

Original article

Severe premenstrual syndrome and bipolar disorder: a tragic confusion

John Studd

London PMS and Menopause Centre, 46 Wimpole Street, London W1G 8SD, UK

Email: laptop@studd.co.uk

Abstract

Bipolar disorder and severe premenstrual syndrome (PMS) have many symptoms in common, but it is important to establish the correct diagnosis between a severe psychiatric disorder and an endocrine disorder appropriately treatable with hormones. The measurement of hormone levels is not helpful in making this distinction, as they are all premenopausal women with normal follicle-stimulating hormone and estradiol levels. The diagnosis of PMS should come from the history relating the occurrence of cyclical mood and behaviour changes with menstruation, the improvement during pregnancy, postnatal depression and the presence of runs of many good days a month and the somatic symptoms of mastalgia, bloating and headaches. Young women with severe PMS do not respond to the antidepressants and mood-stabilizing drugs typically used for bipolar disorder.

Keywords: Premenstrual depression, bipolar disorder, postnatal depression, estrogens, hysterectomy

The treatment of severe premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) by ovulation suppression using transdermal estradiol or gonadotrophin-releasing hormone (GnRH) analogues is usually successful because it is essentially an endocrine condition caused by hormonal changes that follow ovulation. Treatment should be based on the suppression of these cyclical hormonal changes. However, it has been observed that longstanding 'bipolar depression' as diagnosed by psychiatrists often disappears when the cyclical premenstrual nature of the condition is treated by suppression of ovarian cycles.

The purpose of this paper is to emphasize that such misdiagnosis is not rare. It is one that frequently leads to many years of inappropriate drug therapy without noticeable improvement. It is also the intention to clarify the ways in which the diagnosis of PMDD can be made and distinguished from bipolar disorder by certain characteristics in the history.

Depression is more common in women than in men and it particularly occurs at times of hormonal fluctuation. There is a triad of hormone-responsive mood disorders such as premenstrual depression, postnatal depression and climacteric depression,¹ which is best referred to as reproductive depression.² These episodes of depression often occur in the same patient and in a depressed perimenopausal patient would be important points in the history to make a diagnosis of hormone responsive depression. The typical life history of these

women is that they will have teenage premenstrual mood swings and when the hormone levels cease to fluctuate as in pregnancy they experience a good mood for the duration of the pregnancy in spite of early problems of nausea or even late pregnancy obstetric complications. After birth this may be followed by postnatal depression, which may last for months or several years. As the periods recur, the cyclical PMS returns. This premenstrual depression worsens towards the menopausal transition and is less cyclical when the many climacteric symptoms are also at their worst in the two or three years before the periods cease completely.³

The long-term health of these women very much depends upon the initial diagnosis made by the psychiatrist or general practitioner and the treatment that they receive. It is a great regret that estrogens are rarely used for treatment of depression in women by psychiatrists,⁴ although there is adequate evidence from randomized trials showing that transdermal estradiol is effective in premenstrual depression,⁵ postnatal depression⁶ and premenopausal climacteric depression.^{7,8} They are often started on antidepressants and if the mood swings are diagnosed as bipolar disorder a variety of mood-stabilizing or antiepileptic drugs may be added. These will not be effective if the diagnosis is incorrect.

It is vital to appreciate that the diagnosis of hormone-responsive depression is made through the history and not through the measurement of hormone levels.¹ It is commonplace for women to believe that their

depression is 'cyclical and hormonal' but the medical attendant may measure estradiol, follicle-stimulating hormone and possibly testosterone levels. As these women are all premenopausal and still having periods the hormone levels would be expected to be normal and meaningless. Thus normal hormonal levels would not be a valid reason for denying that there is a hormonal causation to the depression and not treating the patient appropriately.

Important items in the history that should clarify the diagnosis are as follows:

- (1) A history of mild or severe PMS as a teenager;
- (2) Relief of depressive symptoms during pregnancy;
- (3) Depression started or recurred postpartum as postnatal depression;
- (4) Premenstrual depression recurred when menstruation and cycles returned after delivery;
- (5) Premenstrual depression became worse with age blending into the menopausal transition and becoming less cyclical;
- (6) Co-existence of cyclical somatic symptoms such as menstrual migraine, bloating or mastalgia;
- (7) Runs of 5–20 good days a month;
- (8) These patients have recurrent episodes of depression, often severe, related to periods but rarely have episodes of mania.

These eight history points will be discussed but initially the following cases are examples of the misdiagnosis and will reinforce these important issues in the history.

