MANAGEMENT FILE

by DR CHARLES SHEPHERD, our medical adviser

This leaflet is based on an article which first appeared in the ME Association's quarterly *ME Essential* magazine.
MEA membership costs £18 a year for people living in the UK/BFPO.
For contact details, see foot of this page.

the ME association

February 2020

PREMENSTRUAL SYNDROME, female hormones and ME/CFS

INTRODUCTION

The premenstrual syndrome (PMS) – also known as premenstrual tension and premenstrual disorder – is a collection of symptoms that appear every month around the time of menstruation.

Some of these symptoms also occur in ME/CFS. So it's not surprising to find that a significant proportion of women with ME/CFS notice an exacerbation of their ME/CFS symptoms at this time. In fact, the NICE guideline on PMS notes that ME/CFS should be considered when making a diagnosis of PMS.

This new MEA information leaflet summarises what we currently know about PMS, how it can overlap with ME/CFS, and the various treatment options that are available.

The information draws on guidance to doctors from NICE, the Royal College of Obstetricians and Gynaecologists (RCOG) and National Association for PMS (NAPS).

WHAT IS PMS?

PMS symptoms start at some point after ovulation – the release of an egg from the ovary each month.

Ovulation occurs about two weeks before the start of a period. Symptoms tend to appear in the five days before the period starts. However, some women have symptoms that occur over the full two weeks or so leading up to the period.

Symptoms tend to worsen as the period approaches and then start to decline/disappear three to four days after the start of the period.

PMS is very common, with NAPS reporting that between 3% and 30% of women have some degree of PMS.

For most women, PMS symptoms are mild and not particularly troublesome and may then disappear. However 5% to 8% have more persistent and severe symptoms. PMS can occur at any age from puberty through to the menopause.

WHAT CAUSES PMS?

The precise cause remains uncertain. The most likely explanation involves the cyclical changes in female hormone patterns that occur during the menstrual cycle – with the release of the egg each month being the main trigger factor.

It appears that women become more sensitive to a female hormone called progesterone, which passes into the blood from the ovaries after ovulation. Over-sensitivity to this hormone reduces the level of two important brain chemical transmitters called serotonin and gamma-aminobutyric acid (GABA).

As the chemical transmitter changes involve serotonin, this may be relevant to ME/CFS because there is research evidence to show that this transmitter is also involved in ME/CFS. And some people with ME/CFS are very sensitive to drugs called SSRIs (selective serotonin uptake inhibitors) that alter serotonin levels in the brain.

Research into possible female hormone abnormalities involving oestrogen and progestogen in ME/CFS is summarised in our leaflet covering the menopause and hormone research.

The ME Association ● 7 Apollo Office Court, Radclive Road, Gawcott, Bucks MK18 4DF ● **Telephone** 01280 818963 ● **email** admin@meassociation.org.uk ● **Registered Charity Number** 801279

WHAT ARE THE SYMPTOMS?

PMS can cause a range of physical and psychological symptoms.

Physical symptoms include:

- Backache
- Abdominal bloating
- Breast tenderness and/or pain
- Clumsiness
- Cognitive dysfunction – problems with memory, concentration, etc
- Fatigue
- Headaches
- Sleep disturbance
- Swollen hands or feet
- Weight gain
- Worsening of pre-existing asthma, migraine-type headaches and cold sores

Psychological symptoms include:

- Irritability, anger, aggression
- Feeling more emotional than usual
- Feeling tense or even 'out of control'
- Food cravings
- Mood swings, anxiety and depression
- Changes in appetite and sexual feelings

Not surprisingly, this combination of physical and psychological symptoms can put a great strain on relationships.

SYMPTOM SEVERITY

As with ME/CFS, there is a wide and sometimes fluctuating spectrum of severity. The NICE guideline on PMS provides a simple classification that obviously relates to women who have no other heath problems:

Mild PMS: symptoms do not interfere with personal, social or professional life.

Moderate PMS: symptoms interfere with personal, social or professional life. Daily functioning is possible but may not be at the normal level.

Severe PMS: symptoms cause withdrawal from social and professional activities and the woman cannot function normally.

THE OVERLAP WITH ME/CFS

We already know from anecdotal reports that some women with ME/CFS experience a significant deterioration in their overall state of health at this time.

When we asked about what effect PMS had on ME/CFS symptoms in a survey on our website in August 2018, the results were as follows:

- No Change in ME/CFS Symptoms 8%, 34 Votes
- Mild Exacerbation 9%, 38 Votes
- Moderate Exacerbation 24%, 99 Votes
- Severe Exacerbation 40%, 165 Votes
- Variable Exacerbation 10%, 43 Votes
- ME/CFS Symptoms Improved 1%, 4 Votes
- Not Applicable – Developed ME/CFS after periods finished 8%, 33 Votes

Total Voters: 416

Two gynaecologists from London – John Studd and Nicholas Panay – have also reported on a small study involving 28 pre-menopausal women with ME/CFS who had a premenstrual exacerbation of symptoms.

