Premenstrual syndrome - Management

Scenario: Diagnosis of premenstrual syndrome

safe practical clinical answers - *fast*

How do I know my patient has it?

- It is generally accepted that, to establish a diagnosis of premenstrual syndrome (PMS), the woman should have symptoms consistent with PMS that regularly recur during the luteal phase (second half) of the menstrual cycle, followed by a symptom-free period that coincides with the onset of menses or soon after [MeReC, 2003].
- Difficulty in diagnosis often occurs because PMS can present with a large number of symptoms which are common to a range of conditions [Rapkin and Mikacich, 2008].
- Ask the woman to record a daily symptom diary for two or three cycles [MeReC, 2003].
- Symptoms which may be reported include [MeReC, 2003; RCOG, 2007; Brown et al, 2009]:

  - Psychological — mood swings, irritability, depressed mood, anxiety, feeling out of control, poor concentration, change in libido, food cravings.
  - Physical — breast tenderness, bloating, headaches, back ache, weight gain, acne, gastrointestinal disturbance, exacerbation of chronic illnesses (for example asthma, epilepsy, or migraine).
  - Behavioural — reduced visio-spatial and cognitive ability, aggression, increase in accidents.

- Investigations are not usually helpful in making the diagnosis of PMS.

What else might it be?

- **Conditions to exclude include:**

  - Depression
  - Anxiety and panic disorders
  - Hypothyroidism
  - Anaemia
  - Dysmenorrhoea
  - Irritable bowel syndrome
  - Interstitial cystitis
  - Endometriosis
  - Chronic fatigue syndrome
  - Fibromyalgia
  - Systemic lupus erythematosus

[Rapkin and Mikacich, 2008]

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scenario: premenstrual syndrome

CKS safe practical clinical answers - *fast*

How should I manage a woman with premenstrual syndrome?

- **Management should be tailored according to the severity and type of symptoms, and the woman's preferences and any desire to become pregnant.**
- **For women with mild symptoms of premenstrual syndrome (PMS), offer lifestyle advice.**

O Regular, frequent (2–3 hourly), small balanced meals rich in complex carbohydrates.

O Regular exercise.

O Smoking cessation.

O Alcohol restriction.

O Regular sleep.

O Stress reduction.

- **For women with moderate PMS, offer lifestyle advice and consider:**

O **A new-generation combined oral contraceptive** (COC; this is off-label use if used solely to treat PMS symptoms), particularly if the woman requires contraception. The COC can be used cyclically or continuously, but the first-line choice of COC is not clear.

O There is more evidence to support the use of drospirenone-containing COCs (for example Yasmin®) than other preparations, but this is not recommended for use in Scotland by the Scottish Medicines Consortium and it is more expensive than competitor products.

O One trial suggests that COCs containing desogestrel (for example Marvelon®) are of similar effectiveness as drospirenone-containing COCs.

O Expert opinion suggests that other COCs, particularly those containing norgestimate (for example Cilest®) or gestodene (for example Femodene®), may also be effective, especially if they have been used before and have been found to be of benefit.

O Inform the woman that it is not possible to predict whether her PMS symptoms will respond.

O **Paracetamol or a nonsteroidal anti-inflammatory drug (ibuprofen, diclofenac, naproxen, mefenamic acid) if the predominant problem is pain** (for example headache, generalized aches and pains).

O If the predominant problem is breast pain — see the CKS topic on Breast pain - cyclical.

O **Cognitive behavioural therapy** (CBT; referral is likely to be required) if it is thought the woman would benefit from psychological intervention.

- **For women with severe PMS, offer lifestyle advice and consider:**

O **The treatment options outlined above for moderate PMS** (a new generation COC, CBT, paracetamol, or a nonsteroidal anti-inflammatory drug).

- **A selective serotonin reuptake inhibitor** (SSRI; this is off-label use).

- Do not prescribe an SSRI if there is doubt about the diagnosis, or a lack of experience in prescribing them. Do not prescribe without the advice of a specialist in people younger than 18 years of age.

- The woman should be informed that this is an off-label use of SSRIs.

- SSRIs can be taken either continuously or just during the luteal phase (for example days 15–28 of the menstrual cycle, depending on its length). Give an initial trial of 3 months' treatment; if there is benefit, continue treatment for 6 months to 1 year.

- Suggested doses (for either continuous or luteal phase dosing) are fluoxetine 20 mg daily, sertraline 50 mg to 100 mg daily, citalopram 20 mg daily, or paroxetine 20 mg daily.

- Monitor the woman's response to treatment closely, including asking about any thoughts of self-harm.

Basis for recommendation

Advice

▪ The recommendation to give lifestyle advice to women with premenstrual syndrome (PMS) is based on a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007]. Specific recommendations on what to advise are based on expert opinion in a practice bulletin from the American College of Obstetrics and Gynaecology [ACOG, 2001] and a review [Bhatia and Bhatia, 2002].

