MI-12-015

Menopause International 2012; **00**: 1–3. DOI: 10.1258/mi.2012.012015

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.[1] There is co-morbidity between premenstrual depression, postnatal depression and later in life as transitional depression.[2] These constitute a triad of hormone-responsive mood disorders grouped together as reproductive depression,[3] 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[4] indicating that it is normal ovarian function that is the driving force behind this syndrome. Endometrial ablation and use of the Lng IUS (levonorgetstrel intrauterine system) can give a similar picture. Perhaps ovarian cycle syndrome[5] 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[6] and the belief is that there is an abnormal central and peripheral response to the normal monthly fluctuations of these gonadal hormones.[7]

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.[8] It is likely that the essential cause of premenstrual depression is the intolerance to endogenous progesterone following ovulation[9] 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).[10] 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 antiandrogenic gestogen drosperinone are being increasingly used in young women with PMS requiring birth control.[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.[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 with PMS. Initially, 100 mg implants were used, a dose that would be regarded as excessive now. A randomized placebo-controlled trial over 10 months showed an improvement in all of the Moos' clusters of symptoms in the active preparation in spite of a small placebo response in 94% of patients.[13]

As such long-lasting implant therapy would be inappropriate in the younger women who may want to become pregnant, the study was repeated with transdermal patches 200 μg twice weekly and shown to be effective against severe PMS in a placebo-controlled cross-over trial.[14] A comparative study was also performed using 100 μg patch in case there was concern about dosage that was also found to be as effective.[15] There has not been a scientific study on using oestradiol gels but this route does produce plasma oestradiol levels similar to those found with the patches.

Currently, the preferred treatment is by transdermal estrogen gels, which do not produce the same skin reaction as the patches and can be discontinued more readily than the oestradiol implant.

The doses of gel would be approximately 1.0–3.0 g daily. For example, Oestrogel 1–3 measures a day or Sandrena 1–3 1 g sachets daily. If using a patch, 200 μg twice weekly is the usual dose. This dose will stabilize plasma oestradiol levels to 300–600 pmol/L and the progestogen levels will remain below 5 ng/mL strongly suggestion anovulation. In spite of the invariably low progestogen in the 100 patients investigated in the study of the lower 100 μg dose,[15] the young women should not be advised that the therapy is an efficient contraceptive and that they should use other methods. Patients having transdermal therapy should be warned that they may occasionally feel less well in the first two weeks rather like the mood changes seen in early pregnancy and it may not work in the first month until ovulation has been suppressed.

In those patients who have already responded well to transdermal estrogens, oestradiol implants of 50 mg every six months will give effective long-term therapy for severe PMS.

The patients will need progestogen to prevent endometrial hyperplasia and irregular bleeding, but because of the progestogen intolerance a smaller dose of shorter duration is recommended, usually in the form of 2.5 mg of norethisterone or 100 mg of utrogestan for the first seven days of each calendar month[1] (see Baker and O'Brien article on progestogen-induced PMS). This will produce a regular withdrawal bleed on about day 10 of each calendar month. Re-setting the periods in this way prevents abnormal bleeding; instead normal, usually scanty bleeding occurs at a predictable time of the month. Another minor advantage of this regimen is that periods now occur 12 times a year rather than 13.

Suppression of ovulation and ovarian function by gonadotropin-releasing hormone (GnRH) analogues is a most useful treatment as well as a diagnostic and therapeutic test for women who may wish to have a hysterectomy and bilateral oophorectomy to solve this problem.[16–18] Such treatment is not inexpensive. Moreover, as the monthly or three-monthly injections produce the menopausal symptoms of hot flushes, sweats and loss of bone density GnRH analogues are usually accompanied by 'add back' of standard HRT preparations of estrogen and progestogen.[19] Once again, although the progestogen is necessary to protect the endometrium, it may produce progestogen PMS-type side-effects. One way to avoid the use of progestogen is to use tibolone,[20] which does not produce a withdrawal bleed and can also by virtue of its progestogen agonist effect bring back symptoms.

If symptoms of progestogen intolerance cannot be ameliorated by a change of progestogen or using a lower dose, then the insertion of a Mirena IUS is recommended. This should be replaced every five years, but it does allow the woman to have effective abolition of the cycles and avoid troublesome irregular 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.[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.[22] The testosterone patch can be used in the dose of 300 μg 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.[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 hysterectomy bilateral oophorectomy with transdermal estrogen and testosterone given to replace the ovarian hormones not forgetting the lost ovarian androgens.[23,24] There is also much evidence in general terms from psychiatrists that depression is less common after hysterectomy.[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.[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.[27]

