) during the follicular phase of the menstrual cycle. FSH then acts on the granulosa cells causing oestrogen production. The excess oestrogen production

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stimulates the growth of the endometrium. It also has negative feedbacks on FSH and triggers an LH surge. The LH surge results in ovulation. After ovulation, the corpus luteum is responsible for the production of progesterone, which results in a secretory endometrium. If the ovum is not fertilised, there should be a synchronous reduction in the production of oestrogen and progesterone as the ovum and corpus luteum degenerate. This results in the shedding of the endometrium (menses).

Women with anovulatory cycles have oestrogenic endometrial stimulation without progesterone to regulate and organise the endometrium. This leads to bleeding that may be irregular, unacceptably heavy or longer than the 7 days expected of normal menses [1] (AUB). Women with ovulatory AUB have a normal HPO axis but poorly functioning haemostatic and vasoconstrictive capabilities of the endometrium.

AUB is an umbrella term encompassing heavy menstrual bleeding (HMB) and intermenstrual bleeding. Prolonged AUB can lead to anaemia, investigations for malignancy, social isolation and relationship breakdown[1]. Most AUB is managed outside the hospital but can also present acutely with anaemia requiring admission. AUB can be classified by PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified) [1]. The causes are grouped according to whether there are structural abnormalities or if the AUB is unrelated to these. Structural abnormalities are covered by PALM and HMB unrelated to structural abnormalities by COEIN [3].

Management can be medical or surgical depending upon the aetiology. First-line investigations include a full blood count, history and examination [11]. If history and examination suggest low risk of fibroids, adenomyosis or histological abnormality progress to pharmacological treatment without further investigation [11]. Excessive pre-menopausal uterine bleeding, not due to pregnancy, systemic disease or uterine cause is dysfunctional uterine bleeding.

Progestins only

Progestins are first-line treatment for HMB in an emergency presentation. Hormonal options: oral norethisterone on days 5–25 of cycle; MPA for 5–10 days of each month (day 16–21 of cycle) or micronized progesterone 200 mg orally once daily for 12 days of each month. Treatment aims to limit blood loss and improve the quality of life for women [2].

Long-acting progestogens

Secondary options include levonorgestrel intrauterine system (LNG-IUS) or etonogestrel subdermal implant. Women using long-term progesterone only hormones, such as the implant, LNG IUS or depot progesterone injection, should be counselled on the likelihood of breakthrough bleeding in the first year. Following this most women will go on to have reduced or absent menses [12]. The IUS is 99% effective at preventing pregnancies and should be changed every 5 years. Long-acting progestogens also provide reversible and effective contraception. The IUS also reduces excessive menstrual bleeding in women with fibroids, with a spontaneous expulsion rate of around 1 in 6 women as compared to 1 in 10 women without fibroids [2]. Contraindications to the IUS include: pregnancy, pelvic inflammatory disease in last 3 months, current uterine or cervical cancer, uterine cavity distorted, current STI, liver disease or tumour [3].

The IUS is more effective in the management of AUB in comparison to luteal phase oral MPA, norethindrone, depot progesterone injection, COCP and mefenamic acid. It was demonstrated to improve both serum haemoglobin and the quality of life compared with standard treatment [13].

Combined oral contraceptives

Although oral progestogens are first line, the most commonly selected treatment remains the combined oral contraceptive pill (COCP) [2]. The COCP contains synthetic/natural oestrogen and progestogen. After the COCP, the IUS is most commonly used [2]. COCP can regulate menstrual cycles and reduce excessive menstrual bleeding [2]. It is therefore useful in oligo/anovulatory cycles as well as HMB. COCP is less effective than higher dose progesterones at reducing bleeding, but blood loss can be

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reduced by up to 50% [2]. COCPs also come in extended-cycle or continuous/tricyclic forms. These reduce bleeding when the traditional 21 days is compared with 7-day hormone-free interval [2]. Breakthrough bleeding on the COCP can be remedied by changing of hormone preparation. If breakthrough bleeding is persistent, they should be further investigated [2].

Contraindications to COCP include [14]:

- Previous Stroke.
- Current or history of ischaemic heart disease.
- Migraine with aura.
- Smoking >15 cigarettes/day or are smokers >35 years old.
- Severe cirrhosis or liver tumour.
- Uncontrolled hypertension ($\geq$160/100 mmHg).
- <21 days post-natal.
- Current breast cancer or breast cancer $\leq$5 years ago.
- History of deep vein thrombosis.
- Major surgery with prolonged immobilisation. Women should stop oestrogen containing contraceptives before 4–6 weeks.
- Certain anticonvulsants (including phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine and lamotrigine)

Non-hormonal pharmacological management: non-steroidal anti-inflammatories and/or fibrinolytics, e.g. tranexamic and mefenamic acids. Other options include uterine artery embolization or myomectomy, endometrial ablation and hysterectomy.

