Journal of Neuroendocrinology
From Molecular to Translational Neurobiology

Journal of Neuroendocrinology 23, 1149–1155

ORIGINAL ARTICLE

Changes in the Maternal Hypothalamic–Pituitary–Adrenal Axis During the Early Puerperium may be Related to the Postpartum 'Blues'

V. O'Keane*, S. Lightman†, K. Patrick‡, M. Marsh§, A. S. Papadopoulos¶, S. Pawlby, G. Seneviratne††, A. Taylor‡‡ and R. Moore§§**

**Trinity Health Sciences Building, Tallaght Hospital (AMNCH), Dublin, Ireland.*

†Henry Wellcome Laboratories for Integrated Neuroscience and Endocrinology, University of Bristol, UK.

‡BMA House, Tavistock Square, London, UK.

§Department of Obstetrics and Gynaecology, King's College Hospital, London, UK.

¶Affective Disorders Laboratory, Bethlem Royal Hospital, London, UK.

***King's College, London, UK.*

††King's College Hospital, London, UK.

‡‡Department of Biochemistry, King's College, London, UK.

§§Burdett House, Mile End Hospital, London, UK.

Journal of Neuroendocrinology

Most women experience time-limited and specific mood changes in the days after birth known as the maternity blues (Blues). The maternal hypothalamic-pituitary-adrenal (HPA) axis undergoes gradual changes during pregnancy because of an increasing production of placental corticotrophin-releasing hormone (CRH). The abrupt withdrawal of placental CRH at birth results in a re-equilibration of the maternal HPA axis in the days post-delivery. These changes may be involved in the aetiology of the Blues given the central role of the HPA axis in the aetiology of mood disorders in general, and in perinatal depression in particular. We aimed to test the novel hypothesis that the experience of the Blues may be related to increased secretion of hypothalamic adrenocorticotrophic hormone (ACTH) secretagogue peptides, after the reduction in negative-feedback inhibition on the maternal hypothalamus caused by withdrawal of placental CRH. We therefore examined hormonal changes in the HPA axis in the days after delivery in relation to daily mood changes: our specific prediction was that mood changes would parallel ACTH levels, reflecting increased hypothalamic peptide secretion. Blood concentrations of CRH, ACTH, cortisol, progesterone and oestriol were measured in 70 healthy women during the third trimester of pregnancy, and on days 1–6 post-delivery. Blues scores were evaluated during the postpartum days. Oestriol, progesterone and CRH levels fell rapidly from pregnancy up to day 6, whereas cortisol levels fell modestly. ACTH concentrations declined from pregnancy to day 3 post-delivery and thereafter increased up to day 6. Blues scores increased, peaking on day 5, and were positively correlated with ACTH; and negatively correlated with oestriol levels during the postpartum days, and with the reduction in CRH concentrations from pregnancy. These findings give indirect support to the hypothesis that the 'reactivation' of hypothalamic ACTH secretagogue peptides may be involved in the aetiology of the Blues.

Key words: placental, CRH, birth, postpartum blues, ACTH.

doi: 10.1111/j.1365-2826.2011.02139.x

Correspondence to:
V. O'Keane, Trinity Health Sciences Building, Tallaght Hospital (AMNCH), Dublin 24, Ireland (e-mail: vokeane@tcd.ie).

Most women experience subjective changes in their emotional states in the days after birth. These emotional experiences are specific to the postpartum period in that they differ phenonemologically from reactions to other major emotional or medical stressors (1). Tearfulness, anxiety and emotional lability are characteristic. Studies of large samples of women demonstrate a trend for these emotional states to peak on day 4 or 5, and to normalise by day 10 (2,3). There is a psychiatric literature on these transient

emotional states and attempts have been made to distinguish a 'syndrome' of 'Postpartum Blues', based on notional cut-off points on scales designed to measure emotional changes (1,4). This literature suggests that, although approximately 70% women have mood changes, 30–35% of women fulfill criteria for Postpartum Blues (5–8). In more recent years, a syndrome of 'Postpartum Highs' has been described, characterised by euphoria, insomnia and irritability, and is conisdered to occur in approximately 10% of women in the days after birth (9,10). Approximately one in 2000 women have a very severe and pathological alteration in their mood typically commencing in the first few days after delivery that evolves into a postpartum psychosis (11). Overall, there appears to be a spectrum of emotional changes occurring in most women in the 10 days after birth, specific to this period, ranging from mild subjective experiences through to more overwhelming emotional states and, rarely, a severe affective psychosis.

