HOW TO TREAT PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

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Introduction

Up to 80% of all women of reproductive age experience some physical, emotional or cognitive change associated with their menstrual cycle.[1] Commonly described as Premenstrual Syndrome (PMS), physical symptoms are common, and include breast tenderness, weight gain, bloating and headaches. Women with PMS also experience irritability and dysphoria and often seek a number of complementary treatments.[2] While PMS still causes considerable regular morbidity, it is on the less severe end of a spectrum of menstrual cycle related disorders. At the other end of the spectrum is PMDD – Premenstrual Dysphoric Disorder -which affects about 2-8% of the reproductive female population and is a severe, debilitating depression with high morbidity and mortality.[3] While the whole spectrum of menstrual cycle related mood disorders remains poorly understood, this article will focus on the severe entity of PMDD.

History

Reports of mood and behaviour relating to the menstrual cycle can be traced back to the ancient Greeks. Hippocrates attributed a number of negative psychological and behavioural symptoms to ‘‘retained menstrual blood’’[4]

In most cultures across time, women’s monthly menstrual cycles have been the subject of taboos, superstitions, and associated with a range of physical and mental symptoms. Isolating the menstruating woman and controlling her behaviour through cultural and religious laws still occurs today. Given the widespread, longstanding historical interest in women’s menstrual cycles; it is curious that the earliest documented psychological changes associated with the premenstrual cycle phase appeared quite late - in 1931, by psychoanalyst Karen Horney.[5] She described increased tension, irritability, depression and anxiety in the week preceding menstruation.

Over the ensuing decades, the existence of Premenstrual Syndrome (PMS) has been debated, with concerns about the medicalisation of biological rhythms by using the illness descriptor ‘syndrome’. Others have argued that epidemiological studies have shown only small incidences [6, 7] of premenstrual mood changes in population studies and hence have called for reconsideration of the entity of PMS. A major confounding factor in such studies is the lack of true measurement of cyclical psychological symptoms in relation to a specific menstrual phase. By contrast, clinical trials [8] aiming to provide treatments for women with PMS, characterise the symptoms and measure their onset and offset. Such work as well as clinical experience underlines the very real existence of hormone related changes in mood and behaviour for some women.

Formal PMDD research can be found in Robert Frank’s 1931 study of 15 women with ‘premenstrual tension’. Frank [9] noted the cyclical occurrence of depressive symptoms associated with the menstrual cycle that would disappear shortly after the onset of

menstruation. The term premenstrual tension was used until the 1950s when it was replaced by the term 'premenstrual syndrome' or PMS which remains widely used today. [10] The first reference to a premenstrual disorder appeared in the DSM-III-R at the end of the manual in 'Additional Codes' under the name 'Late Luteal Phase Dysphoric Disorder' (LLPDD).[11] The condition's name was changed to Premenstrual Dysphoric Disorder (PMDD) and included in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) in 1994.[12] PMDD is recognised as a clear depressive disorder in DSM 5 with strict criteria for its diagnosis.[13]
Controversies surround the diagnosis of PMDD. Feminist theorists have offered the most vociferous critique of the PMDD diagnosis. The main contention is that the inclusion of the disorder in the DSM reflects a destructive view that a woman's biology can make her psychiatrically disordered and that a woman's naturally occurring cyclical changes will be unnecessarily pathologized.[14] It is further contended that a diagnosis of PMDD will lead to the ''medicalization'' and subsequently, marginalization of women's premenstrual experiences.[15]

Arguments are still made that premenstrual mental health challenges are not biologically driven, but socially learned. For example, young women may be influenced by religious and cultural beliefs that menstruation is a 'dirty 'time and that premenstrual changes are associated with negative physical and psychological effects.[16]

While the sociocultural theoretical debates continue, the very real suffering and hence the need for effective treatments for a significant number of women, has been the driving force for neuroscience research and clinical practice.