Case history 1

Was first seen in 2004, aged 36. She had always had PMS since a teenager. She has two children, aged 3 and 4, and was very well with good mood during pregnancy but developed postnatal depression on each occasion. Many selective serotonin re-uptake inhibitors had not helped and she was admitted to a private psychiatric hospital on two occasions for manic depression. She was prescribed lithium but did not take it. As the depression was cyclical she was given a 200 µg estradiol patch twice weekly and was '99% better' after one month, feeling in a good mood, like in her pregnancy. She subsequently has had estradiol gels and an estradiol and testosterone implant. She needed cyclical oral progestogen to protect the endometrium but progestogen intolerance produced a recurrence of her PMS-type symptoms. She therefore had a hysterectomy and bilateral salpingo-oophorectomy in October 2007 with transdermal estradiol and testosterone replacement.

She is now well with no depression, no cyclical mood changes and no antidepressants.

Her summary of the problem is that doctors do not understand what a near-death experience, cycles can produce.

Case history 2

Was first seen in 2006, aged 46. This patient had a history of depression and chronic fatigue for 25 years. She had

been an inpatient in a psychiatric hospital on three occasions and for 10 years had been prescribed antidepressants and mood-stabilizing drugs in the form of sodium valproate, Ritalin, lithium, Prozac, Rovotril, Assendine, Amoxapine and Tegretol from 1987. For three years she was taking seven of these drugs at the same time.

She had a hysterectomy with ovarian conservation in the year 2000 and was not improved as the cyclical depression persisted. She was given transdermal estrogens in October 2006 and 'had the best summer for years' without any depression. She now is undergoing estradiol and testosterone implants every six months. She is no longer on any antidepressants and is well with no depression and plenty of energy.

Her summary of the problem is that she had 20 years of unnecessary mind-destroying psychoactive drugs and is now unhappy because she cannot remember her children growing up.

Case history 3

First seen at age 48 in 2008 with depression for 14 days a month. She had heavy painful periods and only about 10 good days a month and was also troubled by poor energy, loss of libido and cyclical headaches. She had episodes of depression as a teenager and had severe postnatal depression lasting for four years after the birth of her only child 10 years earlier. She was treated with antidepressants, lithium and electroconvulsive therapy (ECT) on eight occasions. Treatment with transdermal estradiol and testosterone resulted in great improvement in mood, energy and libido. She had PMS-type symptoms with her seven days of cyclical norethisterone and her heavy periods continued to be a problem. She had a laparoscopic hysterectomy and bilateral oophorectomy in 2010 and now has no depression, has a good marriage and libido is not on antidepressants but continuing with transdermal estradiol and testosterone.

Her summary of the problem: she is pleased to be normal again having returned to the human race and wishes that her postnatal depression had been treated more effectively with hormones.

Case history 4

This 63-year-old woman suffered from the age of 20. Her twin sister and mother had the same type of cyclical depression. She was diagnosed bipolar in the USA and was given lithium for two years and antidepressants for 20 years. She chose to be sterilized aged 28 during her PhD studies and has no children. She started using estradiol and testosterone for PMS/depression at the age of 32 with good success. She now has had this hormone therapy for 30 years and will not come off it in spite of advice from her general practitioner. This treatment prevents mood swings and allows her to continue her work as a successful author and academic. She is no longer taking antidepressants or mood-stabilizing drugs.

Her summary of the problem: she is happy with her life and marriage and has no regrets about her early sterilization. She still thinks that the problem was not entirely

hormonal as two uncles with depression committed suicide.

Case history 5

First seen in February 2011, aged 50. Diagnosed as bipolar at age 30 and treated with antidepressants and mood stabilizing drugs. She had two one-month admissions to a private psychiatric hospital. She had a history of severe PMS as a teenager but no depression during her two pregnancies that were followed by severe postnatal depression requiring more antidepressants without benefit. Depression became cyclical with somatic symptoms of migraine, mastalgia and bloating. There were no episodes of mania. Severe PMS was diagnosed and treated with transdermal estradiol and testosterone. She was well after one month and continues the hormone therapy having discontinued all antidepressants and sleeping tablets.

Her summary: although very pleased to be cured of this longstanding depression she and her family are angry at the misdiagnosis, inappropriate treatment and 10 wasted years.

Case history 6

First seen at age 45. She developed depression in the two or three days before her periods start and had frequent psychotic episodes on the first day of the period. The symptoms were cyclical but when first seen had no good days a month. She was well during both of her pregnancies and had postnatal depression on two occasions. The psychiatric problems became worse and more prolonged with age. She was given Citalopram and Quetiapine and the diagnosis of bipolar disorder was done two years ago. She was treated with transdermal estrogen and testosterone with considerable improvement, despite there being a recurrence of her depression during the seven days of progesterone. She had a hysterectomy and bilateral salpingo-oophorectomy in May 2011. She is now totally free of cyclical symptoms. There is no depression, no psychosis and she is not taking any antipsychotic drugs or antidepressants. She is now back at work as Chief Executive of a Charity after not being able to work for 14 months.