These mood shifts are considered to result from the effects of rapid hormonal changes on brain emotional centres. Methods of investigation have tended to dichotomise women into groups with and without Postpartum Blues. The hypotheses generally tested in previous studies were that there would be differences between the groups in blood concentrations, or gradients of decline, of the sex hormones. Inconsistent, and sometimes contradictory, findings have emerged from these endocrine studies (5,7). An abrupt decline in either progesterones or oestrogens alone does not explain differences between 'cases' and controls. We aimed to use a novel approach and examine the hormonal changes in relation to mood shifts in women without using categories of 'caseness' because there is insufficient evidence to indicate that a syndrome of Postpartum Blues exists. We use the term 'Blues' to describe the mood swings that typically occur in women during the postpartum week. Individual experiences appear to represent individual affective responses and diatheses to a common endocrine trigger. This affective diathesis is compatible with the observations that Postpartum Blues and Highs predict postnatal depression at 8 weeks postpartum (3,8,9).

Abnormal hypothlamic-pituitary-adrenal (HPA) axis function is found in depression. Compared to nondepressed controls, those with depression tend to have increased activity of the HPA axis; although this is not true for all tests of HPA axis function and only for more severe types of depression (12,13). There is much evidence that the increased output from the HPA axis in depressed states is driven by hypersecretion of corticotrophin-releasing hormone (CRH) and/or arginine vasopressin (AVP), as a consequence of impaired negative-feedback at glucorticoid and/or mineralocorticoid receptors in the hypothalamus. There is a rapidly expanding interest in the HPA axis in depression during pregnancy because of the gathering evidence of the harmful effects of prenatal stress on fetal/-baby development and on the length of pregnancy (14). CRH is secreted by the placenta during pregnancy, leading to the formation of placental-pituitary-adrenal endocrine circuits in mother and baby. This results in a cushingoid state in pregnant women during late pregnancy. After delivery, CRH is rapidly eliminated from the peripheral circulation and a gradual decline in cortisol secretion ensues (15,16). The hypothalamic suppression of CRH secretion that should occur during the end stages of pregnancy is therefore removed during the early puerperium. This should cause increased secretion of the activating brain peptides CRH and/or AVP.

We aimed to test the hypothesis that the loss of the negative-feedback from the autonomous maternal placental CRH-adrenocorticotrophic hormone (ACTH)-cortisol system on hypothalamic CRH and/or AVP output results in increased secretion of these hypothalamic peptides; and that these changes may cause the early puerperal mood changes. We tested this hypothesis indirectly by measuring changes in circulating CRH, ACTH, cortisol, oestriol and progesterone, as well as mood changes over time during the risk period, in a group of healthy women.

Materials and methods

Subjects

Women were recruited from the antenatal outpatient clinics in King's College Hospital, London, at their week-36 scan. Women were eligible for inclusion if they had no history, or no current evidence, of psychiatric disorder. Other exclusion criteria for participants were having a major obstetric, medical or neurological problem; a multiple pregnancy; being on medication other than nutritional supplementation; or being aged < 19 years or > 45 years. Volunteers read the Patient Information Sheet provided their written informed consent. The study was approved by the South London and Maudsley Ethics Committee.

Design

Subjects were tested at week 36 of their pregnancy and on 3 days after the delivery of their babies. Each women was tested on alternate days (i.e. either days 1, 3 and 5 or days 2, 4 and 6 post-delivery). We considered that it would have been too demanding on newly-delivered mothers to request daily blood samples. Thus, 35 samples were collected on each postpartum day. After the week-36 assessment, the main research worker (R.M.) kept in telephone contact with the volunteers and so was aware of when they went into labour. On each test day, blood was drawn for analysis of oestriol, progesterone, CRH, ACTH and cortisol. The mood scale was completed on each test day.

Psychiatric rating scales

All study participants were interviewed at the first meeting by the clinical researcher (R.M.) who conducted a Structured Clinical Interview for the Diagnostic and Statistic Manual (IV) to exclude any formal psychiatric disorder (17). The Edinburgh Postnatal Depression Score (18), which is the most commonly used scale for measuring depression during pregnancy, was also competed by participants. A cut-off point of > 11 was used as a criterion for exclusion. We used the 28-item Blues Questionnaire (1) to measure mood postpartum. This scale is sensitive to changes in emotional states over short time periods and was designed to capture the specific mood changes in the 10 days post-delivery. The Blues Questionnaire has been demonstrated to discriminate between Blues and nonspecific reactions to physical and emotional stress (19) and to be correlated with the occurrence of premenstrual tension and not depression (20). The latter is an important distinction because we aimed to separate symptoms of depression, common during the peripartum period, from fluctuations in emotional states. The

scale takes approximately 15 min to complete and, although self-administered, may need some explanation from the clinician.

