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Editorial

Biological and Hormonal Aspects of Postpartum Depressed Mood

Working Towards Strategies for Prophylaxis and Treatment

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Depressed mood in the year following delivery is associated with three main syndromes.

Firstly, *'maternity blues'* refers to the depressed mood, tearfulness, emotional lability, anxiety and sleep disturbance which up to 60% of women experience in the 10 days or so after delivery (Victoroff, 1952; Pitt, 1973). The phenomenon shows some evidence of links with many biological factors, including: a history of premenstrual syndrome (O'Hara *et al*, 1991); body weight, fluid and electrolytes (Stein, 1980; Stein *et al*, 1981); serum calcium levels (Riley, 1979); monoamines (Treadway *et al*, 1969); serum tryptophan (Handley *et al*, 1980); platelet α_2-adrenoceptors (Metz *et al*, 1983); and with progesterone withdrawal following delivery (Nott *et al*, 1976; Harris *et al*, 1994).

Secondly, *postnatal depression*, of mainly neurotic/reactive type, occurs in at least 10% of postpartum women and is associated with a history of psychiatric illness/neurotic personality, marital dysharmony and lack of confiding relationship, maternal age, and the number of life events in the previous year (Cox *et al*, 1982; Kendell, 1985). A hormonal association has also been defined, in that women who have episodes of postpartum thyroiditis and who are positive for thyroid antibodies are prone to episodes of postpartum depression (Pop *et al*, 1991; Harris *et al*, 1992).

Thirdly, *puerperal psychosis* may present as depression, and occurs in 0.2% of child-bearing women. It is associated with primiparity, a history of manic–depressive illness, Caesarean section, and perinatal infant death (Brockington *et al*, 1981; Kendell *et al*, 1987). Such women have been shown at the time of onset of the condition to have increased hypothalamic dopamine receptor activity, which may be due to the sudden fall in plasma oestrogen following delivery (Wiek *et al*, 1991).

There are associations between these mental states, in that severe blues can progress to postnatal depression (Cox *et al*, 1982), and also there may be a connection between blues and puerperal psychosis, since there is an excess of onset of the latter towards the end of the first week after delivery (Kendell, 1985). Any hormonal associations with these conditions must be seen against the background of normal pregnancy, particularly if treatment strategies are to be devised.

Steroid hormones

Pregnancy is accompanied by a slow rise in progesterone and oestradiol to several hundred times the normal levels, followed by a sudden drop after delivery. Only a small fraction of these steroids are 'free' and biologically active (Anderson *et al*, 1985), and the amount of free progesterone for example in late pregnancy is a maximum of 2.8% of the total, the same being true for oestradiol. Cortisol rises more slowly during pregnancy, maintaining a diurnal variation (although reduced) until parturition, rising during labour then returning to normal levels within about 15 days (Nolten *et al*, 1980; Demey-Ponsart *et al*, 1982; Harris *et al*, 1993). Many studies of steroid hormones and perinatal mood have examined total plasma hormones, so that important associations of mood with changes in the levels of free hormones may be missed. Further problems relate to the small numbers of women studied and failure to monitor mood and hormone changes during pregnancy and on into the postpartum period (e.g. Feksi *et al*, 1984).

Progesterone

Progesterone had been shown as early as 1941 to have a sedative action in rats (Selye, 1941), and later the pregnane anaesthetics were developed (Gyermek & Soyka, 1975). There is evidence that progesterone has both genomic and rapid membrane actions on neurones (McEwen, 1991). The former consists of its action on intracellular receptors at a nuclear level, with resulting changes in the synthesis of enyzmes and neurotransmitters. The rapid membrane action is thought to be responsible for the anaesthetic action of progesterone, shown by the sedation produced by the intravenous injection of micronised progesterone (Arafat *et al*, 1988), probably facilitating gamma-aminobutyric acid (GABA) centrally.