▪ Most lifestyle changes have no strong evidence to support them, but may benefit the overall health of women with mild symptoms. There is weak evidence that exercise improves PMS symptoms [Daley, 2009].

Choice of treatment

▪ The recommended treatment options are based on a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007] and the available evidence for individual treatments.

▪ CKS found no comparative studies of interventions; therefore CKS recommends that choice of treatment should be based on clinical judgement and the woman's preference.

Combined oral contraceptive (COC)

▪ Drospirenone is a synthetic progestogen which has antimineralocorticoid properties. COCs containing drospirenone (for example Yasmin®) produce fewer adverse effects than those with other progestogens and are likely to be effective at improving PMS symptoms. However, evidence of efficacy for the treatment of PMS symptoms discussed in a Cochrane systematic review [Lopez et al, 2009] comes from small, short-term (three cycles of treatment), randomized controlled trials (RCTs). A lower-dose COC containing 20 micrograms of ethinylestradiol and 3 mg drospirenone is licensed in the US, but is not currently available on the NHS in the UK [RCOG, 2007]; this treatment is therefore not recommended by CKS.

▪ Second-generation COCs are considered by experts to be less useful because the progestogens they contain (for example levonorgestrel or norethisterone) can reproduce PMS-type symptoms in some women [RCOG, 2007]. Evidence from one RCT found COCs containing drospirenone to be more effective at reducing PMS than those containing levonorgestrel.

▪ Evidence from a prospective study supports the continuous use of COCs, which is more effective in reducing PMS symptoms compared with the standard 21-day regimen. More research is needed to confirm this [RCOG, 2007].

Selective serotonin reuptake inhibitor (SSRI)

▪ Treatment with an SSRI is only recommended for women with severe PMS symptoms; this is in line with a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007], a practice bulletin from the American College of Obstetrics and Gynaecology [ACOG, 2001], and expert opinion [Rapkin and Mikacich, 2008]. Only a minority (3–5%) of women of reproductive age have PMS symptoms of a severity that has been shown to benefit from treatment with an SSRI [DTB, 2002].

▪ A Cochrane systematic review found evidence to support the use of SSRIs in women with severe PMS symptoms [Brown et al, 2009]. However, SSRIs are associated with adverse effects (for example nausea, insomnia, fatigue, dizziness, sweating, decreased concentration, and sexual dysfunction) [DTB, 2002]. They should not be prescribed without the advice of a specialist in people younger than 18 years of age; evidence of efficacy is lacking and there is an increased risk of harmful outcomes (such as self harm and suicidal thoughts) [BNF 57, 2009].

▪ The recommended doses are based on those most commonly used in clinical studies [Brown et al, 2009]. For paroxetine, doses of 12.5 mg to 25 mg daily have been most commonly studied. However, this formulation is not marketed in the UK so a dose of 20 mg is suggested instead.

▪ Evidence to support giving SSRIs during the symptomatic premenstrual phase is increasing [RCOG, 2007]. Evidence from a Cochrane systematic review found luteal phase-only SSRI regimens and continuous SSRI regimens were both effective, although comparative data were lacking.

Analgesia

▪ CKS found no evidence on the efficacy of paracetamol and commonly used nonsteroidal anti-inflammatory drugs for the treatment of PMS symptoms; they have been recommended for headache and general aches and pains associated with PMS in line with accepted clinical practice. Evidence from small RCTs of mefenamic acid suggests improvement in a wider range of PMS symptoms.

Cognitive behavioural therapy (CBT)

▪ The recommendation to consider CBT as a treatment option is based on a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007].

▪ A systematic review found evidence that CBT produces beneficial effects on anxiety, depression, and daily activities (and behaviour over a longer time period). However, the evidence was limited by methodological problems and differences between studies [Busse et al, 2009].

When should I refer a woman with premenstrual syndrome?

- Refer the woman to a psychiatrist if there is marked underlying psychopathology in addition to premenstrual syndrome (PMS).
- Consider referral to a clinic with a specific interest in PMS (or a general gynaecology clinic if this is not available) if the symptoms are severe and appropriate primary care measures have been explored but have failed.

Basis for recommendation

This recommendation is based on expert opinion in a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007] and feedback from CKS expert reviewers.

What treatments are not recommended for initiation in primary care?

- Treatments which are not recommended for initiation in primary care for premenstrual syndrome (PMS) are:
  - Progesterone or progestogens used alone.
  - Antidepressants other than selective serotonin reuptake inhibitors (SSRIs).
  - Alprazolam.
  - Diuretics.
  - Danazol.
  - Transdermal oestrogen.
  - Gonadotrophin releasing hormone analogues.
  - Complementary therapies and dietary supplements (such as vitamin B_6, calcium and vitamin D, magnesium, evening primrose oil, and agnus castus).
- Hysterectomy and bilateral salpingo-oophorectomy may be considered under certain circumstances in secondary care for women with severe PMS.