DSM 5 Symptoms & Signs of PMDD

The table below shows the signs and symptoms of PMDD according to DSM 5 [13] criteria:
Diagnostic Criteria for Premenstrual Dysphoric Disorder (PMDD)

Timing of symptoms **A**) In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week post menses
Symptoms **B**) One or more of the following symptoms must be present:1) Marked affective lability (e.g., mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection)2) Marked irritability or anger or increased interpersonal conflicts 3) Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts 4) Marked anxiety, tension, and/or feelings of being keyed up or on edge **C**) One (or more) of the following symptoms must additionally be present to reach a total of 5 symptoms when combined with symptoms from criterion B above 1) Decreased interest in usual activities

2) Subjective difficulty in concentration 3) Lethargy, easy fatigability, or marked lack of energy 4) Marked change in appetite; overeating or specific food cravings 5) Hypersomnia or insomnia 6) A sense of being overwhelmed or out of control 7) Physical symptoms such as breast tenderness or swelling; joint or muscle pain, a sensation of “bloating” or weight gain
Severity **D)** The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others.
E) Consider Other Psychiatric Disorders The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia) or a personality disorder (although it may co-occur with any of these disorders).
Confirmation of the disorder **F)** Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (although a provisional diagnosis may be made prior to this confirmation)**Exclude other Medical Explanations** **G)** The symptoms are not attributable to the physiological effects of a substance (e.g., drug abuse, medication or other treatment) or another medical condition (e.g., hyperthyroidism).

Clinical Presentation

The symptoms detailed in the DSM5 criteria particularly emphasise cyclicity, and confirmation of the disorder relies on two symptomatic cycles as a minimum validation for PMDD. A standardised rating scale - the Carolina Premenstrual Assessment Scoring System (C-PASS)[17] has been proposed to validate PMDD as a diagnosis. The C-PASS is a standardized scoring system for making DSM-5 PMDD diagnoses using 2 or more menstrual cycles of daily symptom ratings using the Daily Record of Severity of Problems (DRSP). The C-PASS is successful in providing a construct validity of the PMDD diagnosis, and a measure of severity**,** by eliminating diagnostician variability and sociocultural considerations raised around the DSM-5 diagnosis. This rating scale is available for clinical and community use in computerised and hard copy formats and is certainly an excellent, objective, measurement tool.

However, the diagnosis of PMDD is often overlooked in women who present with cyclical mood disturbances that are not in the exact premenstrual (luteal) phase of a regular cycle. Indeed, the very name of this condition deters clinicians from diagnosing PMDD if women

present with irregular cycles or with different onset times for intermittent severe depression. Here, it is critical for clinicians to work in an empowering manner with their women patients to elucidate a full history and listen to her observations. Importantly, key points underlining a clinical diagnosis of PMDD, (but not necessarily strictly according to DSM5 criteria) are:

1) A rapid, sudden onset of 5 of: depression, irritability, anxiety, affect lability, decreased interest, difficulty concentrating, fatigue, feeling out of control, insomnia, change in appetite, breast tenderness or breast swelling: that interfere with usual activities - work, family, social life.

2) A rapid, sudden offset of the above mood and associated symptoms after 7-10 days. This may coincide with menstrual bleeding, but in women with irregular, amenorrhoeic or medication impacted cycles – the bleeding may not necessarily signal improvement in mood.

3) An absence of new stressors or clear precipitating psychosocial factors causing depression.

Above all, the patient will often detail her observations that about every month, she has a 'sudden depression for no reason.' Many of my patients have clicked their fingers to demonstrate the sudden onset and offset of this condition – which is an important diagnostic clue. It is important to act on her information and make a presumptive diagnosis of mood disorder related to gonadal hormone fluctuation, as a more broad-spectrum diagnosis. Ensure that details of any and all suicidal ideation, plans and attempts are carefully noted. Just because her depression is cyclical does not mean it is less serious and PMDD has an associated mortality by suicide.

By recognising that her cyclical depression may be due to a different set of biological variables than those factors causing standard Major Depressive Disorder, or Bipolar Affective Disorder, we can consider different treatment options and validate our patient's observations – all leading to hopefully improved outcomes.