This group had a premenstrual exacerbation of fatigue, headaches and loss of concentration. 22/28 had a severe premenstrual syndrome. Five of the group also reported post-natal depression and nine reported that they had been 'very well' during pregnancy.

Interestingly, a random female hormone profile of the 28 showed that some had a low level of plasma oestradiol – the main natural female oestrogen – with a normal level of follicle-stimulating hormone (FSH). Five of the hypo-oestrogenic patients also had low bone density (a risk factor for osteoporosis) involving the spine and hip.

Studd and Panay concluded that a sub-group of women with ME/CFS have chronic oestrogen deficiency, which may well improve during pregnancy when oestrogen levels are high.

They also reported that 80% of this group had improved when treated with an oestradiol patch and cyclical progestogen therapy. Unfortunately, no other clinical trials have taken place to try and confirm these observations about PMS and ME/CFS.

Reference: Studd J and Panay N. Chronic fatigue syndrome, *Lancet* 1996, 348, 1384.

DIAGNOSIS

Guidelines produced by NAPS, NICE and the RCOG state that a prospective symptom diary should be completed for at least two consecutive months before any treatment is started. A downloadable symptom diary can be used *(see Further Information, page 4)* and continued once treatment has started. Any improvement can also be objectively assessed.

Where the diagnosis remains unclear after using a two-month symptom diary, the RCOG advises that a three-month trial of a hormonal drug (ie a gonadotrophin-releasing hormone analogue such as goserelin or leucoprelin) can be considered.

As with ME/CFS, there are no tests and examination features that can diagnose PMS.

MANAGEMENT

NICE has concluded that PMS is undertreated with only one in five women seeking medical help for their symptoms. NAPS reports that certain ethnic groups are far less likely to report symptoms.

For mild symptoms, simple self-help measures may be all that are required. For moderate or more severe symptoms,

speak to your doctor about the various prescription-only drug treatments that may be worth trying. There are also some alternative and complementary approaches that can help.

DRUG TREATMENT OPTIONS

Various forms of treatment have been recommended over the years. So finding one that helps can be a matter of trial and error. These treatments may take a while to work – so do not give up too early.

None of the treatments described below are contra-indicated if you have ME/CFS. But some of them (SSRI drugs in particular) need to be used with care because some people with ME/CFS are very sensitive to drugs that increase the level of serotonin.

SSRI drugs (eg fluoxetine or citalopram, etc)

The RCOG advises that SSRI drugs which increase the level of serotonin in the brain should be considered as one of the first-line treatment options in more severe PMS. This is because PMS has been associated with low serotonin levels. SSRIs seem to be effective for psychological and physical symptoms.

SSRIs can be taken continuously, or just during the second half of the cycle (the luteal phase). Both regimes are said to work equally well. If a woman using a continuous SSRI wants to stop, this should be reduced gradually, as is the case when these drugs are used to treat depression. However, the use of an SSRI to treat PMS is unlicensed in the UK.

The RCOG also advises that **venlafaxine** can be considered. NICE says that this drug should not be started in primary care.

Combined oral contraceptive (COC) pill

For a disorder related to the menstrual cycle, preventing ovulation and the release of the hormone progesterone – the main trigger for symptoms – this in theory should help. The combined oral contraceptive pill will do this for women who do not have any contra-indications to its use.

The RCOG recommends a pill containing **drospirenone** – this is a progesterone that does not have the downside of other progestogens.

NICE states that other combined pills, particularly those containing **norgestimate**, **gestodene** or **desogestrel** may also be effective, especially if they have been used before and have been found to be of benefit.

So the doctor's clinical judgement has to be used when deciding which contraceptive pill to try, along with any clinical commissioning group restrictions on the use of drospirenone-containing pills, which tend to be more expensive.

The RCOG advises that continuous use of a combined pill may be more effective than its cyclical use, but more evidence is needed to test this theory.

Other approaches

Oestrogen can be given via a patch or gel and has been shown to improve symptoms by suppressing egg production. Oestrogen tablets are not effective.

This type of oestrogen supplementation also involves taking progestogens if you have not had a hysterectomy. Progestogens can be taken as tablets or an intrauterine system IUS) can be inserted. The dose of oestrogen in a patch (100 micrograms) is much lower than in the combined pill. So the patch is not a method of contraception.

Gonadotrophin-releasing hormone analogues will also suppress ovulation. These drugs are normally reserved for very severe PMS. They are usually advised by specialists and given by injection and with hormone replacement therapy to protect bones and prevent symptoms of the menopause.

Danazol is also occasionally used by specialists. But it can cause distressing side-effects such as weight gain, excess hair, acne and a deeper voice.

It is extremely important to use contraception when taking danazol because it can cross the placenta and damage the unborn baby if a pregnant woman takes it.

Surgery to remove the womb and ovaries (hysterectomy and bilateral salpingo-oophorectomy) is a drastic but effective option that prevents ovulation. It is therefore only carried out in the most severe cases where nothing else has helped.