Summary adapted from the medical management of abnormal uterine bleeding in reproductive-aged women – American Journal of obstetrics and gynaecology [3]

Medical treatment of HMB can also be guided by age group. Age group will also give an indication of likely cause [3]. PCOS and obesity will be causes in pre-menopausal women and are best managed in those not wishing to conceive with COCP and weight loss. Younger patients less than 19 years old are more likely to have bleeding caused by an immature HPO axis or an inherited bleeding disorder, which are both most commonly managed by the COCP if there are no contraindications, but can also be managed by progesterone only options and non-hormonal options[15]. Women aged 19–39 years can be managed first line by an IUS, second line by COCP, third-line progesterone only options. Premenopausal women aged over 39 years can be managed first line by an IUS, second line by progesterone only options and third-line COCP. Women in this category have AUB that is most likely to be caused by perimenopause or pre-malignant/malignant endometrial pathology [3,11] (Table 1).

We have tried to condense the management of AUB into the flow chart below, unfortunately we do not have the scope in this chapter to cover haemodynamically unstable AUB or bleeding during pregnancy. Unexplained post-menopausal bleeding should always be further investigated, the charts below assume women are pre-menopausal and HCG -ve.

Fig. 1 [3,11,16]:

Effect on different tissue types

Schindler et al. produced a table summarising the effects of the 'newer' progestogens in their 2013 paper 'Classification and pharmacology of progestins'. It is a useful summary of the partial effects of progestogens [14]. In Table 2 we have adapted this to include norethisterone and MPA, as well as a summary of the known long-term risks associated with specific progestins [17–20].

Progestogens mainly function by activating progesterone receptors A and B (PR). Differential binding with the PR-A and PR-B receptor subtypes is determined by the structure of the progestins [14] and modulates gene expression with wide-ranging effects.

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Table 1
Summary adapted from The medical management of abnormal uterine bleeding in reproductive-aged women – American journal of obstetrics and gynaecology [1].

Scenario	Pharmacological management:
Acute AUB (normal uterus without underlying systemic cause)	• Fibrinolytic e.g. tranexamic acid • Combined oral contraceptive pill • Oral Progesterogen e.g. norethisterone, MPA • LNG-IUS
HMB (normal uterus without underlying systemic cause): Ovulatory AUB	• Fibrinolytic e.g. tranexamic acid • COCP • Oral progestin e.g. norethisterone • Injectable progestin (Depot MPA) • NSAIDs • GnRH agonist • Androgen receptor agonists e.g.Danazol
HMB (normal uterus without underlying systemic cause): AUB with ovulatory dysfunction	• COCP • Progestin e.g. MPA • NSAIDs
Symptomatic uterine fibroids	• IUS (in women with normal uterine cavity) • COCP • Androgen receptor agonists • NSAIDs • Fibrinolytic e.g. tranexamic acid
Inherited bleeding disorder	• IUS • PO Fibrinolytic e.g. tranexamic acid • COCP • Androgen receptor agonists e.g.Danazol • GnRH agonist • Desmopressin (von willebrand's disease)