Endocrine samples

Collection

Blood samples were collected between 11.00 h and 15.00 h, at least 4 h after waking, and 1 h after breast feeding. Women were seated or supine, an i.v. cannula was inserted and blood was drawn 15 min later. CRH and ACTH samples were collected in chilled ethylenediaminetetraacetic acid tubes: the CRH tube also contained aprotinin. Blood for progesterone, oestriol and cortisol analysis was collected in a plain 10-ml bottle. Most blood samples were taken in the womens' homes. Blood bottles were put in ice and transported in an ice box to the laboratory where they were centrifuged. Serum or plasma was then split into duplicate aliquots and immediately frozen at −80 °C until being thawed in ice before analysis.

Hormone analysis

All hormones were assayed blind to subject status. CRH was analysed in research laboratories at Imperial College, London, by A.T. and the other hormones were analysed by A.P. in the research laboratory on the hospital site. CRH samples were analysed using ^{125}I radioimmunoassay kits obtained from Peninsula Laboratories Inc. Bachem Group (21). The detection limit of the assay is 10 pg/ml serum, the interassay and intra-assay coefficients of variation (CV) are 10.5% and 5%, respectively. ACTH, cortisol, oestriol and progesterone assays were performed using an anonisotopic, automated, 'Immulite'™ chemiluminescence (DPC) immunoassay system (Siemens AG, Munich, Germany). Plasma ACTH requires a solid-phase, two-site sequential assay. Intra- and interassay CVs for ACTH were < 9.6% and < 9.4%, respectively. The assay for serum cortisol has a detection limit (sensitivity) of 5.5 nM and intra- and interassay CVs of < 8.8% and < 10%, respectively. The assay for progesterone has an analytical sensitivity of 0.6 nM and the intra- and interassay CVs are both < 10% (range 5.4–22 nM). High concentration specimens were diluted before analysis as appropriate.

Saliva cortisol concentrations were determined using the DPC Immunoassay analyser. This has a sensitivity of 0.2 nM and an inter/intra-assay precision (% CV) of < 10% (cortisol concentration range 5–25 nM).

Statistical analysis

Hormonal changes were evaluated in two ways: using actual blood concentration values and using delta values (differences between the hormone concentration during the third trimester and on each day post-delivery). Repeated measures ANOVA was used to analyse trends over time, with post-hoc analysis where appropriate using Tamhane's T_2 test. Correlational analysis (Spearman's) was used to examine possible relationships among the data. Measures are presented as the mean ± SEM.

Results

Seventy-six women entered the study, six of whom dropped out before the birth of their baby. Data are given for the 70 volunteers who continued to participate post-delivery. Some of these women were unable or unwilling to supply blood samples on specific days, leaving 14% of samples 'missing'. Missing values were substituted by the mean group value of the hormone for all days combined.

Most of the participants were primiparous (n = 44), 22 had one child and four had two or more children. The mean ± SE age of the women was 33.1 ± 0.57 years. None of the participants delivered at < 37 weeks' gestation. Forty-six women had normal vaginal deliveries, 21 women were delivered by Caesarian section and three had assisted deliveries- either forceps or vontouse. The mean ± SE weight of the babies was 3.3 ± 0.49 kg.

Endocrine data

Table 1 outlines the mean hormonal values on the test days, along with the ANOVA analysis. There were significant reductions in all hormones from pregnancy to day 6; with progesterone, oestriol and CRH levels falling by 95–98%. Analysing the six post-delivery days only demonstrated significant declines for oestriol and progesterone, but no significant fall in CRH, concentrations. The decline in cortisol from week 36 to day 6 postpartum, although significant, was more modest (22%). Cortisol values fell only be 19% during

Table 1. Hormone Concentrations During Late Pregnancy and the Early Puerperium (n = 70 Women).

