Menstrual cycle disorders

**Premenstrual syndrome (PMS)**

* PMS encompasses both ***mood changes***and ***physical symptoms***. Symptoms may start up to 14 days before menstruation, although more usually they begin just a few days before and disappear at the onset of, or shortly after, menstruation.
* Numerous studies have demonstrated that this condition can cause substantial impairment of normal daily activity, including reduced occupational activity and significant levels of work absenteeism.
* Severity varies from cycle to cycle and may be influenced by other life factors such as stress and tiredness.
* The most severe form of PMS may be referred to as premenstrual dysphoric disorder (PMDD).

***Diagnostic criteria for premenstrual dysphoric disorder (PMDD):***

1. One-year duration of symptoms which are present for the majority of cycles (occur luteal/remit follicular)
2. Five of the following symptoms must occur during the week before menses and remit within days of menses:

• Irritability

• Depressed mood or hopelessness

• Affective lability (sudden mood swings)

• Tension or anxiety

• Decreased interest in activities

• Change in sleep patterns

• Difficulty concentrating

• Feeling out of control or overwhelmed

• Lack of energy

• Other physical symptoms, for example, breast tenderness, bloating

• Change in appetite, for example, food cravings.

* This seriously interferes with work, social activities, and relationships.

**Etiology**

 PMS is not seen before puberty, during pregnancy or in postmenopausal women, and therefore, the ***ovarian hormones*** have been implicated.

* *The mineralocorticoids, prolactin, androgens, prostaglandins, endorphins*.
* *Nutritional factors* (e.g. pyridoxine, calcium and essential fatty acids)
* *Hypoglycaemia* may be involved. In addition:
* Changes in CNS function have been implicated as cerebral blood flow in the temporal lobes is decreased premenstrually in PMS sufferers.

 As symptoms vary so much from cycle to cycle, and from individual to individual, it is likely that different etiological factors apply to different women.

**Hormones**

* The cyclicity of PMS suggests an ovarian involvement. This is substantiated by the fact that it is still experienced after hysterectomy if the ovaries are left intact and that it disappears during pregnancy and after the menopause.
* *One theory attributes PMS to luteal phase* ***progesterone*** *deficiency leading to a progesterone/estradiol imbalance,* but there is no direct clinical evidence to support this in terms of serum progesterone levels.

  **Estradiol** increases neuronal excitability possibly via increasing the activity of glutamate (an important excitatory neurotransmitter). **Progesterone**, and its metabolites, can bind to the γ-aminobutyric acid A (GABA-A) receptor. The **mineralocorticoid, aldosterone**, may be associated with the increase in fluid retention as serum levels of this hormone are elevated in the luteal phase.

 **Prolactin** is secreted from the *decidual cells* at the end of the luteal phase of the menstrual cycle as well as from the *anterior pituitary*. This hormone has a direct effect upon *breast tissue* and hence may be associated with *breast tenderness*. Prolactin is also associated with *stress* and has an indirect relationship with *dopamine metabolism* and release in the CNS. It promotes *sodium, potassium and water retention.*

 **Prostaglandins** may also be implicated in the etiology of PMS as synthesis of these autocoids can be affected by the sex hormones. Prostaglandin imbalance is implicated in PMS as increased synthesis of certain prostaglandins, for example, PGE2, have *antidiuretic and central sedative* effects as well as promoting capillary permeability and vasodilation.

**Vitamins and minerals**

* Pyridoxine phosphate is a co-factor in a number of enzyme reactions, particularly those leading to production of dopamine and serotonin (5HT).
* It has been suggested that disturbances of the oestrogen/progesterone balance could cause a relative deficiency of pyridoxine, and supplementation with this vitamin appears to ease the depression sometimes associated with the oral contraceptive pill.
* Decreased dopamine levels would tend to increase serum prolactin, and decreased serotonin levels could be a factor in emotional disturbances, particularly depression.

**Essential fatty acids**

 Essential fatty acids, such as γ-linolenic (or gamolenic acid/ GLA), provide a substrate for prostaglandin synthesis. γ-Linolenic is converted into dihomo-γ-linolenic acid, which forms the starting point for the synthesis of prostaglandins of the 1 series (e.g. PGE1).

 It has been suggested that women with PMS are abnormally sensitive to normal levels of prolactin, and that PGE1 is able to attenuate the biological effects of this hormone.

 Hence, if there is a *γ-linolenic deficiency*, then there is less substrate for PGE1 synthesis. Therefore, the effect of prolactin with respect to breast tenderness, fluid retention and mood disturbances may be exaggerated.