Q6 **Competing interests:**

Accepted: 9 March 2012

References

1 Studd J. A guide to hormone therapy for the treatment of depression in women. *Climacteric* 2011;**n 1**:14637–42
2 Studd J, Nappi RE. Reproductive depression. *Gynecol Endocrinol* Q7 2012
3 Burger HG, Hale GE, Robertson DN, Dennerstein L. A review of hormonal changes during the menopausal transition. *Human Reprod Update* 2007;**13**:559–65
4 Backstrom T, Boyle H, Boyle DT. Persistence of symptoms of premenstrual tension in hysterectomized women. *Br J Obstet Gyaecol* 1981;**88**:530–6
5 Studd J. Ovarian cycle syndrome. *Gynaecol Endocrinol* 2009;**25**:74–5
6 Schmidt PM, Nieman LK, Danaceau MA, *et al*. Differential behavioral effects of gonadal hormones in women with and without premenstrual syndrome. *N Eng J Med* 1998;**338**:209–16
7 Nappi RE, Tonani S, Santamaria V, Ornati A, Albani F, Pisani C, Polatti F. Luteal phase dysphoric disorder and premenstrual syndrome. *Int J Psych* 2009;**28**:27–33
8 Studd J. Suppression of cyclical ovarian function in the treatment of severe premenstrual syndrome. *Menopause Int* 2007;**13**:182–4
9 Magos AL, Brewster E, Singh R, *et al*. The effects of norethisterone in postmenopausal women on oestrogen therapy: a model for the aetiology of premenstrual syndrome. *Br J Obstet Gynaecol* 1986;**93**:1290–6
10 Panay N, Studd J. Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. *Hum Reprod Update* 1997;**3**:159–71
11 Rapkin AJ. Yaz in the treatment of premenstrual dysphoric disorder. *J Reprod Med* 2008;**53**:729–41
12 Renoux C, Dell'Aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke. *BMJ* 2010;**340**:c2519
13 Magos AL, Brincat M, Studd JW. Treatment of the premenstrual syndrome by subcutaneous oestradiol implants and cyclical oral norethisterone: placebo controlled study. *Br Med J (Clin Res Ed)* 1986;**292**:1629–33
14 Watson NR, Studd JWW, Savvas M, Garnett T, Baber RJ. Treatment of severe premenstrual syndrome with oestradiol patches and cyclical oral norethisterone. *Lancet* 1989;**8665**:730–2
15 Smith RN, Studd JW, Zamblera D, Holland EF. A randomised comparison over 8 months of 100 micrograms and 200 micrograms twice weekly doses of transdermal oestradiol in the treatment of severe premenstrual syndrome. *Br J Obstet Gynaecol* 1995;**102**:475–84
16 Leather AT, Studd JW, Watson NR, Holland EF. The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. *Gynecol Endocrinol* 1999;**13**:48–55
17 West CP, Hillier H. Ovarian suppression with the gonado-trophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. *Hum Reprod* 1994;**6**:1058–63
18 Wyatt KM, Dimmock PW, Ismail KM, Jones PW, O'Brien PM. The effectiveness of GnRH analogue with and without 'addback' therapy in treating premenstrual syndrome: a meta analysis. *BJOG* 2004;**111**:585–93
19 Leather A, Studd J, Watson NR, Holland EF. The prevention of bone loss in young women treated with GnRH analogues and add back estrogen therapy. *Obstet Gynecol* 1993;**81**:104–7
20 Di Carlo C, Palomba S, Nappi C. Use of leuprolide plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001;**75**:380–4
21 Elovainio M, Teperi J, Aalto AM. Depressive symptoms as predictors of discontinuation of levonorgestrel releasing intrauterine system. *Int J Behav Med* 2007;**14**:70–5
22 Davis SR, Burger HG. The rationale for physiological testosterone replacement in women. *Baillieres Clin Endocrinol Metab* 1998;**12**:391–405
23 Casson P, Hahn PM, Van Vugt DA, Reed RL. Lasting response to ovariectomy in severe entractable premenstrual syndrome. *Am J Obstet Gynecol* 1990;**162**:99–105
24 Cronje WH, Vashisht A, Studd JW. Hysterectomy and bilateral oophorectomy for severe premenstrual syndrome. *Hum Reprod* 2004;**19**:2152–5
25 Gath D, Rose N, Bond A, *et al*. Hysterectomy and psychiatric disorder. *Psycho Med* 1995;**25**:277–83
26 Studd J. Hysterectomy A life saving as well life enhancing operation. *Menopause Int* 2009;**15**:2–3
27 Rousseau JE, Prentice RL, Manson JE, *et al*. Post menopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;**297**:1465–77

QUERY FORM

Royal Society of Medicine

Journal Title: **MI**
Article No: **12-015**

AUTHOR: The following queries have arisen during the editing of your manuscript. Please answer the queries by making the requisite corrections at the appropriate positions in the text.

Query No.	Nature of Query	Author's Response
Q1	Please check and confirm the suggested running title.	
Q2	Please check the sentence "The understanding....ovulation is not clear."	
Q3	Please check the term "gestogen" in the sentence "It is for this... control. Should this be gestagen?	
Q4	Please check the phrase "strongly suggestion anovulation" in the sentence " This dose will... anovulation".	
Q5	Please provide the manufacturer name and location details for Mirena IUS.	
Q6	Please provide the Competing interest statement.	
Q7	Please provide the missing Volume number and page range in the reference 2.	