	Week 36	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Oestriol (ng/ml)	79.1 ± 8.7	8.6 ± 1.1	7.4 ± 0.95	2.9 ± 0.54	1.8 ± 0.6	1.9 ± 0.19	0.9 ± 0.05
F = 380, d.f. = 6,272, P < 0.01		F = 7.47, d.f. = 5,201, P < 0.01; P < 0.01 (days 1 and 3; days 1 and 4; days 1 and 5; days 1 and 6)					
Progesterone (nM)	602 ± 37.5	50.8 ± 6.1	56.6 ± 5.9	40 ± 5.1	43.6 ± 4.7	25.6 ± 4.4	30.3 ± 4.6
F = 103, d.f. = 6,272, P < 0.01		F = 2.9; d.f. = 5,201; P = 0.04; P < 0.05 (days 1 and 4; days 1 and 5; days 2 and 5; days 2 and 6)					
CRH (pg/ml)	556 ± 40.2	79 ± 8.7	72.6 ± 9.6	71.8 ± 9.5	73 ± 10.2	70.51 ± 9.8	62.7 ± 9.3
F = 97.4, d.f. = 6,272, P < 0.01		F = 0.36, d.f. = 5,201, P = 0.9					
ACTH (pM)	7.3 ± 0.8	2.7 ± 0.36	3.5 ± 0.21	3.1 ± 0.42	4 ± 0.26	4.5 ± 0.44	4.63 ± 0.37
F = 85; d.f. = 6,272, P < 0.01		F = 4.4, d.f. = 5,201, P = 0.001; P = 0.05 (days 1 and 4; days 1 and 5); P = 0.006 (days 1 and 6)					
Cortisol (mM)	506.6 ± 40.1	491.4 ± 35.8	522.4 ± 33.7	467.2 ± 25.7	474.5 ± 19.8	460 ± 38.1	397.8 ± 21.3
F = 13, d.f. = 6,272, P < 0.01		F = 3, d.f. = 5,201, P = 0.01; P = 0.04 (days 1 and 5); P = 0.02 (days 1 and 6)					

Mean ± SD hormone concentrations (with units of measurement) at week 36 gestation, and from days 1–day 6 in a sample of 70 women. Overall differences over time for each hormone is presented in the left column under the hormone name. Analysis over time for the postpartum days only, with significant post-hoc results, is presented in the row under the data entries. CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophin hormone.

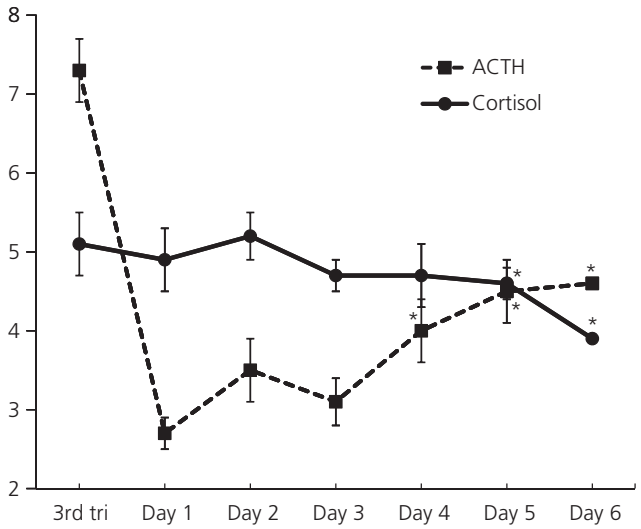

Fig. 1. Scaled graph of mean ± SEM adrenocorticotrophic hormone (ACTH) and cortisol concentrations in 70 women during the third trimester (3rd tri) of pregnancy and on days 1–6 after birth. *Statistically significant ($P < 0.05$) difference from day 1 values for each hormone separately.

the postpartum days, although these changes were statistically significant. ACTH values had a different pattern: initially declining from pregnancy for the first 3 days, and increasing thereafter, with significant differences between day 1 and days 4, 5 and 6. Figure 1 illustrates the cortisol and ACTH changes. Analysis using delta hormone values did not alter the findings. There were no differences between any hormone values in relation to parity (primiparous versus all other). There were no differences in pregnancy hormones between women who gave birth to male compared to female babies.

Mood data

Blues scores increased from day 1 to day 6 ($F = 5.36$, d.f. = 5,204, $P < 0.01$), with the highest scores on day 5 (Fig. 2). There were significant differences between day 1 and days 3, 4 and 5 (all $P < 0.01$). There were no differences between primparous and mutiparous women in relation to peak mood scores.

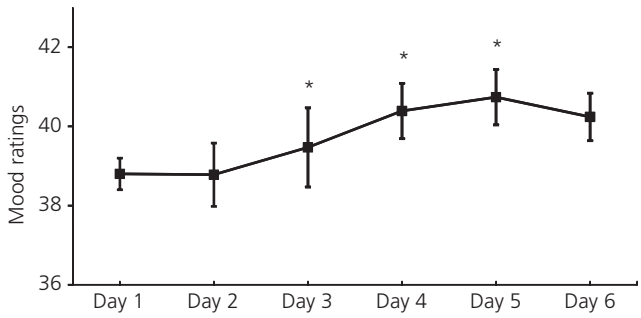

Fig. 2. Mean ± SEM mood scores, as evaluated using the Kennerley and Gath Scale over the first six postpartum days in 70 healthy newly-delivered women. *Statistically significant difference from day 1.