**Symptoms**

 Symptoms occur 1–14 days before menstruation begins and disappear at the onset or shortly after menstruation begins.

 For the rest of the cycle, the woman feels well. Symptoms are cyclical; although they may not be experienced every cycle, and can be either physical and/or psychological (see Boxes 45.1. and 45.2).

***Diagnostic criteria for premenstrual syndrome (PMS)***

Patient reports ≥1 of the following affective and somatic symptoms during the 5 days before menses in each of three prior menstrual cycles:

**Affective**  **Somatic**

Depression Breast tenderness

Angry outbursts abdominal bloating

Irritability Headache

Anxiety Swelling of extremities

Confusion

Social withdrawal

**Management**

**Non-pharmacological strategies**

* Maintenance of good general health is important, especially with respect to diet and possible deficiencies.
* Dietary modifications that may be helpful include restricting caffeine and alcohol intake.
* Smoking can also exacerbate symptoms.
* Exercise may help, as may learn simple relaxation techniques.
* If fluid retention is a problem, then reducing fluid and salt intake may be of value.

**Pharmacological management**

**Progestogens:**

* Synthetic progestogens, in preparations such as Cyclogest® and Duphaston®, have been used in the past.
* However, because of the lack of convincing trial evidence and the risk of side effects, the use of progestogens is no longer recommended.
* Possible side effects include weight gain, nausea, breast discomfort, breakthrough bleeding and changes in cycle length.
* Problems arise because some synthetic progestogens, especially 19-nor compounds such as norethisterone and levonorgestrel, also display some affinity for glucocorticoid, mineralocorticoid and androgen receptors.
* *Third-generation progestogens* that have an ethyl group at C13 on the steroid nucleus (gestodene, desogestrel and norgestimate) have the least androgenic activity. However, all the 19-nor compounds are still orally active.

**Combined oral contraceptives (COC):**

* Some women are helped by the COC pill because it prevents ovulation from taking place.
* However, the use of exogenous oestrogen may be contraindicated in some cases because it can increase the risk of venous thromboembolism. This occurs because oestrogen decreases blood levels of the potent natural anticoagulant antithrombin III and at the same time increases serum levels of some clotting factors.
* It is thought that use of third-generation progestogens is associated with increased resistance to the anticoagulant action of activated protein C. Oral contraceptive treatment diminishes the efficacy with which activated protein C downregulates *in vitro* thrombin formation.
* The combination of ethinylestradiol with drospirenone is available as an oral contraceptive and appears to be useful in the management of PMS. Drospirenone is a derivative of spironolactone, with affinity for progesterone receptors, but it also acts as a mineralocorticoid antagonist.

**Bromocriptine:**

* Bromocriptine stimulates central dopamine receptors and thus inhibits the release of prolactin. It may be useful for breast tenderness and occasionally has beneficial effects upon fluid retention and mood changes.
* It should be used in small doses, for example, 1–1.25 mg at bedtime with food, to avoid the side effects of nausea and faintness due to hypotension. The dose can be slowly increased to 2.5 mg twice a day if required.

**Danazol:**

* Danazol is a synthetic steroid derived from ethisterone.
* Danazol interacts with androgen receptors (weak agonist), but it also has some affinity for the progesterone receptor (weak agonist & antagonist).
* It inhibits the pulsatile release of gonadotrophins from the anterior pituitary and so abolishes cyclical ovarian activity (anti-gonadotrophin), leading to *amenorrhoea* in the majority of women and a *subsequent fall in serum estrogen levels* (anti-estrogen).
* However, because of the high incidence of side effects, it tends to be used as a last resort for relief of severe mastalgia and mood changes.

**Gonadotrophin-releasing hormone analogues:**

* GnRH analogues, sometimes referred to as gonadorelin analogues, are useful for managing the physical symptoms, but are less effective with respect to emotional symptoms.
* These agents inhibit the hypothalamic pituitary–gonadal axis. However, they can only be used for short periods of time, no more than 6 months, because they induce a hypo-oestrogenic state, and therefore bone loss becomes significant after 6 months' treatment.

**Prostaglandin synthesis inhibitors:**

* Improvements in tension, irritability, depression, headache and general aches and pains can be seen in some women who take prostaglandin synthesis inhibitors.
* Most of the information available centers upon the use of mefenamic acid at doses of 250 mg three times a day 12 days before a period, increasing to 500 mg three times a day 9 days before the period and continuing until the third day of menstruation.

**Antidepressants**

The selective serotonin reuptake inhibitors (SSRIs) are becoming more popular in the treatment of PMS-related depression because they are effective and well tolerated.