Causes of PMDD

It is important to take a holistic approach to understand and manage mental health issues. PMDD is a severe form of depression and is influenced by psychological and environmental factors. However, the most obvious factor in the onset and offset of PMDD is the hormonal fluctuations that control the menstrual cycle and the impact of these on neurochemistry. It is important to note that the reproductive (gonadal) hormones - estrogen, progesterone and testosterone are potent 'brain hormones. These reproductive hormones have great influence over the neurochemistry responsible for thoughts, behaviours and emotions. Hence, the connection between reproductive hormones and mental health is clear. It is not surprising that some women experience depression, anxiety and other mental health issues associated with their menstrual cycles.[18] Above all, it is critical to underline that PMDD is a brain disorder, not a reproductive organ disorder.

There is no single clear theory yet to explain exactly which hormones trigger particular chemicals – or why only some women experience PMDD. However, we know that some women are susceptible to mood changes with very small swings in gonadal hormones due to changes in the activity of central neurotransmitters (GABA, serotonin and dopamine) that influence mood and behaviour. At the same time, many of the physical symptoms (breast tenderness, bloating, headaches, constipation) are the direct effect of gonadal hormones, so that overall - both mind and body are affected. From both the animal work and human studies conducted to date, it appears that estrogen is a 'protective' hormone and can improve psychotic symptoms as well as depression.[19, 20] Estrogen directly influences the key neurotransmitters of serotonin and dopamine to achieve this positive effect. Hence, during low estrogen phases of the menstrual cycle (premenstrual phase and during the transition into menopause), depression and other adverse mental symptoms worsen. Progesterones can have the opposite effect. Many susceptible women who take a progesterone – only contraceptive pill (the 'mini-pill') experience worse depression, and there are certain types of progesterones in the combined oral contraceptive pill that can be very depressive.[21]
Interesting recent work about the cause of PMDD reveals that a breakdown product of progesterone – called allopregnanolone (ALLO) – is a critical stimulator of the GABA –A receptors. The GABA system when stimulated can alleviate anxiety. Benzodiazepine drugs like diazepam (Valium) stimulate the GABA system and help to calm down agitation. In this way, ALLO is an 'anti-anxiety' hormone. Just like estrogen, progesterone levels and its metabolite – allopregnanolone (ALLO) levels, fall in the premenstrual phase. Women who have PMDD are often agitated and anxious as well as depressed, and a newer theory is that their brain chemistry is not reacting normally to ALLO, hence they become anxious. This is important to explore further and already new drugs that impact on ALLO are being developed and tested.[22]

Early Life Trauma & PMDD

Posttraumatic stress disorder (PTSD), often occurs as a result of repeated early life emotional neglect, invalidation or abuse, or physical/sexual abuse. Complex PTSD (cPTSD) [23, 24] is a good descriptor of this mental disorder and is often comorbid with premenstrual dysphoric disorder (PMDD) in women; however, it is unclear whether this relationship is driven by the trauma that may lead to PTSD or if PTSD is uniquely associated with PMDD. [25] The psychophysiological mechanisms linking PMDD and PTSD have not been investigated well enough to date. However, a number of studies have found evidence of autonomic nervous system dysregulation in both patients with PMDD and patients with PTSD [23]. Our research has shown that the endocrine Hypothalamic-Pituitary -Adrenal (HPA) axis, a key mediator of stress, initiates a series of neural and hormonal cascades that, in addition to other metabolic functions such as increasing blood sugar levels, and suppressing immune function, serves to regulate the response to stress. The metabolic feedback links between the HPA axis and the Hypothalamic-Pituitary- Gonadal (HPG) axis may well explain the relationship between HPA dysregulation in women with cPTSD, who experience PMDD.[26] Furthermore, the autonomic nervous system dysregulation characteristic of cPTSD may be a risk factor for PMDD.[23]

While the mechanisms linking early life trauma or repeated traumatic events and PMDD remain unclear, it is important for clinicians to take a detailed developmental history from their PMDD patients, to better understand her illness and management context