Table 2. Correlations Analysis of Endocrine and Blues Scores (n = 70 Women).

	Delta values	Absolute concentrations
CRH	*CC = 0.15, P = 0.03	CC = 0.03, P = 0.72
ACTH	CC = −0.01, P = 0.87	*CC = 0.23, P < 0.01 RA (β = 0.13, P = 0.05)
Cortisol	CC = 0.4, P = 0.58	CC = −0.008, P = .83
Oestriol	CC = 0.08, P = 0.24	CC = −0.3, P < 0.01* RA (β = −0.27, P < 0.01)
Progesterone	CC = 0.05, P = 0.67	CC = −0.07, P = 0.1

Results of correlational analysis among the endocrine (day 1–6 postpartum) and Blues scores: each cell contains the correlation coeffecient (CC) and its significance, of the intersecting endocrine and blues scores. Endocrine data are analysed both as 'absolute' values (blood concentrations) and 'delta' values (differences between the week-36 concentration and each value on the days after birth). The significance after regression analysis (RA) is shown under the 'CC' as appropriate. *Statistically significant. CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophin hormone.

Correlational analysis

The only significant correlation between Blues scores and delta hormone concentrations was with CRH values (Table 2). There were significant linear relationships among Blues scores and the postpartum concentrations for both ACTH (positive correlation) and oestriol levels (negative correlation): both of which were significant after regression analysis. There were no significant correlations between either cortisol or progesterone values and Blues scores.

Discussion

Mood scores in this group of healthy women in the first 6 days after birth confirms previous findings of a significant shift in emotional states during these days, peaking on days 4–5. There was a predictable dramatic decline in CRH, oestriol and progesterone levels post-delivery, and Blues scores were correlated with the fall in CRH levels from pregnancy to the early puerperium. Our findings of a modest fall in cortisol levels after birth is consistent with findings reported in the literature (15,16,22). The pattern of ACTH secretion during the first week postpartum, however, has not previously been described. Levels dropped for the first three postpartum days and then started to climb. Mood scores were correlated positively with ACTH, and negatively with oestriol values postpartum. Analysis of delta hormone values, which measured hormone values as the decline in each hormone from pregnancy to the the index postpartum day, demonstrated a significant association between CRH changes and the Blues scores. We discuss the possible meaning of these findings.

The placental-pituitary-adrenal axis

Specific changes in the HPA axis occur during pregnancy. These changes are brought about by the secretion of CRH from the

placenta (16,23). Although CRH is normally an almost completely brain-bound peptide, and unable to cross the blood–brain barrier, placental CRH is secreted into the maternal and fetal circulations. The synthesis of placental CRH is stimulated by maternal cortisol and in turn cortisol stimulates placental CRH synthesis: creating a positive-feedforward drive (16). We have recently reported that women who are depressed during pregnancy have higher cortisol production and higher CRH levels during the second trimester (14). Higher CRH levels in depressed pregnant women has also been recently reported by another group (24); whereas a third recent study reported no difference in CRH concentrations between depressed and nondepressed pregnant women (25). Circulating CRH concentrations increase as pregnancy advances and a critically high level of CRH is considered to be a key trigger for the initiation of the process of parturition (26,27). After the delivery of the placenta, levels of circulating CRH rapidly reduce over 24 h (15).

Diurnal cortisol secretion gradually increases in the 30 days leading up to birth, with a blunting of the diurnal rhythm of cortisol secretion (7). This may result from the reduction of CRH binding protein and the exponential rise in free CRH concentrations that begins at week 36 (28). The adrenal glands become hypertrophied during pregnancy and cortisol levels gradually decline after birth, with high rates of cortisol nonsuppression to dexamethasone being present for the first three postpartum weeks (22). The HPA axis remains relatively hyporesponsive overall during the postpartum period: probably as a consequence of this adrenal hypertrophy and other inhibitory brain factors, such as oxytocin or prolactin (15,29). Our cortisol results are compatible with these findings (i.e. a small decline in the first postpartum week). Two studies have found differences between cortisol levels in women who had Postpartum Blues compared to groups who did not fulfill these criteria (6,30). Other studies have reported that there are no differences in cortisol between groups of women with and without Postpartum Blues (5,7).