Studies of mood and progesterone are particularly important, since the latter has been advocated (without supporting scientific evidence) for treatment of postnatal depression (Dalton, 1989). Some weak associations with blues have emerged, in that women reporting more severe blues have a greater fall in plasma (total) progesterone after delivery (Nott *et al*, 1976). A much larger study (O'Hara *et al*, 1991)

examined total plasma progesterone and mood from the second trimester of pregnancy to the ninth postpartum week, but failed to find any association between the two. Saliva progesterone (and cortisol) levels accurately reflect plasma free hormone levels, and by implication levels in cerebrospinal fluid (CSF), the latter closely reflecting plasma free hormone levels (Backstrom *et al*, 1976). In a recent study (Harris *et al*, 1994) 120 primiparous women collected saliva samples twice daily from two weeks before the expected date of delivery through the peripartum period until the 35th day postpartum, together with frequent monitoring of mood. Higher blues scores on the Stein questionnaire (Stein *et al*, 1980) showed modest associations with: higher antenatal progesterone levels; a steeper rise in the last two weeks of pregnancy; a bigger decrement from antenatal levels to the day of peak blues score; and lower progesterone levels on the day of peak blues. Finally, higher blues score was associated with the continuing fall in progesterone levels after delivery (postnatal days 2 to 10). The importance of this finding from a clinical point of view is debatable. More importantly, the same women were assessed at 35 to 40 days postpartum according to DSM–III criteria for major depression, and rated on a variety of depression questionnaires. In this study, in which almost 10 000 estimations of salivary progesterone were made, no direct association was shown between postnatal depression, or later depressed mood in general, and progesterone.

Oestrogen

Peripartum oestrogen and progesterone changes have been suggested as being responsible for increased platelet α_2-adrenoceptor binding capacity at 7–10 days postpartum in women with blues, possibly reflecting similar receptor changes in the brain, and furthermore a link with depression (Metz *et al*, 1983), although later work by the same group casts doubt on this (Best *et al*, 1992). However, most studies have failed to show an association between blues and oestradiol changes (O'Hara *et al*, 1991; Harris *et al*, 1994). A weak association has been shown between blues and higher prenatal total and free oestriol, and also with a bigger drop in its concentration postpartum day 1 (O'Hara *et al*, 1991). This provides limited support for oestrogen withdrawal as a factor in generating blues.

On the other hand, encouraging results have been obtained in the context of puerperal psychosis. Oestrogens have been shown to affect dopaminergic transmission in the central nervous system (Deakin, 1988), and their precipitate drop after delivery may well be responsible for episodes of psychosis (and therefore depression) in predisposed women. In a prospective study of 15 women at risk (Wieck *et al*, 1991), the growth hormone response to an apomorphine challenge test on day 4 postpartum in eight women who had a recurrence of illness was significantly greater than that of the seven at-risk women who remained well, and than that of a control group of 15 postpartum women who were not at risk. The finding is of importance in terms of a treatment strategy, since oestrogen therapy may well prove to be a prophylactic in women prone to puerperal psychoses. Some support for the role of oestrogen as a treatment has been shown in women with postnatal depression (Henderson *et al*, 1991).

Cortisol

Elevated cortisol and depressed mood occur in Cushing's syndrome (Blake Tyrell & Forsham, 1986), and hypercortisolaemia often accompanies major depression (Carroll *et al*, 1981). Similarly, Addison's disease is often accompanied by depressed mood, and withdrawal of steroid medication has the same association (Fricchione *et al*, 1989).

Early studies actually suggested oral prednisone as a treatment for puerperal depression (Railton, 1961). From the studies which have assessed mood, plasma cortisol and urinary corticosteroids during pregnancy and the postpartum period, one robust finding to emerge is that puerperal women, whether depressed or not, are non-suppressors in terms of the dexamethasone suppression test (Singh *et al*, 1986; O'Hara *et al*, 1991). However, most studies have failed to show any associations of blues with plasma or saliva cortisol, or with urinary metabolites (Kuevi *et al*, 1983; O'Hara *et al*, 1991; Harris *et al*, 1994). Among the few exceptions is the report that higher plasma cortisol levels at the end of pregnancy are associated with more severe blues (Handley *et al*, 1980).