Investigations

There are no specific laboratory investigations for PMDD. However, it is important to perform tests for three reasons: to rule out other causes for PMDD symptoms, to obtain general health baseline measures prior to starting treatment and to monitor general health once treatment is ongoing

Possible Differential Diagnoses for PMDD include endometriosis, fibroids, fibromyalgia, thyroid disorders, major depression, borderline personality disorder,bipolar affective disorder – type 2, migraines, menopause and panic disorder. Investigations include routine blood tests measuring thyroid, liver and renal function as well as full blood examination, iron studies (for anaemia due to menorrhagia), clotting factors (prior to starting hormone therapy) B12, electrolytes and measures of the hypothalamic-pituitary – gonadal (HPG) axis. HPG measures include oestradiol, progesterone, FSH, LH, prolactin, testosterone, SHBG, DHEA and are done to exclude menopause changes or polycystic ovarian syndrome or any other hormonal abnormalities. The HPG axis investigations are not a test for PMDD itself. Other investigations need to be done as per the patient's health status, age and lifestyle and risk factors. Gynaecological investigations include routine Pap smear and special investigations for endometriosis if clinical symptoms and signs are present.

If the patient is to receive hormone treatments, then routine breast health screening with breast ultrasound or mammogram, and cardiovascular health screening should occur according to the patient's age and risk factors.

Management

Understanding the body-mind connections in PMDD are critical to develop effective management strategies for the many women who suffer from significant depression and other issues every month. Gonadal hormones are potent brain hormones too and there is a valid biological basis to explain the relationship between menstrual (and menopausal) phases and mental health. Management options need to include the holistic consideration of all aspects of the woman's life including her work, relationship stresses, past traumas, current physical health and daily demands. Many women experiencing PMDD require hormone treatment and other strategies to assist them to improve their quality of life. Clinical experience suggests that women are more likely to try and respond to hormone strategies compared with psychotropic medications alone, the latter having associated stigma and side effects, plus withdrawal symptoms when ceased. Concomitant psychotherapy is critical for women with PMDD and the nature of this therapy depends on her past history, current social context and psychological insight. Healthy eating, regular exercise, a good sleep pattern, limited alcohol intake, no cigarette smoking and no illicit drug use are all part of a healthy lifestyle approach required to manage PMDD. Importantly, interpersonal violence/ bullying in the woman's domestic or workplace environment needs to be addressed urgently to ensure her safety and promote her self-esteem.

Staged Treatment of PMDD

Tier 1:

1) 'Complementary Treatments' – such as exercise, primrose oil, cognitive behavioural therapy, vitamin B6, magnesium, can be useful for PMS but not PMDD.
2) Combined Oral Contraceptive pill (COC) – taken continuously for 3 or more cycles

(ie: without placebo pills). Newer generation COCs (Zoely, Yaz, Diane) are more effective than the older COCs, but differential depressive responses can occur in individual women.

3) COC (continuous) + Antidepressant (intermittent SSRI or SNRI or agomelatine)

Tier 2:

4) COC + Estradiol patches (25 or 50 or 100 micrograms) + Antidepressant (intermittent SSRI or agomelatine)
5) Estradiol patches (50 or 100 micrograms) + micronised progesterone (100 mg or 200 mg [day 17–28], orally *or* vaginally) + Antidepressant (intermittent SSRI or SNRI or agomelatine)
6) Estradiol patches (100 micrograms) + micronised progesterone (100 mg or 200 mg [day 17–28], orally *or* vaginally) + Higher dose SSRIs or SNRIs continuously e.g. citalopram/escitalopram 20–40 mg, venlafaxine

Tier 3:

7) GnRH analogues (Synarel) + add-back HRT (continuous combined estrogen + progesterone
[e.g. 50–100 micrograms estradiol patches *or* 2–4 doses of estradiol gel combined with micronised progesterone 100 mg/day] or tibolone 2.5 mg/day

Tier 4:

8) Surgery + HRT

(Adapted from the RCOG [27] UK treatment guidelines)