**Menorrhagia**

 Blood loss is considered to be excessive if it exceeds 80 mL per period, any change in menstruation, whether real or perceived, may be disturbing with respect to social, occupational or sexual activities and can lead to other problems including depression and concern about an undiagnosed problem such as cancer. Physically excessive blood loss will precipitate iron deficiency anemia (haemoglobin <12 g/dL) which, if left undiagnosed and untreated, will compound the problems outlined earlier.

**Etiology and investigation**

 The etiology of menorrhagia can be divided into three categories:

* underlying pelvic pathology
* systemic disease
* dysfunctional uterine bleeding

**Causes of menorrhagia (percentage frequency)**

* Dysfunctional uterine bleeding (60%), that is cause is unknown
* Other gynecological causes (30%):
* Uterine or ovarian tumours
* Endometriosis
* Pelvic inflammatory disease
* Intrauterine contraceptive devices
* Early pregnancy complications
* Endocrine and hematological causes (<5%)
* Thyroid disorders, for example hypothyroidism
* Platelet problems and clotting abnormalities

 **Pelvic pathologies** associated with menorrhagia include myomas (fibroids, common benign tumours of the myometrium), endometriosis, adenomyosis (penetration of endometrial tissue into the myometrium), endometrial polyps, polycystic ovarian disease and endometrial carcinoma.

 Although endometrial cancer is more typically seen in postmenopausal women, approximately 50% of those patients diagnosed with it premenopausally will have associated menorrhagia.

 **Systemic diseases** from which menorrhagia may stem include hypothyroidism, disorders involving the coagulation system such as elevated endometrial levels of plasminogen activator, and systemic lupus erythematosus (SLE).

 About 60% of menorrhagia sufferers have no underlying systemic or pelvic pathology and have ovulatory cycles, these patients are said to have **dysfunctional uterine bleeding**. Occasionally, cycles may be anovulatory, with heavy blood loss because the endometrium has become hyperplastic under the influence of oestrogen. In addition, use of an intrauterine contraceptive device may also increase menstrual blood loss.

 **Prostaglandins** appear to play a role in the local mechanisms and have been implicated in menorrhagia. Studies have suggested an association between the type and quantity of endometrial prostaglandin synthesis and the degree of menstrual blood loss.

 Women with heavy periods had raised endometrial levels of PGF2α and PGE2 and that blood loss could be reduced by the use of drugs inhibiting prostaglandin formation.

 The availability of arachidonic acid, a substrate for prostaglandin synthesis, is also greater in women with menorrhagia.

 Levels of the vasodilators or their metabolites, PGI2 and nitric oxide (NO), are also increased in the menstrual blood collected from women with excessive blood loss.

 It has been suggested that menorrhagia is an angiogenesis-related disease associated with changes in the pattern of vascular fragility involving the up-regulation of various vascular endothelial growth factors (VEGF).

 Excessive menstrual blood loss is the most common cause of **iron deficiency anemia** in women of reproductive age. While in healthy, well-nourished woman, it has been estimated that menstrual blood loss would have to exceed 120 mL to precipitate iron deficiency anemia, so measurement of full blood count (including red blood cell and serum ferritin levels), and in particular, haemoglobin concentration.

 **Thyroid** function should also be assessed.

 If **fibroids** are suspected, then pelvic ultrasound may be required.

 Endometrial biopsy is needed if there is an associated irregularity of menstruation or if intermenstrual or postcoital bleeding is present.

**Treatment**

 The management of menorrhagia depends upon the cause of the condition.

* Drug treatment is also influenced by a woman's contraceptive needs; for example, **COCs** can reduce menstrual blood loss by up to 50%, but in women over 35 years of age who smoke, this form of therapy would need careful consideration.
* Long-term, long-acting **progestogens**, however, may render a woman amenorrhea.
* Other hormonally based therapies include the **GnRH** analogues; although their propensity to induce a hypo-oestrogenic state with long-term use may be problematic (a 6-month course would reduce trabecular bone density by 5–6%).
* **Danazol** can reduce menstrual blood loss but its use is generally prohibited by its side-effect profile.
* Prostaglandins have been implicated in the etiology of several forms of menorrhagia. Therefore, **NSAIDs** may be of use in some patients, especially if there is pain associated with menstruation. The NSAIDs appear to be most effective in women with the heaviest blood loss, for example, mefenamic acid 500 mg three times daily from day 1 until heavy flow ceases.
* Women with menorrhagia have greater endometrial fibrinolytic activity, hence the use of **antifibrinolytic drugs**, which are plasminogen activator inhibitors. ***Tranexamic acid*** reduces menstrual blood loss by up to 50%, the recommended dose being 1 g three times daily starting on the first day of menses for up to 4 days of menses. This class of drugs decreases menstrual blood loss better than NSAIDs and oral luteal phase progestogen.
* The levonorgestrel intrauterine contraceptive devices (also known as intrauterine systems or **LNG-IUS**) can be left in place for up to 5 years following insertion. They reduce menstrual blood loss by up to 90% after 12 months of use.