Basis for recommendation

Progesterone and progestogens

- It is postulated that treatment with progesterone may restore a deficiency, balance menstrual hormone levels, or reduce the effects of decreasing progesterone levels on the brain, or on electrolytes in the blood [Ford et al, 2009].
- The Royal College of Obstetricians and Gynaecologists does not recommend progesterone or progestogens for women with premenstrual syndrome (PMS) on the basis of insufficient evidence [RCOG,

2007]. A Cochrane systematic review [Ford et al, 2009] also found insufficient evidence to conclude that progesterone is effective for treating PMS.

▪ The adverse effects of progesterone and progestogens include alteration of menstrual cycle length, breakthrough bleeding, and occasional soreness on topical application [Ford et al, 2009].

Antidepressants other than selective serotonin reuptake inhibitors (SSRIs)

▪ The Royal College of Obstetricians and Gynaecologists' guideline on the *Management of premenstrual syndrome* did not cover the use of antidepressants other than SSRIs for women with PMS [RCOG, 2007]. Tricyclic antidepressants have a significant adverse effect profile.

Alprazolam

▪ Low dose alprazolam has been used for women with severe PMS and has been found to be effective, but this is an off-label use and there is a possibility of dependence [Bhatia and Bhatia, 2002; MeReC, 2003]. It cannot be prescribed on the NHS [BNF 57, 2009].

Diuretics

▪ Guidelines from the Royal College of Obstetricians and Gynaecologists and the American College of Obstetrics and Gynaecology did not cover the use of diuretics for treating PMS. Limited evidence from small trials suggests that spironolactone may be beneficial, particularly for women with bloating symptoms.

Transdermal oestrogen

▪ Oestrogen patches (given with a progestogen to prevent endometrial hyperplasia) may help with PMS and are offered as an option in a guideline from the Royal College of Obstetricians and Gynaecologists [RCOG, 2007]. However, in view of the fact that there is little evidence for this, and insufficient evidence to determine whether premenopausal women using percutaneous oestradiol patches and cyclical progestogen are at increased risk of endometrial or breast cancers [RCOG, 2007], CKS does not recommend their use in primary care.

Danazol

▪ Although it is effective for treating PMS, danazol is not recommended for use in primary care as this is an off-label use and there is a risk of virilizing adverse effects (such as weight gain, acne, hirsutism, and voice changes). Long-term use can also reduce high-density lipoprotein levels [RCOG, 2007].

Gonadotrophin-releasing analogues (GnRH analogues)

▪ GnRH analogues are not recommended for use in primary care for PMS because this is an off-label use, treatment is limited to 6 months, and there is a need for additional hormone replacement therapy to reduce trabecular bone loss [RCOG, 2007]. Long-term use of GnRH analogues is limited by their adverse effects (for example hot flushes and osteoporosis) and high cost [MeReC, 2003].

Complementary treatments and dietary supplements

- For most complementary treatments and dietary supplements the evidence of benefit is weak or inconclusive; for some there is little regulation ensuring efficacy or safety [RCOG, 2007].

- For further discussion of the evidence on specific treatments, see agnus castus, calcium and vitamin D, evening primrose oil, magnesium, and vitamin B6 (pyridoxine).

Hysterectomy and bilateral salpingo-oophorectomy

- Surgical interventions are discussed as an option for women with severe PMS in the Royal College of Gynaecologists and Obstetricians' guideline, on the basis of observational studies [RCOG, 2007]. However the expertise and facilities necessary are only available in secondary care.

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

1st line: lifestyle advice

Age from 12 years onwards

Advice note: lifestyle advice

Age: from 12 years onwards
Licensed use: no

Patient information: The following things may help to ease PMS. Eat regular, frequent, small balanced meals rich in complex carbohydrates. Take regular exercise. Stop smoking. Don't drink too much alcohol. Get regular sleep.

COCs monophasic: EE 30-35mcg with drospirenone or norgestimate

Age from 13 to 50 years

Yasmin: drospirenone 3mg + ethinylestradiol 30mcg

Yasmin tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £14.70
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a healthcare professional.

Cilest: norgestimate 250mcg + ethinylestradiol 35mcg

Cilest 250microgram / 35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £2.99
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a healthcare professional.

COCs monophasic: EE 30mcg with gestodene or desogestrel

Age from 13 to 50 years

Femodene: gestodene 75mcg + ethinylestradiol 30mcg

Femodene tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £7.18
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Femodene ED: gestodene 75mcg + ethinylestradiol 30mcg

Femodene ED tablets
Take one tablet once a day. See package insert for full instructions.
Supply 84 tablets.

