Review

Treatment of premenstrual disorders by suppression of ovulation by transdermal estrogens

John Studd

London PMS and Menopause Centre, 46 Wimpole Street, London, UK

Email: laptop@studd.co.uk

Abstract

The understanding of the cause and treatment is confused but it is essentially the result of cyclical ovarian activity, usually ovulation, and an effective treatment should be by suppressing ovulation. This can be done by an oral contraceptive but as these women are progestogen intolerant the symptoms may persist becoming constant rather than cyclical. Alternatively, transdermal oestradiol by patch, gel or implant effectively removes the cyclical hormonal changes, which produce the cyclical symptoms. A shortened seven-day course of a progestogen is required each month for endometrial protection but it can reproduce premenstrual syndrome-type symptoms in these women. Gonadotropin-releasing hormone with ‘add-back’ is effective in the short term. Laparoscopic hysterectomy and bilateral oophorectomy with adequate replacement of estrogen and testosterone should be considered in the severe cases with progestogenic side-effects.

Keywords: Premenstrual disorders, PMS, PMDD, ovulation, estradiol, testosterone, depression, hysterectomy, hormones

Premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) is a complex group of many psychiatric, behavioural and somatic symptoms that have defied a single simple aetiology but an understanding of hormonal changes seems to be the key. Depression is twice as common in women than in men and these peaks of depression occur at times of hormonal fluctuations rather than low estrogen levels. There is co-morbidity between premenstrual depression, postnatal depression and later in life as transitional depression. These constitute a triad of hormone-responsive mood disorders grouped together as reproductive depression, which can be helped by estrogen therapy. Regrettably, the association of endocrine factors and severe mood disorders is often unrecognized and the women are subjected to diverse psychiatric treatments because the relationship to cycles, periods and physical symptoms has been ignored.

It is not necessary for women to have periods to suffer cyclical symptoms as was demonstrated after hysterectomy with ovarian conservation indicating that it is normal ovarian function that is the driving force behind this syndrome. Endometrial ablation and use of the Lng IUS (levonorgestrel intrauterine system) can give a similar picture. Perhaps ovarian cycle syndrome is a more accurate and descriptive name but it is too logical and too gynaecological to be accepted by the American Psychiatric Association, which prefers PMDD. Patients with PMS do not have abnormal hormone levels compared with asymptomatic controls and the belief is that there is an abnormal central and peripheral response to the normal monthly fluctuations of these gonadal hormones.

As premenstrual depression and other cyclical disorders of this condition are related to ovulation, it is logical that the mainstay of treatment should be the suppression of ovulation and the removal of the cyclical hormonal changes, whatever they are, which produce the cyclical symptoms of this condition. It is likely that the essential cause of premenstrual depression is the intolerance to endogenous progesterone following ovulation and it is regrettable that such patients are also progestogen intolerant to any progestogens administered, and that these progestogenic side-effect are both dose- and duration-dependant. This is a frequent problem with postmenopausal women receiving sequential hormone replacement therapy (HRT). Any progestogen used for endometrial protection in these patients should be one that produces the least symptoms given in the lowest effective dose and the least number of days. Younger women particularly those with PMS are particularly intolerant to
progestogen-only contraception or to a combined oral contraceptive (OC) containing an androgenic progestogen. It is for this reason that OCs containing the antianabolic progestogen drospirenone are being increasingly used in young women with PMS requiring birth control.\textsuperscript{11}

If the medical solution to PMS is the abolition of cyclical hormonal changes and reducing progesterone levels, an effective hormone therapy for severe PMS is the use of transdermal estrogens for the suppression of ovulation. Transdermal oestradiol is considered safer than oral estrogens due to the avoidance of the first-pass effect and production of hepatic coagulation factors.\textsuperscript{12} There are also no data reporting the efficacy of the oral route. It probably is effective in the appropriate dose but the studies have not been performed.

