

From Stress to Postpartum Mood and Anxiety Disorders: How Chronic Peripartum Stress Can Impair Maternal Adaptations

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Key Words

Oxytocin · Prolactin · HPA axis · Anxiety · Maternal behaviour

Abstract

The peripartum period, in all mammalian species, is characterised by numerous adaptations at neuroendocrine, molecular and behavioural levels that prepare the female for the challenges of motherhood. These changes have been well characterised and, while they are necessary to ensure the survival and nurturance of the offspring, there is growing belief that they are also required for maternal mental health. Thus, while increased calmness and attenuated stress responsiveness are common characteristics of the peripartum period, it also represents a time of increased susceptibility to mood disorders. While a number of risk factors for these disorders are known, their underlying aetiology remains poorly understood, due at least in part to a lack of appropriate animal models. One translatable risk factor is stress exposure during the peripartum period. In the following review we first describe common peripartum adaptations and the impact postpartum mood disorders have on these. We then discuss the known consequences of peripartum stress exposure on such maternal adaptations that have been described in basic research.

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Introduction

In all mammalian species the transition from virginity to motherhood represents a time when a host of changes occur in order to prepare the female for the challenges of maternity. Thus, the onset of maternal behaviours, such as maternal care and aggression, lactogenesis and milk ejection, represent such essential alterations in behaviour and physiology from virgins to the lactating mother [1–3]. These changes together with numerous other alterations at physiological, cellular and molecular levels act in concert to ensure the healthy survival and nurturance of the offspring [4, 5]. Thus, towards the end of pregnancy, and into lactation, a dampened (re)activity of the hypothalamo-pituitary-adrenal (HPA) axis appears to be essential for the healthy development of the offspring, as high levels of circulating corticosteroids can have severe consequences on fetal development [6]. This has been reported in various mammalian species including mice, rats, sheep, non-human primates and cows [1, 2, 7–10]. However, most of our basic knowledge regarding peripartum adaptations comes from studies on laboratory rodents. For example, in rats, there are changes in behaviour, with increased anxiety reported in mid-late pregnancy [1, 11], whereas reduced anxiety is found in lactation [1, 3, 12, 13]. These findings are in agreement with human studies, as an increased calmness has been reported in lactating women [14, 15].

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Table 1. Examples of neuroendocrine and behavioural alterations observed in pregnancy and lactation as assessed in rodent and human studies

Common peripartum adaptations	Time of occurrence	References animal studies	References human studies
<i>Neuronal and neuroendocrine adaptations</i>			
Chronic basal hypercorticism/hypercortisolism	lactation	3, 8, 36, 210, 211	29, 30, 130, 212
Decreased responsiveness of HPA axis to stressors	lactation	11, 36, 40, 41, 213, 214	15, 204, 215
Decreased CRH mRNA expression in the PVN	lactation	9, 37, 39–41	n.a.
Decreased CRH binding in the adenohypophysis	pregnancy and lactation	9, 11, 38	n.a.
Decreased noradrenergic input to PVN neurons	end of pregnancy and lactation	7, 44	n.a.
Attenuated pituitary sensitivity to CRH	pregnancy and lactation	11, 38	n.a.
Altered size and branching pattern of dendritic trees in the PVN	lactation	50	n.a.
Altered synaptic neuronal-glia interaction	lactation	51, 52	n.a.
Increased OXT mRNA and OXT-R mRNA expression in the PVN	lactation	5, 41, 53, 54, 77, 216	n.a.
Decreased ACTH secretion by systemic OXT after stress	lactation	217	n.a.
<i>Behavioural alterations</i>			
Increased maternal behaviour	lactation	1, 2, 48, 81	2, 218
Increased maternal aggression	lactation	1, 76, 82, 89, 219	n.a.
Increased calmness, decreased anxiety and responsiveness to stressors	lactation	12, 34, 49, 90	15, 29

ACTH = Adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; HPA = hypothalamo-pituitary-adrenal axis; n.a. = not assessed; OXT = oxytocin; OXT-R = oxytocin receptor; PVN = paraventricular nucleus of the hypothalamus.