Our findings of an immediate fall in ACTH levels after birth indicate that placental CRH stimulates the production of maternal ACTH during pregnancy (16). The increase in ACTH levels, commencing on day 3–4 post-delivery, has not been previously described and suggests that maternal ACTH secretagogues, hypothalamic CRH or AVP, are mediating this secretion. The findings from our study that the Blues scores are negatively correlated with a drop in CRH concentrations from pregnancy, and a rise in ACTH concentrations post-delivery, supports the speculative hypothesis that the emotional shifts over the first puerperal days may be related to the central release of these behaviourally activating peptides.

CRH and the brain

Animal work indicates that when CRH is released secondary to stress, and apart from the effects that it has on ACTH release from the pituitary, it can stimulate CRH-1 receptors in many brain limbic structures, including the amygdla and hippocampus (31), altering cognitive function and behaviour. CRH has neuromodulatory and neuroregulatory actions at neuronal synapses (32). Intracerebroventricular injection of CRH in rats results in increased locomotor activity, reduced appetite, reduced sleep, increased alertness and reduced sexual drive: behaviours compatible with the overaroused emotional states of the puerperium. Reactivation of CRH would be likely to cause comparable behavioural experiences in humans. This is supported by the convincing evidence obtained in humans indicating that melancholic depression is associated with hypersecretion of CRH and/or AVP (12,13). Much exploration in clinical depression is now focused on impaired cortisol feedback mechanisms, although the direct effects of CRH on brain function are also being explored and CRH antagonists are being investigated as possible antidepressant agents (33).

Gestational steroids and the Blues

The inverse relationship of oestriol levels with Blues scores during the 6 days after birth is interesting because of the relationship between oestriol and the gestational HPA axis. During pregnancy, oestriol is synthetised in the placenta from dehydroepiandrosterone sulphate (DHEAS) derived from the fetal adrenal glands (34). DHEAS is the main product of the fetal adrenals and its secretion is partly controlled by placental CRH secretion (35). Thus, the decline in CRH from pregnancy and the decline in oestriol post-delivery are different measures of the placental-fetal-maternal pituitary-adrenal system.

One previous study has reported on oestriol levels in groups of women divided into those with and without the 'Postpartum Blues'. Oestriol levels dropped more significantly in the Postpartum Blues group from the third trimester of pregnancy to day 1 postpartum (5). The authors interpreted their findings as providing 'weak support' to a hypothesis of oestrogen withdrawal as a cause of postpartum blues, acknowledging that oestriol is a weak oestrogen. The findings do suggest that the size of the decline in oestriol is related to the severity of the emotional shifts and is compatible with the findings of the present study.

One other study dichotimising women into those with and without 'Maternity Blues' had an impressive sample size (n = 39 with; n = 78 without Maternity Blues) (7). It was found that the decline in progesterone concentrations from delivery to day 5, when Blues scores peaked, was greater in the group classified as having the Maternity Blues. The authors concluded that the Maternity Blues was related to progesterone withdrawal. These findings could also indicate that a steeper decline in progesterone, rather than being causal, is related to the presence of more Maternity Blues symptoms. Progesterones and oestrogens also have effects on CRH production, with oestrogens probably having stimulatory, and progesterones having inhibitory, effects (36,37).

Downstream effects of hormones on neurotransmitter function

It is probable, given the complexity of the changes during the puerperium and the inter-relatedness of the systems involved, that many factors are involved in the mood changes during the puerperium. For example, the effects of hormone changes on

neurotransmitter function could be responsible; for example, declining oestrogen levels have been shown to increase brain monoamine oxidase A binding capacity in puerperal women (38); progesterone has an anaesthetic effect that animal work shows to be partly mediated through GABA receptors (39) and possibly dopamine receptors in women (40); and there is much animal and human evidence that oestrogens effect brain monoamine function (41,42). The immediacy and predictability of the timing of the Blues, however, suggests a direct effect on brain function rather than a downstream effect that could take a variable amount of time.

Study limitations

The present study has several limitations. Hormones were measured at week 36 but are known to increase until term. We did not have a pre-delivery level for the hormones and so the delta scores were probably undervalued. The HPA axis hormones that were measured increase commensurately during the final weeks, however, suggesting that the hormones were proportionately undervalued. The HPA axis does not return to homeostasis for approximately 3 weeks after birth and we therefore did not establish a post-pregnancy endocrine baseline for our participants. The same is true for the mood scores. Although we captured interesting changes over a small period of time, the findings would be strengthened by having exact pre-delivery and stable post-delivery mood and endocrine values.