Her summary: pleased to be cured by removal of uterus and ovaries and by medication with estrogen and testosterone.

Case history 7

First seen at the age of 37. She had severe premenstrual depression with 'insanity', aggressiveness, loss of libido and loss of energy from the age of 14. She was diagnosed as bipolar and has had lithium for 10 years from the age of 17 and Prozac for two years. The symptoms have become worse to the point where she only had five good days per month. She has never worked because of her psychiatric problems. She was given transdermal estrogen and testosterone gel with improvement within a month. After one year, she has no depression and is maintained on

60 mg of Prozac and is unable to reduce the dose. The loss of libido was the slowest problem to resolve but is now normal. She is now at college and to be married soon.

Her summary: disbelief at 20 wasted drugged years as the psychiatrists referred to the monthly relationship of depression with periods as a red herring and amazement at the simplicity of the ultimate cure.

Case history 8

Patient now aged 30. Had severe depression during her undergraduate years and was treated as an inpatient for three months. A diagnosis of bipolar disease was made and she was given many antidepressants and lithium. She had a history of moderate premenstrual depression as a teenager and had never had any pregnancies. After graduation from Oxford with a good degree she was not able to hold down a job and even avoided going to interviews. She was given estradiol patches 200 µg twice weekly, which helped her depression, energy and libido somewhat, but every month had recurrence of symptoms during her monthly progesterone. She was given GnRH analogue, Zoladex, with considerable improvement but had problems with the progesterone component of the add-back hormone replacement therapy. After one year the 'add-back' was changed to tibolone 2.5 mg, which produced a considerable improvement that has been maintained. After six years of this treatment she now has no cyclical symptoms, no cycles, no bleeding and keeps down a very responsible job working in Asia. She is seen once a year and is still receiving monthly GnRH and daily tibolone, has no complaints and no depression after six years of this therapy. The most recent information is that she is pregnant following ovulation induction with no sign of depression or mental instability.

Her summary: after several years of inpatient and outpatient treatment for bipolar depression she thought that the doctor suggesting that she had PMS was crazy.

Case history 9

First seen aged 50 one year after last period and treated with estrogens and testosterone successfully for 10 years for climacteric symptoms, loss of libido and moderate depression. She previously had severe premenstrual syndrome as a teenager. She was well with a good mood during her three pregnancies but had severe postnatal depression after all pregnancies and was given antidepressants for eight years, lithium for three years and had ECT on six occasions. She is now well, a successful novelist with no depression and no longer receiving any treatment but transdermal estradiol and testosterone.

Her summary: it is reassuring that profound depression can have a biophysical cause and can be treated so easily.

Case history 10

First seen at age 40, having developed postnatal depression after the birth of her only child 10 years ago. Antidepressants were ineffective and she took various

antidepressants for 10 years. After five years of non-response she was diagnosed with bipolar disorder and had five years of lithium without benefit. She had a history of PMS since the menarche, which was becoming worse. Her mood was good during pregnancy until she developed postnatal depression three months afterwards. After six months of transdermal estrogens she is no longer depressed and off all psychiatric drugs.

Her summary: anger that she had 10 years of wrongly diagnosed and incorrectly treated depression and had to be persuaded not to sue her four psychiatrists.

But there can be failures in women who seem to have the typical past history of reproductive depression.

Case history 11

A 50-year-old woman diagnosed with acute mental issues initiated in 1988 by postnatal depression/puerperal psychosis with attempted suicide 19 months after giving birth to her baby. She survived but the baby died. Severe depression started in 1987 but there had been a history of moderate premenstrual depression. She was very well during pregnancy, breastfed for one year and had good bonding with the child. She was admitted to hospital for one year. She has had many drugs for 20 years including Dothiepin and lithium. She had eight episodes of ECT during this time. In 2010, she was started on transdermal estradiol but a week later her psychiatrist refused to see her anymore and removed all the National Health Service psychiatric support because she was undergoing treatment elsewhere. She has only had nine months of transdermal hormone therapy and is improving a little but no longer being suicidal. Although her case history fitted perfectly into one of hormone-responsive reproductive depression rather than a depression-related disorder, it was not possible to assess the response as she has stopped hormones and is still taking the drugs from her psychiatrist.

Her summary of the problem: she experienced considerable levelling of mood but also anger, which was new. She stopped hormone therapy and reduced antidepressants, but still has some anger and doesn't know where it comes from.

In all cases, suppression of ovulation with high dose estradiol in non-hysterectomised women, requires the addition of progestogen for endometrial protection. As described in other papers in this issue, the addition of progestogen can cause recurrence of premenstrual symptoms and so great care must be taken to minimise the progestogenic effect.