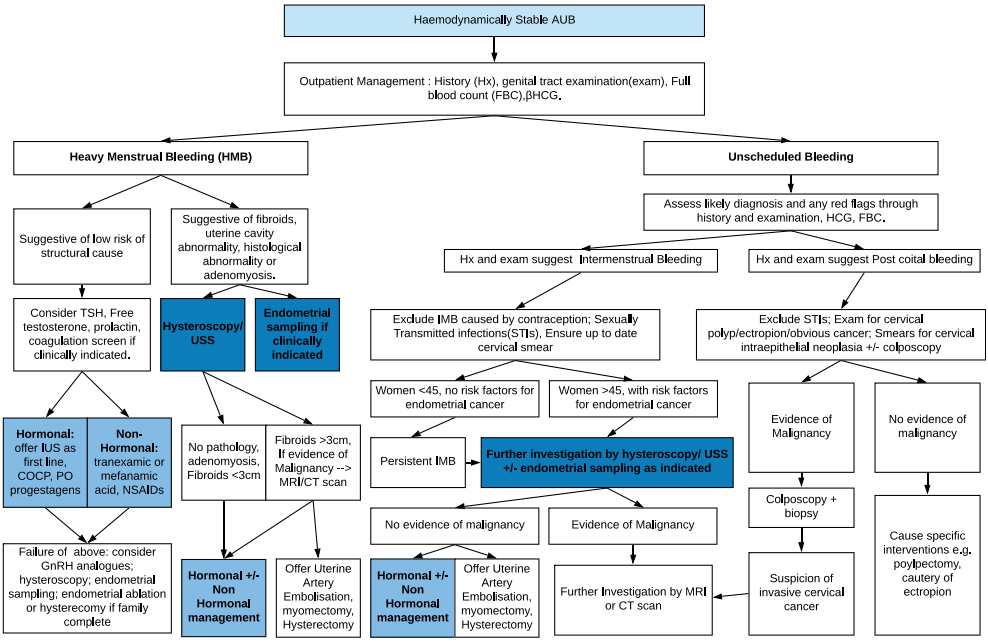

Fig. 1. Flowchart outlining managements of Haemodynamically Stable AUB.

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Table 2
Summary of partial effects of progestogens.

Progestogens	Progesto-genic	Anti-oestrogenic	Anti-androgenic	Androgenic	Glucocorticoid	Anti-Mineralocorticoid	Increased Risks
Progesterone	+	+	(+)	-	(+)	+	Hirsutism,
Dienogest	+	+	+	-	-	-	Used with oestrogen, specific profile not available
Drospirenone	+	+	+	-	-	+	Used with oestrogen, specific profile not available, some speculation may be decreased cardiac risk due to anti-androgenic effects.
Nomegestrol acetate	+	+	(+)	-	-	-	Used with oestrogen, specific profile not available
Norethisterone	+	-	-	(+)	-	-	Thromboembolism, hepatic cancer and breast cancer
MPA	+	+	-	(+)	(+)	-	Breast cancer, lipid profile and coronary heart disease

HRT utilises a range of different progestogens [14]. In August 2019, the National Institute of Health and Care Excellence (NICE) collated the evidence of the multi-system effects of HRT [4] when compared with placebo. As discussed earlier, differences in progestin structure result in a variety of effects of different preparations. Heterogenicity of studies coupled with some studies not defining the type, dosage or duration of HRT, creates a challenge to associate specific progestins with an individual physiological benefit or risk. However, we have discussed the established impact upon a range of tissue types below.

Endometrium

Progesterone exerts its effect on the endometrium through PR-A and PR-B receptors, which results in the conversion of proliferative endometrium to secretory endometrium in an oestrogen-primed uterus [21]. Progestogens vary in their ability to decidualise endometrium, and this determines their efficacy in decreasing or stopping endometrial bleeding. An excessively proliferative endometrium can lead to endometrial hyperplasia, which has the potential of progression to, or can occur coincidentally with endometrial carcinoma [22]. Reversion of hyperplasia to normal endometrium represents the key conservative treatment for the prevention of the development of endometrial cancer.

Breast

It is well established that some popular forms of combined HRT are linked to the increased risk of breast cancer development [23]. However, increased endogenous progesterone does not appear to correlate with increased breast cancer risk [17], this suggests that increased progesterone levels alone do not increase risk. Also, high-dose progestogens like MPA or megestrol acetate were used to treat advanced breast cancer and are still used in the treatment of PR-negative breast cancers. It is not clear, whether increased breast cancer risk has not been demonstrated in patients with naturally higher progesterone levels due to study design or true lack of a link between increased endogenous production of progesterone [17].

Breast tissue is also affected by other hormones such as oestrogen, androgens and prolactin, this makes the exact role of progesterone difficult to elucidate [17]. The complex systems in which the hormones interact are yet to be recreated in vitro and are challenging to study in vivo. Synthetic

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progestogens differ in their affinity for androgen and mineralocorticoid receptors. Hence, combined HRT containing different progestogens may have differing effects on breast cancer risk.

During pregnancy, when progesterone levels are highest, the increased expression of PRs is induced by higher oestrogen levels, allowing for lobuloalveolar maturation. Progesterone is also involved in the ductal development of the mammary glands (although to a lesser extent than lobuloalveolar maturation during pregnancy). It is possible that the synthetic progestins are creating a similar effect of increased tissue simulation leading to increased cancer risk.