Conclusions and implications for future research

We found indirect support for our 'hypothalamic re-activation hypothesis' being a possible causal factor in the Blues, although this hypothesis must remain speculative. It is an attractive hypothesis because of the large literature on probable CRH and/or AVP over-secretion in depression. The central effects of the disassembling of the placental-pituitary-adrenal circuit after birth open up novel ways for our further understanding of the increasingly complex changes that give rise to the mood disturbances occurring during this period. The pattern of ACTH secretion, probably reflecting hypothalamic peptide secretion, has not been previously described. A hypothesis of CRH reactivation opens up the possibility of treating puereral psychosis with CRH antagonists. Similarly, if severe blues herald the onset of postpartum depression, CRH antagonists may arrest the processes that occur after this 'trigger'.

The early puerperal days are a unique period of predictable mood instability and represent a naturally occurring phenomenon that could inform us about depression outside of pregnancy. Reduced glucocorticoid feedback on hypothalamic ACTH secretagogues is widely hypothesised to be central to the aetiology of clinical depression. Our preliminary study suggests the possibility that oversensitive feedback mechanisms may give rise to extreme emotional/mood experiences.

Received 5 January 2011,
revised 16 March 2011,
accepted 12 April 2011

References

1 Kennerley H, Gath D. Maternity blues. I. Detection and measurement by questionnaire. *Br J Psychiatry* 1989; **155**: 356–362.
2 Stein G, Marsh A, Morton J. Mental symptoms, weight changes, and electrolyte excretion in the first post partum week. *J Psychosom Res* 1981; **25**: 395–408.
3 Kendell RE, McGuire RJ, Connor Y, Cox JL. Mood changes in the first three weeks after childbirth. *J Affect Disord* 1981; **3**: 317–326.
4 Stein GS. The pattern of mental change and body weight change in the first post-partum week. *J Psychosom Res* 1980; **24**: 165–171.
5 O'Hara MW, Schlechte JA, Lewis DA, Wright EJ. Prospective study of postpartum blues. Biologic and psychosocial factors. *Arch Gen Psychiatry* 1991; **48**: 801–806.
6 Okano T, Nomura J. Endocrine study of the maternity blues. *Prog Neuropsychopharmacol Biol Psychiatry* 1992; **16**: 921–932.
7 Harris B, Lovett L, Newcombe RG, Read GF, Walker R, Riad-Fahmy D. Maternity blues and major endocrine changes: cardiff puerperal mood and hormone study II. *BMJ* 1994; **308**: 949–953.
8 Adewuya AO. Early postpartum mood as a risk factor for postnatal depression in Nigerian women. *Am J Psychiatry* 2006; **163**: 1435–1437.
9 Glover V, Liddle P, Taylor A, Adams D, Sandler M. Mild hypomania (the highs) can be a feature of the first postpartum week. Association with later depression. *Br J Psychiatry* 1994; **164**: 517–521.
10 Heron J, Craddock N, Jones I. Postnatal euphoria: are 'the highs' an indicator of bipolarity? *Bipolar Disord* 2005; **7**: 103–110.
11 Kumar R. Postpartum psychosis. *Baillieres Clin Obstet Gynaecol* 1989; **3**: 823–838.
12 Claes S. Glucocorticoid receptor polymorphisms in major depression. *Ann NY Acad Sci* 2009; **1179**: 216–228.
13 Lightman SL. The neuroendocrinology of stress: a never ending story. *J Neuroendocrinol* 2008; **20**: 880–884.
14 O'Keane V, Lightman S, Marsh M, Pawlby S, Papadopoulos AS, Taylor A, Moore R, Patrick K. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: a pilot study. *J Affect Disord* 2011; **130**: 300–305.
15 Mastorakos G, Ilias I. Maternal hypothalamic-pituitary-adrenal axis in pregnancy and the postpartum period. Postpartum-related disorders. *Ann NY Acad Sci* 2000; **900**: 95–106.
16 Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Ann NY Acad Sci* 2003; **997**: 136–149.
17 American Psychiatric Association. *Work Group to Revise DSM-III. Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R*, 3rd edn. Washington, DC: American Psychiatric Association, 1987.
18 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782–786.
19 Iles S, Gath D, Kennerley H. Maternity blues. II. A comparison between post-operative women and post-natal women. *Br J Psychiatry* 1989; **155**: 363–366.
20 Kennerley H, Gath D. Maternity blues. III. Associations with obstetric, psychological, and psychiatric factors. *Br J Psychiatry* 1989; **155**: 367–373.
21 Dwenger A. Radioimmunoassay: an overview. *J Clin Chem Clin Biochem* 1984; **22**: 883–894.
22 Owens PC, Smith R, Brinsmead MW, Hall C, Rowley M, Hurt D, Lovelock M, Chan EC, Cubis J, Lewin T. Postnatal disappearance of the pregnancy-associated reduced sensitivity of plasma cortisol to feedback inhibition. *Life Sci* 1987; **41**: 1745–1750.
23 Magiakou MA, Mastorakos G, Rabin D, Margioris AN, Dubbert B, Calogero AE, Tsigos C, Munson PJ, Chrousos GP. The maternal hypothalamic–pituitary–adrenal axis in the third trimester of human pregnancy. *Clin Endocrinol (Oxf)* 1996; **44**: 419–428.