In contrast to the amount of attention that has been given to major depression in general and the hypothalamic–pituitary–adrenocortical (HPA) axis, comparatively few studies have examined the relationship between puerperal depressive illness, cortisol, and cortisol suppression to dexamethasone. No major associations have emerged (Owens *et al*, 1987; Smith *et al*, 1987; O'Hara *et al*, 1991). A similar negative finding has been shown for puerperal psychosis (Singh *et al*, 1986). More recently, a small pilot study involving 26 women has shown a slower fall in postpartum morning cortisol levels in depressed compared with non-depressed women,

although there were no differences between the groups in terms of 24-hour urinary free cortisol excretion, indicating that 24-hour HPA axis activity may in fact be the same in the two groups (Pederson *et al*, 1993). Further elucidation of this finding is awaited.

Thyroid hormones

Thyroid hormones also change during pregnancy, mostly reflecting the increase of binding globulins, so that there is an overall increase of the total T3 and T4, but free thyroid hormone levels remain within normal limits. After delivery there are fairly rapid changes in the same hormones (Rodin, 1989). Transient hypothyroidism, sometimes preceded by hyperthyroidism, occurs in up to 5% of women in the postpartum year, reaching a peak at four to five months (Amino *et al*, 1981; Jansson *et al*, 1984; Gerstein, 1990). Such postpartum thyroid dysfunction has been shown to be associated with depression (Harris *et al*, 1989; Pop *et al*, 1991). Furthermore, an association has been shown between positive thyroid antibody status, which occurs in approximately 10% of normal women (Prentice *et al*, 1990), and episodes of postnatal depression (Harris *et al*, 1992). In a study in which over 100 women positive for thyroid antibodies were compared with a similar number of antibody-negative women and interviewed and rated on depression rating scales over eight months postpartum, a clear association between depressed mood and positive antibody status emerged. The cause of the depressed mood is debatable, and may be related to changes in thyroid hormones, in that the latter are subject to rapid flux in women with positive thyroid antibody status. The importance of this finding is that thyroid antibody status can be identified in pregnancy or in the immediate postpartum period (Pop *et al*, 1993), and women at risk may be monitored more carefully, appropriate treatment being instituted if necessary. An estimated 1% of postpartum women in the general population will experience such a major depressive episode (Harris *et al*, 1992). There is also serious risk of developing permanent hypothyroidism (Tachi *et al*, 1988).

Major depression in general is known to be associated with changes in thyroid function (Prange *et al*, 1972; Kirkegaard & Faber, 1980; Nemeroff, 1989), and a small pilot study has shown that a group of 12 puerperal women with a history of major depression tended to have higher levels of T3, T4, and thyroid-stimulating hormone in the puerperium compared with 14 women with no such history. The same study also showed that women with puerperally depressed mood tended to have lower total T4, free T4 and higher T3 uptake at 38 weeks' gestation.

Conclusions

Many interesting associations between hormonal/biological factors and postnatal mood have emerged; a few prompt review of current practice, and a few suggest new strategies for prophylaxis and treatment. A causal link between progesterone withdrawal and *serious* postpartum mood disorder has never been shown, and although many agree with the largely anecdotal accounts of the usefulness of progesterone administration as a prophylactic and treatment strategy in the puerperium, an adequate controlled, double-blind trial comparing progesterone with placebo is still awaited.

On the other hand, two useful strategies have emerged. Firstly, women who are thyroid-antibody positive should be identified, and subsequently monitored in the postpartum period, in anticipation of some of this subgroup developing postnatal depression (a double-blind trial of thyroxine versus placebo in the postpartum six months is currently being carried out by the author). Secondly, oestrogen therapy is proving its usefulness as a prophylactic and treatment for the more severe episodes of depression, the latter probably representing manic-depressive illness, depressed type. These strategies will be used in conjunction with standard antidepressant treatment. They will also aid the investigation of the many other background factors known to be associated with depressed mood in the puerperium.

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