Use in gynaecology – Hormone replacement therapy

Aside from the cessation of menses, menopause has several reported negative symptoms, which include vasomotor symptoms like hot flushes and night sweats, vaginal discomfort and dryness, recurrent lower urinary tract infections, sexual dysfunction and sleep disturbance. HRT is shown not only to relieve these symptoms but also to improve the quality of life and maintain physical and mental activity levels [24]. Combined (progestogen containing) HRT is used in women with a preserved uterus to avoid adverse effects of chronic endometrial stimulation such as abnormal bleeding and cancer development.

Safety of HRT

HRT was largely considered to be safe for the treatment of menopausal symptoms until the 2002 Women's Health Initiative (WHI) trial and 2004 Million Women Study, which demonstrated a significantly increased risk of breast cancer. WHI assessed the value of HRT in chronic disease prevention and included postmenopausal women with a mean age of 63 years (range: 50–69 years). The arm comparing combined HRT (CEE and MPA) was stopped early when it was considered that the harm outweighed the benefit in terms of disease prevention. It reported that CEE + MPA increased the risk of breast cancer, coronary artery disease, stroke and venous thromboembolism when compared with placebo [19]. This coincided with the publication of the Million Women Study reporting a significant risk of breast cancer with all types of HRT, with oestrogen in combination with progestogen outweighing oestrogen alone. However, later analysis of results from the WHI study suggested that the safety profile may vary depending on the age group with substantial benefits in terms of cardiovascular disease prevention for those starting HRT at the time of menopause and significantly more harm being encountered in women over 60 years or more than 10 years post menopause. WHI also investigated only one type of progestogen (MPA). Overall, WHI suggested that the absence of increased breast cancer risk with oestrogen alone suggested that the problem was related to the progestogen component of the HRT.

The 2019 meta-analysis published in the Lancet by the Collaborative group on hormonal factors in breast cancer made headlines. The group found that all types of systemic HRT are associated with an increased risk of breast cancer [18]. This effect was only significant after use for a year or longer [18]. The risk of developing breast cancer increases with the duration of use and risk is not oestrogen specific – it is higher with combined HRT than in those women taking oestrogen only HRT. Th increase in risk is duration dependent. There was no evidence of an effect on breast cancer risk with low doses of vaginal oestrogens. The risk begins to decline 10 years after the cessation of HRT [18]. Overall this equates to 1 extra case of breast cancer per 70 women studied who used cyclical HRT and 1 extra case of breast cancer per 50 women studied who used continuous combined HRT [18].

Current clinical classification of breast cancers reflects the important role of ovarian sex steroid hormones in cancer development and treatment. Cancers are classified by their oestrogen receptor (ER) and PR status. It has been well established that women with 'double positive' receptors have better outcomes [25]. Until relatively recently, treatment focus has been on targeting the ER with receptor agonists such as tamoxifen. Various challenges have meant that studying the exact role of progestogens in breast cancer pathogenesis is difficult. These include the difficulty of recreating the complex interactions between progestogens and other hormones, significant cyclical variation in progesterone (pre-menopausal women), limited data surrounding the role of progesterone metabolites, sensitivity of assays and difficulties in assessing isotypes of PR from clinical specimens, paracrine action of progesterone meaning its levels in circulation are unlikely to reflect levels in target tissues [17].

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As the effects of oestrogens and progestogens are so heavily linked, separating the role of progestogens without oestrogen has been one of the largest research challenges. It has been shown that both oestrogen and progesterone work together to affect transcription (contributing to breast cancer risk). As mentioned above, this combined with the large number of different metabolites for progesterone makes studying its role in pathogenesis extremely difficult. Mouse models and human trials have shown that only the combination of oestrogen and progestogens can induce mammary gland and epithelial proliferation [17]. Guidance for women with a current diagnosis or personal/strong family history of breast cancer state that hormone replacement therapy is generally contraindicated.

Cardiovascular system

The mechanisms by which sex hormones and specifically progesterone affect the cardiovascular system are not fully understood [26]. It is known that progesterone has both vasodilatory and vasoconstrictor effects depending upon the site of action. Women are at lower risk of cardiovascular disease compared to men during their reproductive years [21]. The reason behind this remains to be elucidated.

Until recently, it was also widely accepted that hormone replacement therapy was cardioprotective. The Heart and Estrogen/progestin Replacement Study (HERS) was the first study to investigate the effect of HRT on women with pre-existing heart disease. The study showed HRT not to be cardioprotective and to increase the risks of venous thromboembolism and gall bladder disease [27].