Age: from 13 years to 50 years
NHS cost: £7.18
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Katya 30/75: gestodene 75mcg + ethinylestradiol 30mcg

Katya 30/75 tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £5.03
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Millinette 30/75: gestodene 75mcg + ethinylestradiol 30mcg

Millinette 30microgram/75microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £4.85
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Marvelon: desogestrel 150mcg + ethinylestradiol 30mcg

Marvelon 150microgram/30microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £6.70
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Gedarel 30/150: desogestrel 150mcg + ethinylestradiol 30mcg

Gedarel 30microgram/150microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £4.93
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Paracetamol

Age from 12 years onwards

Paracetamol tablets: 500mg to 1g up to four times a day

Paracetamol 500mg tablets
Take one or two tablets every 4 to 6 hours when required for pain relief. Maximum of 8 tablets in 24 hours.
Supply 50 tablets.

Age: from 12 years onwards
NHS cost: £0.78
Licensed use: yes

Nonsteroidal anti-inflammatory drugs

Age from 12 years to 15 years 11 months

Ibuprofen tablets: 200mg to 400mg three to four times a day

Ibuprofen 200mg tablets
Take one or two tablets 3 to 4 times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 12 years to 15 years 11 months
NHS cost: £2.78
OTC cost: £3.26
Licensed use: yes

Age from 12 years onwards

Mefenamic acid tablets: 500mg three times a day when required

Mefenamic acid 500mg tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 12 years onwards
NHS cost: £5.94
Licensed use: yes

Age from 16 years onwards

Ibuprofen tablets: 400mg three or four times a day when required

Ibuprofen 400mg tablets
Take one tablet three or four times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.72
OTC cost: £3.30
Licensed use: yes

Naproxen tabs: 500mg immediately then 250mg three to four times a day

Naproxen 250mg tablets
Take two tablets initially, then take one tablet every 6 to 8 hours when required for pain. Maximum of 5 tablets in 24 hours.
Supply 112 tablets.

Age: from 16 years onwards
NHS cost: £3.52
Licensed use: yes

Diclofenac sodium e/c tablets: 25mg three times a day when required

Diclofenac sodium 25mg gastro-resistant tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.14
Licensed use: yes

Diclofenac sodium e/c tablets: 50mg three times a day when required

Diclofenac sodium 50mg gastro-resistant tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.31
Licensed use: yes

Continuous selective serotonin reuptake inhibitors (SSRIs)

Age from 18 years onwards

Fluoxetine capsules: 20mg each morning

Fluoxetine 20mg capsules
Take one capsule each morning.
Supply 30 capsules.

Age: from 18 years onwards
NHS cost: £1.15
Licensed use: no - off-label indication

Sertraline tablets: 50mg once a day

Sertraline 50mg tablets
Take one tablet once a day.
Supply 28 tablets.

Age: from 18 years onwards
NHS cost: £1.37
Licensed use: no - off-label indication

Paroxetine tablets: 20mg each morning

Paroxetine 20mg tablets
Take one tablet each morning.
Supply 30 tablets.

Age: from 18 years onwards
NHS cost: £2.58
Licensed use: no - off-label indication

Citalopram tablets: 20mg once a day

Citalopram 20mg tablets
Take one tablet once a day.
Supply 28 tablets.

Age: from 18 years onwards
NHS cost: £1.25
Licensed use: no - off-label indication

Luteal phase selective serotonin reuptake inhibitors (SSRIs)

Age from 18 years onwards

Fluoxetine capsules: 20mg each morning on days 15-28 of cycle

Fluoxetine 20mg capsules
Take one capsule each morning on days 15 to 28 of your menstrual cycle.
Supply 14 capsules.

Age: from 18 years onwards
NHS cost: £0.37
Licensed use: no - off-label indication

Sertraline tablets: 50mg once a day on days 15 -28 of cycle

Sertraline 50mg tablets
Take one tablet once a day on days 15 to 28 of your menstrual cycle.
Supply 14 tablets.

Age: from 18 years onwards
NHS cost: £0.69
Licensed use: no - off-label indication

Citalopram tablets: 20mg once a day on days 15-28 of cycle

Citalopram 20mg tablets
Take one tablet once a day on days 15 to 28 of your menstrual cycle.
Supply 14 tablets.

Age: from 18 years onwards
NHS cost: £0.65
Licensed use: no - off-label indication

Paroxetine tablets: 20mg each morning on days 15 to 28 of cycle

Paroxetine 20mg tablets
Take one tablet each morning on days 15 to 28 of your menstrual cycle.

Supply 15 tablets.

Age: from 18 years onwards
NHS cost: £1.46
Licensed use: no - off-label indication