Current Evidence for the Staged Treatment Guidelines

Complementary Therapies

The evidence for complementary treatments for PMDD has limited efficacy to date. While less severe symptoms may respond, trials of evening primrose oil, showed minimal response in the depressive symptoms of PMDD.[27] Interestingly a systematic review into herbal remedies for PMS supported the use of Vitex agnus castus L. (also known as chasteberry) but contradictory evidence exists for the use of calcium, vitamin B6 and gingko biloba.[27] There are not enough published controlled trials to comment on the efficacy of saffron, curcumin, lemon balm, wheat germ and isoflavones in PMDD. [27] A trial of St John's Wort in mild PMS showed significant improvements in physical and behavioural symptoms but no improvement in mood or pain-related symptoms.[28] St John's Wort interacts with other medications, in particular it should not be used concurrently with SSRIs and can render low dose COCs ineffective. Exercise is thought to have some benefit for the milder PMS symptoms.[29]

Combined Oral Contraceptives

Studies investigating the efficacy of the combined oral contraceptive (COC) pill use to alleviate premenstrual mood symptoms have had mixed results.[30, 31] Joffe and colleagues compared pre- menstrual symptoms in women prior to first OC pill use with symptoms experienced while using an OC pill [31]Of the 658 women, 12.3% reported an improvement in mood, while 16.3% reported mood deterioration. These results suggest that OC pills do not necessarily influence mood symptoms. It should be noted that OC pill type (i.e., mono-/triphasic, high/low dose) were not factored into the analysis; however, considering the age range in that study (36–44 years of age), it is likely that higher-dose OC pills were being taken. It has been suggested that newer, low-dose OC pills have more positive effects on mood and that monophasic OC pills could help stabilize mood better than triphasic pills.[32, 33] Recent trials using a combination OC pill (drospirenone and ethinylestradiol) have demonstrated improvement of mood symptoms in women with PMDD.[34, 35] For example, Pearlstein and colleagues [34] examined the effects of a low-dose OC pill (drospirenone 3 mg/ethinyl estradiol 20 mcg) for the treatment of PMDD in a double-blind, placebo-controlled, crossover study. Subjects (n = 64) were treated with the monophasic OC pill or placebo for 3 months, with a 1-month washout period before switching treatment regimens. Response to treatment occurred in 62% of the active-treatment group and 32% of the placebo group. Although these results suggest that certain OC pills might improve mood, future studies investigating dose and dose regimen should clarify the role of OC pills for the treatment of PMS/PMDD. Newer pills that include 17 – beta estradiol 1.5mg + nomegestrol acetate 2.5mg or combinations of estetrol (E4) + drospirenone appear promising in clinical practice for the treatment of PMDD but are yet to be trialled for this indication.

<u>*Continuous COC therapy*</u> compared to 21/7 dosing, showed that a 168-day extended regimen of drospirenone 3 mg and ethinylestradiol 30 micrograms led to a significant decrease in premenstrual-type symptoms compared with a standard 21/7-day regimen [36]. Phase II of this trial extended the continuous use of this COC for a total of 364 days. Menstrual symptoms were recorded using DRSP charts. The results concluded that mood, headache and pelvic pain scores improved when compared with a 21/7-day regimen. There was a high level of satisfaction, with most women.

Antidepressants

Studies suggest that 60–70% of women respond to SSRIs while approximately 30% of women respond to placebo.[37] SSRIs may be taken continuously (every day of the menstrual cycle), during the luteal phase, or intermittent dosing (from ovulation to the first day of menses), or symptom- onset (from the day that symptoms start during the luteal phase to the first day of menses). Fluoxetine, sertraline, and paroxetine (both continuous and luteal phase administration) are approved by the US Food and Drug Administration (FDA) for the treatment of PMDD. SNRIs are commonly associated with significant withdrawal symptoms, hence are more difficult to use in an intermittent fashion. If the woman is stabilised on an SNRI, then continuous use of this is better with respect to withdrawal symptoms. More recently, agomelatine appears to be a useful antidepressant for PMDD with decreased side effects on intermittent use and increased efficacy in treating sleep disturbances.[38]