While such changes are essential to ensure the healthy development of the offspring, there is growing evidence that they are also required for maternal mental health [5]. Thus, it has been shown that the peripartum period represents a time with high risk for women to develop mood and anxiety disorders, such as postpartum anxiety [16], postpartum depression (PPD) [17, 18] or the much rarer postpartum psychosis (PPP) [19, 20]. A number of risk factors for the development of these postpartum mood and anxiety disorders are known, including smoking [21] and alcohol abuse [22]. More translational risk factors that can be modelled in preclinical research include a history of anxiety or depression [23, 24], the social status of the mother [25, 26], or stressful events during pregnancy [18]. Although the physiological adaptations that occur throughout the peripartum period are well known, the mechanisms underlying postpartum mood and anxiety disorders remain elusive. However, given the clear association between stress and mood and anxiety disorders [27], recent research assessing the impact of stress during the peripartum period is beginning to shed light on potential mechanisms that may be involved in these disorders. Therefore, in the following review, we will describe the known consequences of chronic or repeated stress during the peripartum period on common adaptations that occur during this sensitive period that will hopefully lead to a better understanding of maternal mental health.

Peripartum-Related Adaptations

Before describing the consequences of chronic stress during the peripartum period, we will first discuss the adaptations that occur during this period. These changes, and the neural circuitry involved in their onset and maintenance, have been extensively discussed elsewhere, and we would direct the interested reader to the following reviews [1, 2, 4, 5, 8, 19, 28] and to table 1, which summarises the findings.

Neuroendocrine and Molecular Alterations

Towards the end of pregnancy, and into lactation, the response of the HPA axis to a variety of stressors has been shown to be severely attenuated in mothers [15, 29]; despite a concurrent hypercortisolism under basal (i.e. normal non-stressed) conditions compared with the respective level in nulliparous animals/virgins [30]. Such a basal elevation in glucocorticoids and attenuated HPA axis response to stress has been identified not only in humans, but also in numerous other species including rats, mice and sheep [8, 11, 31–36]. Increased expression of the neuropeptide vasopressin (AVP) in parvocellular paraventricular nucleus (PVN) neurons [37], accompanied by an enhanced sensitivity of the pituitary to AVP [38], may contribute to the heightened basal activity of the HPA axis in lactation. Moreover, animal studies have shown that the reduced peak HPA axis activity predominantly

results from a markedly reduced corticotrophin-releasing hormone (CRH) mRNA expression in the PVN [37, 39–41], as well as a reduced CRH binding in the adenohypophysis during pregnancy [11] and lactation [38]. Taken together, these alterations lead to a reduced CRH production and CRH release by PVN neurons, which is also accompanied by a decreased ACTH secretory response to CRH [38, 42].

Further central changes which occur to attenuate the HPA axis responsiveness include an altered pattern of the excitatory inputs to the hypothalamus [43]. For example, there are excitatory noradrenergic projections from the brainstem that project to CRH neurons of the PVN that promote CRH release, which in turn increases HPA axis activity [7]. However, during the peripartum period these projections exhibit a reduced influence on PVN neurons [7], which, in addition to a decreased expression of noradrenergic α_{1A} -adrenoceptors, leads to decreased basal noradrenergic tone within the PVN [44]. A further excitatory pathway that is altered in the peripartum period is that of the opioidergic system, which is actually reversed to inhibit HPA axis activity around birth [30, 43, 45, 46].

In parallel with the reduction of these excitatory inputs to the hypothalamus, inhibitory pathways, including those of oxytocin (OXT) and prolactin (PRL), are highly activated. These two neuropeptide systems mediate key roles in reproductive functions, such as the promotion of labour, lactogenesis, milk ejection and maternal behaviour [19, 28, 47, 48], but have also been shown to modulate the HPA axis response to stress [34, 49]. The oxytocinergic system within the hypothalamus undergoes fundamental structural and functional reorganisation in the peripartum period. This is reflected by altered size and branching patterns of dendritic trees within the PVN and SON [50] and increased synaptic and neuronal-glial interaction [51, 52]. Further, it has been shown that OXT mRNA, OXT receptor (OXT-R) expression in the PVN [53, 54] and central OXT release [34, 55–58] are increased in the peripartum period. It has been shown, in males and females, that such an activated OXT system is accompanied by a decreased ACTH and corticosterone response to acute stressors [59–61].