 Slow-release progestogenic devices such as **nesterone** implants and vaginal rings also reduce menstrual blood loss and promote amenorrhoea.

* **Surgery**: including hysterectomy & endometrial ablation, this can be done by electrosurgical, laser, microwave or thermal techniques.

 Pre-treatment with a single dose of a GnRH agonist before the ablation procedure gives a better result. These preparations cause an initial stimulation of gonadotrophin release which then suppresses the hypothalamic-pituitary axis, producing a hypo-oestrogenic state. If circulating levels of oestrogen are low, then endometrial growth will not be stimulated; thus, it will be thinner, making the surgical endometrial destruction more effective.

**Endometriosis**

 Endometriosis is a condition in which endometrial tissue is found outside the uterus. These so-called ectopic endometrial foci have been found outside the reproductive tract; in the gastro-intestinal tract, the urinary tract and even the lungs.

**Etiology**

* Endometriosis is found in women in whom the normal route for the menstrual flow is disrupted, such as when there is some genital tract abnormality.
* Women who have frequent and heavier periods also seem to be more likely to suffer from endometriosis.
* Endometrial tissue from women with endometriosis has aromatase activity which can be stimulated by PGE2. Aromatase enzyme converts androgenic precursors into oestrogen and oestrogen stimulates biosynthesis of PGE2.

**Symptoms**

Although not all women with endometriosis are symptomatic, the pelvis is the most commonly affected site. Consequently, most of the symptoms of endometriosis relate to this region.

* Symptoms take the form of dysmenorrhoea and pelvic pain.
* Dyspareunia often with postcoital discomfort is also common and there may also be menstrual irregularities.
* The link between endometriosis and infertility is recognised, but the mechanisms involved have not been established. If the ovaries or fallopian tubes themselves are directly affected by the endometriotic lesions, then fertility may be compromised by different ways including ovulation disorders such as luteinized unruptured follicle syndrome, anovulation, premature ovulation; hyperprolactinaemia.
* Prostaglandin levels, along with macrophage concentrations, are raised in the peritoneal fluid of women with endometriotic explants, and these may alter tubular and uterine motility within the abdomen.
* **Outside** the reproductive tract, endometrial deposits can be found along the urinary and gastro-intestinal tracts.
* If the urinary tracts are involved, then the patient may suffer from cyclical haematuria, dysuria or even ureteric obstruction.
* If there is gastro-intestinal tract involvement, then symptoms could include dyschezia, cyclical tenesmus and rectal bleeding or even obstruction.
* Very rarely, the lesions are found at more distant sites such as the lungs, where they could cause cyclical haemoptysis.

**Diagnoses of endometriosis**

* These include ultrasound, MRI scans, and gynecological examinations.
* Definitive diagnosis is made via visualization of lesions during surgery (laparoscopy or laparotomy).

**Treatment**

 The aims of treatment in endometriosis are to relieve symptoms and improve fertility if pregnancy is desired; treatment can be either **surgical** or **medical**.

 Medical treatment utilizes the fact that endometriotic tissue is oestrogen dependent, and any drug therapy that will oppose the effects of oestrogen should, among other things, inhibit the growth of the endometriotic tissue. Hence, the choices of drug treatment are as follows:

* **GnRH analogues** such as buserelin, goserelin, leuprorelin and nafarelin. These initially stimulate the hypothalamic–pituitary–ovarian axis but thereafter induce a hypo-oestrogenic state by paradoxically inhibiting follicle-stimulating hormone (FSH) and LH release.
* Low-dose **COC** (20–30 μcg of ethinylestradiol) monophasic preparations have been found to be as effective as GnRH analogues, and they may slow down disease progression in young women and preserve future fertility.
* Compounds with androgenic activity such as **danazol** also inhibit pituitary gonadotrophin release by interfering with the negative feedback and cause atrophy of endometrial tissue.
* **Progestogens** such as dydrogesterone, medroxyprogesterone acetate and norethisterone initially cause decasualization of the endometrial tissue followed by glandular atrophy.