The issue of the relationship between cardiovascular risk remains unsolved. Again, studies on the effect of HRT on the cardiovascular system are heterogeneous. The most recent Cochrane review in 2017 [28], in fact, showed that even short-term use of HRT (up to a year) resulted in a very small increased risk of heart attack and venous thrombosis and in longer term increased the risk of stroke with combined HRT. Studies published since then remain heterogeneous and overall inconclusive on the exact risks and rewards of HRT therapy's effect on the cardiovascular system. The most recent NICE update (2015) concluded that the risk of cardiovascular disease with oestrogen alone is neutral or may be decreased, this is not the case with combined HRT. Additionally, a Cochrane review concludes that the impact of HRT on the risk in younger women starting HRT is either reduced or neutral [4].

An adverse lipid profile consisting of a higher ratio of low-density lipoprotein to high-density lipoprotein combined with overall raised cholesterol level significantly increases the risk of coronary artery disease. It is thought that HRT may alter lipid profile but the impact of this on the incidence of CVD is unclear.

A 2017 review 'progestogens and lipids' summarised the results of the studies [29] (Table 3):

However, these studies only investigate the short-term effect on lipid profile.

Bone

Although oestrogen is the dominant female sex hormone linked to the maintenance of bone mineral density (BMD) [30], progesterone plays a key role. It is thought that the differentiation of osteoblasts is dose dependent upon physiological progesterone levels [31]. Osteoblasts 'build bone' to increase BMD. Maintenance of BMD is important in reducing osteoporotic fractures in elderly women. A climacteric Meta-analysis showed that women lose almost 1% of spinal BMD per year if around a third of their ovulatory cycles are disturbed, e.g. in the perimenopause [25]. A meta-analysis in postmenopausal

Table 3
Progestogens and their effects upon Lipid profile.

Effect on lipid profile	Progestogen
Neutral	Progesterone, Dydrogesterone, Nomegestrol acetate
No conclusion – may mitigate beneficial effects of CEE	MPA
Reverses the beneficial effect on HDL but also favourably influences the TG, VLDL and LDL	NETA
Favourable effects	Drospirenone

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women demonstrated a 0.4% increase per year in BMD when receiving combined hormone replacement therapy compared with unopposed oestrogens [26]. The exact role of progesterone in the maintenance of BMD requires further study. The reduction in the risk of osteoporosis has only been shown whilst women are taking HRT.

Summary of progestagen-containing hormone replacement therapy options [32]

- **Medroxyprogesterone acetate (MPA)**:
  - Historically, one of the most commonly prescribed and studied progestin [27].
  - Ability to prevent endometrial hyperplasia has been overshadowed recently as multiple studies show increased breast cancer and coronary heart disease risk.
  - Likely to have adverse effects on the lipid profiles of women (see Table above).
- **Micronized progesterone** [3]:
  - Bioidentical to ovarian progesterone.
  - Frequently prescribed, protects endometrium [33] and has little impact upon serum lipids and hepatic metabolism [28].
  - Effect on the cardiovascular system is neutral and may even decrease BP [34].
  - Appears to have less impact on the breast with a lesser increase in breast cancer risk [35].
  - Favourable bleeding pattern compared with MPA when used in combined HRT. In 2002, Linfield et al. demonstrated a decreased number of days bleeding, quantity of bleeding and number of episodes of 'excessive bleeding' in women using micronized progestin + CEE [36], compared with MPA + CEE.
- **Levonorgestrel-releasing intrauterine system (IUS), e.g. Mirena, Jaydess**:
  - Originally marketed as long-acting reversible contraceptive agents; however, also effective endometrial protection for menopausal women taking oestrogen [37].
  - Meta-analysis of ability to prevent or reduce endometrial hyperplasia concludes that the IUS is as good as or better than oral equivalents [38,39].
  - Side effects include irregular bleeding, nausea and abdominal pain. However, a recent Cochrane review suggests that there is no reported difference in tolerance vs oral progestins [40].
  - Useful in women with oral progestin intolerance or likely to require endometrial protection for 4 years.
  - Effective as a contraceptive, the treatment of HMB and endometrial protection in women with breast cancer on adjuvant tamoxifen [41].
  - Acts locally with minimal systemic concentrations, it is hypothesized that impact on long-term cardiovascular and breast cancer risk would be insignificant. However, there is minimal evidence of these long-term outcomes [23] and would require further study.
- **Quarterly progestin regimens**:
  - Investigated initially for those women intolerant of progestin.
  - However, these do not increase compliance [42] and are associated with higher risk of endometrial hyperplasia and progression to endometrial cancer compared with conventional HRT cycles [36]. As such their use is not recommended at present.
- **Combination oestrogen-progestin products (oral):**
  - Drospirenone:
    - 17-alpha spironolactone derivative drospirenone (see above).
    - Decreases the risk of endometrial hyperplasia when compared with unopposed oestrogen [43].
    - Reduces the risk of osteoporosis [38].
    - Combined drospirenone/oestrogen therapy has a favourable impact on cholesterol and triglyceride levels [37].
    - Drospirenone is also anti-aldosterone and lowers BP.
  - Testosterone derivatives:
    - Have variable effects depending on structure as discussed above.
    - Overall strongly progestogenic and moderately anti-gonadotropic [9].
  - Pregnane derivatives (17α- Hydroxyprogesterone derivatives):