Evaluation of the 8 questions and the diagnosis of PMDD

The clinical characteristics of the 10 successful cases have been analysed to test the hypothesis that these eight items in the history can clarify the diagnosis of a hormone-responsive depression rather than bipolar disorder. All patients had been diagnosed as having bipolar

disorder by a psychiatrist and had been prescribed mood stabilizing drugs such as lithium.

- (1) *There was a history of mild or severe PMS as a teenager.* All 10 patients had such a history involving cyclical depression starting soon after puberty. In five cases this was recognized as being a result of simple teenage behavioural and period problems that were not regarded as abnormal but four cases were given antidepressants before the age of 20.
- (2) *There was a relief of depressive symptoms during pregnancy.* Of the eight patients who became pregnant, depression was not a problem in six who claimed to experience good mood during pregnancy in spite of first trimester problems such as nausea and tiredness but two remained on their antidepressants throughout. All eight patients reported that they were at their best with least or no depression during their pregnancies.
- (3) *Depression started or recurred postpartum as postnatal depression.* Postnatal depression was a feature in all eight women who had been pregnant but not in every pregnancy. All had antidepressants for postnatal depression and six patients started antidepressants at this time.
- (4) *Premenstrual depression recurred when menstruation and cycles returned after delivery.* All eight women with a pregnancy developed cyclical depression when periods returned with the depression often being more severe than formerly. It was this cyclical depression and lack of response to antidepressants that led to the diagnosis of bipolar disorder.
- (5) *Premenstrual depression became worse with age blending into the menopausal transition and becoming less cyclical.* Although this usually is the case, it is the least helpful of all the questions. The depression can be worse in the menopausal transition and improve when the periods stop after the menopause. It is also advisable to make the diagnosis early and avoid 20 years of inappropriate therapy.
- (6) *There is often co-existence of cyclical somatic symptoms such as menstrual migraine, bloating or mastalgia.* These women all had cyclical somatic symptoms lasting from two to 14 days each month. All had bloating or mastalgia and six had premenstrual or menstrual headaches. These cyclical, mostly progestogenic symptoms are invariable in PMS/PMDD but do not usually occur in bipolar disorder.
- (7) *They usually have runs of 5–20 good days a month* Although these women may or may not have heavy and painful periods as well as one or two weeks of depression, anxiety, loss of energy and libido, etc., all 10 patients had runs of between 5 and 15 good days a month.
- (8) *These patients have recurrent episodes of depression, often severe, related to periods but rarely have episodes of mania.* Nine patients had had no episodes of mania but one (Case 6) had occasionally one or two manic days before a period but none following treatment.

Pre-menstrual syndrome (PMS) is frequently misdiagnosed. It can be over diagnosed in women with normal mood changes, as an explanation for behaviour problems or depressive illness. In this case, hormone therapy will not help. That it can be under diagnosed and wrongly diagnosed as bipolar disorder is indisputable but there is little way of knowing the frequency of this error. It is clear that these women may suffer the full range of psychiatric care including antidepressants, mood-stabilizing drugs, hospitalization and even ECT without clear benefit but experiencing many side-effects of years of ineffective and inappropriate therapy. Various types of hormone therapy or surgery suppressing the cyclical hormone changes of ovulation can cure them.

It is important to distinguish the endocrine condition of 'PMDD' treatable by hormonal manipulation of the cycle from other psychiatric and personality problems. A case is made for the value of specific questions relating to the woman's depression to the timing of the menstrual cycle, pregnancy, the postpartum state and the presence of cyclical somatic symptoms such as bloating and mastalgia, which do not occur with bipolar disorder.

There may be premenstrual exacerbations of all mood disorders⁹ and therefore cases of co-morbidity and overlap between conditions may occur but even so elimination of the endocrine causes of mood swings will facilitate effective treatment by a combination of estrogens and antidepressants.¹⁰ The family history can be helpful with mother and sisters with PMS and postnatal depression, suggesting a familial hormonal basis for the symptoms, but alternatively a history of bipolar disorder and suicide in male relations would suggest a mixed aetiology (Case 4).

Fornaro and Perugi¹¹ have reported the frequent co-morbidity of PMDD on bipolar patients particularly those with BD-11 or cyclothymia but did not suggest a modification of treatment or an aid to differential diagnosis. Moreover, they did find a greatly increased incidence of postnatal depression in women with PMDD which would support the findings in the case histories.

The failure to diagnose the true cause and best treatment of hormone-related cyclical depression is due to the failure to relate these psychiatric and frequently somatic symptoms to the menstrual cycle and lack of appreciation

that PMDD disappears during pregnancy and often re-appears as postnatal depression, which is too often treated with antidepressants rather than estrogens.⁶ This too often leads to many years of prolonged psychotherapy, mood stabilizing drugs and ECT when antidepressants fail to bring benefit.

It is hoped that the eight questions relating to the timing of symptoms will help to distinguish PMDD from bipolar disorder.

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