During the peripartum period there is also an upregulation of the PRL system, as evidenced by heightened central PRL tone and receptor expression in various regions including the PVN, SON and medial preoptic area (both the long- and short-receptor forms) – areas that are all important for maternal behaviour [62–65]. It has been shown that this activation is also involved in the stress attenuation observed in the peripartum period. In more

detail, downregulation of PRL receptors (PRL-R) in dams, via chronic intracerebroventricular infusion of a PRL-R antisense oligonucleotide probe, resulted in a greater stress-induced plasma ACTH and OXT levels compared with controls [49, 66]. This finding demonstrates the causal relationship between the increased activity of the PRL system and decreased stress responsiveness in the peripartum period. Given the similarity in the actions of these neuropeptides, it is perhaps not surprising to find that there is substantial evidence for an interaction between the two. Thus, PRL-Rs have been described on OXT (and AVP) magnocellular PVN neurons [63, 64]. Further, it has been demonstrated that PRL can stimulate OXT release from isolated neural lobes, but only during parallel electrical stimulation [67]. Additionally, PRL administration to hypothalamo-neurohypophyseal system explants, from rats in mid-lactation, was shown to increase OXT release and OXT mRNA expression, but again only under conditions that stimulated OXT release [68, 69]. Increased OXT mRNA expression within the PVN has also been observed in pseudo-pregnant rats (e.g. treated with steroids to mimic late pregnant levels), an effect that can be blocked by administration of bromocriptine, an agent that decreases PRL secretion [70]. Moreover, OXT administration can increase PRL release from the pituitary of oestrogen-primed ovariectomised rats [71]. These effects may be mediated via a PRL-induced increase in nitric oxide synthase activity, as has been shown in pregnant rats and in males [70, 72]. However, it was recently demonstrated that the cells that increase in PRL sensitivity, as assessed 5 weeks after weaning, were non-oxytocinergic neurons suggesting that the upregulation observed in the peripartum period may be in CRH or AVP neurons [73]. Taken together, the majority of available evidence suggests that the OXT and PRL system act synergistically in the peripartum period, to protect the late pregnant and lactating mother from over-responding to a stressor, such alterations are likely in turn to alter the behavioural repertoire shown during this time.

Behavioural Alterations

Obviously, one key behavioural change that occurs in the peripartum period is the display of maternal behaviour, including maternal aggression. The majority of animal species are not spontaneously maternal, and require repeated exposure to young in order to display maternal behaviour, whereas almost all new mothers immediately

display such behaviour. Brain factors that have been shown to significantly contribute to the onset and maintenance of the complex repertoire of maternal behaviours include the elevated availability of the neuropeptides OXT [2, 74], PRL [49, 75], as well as AVP [76–80] and their receptors. Moreover, the rapid fall in plasma progesterone and testosterone (that occurs between pregnancy days 18 and 21 in rodents), as well as the decreased activity of the CRH system, have been shown to be of importance for the onset of maternal behaviour and aggression [48, 81, 82]. These alterations act in concert to result in an increased display of aggression towards intruders with a concurrent decrease in anxiety [34, 37, 49, 83]. In detail, treatment with an OXT antagonist 10 min prior to elevated plus maze testing enhanced the anxiety-related behaviour in pregnant and lactating, but not virgin rats, suggesting that the anxiolytic action of endogenous OXT is restricted to the peripartum period, i.e. to when its activity is elevated [34]. Chronic administration of a PRL-R antisense oligonucleotide increased anxiety-related behaviour in lactating dams [49], while administration of bromocriptine during early pregnancy was shown to lead to elevated levels of anxiety in the postpartum period [83]. These two studies suggest that the increase in PRL activity during the peripartum period, at least in part, mediates the decreased anxiety observed at this time. Moreover, an inverse relationship between decreased anxiety and increased aggression during the lactation period has been shown in rodents [84–86]. Thus, increasing CRH availability, either by intracerebroventricular infusion of CRH, or knocking out CRH binding protein, results in lower levels of maternal aggression [87, 88]. These findings suggest that the peripartum-associated decrease in CRH system activity is important for the expression of maternal aggression and reduced anxiety. Both increased maternal offensive behaviour, as well as a reduction in anxiety, are important to ensure the protection of the offspring [89, 90]. However, it is also likely that this peripartum-associated anxiolysis, as well as increased calmness observed particularly in breast-feeding mothers [12, 15, 29], are important for maternal mental health.