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- For example, Cyproterone acetate
- Competitively binds to androgen receptors, resulting in the most anti-androgenic properties of all progestins [9].
- Can be used to treat hirsutism, androgenic alopecia and androgen-induced acne resistant to other anti-androgenic drugs [9].

- Bioidentical Progesterone – Compounded vs Regulated [44,45]:
  - 'Bioidentical hormones' are preparations made from plant sources. Identical in structure and action to hormones such as oestradiol, progesterone, dehydroepiandrosterone, testosterone and levothyroxine as synthesised by the human ovary, adrenal and thyroid, respectively. Hormones identical to those produced within the body form an important component of HRT with high benefits particularly in women with risk factors.
  - However, it is very important to differentiate between 'compounded' bioidentical hormone replacement therapy from conventionally prescribed 'regulated' bioidentical hormone replacement therapy. In UK, MHRA (Medicines and Healthcare products Regulatory Agency) has developed regulatory pathways and rigorous processes for drug development and evaluation. The biggest drawback with compounded hormones is that they are not subjected to these and are not scientifically evaluated through randomised controlled trials for optimum dosage, safety and efficacy.
  - This particularly is very important while using combined HRT. If the total amount, efficacy and side effect profile of a progestin within a compounded combined HRT preparation is unknown, this can cause significant side effects. For example, the effect on endometrial protection and avoidance of breakthrough bleeding may not be as consistent. The cardiovascular profile and breast cancer risks will remain uncertain and may be even high in certain cases.
  - Most of the international Menopause and Endocrine societies including BMS (British Menopause Society) do not endorse or recommend the use of compounded HRT as they are not evidence-based for effectiveness and safety, and because effective regulated bioidentical HRT options are available.

- Transdermal —
  - Patches containing oestrogen and norethisterone are also available.
  - Preparations vary but they appear to be comparable to oral and IUS in the relief of hot flushes and reduction of endometrial hyperplasia.
  - They do not increase coagulation.

Summary

Progesterone plays a pivotal role in the management of abnormal uterine bleeding. Its role is diverse and encompasses the reduction or cessation of excessive menstrual bleeding as well as the endometrial protection and treatment of endometrial hyperplasia. The preparation of progestin can be extremely important in hormone replacement therapy, but the route of administration is also important in both the treatment of AUB and endometrial hyperplasia. The route can be selected based on patient preference, side effect profile and the expected duration of use. The IUS has emerged as a well-accepted, cost effective, lower risk alternative for endometrial protection and the management of AUB.

Studies linking HRT to side effects such as breast cancer, venous thromboembolism and cardiac disease will need to expand to explore the effects of the different progestins in detail. If this were to be undertaken, then it would allow the individualised selection of HRT based on a woman's specific past medical history and risk profile.

Declaration of Competing Interest

My colleagues, Professor Mary Ann Lumsden, Dr Prashant Purohit and I have no conflict of interest to declare with regards to our submission: Progesterone and Abnormal uterine Bleeding/

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Practice points

- Acute presentations of abnormal uterine bleeding should be managed according to women's individual risk profile and preference. General principles are a strategy of hormonal, e.g. norethisterone or COCP and/or non-hormonal options, e.g. tranexamic acid.
- Longer term management of abnormal uterine bleeding follows similar principles; however, the progesterone intrauterine system (IUS) is emerging as an increasingly popular and efficacious option.
- MPA-containing HRT has been linked to increased breast cancer and cardiovascular risk. It may be advisable to try a local progesterone such as the IUS or a micronized oral or topical progesterone as first line.

Research agenda

- Current best clinical practice of progesterone use
- Development and types of progestogens
- Summary of research surrounding safety of progestogens – particularly in Hormone Replacement Therapy (HRT)

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