Estradiol + Progesterone Treatments

Percutaneous estradiol combined with cyclical progestogens has been shown to be effective for the management of physical and psychological symptoms of PMDD. Percutaneous

preparations give sufficient estradiol levels to suppress ovarian activity. Clinical trials have demonstrated that 17b-estradiol combined with cyclical progestogens are effective for the management of severe PMS symptoms.[39, 40] When treating women with percutaneous estradiol, treatment with oral or vaginal progesterone should be used for the prevention of endometrial hyperplasia. Increased frequency of breast screening is needed for women receiving hormone treatment

Micronised oral progesterone (100 or 200 mg) has fewer androgenic and unwanted adverse effects compared with progestogens such as norethisterone and levonorgestrel. Progesterone may act as a diuretic and a central nervous system anxiolytic and so in theory could also alleviate PMS symptoms [41], although there is currently little evidence to demonstrate this. Micronised progesterone can also be administered vaginally, which may be better tolerated by avoiding first-pass hepatic metabolism. Vaginally administered progesterone avoids the formation of psychoactive metabolites such as allopregnanolone.[42] Of great interest are the new allopregnanolone modulators that are currently being trialled in the future treatment of PMDD.[22]

GnRH Analogues

GnRH analogues are highly effective in treating severe PMDD. When treating women with PMS, GnRH analogues should usually be reserved for women with the most severe symptoms and not recommended routinely unless they are being used to aid diagnosis or treat particularly severe cases. GnRH analogues suppress ovarian steroid production and therefore cause a drastic improvement or complete cessation of symptoms in patients with core PMDs, but their effects on bone mineral density (BMD) mean that they should only be considered for severe cases. A meta-analysis identified 71 women on active treatment in seven trials. GnRH analogue therapy did not result in elimination of premenstrual symptoms, but the lack of efficacy was in part due to diagnostic difficulties rather than a limitation of the therapy. [43] When treating women with severe PMS using GnRH analogues for more than 6 months, add-back hormone therapy should be used. Add-back hormone therapy includes continuous combined HRT or tibolone and is important to maintain healthy bone mineral density.[43]

Surgery + Hormone Therapy

Severe PMDD is in most cases treated successfully with medical management, but hysterectomy with bilateral oophorectomy can be justified in women in whom medical management has proven unsuccessful, where long-term GnRH analogue treatment would be required, or if gynaecological comorbidities indicate hysterectomy.[44] Women being surgically treated for PMDD should be advised to use HRT, particularly if they are younger than 45 years of age. Following hysterectomy, estrogen-only replacement can be used. The avoidance of progestogen prevents reintroduction of PMDD-type adverse effects. Consideration should also be given to replacing testosterone, as the ovaries are a major production source (50%) and deficiency could result in distressing low libido (hypoactive sexual desire disorder).[45]

Case Study

Sarah is a 35-year-old, secondary school teacher and a talented artist. She said “About every month I feel suddenly depressed – for no reason, and then I get overwhelmed by incredible tiredness and brain fog. I just can’t do my work, can’t be bothered talking to my partner or

doing anything – even brushing my hair seems too hard. And then after about a week or ten days, I suddenly feel fine. Usually, I feel better when I start to have a period. This started in my teens and keeps happening. I feel like I am only alive for part of each month – it's horrible."

Sarah's symptoms are typical of premenstrual dysphoric disorder, or PMDD, but were not recognised as such for 15 years. As a result, Sarah lost key jobs, friendships and intimate relationships over the years as well as experiencing side effects of many psychotropic medications - with little respite from the relentless severe cyclical depression.