Postpartum Mood and Anxiety Disorders

Although, in general, the peripartum period is a time of reduced stress responsivity and increased calmness, as described above, for a large percentage of mothers it can represent a time of increased susceptibility to mood disorders. Indeed, the peripartum period is believed to rep-

resent the time when a woman is at most risk to develop a mood disorder, such a depression.

Postpartum mood and anxiety disorders can be divided into four main groups [91], which are summarised below.

Postpartum Blues or Baby Blues

30–75% of mothers are affected by this short-lasting mood disturbance [92]. It appears between the 3rd and 5th day postpartum as a normal reaction to the changing steroid-hormone levels and disappears in most of the cases within a week without any treatment. Symptoms include mood lability, frequent crying, sleep disturbance, irritability and anxiety [92–94].

Postpartum Depression (PPD)

This major depressive disorder, which starts within the first 4 weeks after birth, occurs in 10–22% of mothers and can be a result of long-lasting PPB [95, 96]. The symptomatology is indistinguishable from depressive episodes occurring at other times during a woman's life [97] and range from depressive mood, loss of general interest – but particularly in the baby, sleep and eating disturbances, physical agitation, cognitive impairments and high anxiety, to thoughts and attempts of suicide. Studies in women with major PPD, using the Postpartum Depression Screening Scale (PDSS) revealed emotional lability, mental confusion and anxiety/insecurity as core symptoms of PPD [98, 99]. Additionally, it is known from human studies that mothers with baby blues or PPD find infant stimuli, including crying, rather aversive [100] and that postpartum depressed women show a reduction in the attachment process as well as an impaired, or even lack of maternal care [101, 102].

Postpartum Anxiety

Often coincident with PPD, postpartum anxiety disorder has an incidence of 5–12% and generally occurs in the first 6 months after birth [23, 103]. There is even some evidence that the rate of anxiety disorders peripartum is higher than the rate for depression [104]. Symptoms of postpartum anxiety often overlap with those of PPD; however, physiological symptoms like clammy hands, tingling or numbness in parts of the body seem to be rather apparent than cognitive/behavioural symptoms of general anxiety disorder symptoms like restless, excessive worries or irritability [105]. Moreover, women who suffer from this postpartum anxiety show diminished feelings of efficacy in their parenting role, a reduction in coping capability, reduced maternal reactivity and sensitivity.

Additionally, a highly protective maternal style, termed 'helicopter parenting', has also been shown [19, 106].

Postpartum Psychosis (PPP)

As arguably the most serious postpartum mood disorder, PPP appears within the first 2 weeks after delivery [107] and has an incidence of 1–2 per 1,000 mothers [108, 109]. Mothers with PPP often have bipolar [108, 110] and manic symptoms (i.e. euphoria, overactivity, irritability, violence) [110, 111]. Others display severe depression with delusions or verbal hallucinations [112]. Some switch from mania to depression (or vice versa) within the same episode. PPP always requires the sufferers to be hospitalised, because of the danger of suicide and infanticide, which is a vital difference to PPD.