ALTERNATIVE AND COMPLEMENTARY APPROACHES

Not surprisingly, a wide range of alternative and complementary treatments, diets and supplements are recommended and used for PMS. But firm evidence of benefit is often lacking.

The alternative treatments to which the RCOG gives the most credence are calcium and vitamin D, agnus castus, vitamin B6 (pyridoxine) and saffron. Evening primrose oil is sometimes recommended for use in PMS but the evidence suggests that its effects are only useful for those with cyclical breast symptoms.

Other ACM remedies which are claimed to help include:

- Acupuncture
- Curcumin
- Evening primrose oil
- Gingko biloba
- Lemon balm
- Magnesium
- St John's Wort
- Wheat germ

Most ACMs are unlikely to do any harm as long as they are taken in the recommended dose although they are not generally available on the NHS.

It should also be noted that some alternative remedies can interact with ordinary drugs – one example being St John's Wort and the oral contraceptive pill.

We don't have space to summarise all these options. This leaflet will therefore concentrate on just three remedies where there is some evidence to support their use in PMS.

Vitex agnus castus is a plant-based remedy that appears to have genuine pharmacological effects on female hormones involved in the menstrual cycle. And there is some evidence from a small clinical trial that it can help to reduce some PMS symptoms.

Agnus castus appears to be well tolerated but side-effects can include nausea, an itchy skin rash, headaches and weight gain.

As it appears to affect female hormone status, it may decrease the effectiveness of the oral contraceptive pill so additional contraceptive methods should be used when taking it. Don't use it if you are pregnant or breast feeding. Various commercial products are available from health food shops, pharmacies and on-line.

Calcium and vitamin D are two important bone-building nutrients and we know that many women are not taking an adequate amount of these essential nutrients in their daily diets.

Research in America has shown that women with a good intake of calcium and vitamin D had a significantly decreased risk of developing PMS. As there is evidence that people with moderate and severe ME/CFS are at risk of vitamin D deficiency, this form of supplementation may be quite relevant. The MEA has a separate information leaflet covering vitamin D deficiency and ME/CFS.

Saffron is one of the world's most expensive cooking spices. But there is also some evidence it has medicinal properties as it appears to have an effect on the level of serotonin – a brain chemical transmitter involved in both PMS and ME/CFS.

Saffron also has antioxidant properties. A small placebo-controlled clinical trial found that saffron capsules produced a 50% reduction in PMS symptoms, including depression, in 75% of women taking the active treatment.

Although saffron is generally well tolerated, side-effects can include anxiety, stomach upsets, headaches and mood swings. Women who are pregnant or breast feeding should not take it. Saffron can interact with some prescription-only drugs, including treatments for blood pressure and blood thinning.

SELF HELP

- Eat a healthy balanced diet with small frequent meals
- Try reducing the amount of sugar, sugary drinks and refined carbohydrates you eat before a period. Carbohydrates that have a lower glycaemic index (eg granary or wholemeal bread rather than white bread) give a slower and steadier release of sugar and may be a better choice
- Try to have seven or eight hours of solid sleep each night
- Reduce stress levels, where present, possibly by using meditation or yoga
- Use ibuprofen (Brufen) or paracetamol for pain relief
- The RCOG recommends regular exercise as there is some evidence for its benefit on PMS. But this clearly has limitations in relation to ME/CFS.
- Stop smoking and reduce the amount of alcohol and caffeine in coffee, tea, cola drinks etc – which should already be part of ME/CFS management.

FURTHER INFORMATION

National Association for Premenstrual Syndrome (NAPS)
Provides information and support for people with PMS.

41 Old Road
East Peckham
Kent TN12 5AP
Phone: 0844 8157311
Email: contact@pms.org.uk

Downloadable symptom diary produced by NAPS:
https://tinyurl.com/y67cy76z

Management of Premenstrual Syndrome; *Royal College of Obstetricians and Gynaecologists* (2016):
https://tinyurl.com/y5wde9uz

Premenstrual syndrome; NICE Clinical Knowledge Summaries, September 2014 (UK access only):
https://tinyurl.com/y64nrh66

Food Fact Sheet: Premenstrual Syndrome (PMS); British Dietetic Association (BDA), 2014

Scientific papers

Marjoribanks J, Brown J, O'Brien PM, et al. (2013) Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev.* Jun 76: CD001396. doi:10.1002/14651858.CD001396.pub3.

Lopez LM, Kaptein AA, Helmerhorst FM. (2012) Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. Feb 152:CD006586. doi:10.1002/14651858.CD006586.pub4.

Verkaik S, Kamperman AM, van Westrhenen R, et al. (2017) The treatment of premenstrual syndrome with preparations of Vitex agnus castus: a systematic review and meta-analysis. *Am J Obstet Gynecol.* Aug217(2): 150-166. doi: 10.1016/j.ajog.2017.02.028 Epub 2017 Feb 22.