24 Rich-Edwards JW, Mohllajee AP, Kleinman K, Hacker MR, Majzoub J, Wright RJ, Gillman MW. Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. *J Clin Endocrinol Metab* 2008; **93**: 1946–1951.
25 Meltzer-Brody S, Stuebe A, Dole N, Savitz D, Rubinow D, Thorp J. Elevated corticotropin releasing hormone (CRH) during pregnancy and risk of postpartum depression (PPD). *J Clin Endocrinol Metab* 2011; **96**: E40–E47.
26 McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. *Nat Med* 1995; **1**: 460–463.
27 Smith R, Nicholson RC. Corticotrophin releasing hormone and the timing of birth. *Front Biosci* 2007; **12**: 912–918.
28 Linton EA, Perkins AV, Woods RJ, Eben F, Wolfe CD, Behan DP *et al.* Corticotropin releasing hormone-binding protein (CRH-BP): plasma levels decrease during the third trimester of normal human pregnancy. *J Clin Endocrinol Metab* 1993; **76**: 260–262.
29 Magiakou MA, Mastorakos G, Rabin D, Dubbert B, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. *J Clin Endocrinol Metab* 1996; **81**: 1912–1917.
30 Ehlert U, Patalla U, Kirschbaum C, Piedmont E, Hellhammer DH. Postpartum blues: salivary cortisol and psychological factors. *J Psychosom Res* 1990; **34**: 319–325.
31 Gallagher JP, Orozco-Cabal LF, Liu J, Shinnick-Gallagher P. Synaptic physiology of central CRH system. *Eur J Pharmacol* 2008; **583**: 215–225.
32 Ivy AS, Rex CS, Chen Y, Dube C, Maras PM, Grigoriadis DE, Gall CM, Lynch G, Baram TZ. Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J Neurosci* 2010; **30**: 13005–13015.
33 Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. *CNS Neurol Disord Drug Targets* 2006; **5**: 453–479.
34 Mesiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. *Endocr Rev* 1997; **18**: 378–403.
35 Weintrob N, Drouin J, Vallette-Kasic S, Taub E, Marom D, Lebenthal Y, Shohat M. Low estriol levels in the maternal triple-marker screen as a predictor of isolated adrenocorticotropic hormone deficiency caused by a new mutation in the TPIT gene. *Pediatrics* 2006; **117**: e322–e327.
36 Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic–pituitary–adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med* 1998; **129**: 229–240.
37 Brunton PJ, McKay AJ, Ochedalski T, Piastowska A, Rebas E, Lachowicz A, Russel JA. Central opioid inhibition of neuroendocrine stress responses in pregnancy in the rat is induced by the neurosteroid allopregnanolone. *J Neurosci* 2009; **29**: 6449–6460.
38 Sacher J, Wilson AA, Houle S, Rusjan P, Hassan S, Bloomfield PM. Elevated brain monoamine oxidase A binding in the early postpartum period. *Arch Gen Psychiatry* 2010; **67**: 468–474.
39 Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. *Neuron* 2008; **59**: 207–213.
40 Mc Ivor RJ, Davies RA, Wieck A, Marks MN, Brown N, Campbell IC. The growth hormone response to apomorphine at 4 days postpartum in women with a history of major depression. *J Affect Disord* 1996; **40**: 131–136.
41 O'Keane V, O'Hanlon M, Webb M, Dinan T. d-Fenfluramine/prolactin response throughout the menstrual cycle: evidence for an oestrogen-induced alteration. *Clin Endocrinol (Oxf)* 1991; **34**: 289–292.
42 Coyle N, Jones I, Robertson E, Lendon C, Craddock N. Variation at the serotonin transporter gene influences susceptibility to bipolar affective puerperal psychosis. *Lancet* 2000; **356**: 1490–1491.