Although these four disorders can be theoretically distinguished, as can be noted from the symptomatology described above, there exists substantial comorbidity across the disorders. For example, while postpartum blues is not a psychiatric disorder, if the symptoms are prolonged for longer than 2 weeks, it is possible that PPD can be diagnosed in the mother. Moreover, diagnosis of postpartum anxiety represents one of the most robust indicators of a mother subsequently developing PPD [16]. Therefore, it is better to think of these postpartum psychiatric disorders as a continuum with overlapping symptomatology in terms of diagnosis and treatment.

While the underlying aetiology of peripartum-associated mood and anxiety disorders is largely unknown, various risk factors have been identified that increase their likelihood. Among those, environmental factors such as smoking [17, 21], alcohol abuse [22] or low socioeconomic status [25, 26, 113] increase the risk of developing a postpartum mood or anxiety disorder. Furthermore, prior history of a mental illness including depressive episodes or experiencing anxiety during pregnancy [23] elevates the chance of developing a postpartum mood and/or anxiety disorder. One hypothesis for the underlying aetiology of postpartum mood and anxiety disorders is related to the fluctuation in steroid hormones and glucocorticoids during the end of pregnancy [97, 113–118]. Thus, oestradiol levels increase 50-fold and progesterone levels 10-fold throughout pregnancy, but drop to early follicular levels within 1 week after delivery [119, 120]. This dramatic drop in steroid hormones may represent a risk factor for postpartum mood and anxiety disorders. For example, a stress-related increase in oestradiol, progesterone and cortisol levels, as well as elevated basal progesterone levels have been observed in mothers with PPD [121].

However, in the majority of depressed patients [122, 123], including PPD [18, 97, 118], chronic stress has been shown to be one of the most prominent single risk factors, after a prior history of depression. Moreover, women have been shown to exhibit a higher susceptibility to stress-related illnesses, such as mood and anxiety disorders, than men [124–126]. Despite the correlation between chronic stress during pregnancy and the development of a depression after birth, studies assessing the effects of chronic stress during pregnancy on peripartum adaptations in humans are largely missing. Thus, the following section details the impact of postpartum mood disorders on the mother and, consequently, impaired mother-infant relationship, regardless of the underlying cause.

Given the profound physiological alterations that occur during the peripartum period at the level of the HPA axis, it has also been speculated that circumstances which prevent these adaptations may underlie, at least in some instances, postpartum mood and anxiety disorders [5, 12]. This is based on the large body of evidence showing that in a subpopulation of depressed women, high levels of cortisol exist, together with an inhibited negative feedback, as well as an abnormal diurnal secretion pattern of cortisol [123, 127, 128]. There is also recent evidence showing that abnormal levels of cortisol, whether too high or too low, resulted in a greater risk of major depression [129]. Interestingly, a recent study demonstrated that women with PPD exhibited a decreased cortisol-awakening response compared with healthy mothers [130]. This finding could imply that PPD is associated with an abolished physiological hypercortisolism and rather resembles a hypocortisol disorder, such as post-traumatic stress disorder or chronic fatigue syndrome [130]. In agreement, postpartum fatigue has been recently demonstrated to be correlated with the amount of perceived stress during the last 2 weeks of pregnancy and, moreover, represents a particularly prevalent symptom of PPD [131, 132]. Furthermore, a more pronounced attenuation of the ACTH response to a CRH bolus was found in women with postpartum blues compared with euthymic women [133]. These findings suggest that prevention of the normal peripartum adaptations at the level of the HPA axis can be detrimental for the mother's mental health.

A strong relationship between PRL and maternal mood has also been reported. For example, high circulating PRL levels in breast-feeding women have been associated with hypoanxiety [134], while lower levels have been linked with an increased incidence of depression [114]. Breast-feeding has been demonstrated to increase plasma PRL and OXT levels in women [59, 135], which is likely to

