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BJOG DEBATE

BJOG PERSPECTIVES

HRT should be considered as first line therapy for perimenopausal depression

FOR: Estrogens are the first line treatment for perimenopausal women

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Perimenopausal women with depression (PMD) suffer the many symptoms of the menopausal transition before the cessation of periods, together with anxiety, poor concentration and loss of libido. These women often have a continuum of depression from an early age with a history of hormone-related depression of premenstrual depression (PMS) and a history of postnatal depression (PND). The PND then becomes cyclical with the return of periods, becoming worse with age until the mid-forties. These women are then denied hormone therapy because they are not post-menopausal. This pattern of depression in women is best called reproductive depression (RD) and cannot be diagnosed or excluded by blood tests because the hormone levels will usually be in the pre-menopausal range (Studd & Nappi. Gynecol Endocrinol 2012;28:42–5).

Transdermal estrogens are safer than oral estrogens in that they do not carry any extra risk of thrombosis and also have been reported as more effective in the treatment of depression. This should be by patches or gels giving a reasonably high dose using estrogen patches of 100 mcg twice weekly (Soares et al. Arch Gen Psychiatry 2001;58:529–34). A similar dose of gels should be used. There is often a loss of libido and loss of energy at the same time and these women will benefit from transdermal testosterone. Although it is unlicensed in women, it can be achieved by testosterone gel, Testim or Testogel using approximately one-tenth of the licensed male dose (Studd. Climacteric 2011;14:637–42). Those women with a uterus have to have cyclical progestogen but as these women are progesterone-intolerant it is justifiable to use a shortened course of Norethisterone, Provera or Utrogestan for 7–10 days each month.

Not all women will have the depression removed by hormone therapy and there will be a case for the use of antidepressants in a few women, but I believe this is second line treatment for these patients who do not respond to the more logical transdermal estrogens. I have tried to arrange a lecture for years at the RCPsych but I am informed that there is no interest in this treatment among senior psychiatrists. Is it a territorial issue? Possibly. Is it a safety objection? This is unlikely as transdermal estradiol is safer than long-term antidepressants (Smoller et al. Arch Int Med 2009;169:2128-39). Essentially, the problem is the failure to recognise the hormonal component of perimenopausal depression. This failure leads to an interesting catalogue of explanations: treatment resistant depression (wrong treatment); borderline personality disorder (a familiar DSM V diagnosis); bipolar disorder (it is cyclical after all!); premorbid history of depression (depression also occurred before the current PMD; it was PMS or PND—usually both). Most psychiatrists are not effective when treating depression in women. I hope Michael Craig will be able to instruct them. I have failed.

Disclosures of interests

None declared. Completed disclosure of interests form available to view online as supporting information. ■

AGAINST: More clinical trials are needed

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Observational community studies have reported that during the perimenopause the incidence of depression increases by up to three-fold. This probably includes a significant subgroup of women who are particularly sensitive to fluctuations and/or decline in sex hormones.

It has been argued that this sensitivity constitutes a discreet nosological entity, sometimes referred to as reproductive depression. This is supported by a number of approaches. These include family and twin studies, which reported high heritability of conditions such as premenstrual dysphoric disorder (PMDD), and postnatal depression (PND). Also, studies that iatrogenically induce estrogen withdrawal have found a specific recurrence of depressive symptoms in women with a history of PMDD, PND and/or perimenopausal depression (PMD), but not in control women. Recently, for example, blinded HRT withdrawal was reported to trigger depressive symptoms in postmenopausal women with past PMD responsive to HRT, but not in postmenopausal women without a history of PMD (Schmidt et al. *JAMA Psychiatry* 2015;72:714–26).

The biological basis of this vulnerability remains unclear. However, it probably includes indirect effects of menopausal symptoms on mood, and a more direct interaction between sex hormones and neurotransmitter systems implicated in depression (Craig. In: Managing the Menopause—21st Century Solutions. Cambridge: Cambridge University Press; 2015: p. 91–102). An important question that follows is whether HRT can be used to treat depression in this subgroup.

In *post*menopausal women who are not clinically depressed, some studies have reported that HRT is associated with improvement in psychological 'well-being' (see Craig. Br J *Psychiatry* 2013;202:9–13). However, other studies have failed to support these findings. In the WISDOM study, for example, 3721 postmenopausal women, aged 50–69, were randomised to HRT or placebo. No significant differences in depression, or overall quality of life, were observed at 1 year. Several studies have also failed to demonstrate superiority of HRT over placebo in clinically depressed menopausal women. However, two RCTs lend greater support to the use of estrogen therapy in *peri*menopausal women.

The first was a 'pilot study' of 16 women randomised to 17-β estradiol patches (50 mcg) and 18 women prescribed placebo patches (Schmidt et al. *Am J Obstet Gynecol* 2000;183:414–20). A full or partial therapeutic response was seen in 80% of subjects receiving estradiol and 22% of those receiving placebo ($P < 0.01$). In the second study, 25 women with depressive disorders were randomised to 17-β estradiol skin patches (100 mcg) and 25 women were prescribed placebo patches (Soares et al. Arch Gen Psychiatry 2001;58:529–34). Remission of depression was observed in 17 (68%) women treated with 17-β estradiol compared with five (20%) in the placebo group ($P = 0.001$). Further, the clinical improvement remained significant after the 4-week wash-out period. However, it remains unclear whether improvements extend beyond this time.

In summary, there is *preliminary* support for the use of estrogen therapy to treat perimenopausal depression. However, larger clinical trials, with longer follow up, and the inclusion/exclusion of other sex hormones are still required before recommending (or advising against) the use of HRT as a first-line medication in perimenopausal depression.

Disclosure of interests

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