The first information concerning suppression of ovulation came following the use of oestradiol implants for menopausal and perimenopausal women. It was noticed that the cyclical depression and other symptoms associated with the menopausal transition were also removed. It was a logical step to extend this treatment to the younger women who may want to become pregnant, the study was repeated with transdermal therapy should be warned that they may occasion-ally present with a withdrawal bleeding. The Mirena IUS is a very effective treatment of progestogen intolerance but alone is not a treatment of PMS although it causes amenorrhoea. The cycles persist. Moreover, systemic absorption does occur, producing continuous symptoms of depression, tiredness and bloating in about 10% of women.\textsuperscript{21} These disappear within 24 hours of removal of the IUS but removal can be avoided in many since the induced symptoms are often transient (weeks rather than days).

These patients often have a problem of loss of energy and loss of libido, particularly if they have been taking antidepressants for some time. This can have a very distressing effect upon their sexual relationships and self-esteem but can be corrected by the use of transdermal testosterone.\textsuperscript{22} The testosterone patch can be used in the dose of 300 $\mu$g twice weekly, or a testosterone gel, which can be given in the appropriate dose, which would be approximately one-tenth of the daily male dose. After improvement is well established and if implants are being used, a 100 mg pellet of testosterone can be added to the 50 mg oestradiol implant. For long-term therapy, an implant every six months and a Mirena IUS every five years is a simple uncomplicated treatment, which can even be continued for many years past the menopause.\textsuperscript{1} If this dose or lesser doses at six or more months’ interval between implants are maintained over the years tachyphylaxis will be avoided.

There are women whose symptoms are much improved but not cured by these regimens, which suppress
ovulation. They may continue to have some cyclical symptoms either due to incomplete suppression of the cycle or due to cyclical progestogenic symptoms or they may have troublesome irregular bleeding associated with other pelvic pathology such as fibroids. Maybe they do not want to have any cycles or progestogen or even normal bleeding. These women will have complete and permanent cure from a hysterectional bilateral oophorectomy with transdermal estrogen and testosterone given to replace the ovarian hormones not forgetting the lost ovarian androgens.\textsuperscript{23,24} There is also much evidence in general terms from psychiatrists that depression is less common after hysterection.\textsuperscript{25} In spite of this, virtually all newspaper and magazine articles on this subject stress the belief that hysterectomy causes profound depression, loss of sexuality and marital break-up. The reverse is true. It should be seen as a life-enhancing procedure removing cycles and the need for progestogen. As 4% of women die of cancer of the ovary, cervix and uterus this also is part of the risk benefit equation and should be seen as a life-saving as well as a life-enhancing procedure.\textsuperscript{26} This should not be seen as a radical last choice – or never choice option.

These regimens of therapy do presuppose that the condition is an endocrine one and not psychiatric. Apart from depression loss of energy, irritability anger and loss of libido PMS is often associated with many cyclical somatic symptoms such as mastalgia, bloating acne headaches and menstrual migraine that would also be removed when the cycles are abolished by any of the regimens described.

As this treatment is so effective in the hands of interested gynaecologists familiar with the use of hormones it is a mystery why it is not used by those practitioners either physicians or psychiatrists who most frequently deal with depression. No doubt we are all products of our training and psychiatrists would be unfamiliar with the minor side-effects of hormone therapy such as mastalgia or normal or abnormal vaginal bleeding. Perhaps the well-publicized and much-criticized Women’s Health Initiative (WHI) or million women study data are used as a justification for withholding estrogen therapy. It should be noted that these patients are all young premenopausal women and the major side-effects in the WHI study only occurred in high-risk women starting Prempro, a combination of oral equine estrogens and daily medroxyprogesterone, over the age of 60. There were no excess side-effects in the age group being discussed.\textsuperscript{27}

Q6 Competing interests:

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References

1 Studd J. A guide to hormone therapy for the treatment of depression in women. \textit{Climacteric} 2011;14:14637–42
2 Studd J, Nappi RE. Reproductive depression. \textit{Gynecol Endocrinol} 2012
8 Studd J. Suppression of cyclical ovarian function in the treatment of severe premenstrual syndrome. \textit{Menopause Int} 2007;13:182–4
17 West CP, Hillier H. Ovarian suppression with the gonado-trophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. \textit{Hum Reprod} 1994;6:1058–63
22 Davis SR, Burger HG. The rationale for physiological testosterone replacement in women. \textit{Baillieres Clin Endocrinol Metab} 1998;12:391–405
26 Studd J. Hysterectomy A life saving as well life enhancing operation. \textit{Menopause Int} 2009;15:2–3
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