Sarah consulted a psychiatrist 8 years ago who diagnosed her as having "Bipolar Affective Disorder (BPAD) – Type 2". The reasons given by the psychiatrist for this diagnosis were that Sarah had cyclical depression and in between episodes, she described herself as 'great, well able to produce meaningful paintings and teach Art to Years 11 & 12. When I am feeling good, I get lots done like cleaning the house, planning lessons, baking and preparing everything I can as a kind of 'stocking up' for when I get depressed and just can't do anything'. This was interpreted as a 'hypomanic' episode and BPAD- Type 2 was diagnosed. Although Sarah tried to discuss her observations that her depression was cyclical and related to her menstrual periods, this was dismissed as irrelevant. To complicate matters, Sarah's menstrual cycle became more irregular, probably due to the medications she was prescribed and her weight gain.

Sarah was treated with a combination of Lithium Carbonate 750mg oral twice daily, plus quetiapine 600mg oral at night, plus fluoxetine 40mg per day. She was admitted to a psychiatry ward on three occasions for medication stabilisation.

Unfortunately, Sarah gained 20kg weight and her BMI was 30. She also developed a tremor in both hands, that interfered with her capacity to paint, and became hypothyroid. She was then treated with 50mcg thyroxine daily. She continued to experience depression in a cyclical fashion. Due to her tremor, she stopped painting, which led to her feeling deprived of an important creative aspect of her life. Her frequent work absences led to her losing a valued teaching job in a Private School that she had enjoyed for six years. A five year - long intimate relationship ended because her partner could not cope with her depression and associated symptoms.

Sarah was born in a metropolitan suburb. Her parents split up when she was 2 and her mother repartnered when Sarah was 5. She had no further contact with her biological father. Her stepfather was a violent man who was physically violent towards Sarah, her two stepbrothers and her mother. Sarah also experienced verbal abuse from her stepbrothers growing up. She discovered that school was a haven for her, particularly Art classes, and eventually left home to attend University, majoring in Fine Art, as well as completing a teaching degree. Sarah was involved in emotionally abusive intimate relationships at ages 19 and 22. She was referred for therapy with a clinical psychologist and came to understand the extent of her early life trauma and the impact it had on her quality of life as an adult. At 27, she met Michael, and they planned a life together. In particular, they both wanted to have children – but due to her diagnosis of 'Bipolar Affective Disorder – Type 2" and the psychotropic drug treatment, she was advised not to become pregnant by her psychiatrist and General Practitioner. After 5 years of recurrent, worsening depression and hospitalisations, the couple separated. Sarah lost her job and during one episode of depression, she attempted suicide by taking an overdose of her medications. The physical consequences of this attempt were

treated, and a different psychiatrist saw her in hospital and referred her to the Women's Mental Health Clinic.

Hearing Sarah's story prompted further exploration of the cyclical nature of her depression. Sarah had kept records of her cycles with mood charts and a pattern of monthly sudden onset of depression and sudden offset emerged. Although the timing of her depression was not always precisely in the premenstrual week, since her periods were irregular, the sudden onset and then offset after 7-10 days was apparent. A working diagnosis of PMDD was made and Sarah was started on the oral contraceptive pill, 'Zoely'(1.5mg 17 beta estradiol +2.5mg nomegestrol acetate), taken in continuous format for 3 cycles. The lithium was gradually decreased over 8 weeks and ceased, as was the quetiapine – although this took 6 months. Once she stopped the lithium, her tremor improved. Sarah began painting again and this resumption of an important creative activity spurred on a great improvement in depression. Sarah was engaged in psychotherapy and continued to make good progress. Since she made a significant improvement but still had some depression every month, 25mcg of transdermal estradiol was added to her treatment, plus continuing with 40mg/day fluoxetine.

Twelve months later, Sarah is doing very well. She has lost 13 kg weight, has very mild depressive symptoms each month – which she copes with in therapy, is painting and teaching Art. She has regular breast ultrasounds, general health screening and Pap smears and is physically healthy. She does not have an intimate relationship yet, but she has discussed her desire to have a baby and it will be important to assist her planning for this goal.

Sarah's story is a great reminder that PMDD is a real entity and the impact of reproductive hormones on mental health is critical in many women. Her case also underlines the importance of listening carefully to our patients, whose observations often hold the key to optimising their diagnosis and management

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