be accompanied by increased central release of these neuropeptides [56, 57, 136]. Interestingly, women who breast-fed their babies prior to acute stress test were shown to have an attenuated stress-induced rise in cortisol compared with non-breast-feeding lactating mothers [15], suggesting an involvement of brain PRL and OXT in the peripartum-related calmness. Similarly, women who display a high-interaction level with their children also exhibit a dramatic rise in plasma OXT [137]. Such an increase appears to be beneficial for the mother, as first-time mothers who display low infant-attachment ratings displayed a reduced plasma OXT response when interacting with their children, as well as reduced activation of the reward circuitry [138]. Furthermore, plasma OXT levels are decreased in cocaine-addicted mothers, who are more likely to have psychiatric disorders and less attachment to their infants [139]. The importance of OXT for a mother's mental health was recently demonstrated in a study showing that low levels of plasma OXT during mid-pregnancy significantly predicted the development of PPD symptoms within 2 weeks of parturition [140]. Finally, while not in the peripartum period, women who had experienced childhood trauma were shown to have lower cerebrospinal fluid levels of OXT than controls; the levels of which negatively correlated their current anxiety ratings [141]. Therefore, taken together, these findings implicate a reduced activity level of the brain OXT and PRL systems in postpartum mood and anxiety disorders due, in part, to the subsequent effect on HPA axis adaptations, behaviour and mother-infant relationship.

Postpartum mood and anxiety disorders are also associated with dramatic alterations in maternal behaviour towards her newborn. Thus, while PPD is associated with reduced interaction between the mother and infant [142–144], postpartum anxiety can rather lead to the opposite. It has been shown in a number of species that highly anxious mothers tend to ruminate over the health and well-being of their babies (helicopter parenting) [19, 77, 145]. More seriously, in the case of PPP, mothers may actually attempt infanticide or suicide [for review, see 146]. In support, rodent studies have shown a close link between the dam's level of anxiety and the display of maternal care and maternal defence behaviour with difference in the brain AVP and OXT systems underlying this correlation (see Bosch [28] for a comprehensive review).

In general, alterations in mother-infant interactions have detrimental long-lasting effects on the children who grow up with a much higher risk of developing a mood disorder, substance abuse and cognitive impairments [147–149]. It is likely that these alterations in maternal

behaviour are related, at least in part, to the neuroendocrine findings detailed above.

Given the complexity of physiological peripartum adaptations, which cannot be readily studied in humans, factors that determine the aetiology of postpartum mood and anxiety disorders need to be clearly identified in relevant animal models.

Chronic Stress Paradigms in Male and Female Rats

In order to examine the effect of stress on peripartum adaptations, appropriate animal models are required. Despite the fact that women are twice as likely to develop stress-related disorders, most basic studies assessing the detrimental effects of chronic stress are performed in males. This is due, in part, to the complexity of studying chronic stress in females, given the differences in a number of factors that are observed across the oestrus cycle, which have to be considered such as OXT-R expression [150] and HPA axis activity [151]. Moreover, chronic stress exposure can lead to a lengthening of the oestrus cycle [152], complicating the choice of appropriate controls. In light of this, it is important to note that forms of stress that are effective in males may not be in females and vice versa. While physiological stressors, such as restraint or swim stress, work in both males and females, there has been a recent shift towards employing chronic psychosocial stressors, which are believed to be more relevant to the human situation than non-social stress paradigms [27, 153]. However, males and females respond differently to social stress paradigms. Hence, it arises that defeat by aggressive male residents induces classical stress-related changes like decreased body weight gain, increased adrenal size and increase in basal corticosterone levels in males [154], but not in females [155]. In contrast, clear-cut signs of chronic stress (i.e. thymus involution, adrenal hypertrophy) are observed in females after exposure to social instability conditions, induced by mixed-sex crowding and alternating isolation phases [155–159]. One reason for the variability regarding the response to different stressors may underlie the fact that it is difficult to obtain strong dominance or high aggression in virgin females. Here, the naturally-occurring high aggression potential found in lactating rat dams has been successfully utilised in order to inflict defeat on virgin (or pregnant) females, resulting in clear signs of acute [160] or chronic [161] stress exposure in the female intruder. Moreover, there have been trials to induce high aggressiveness in females by performing medio-basolat-

eral hypothalamic lesions [155]. Therefore, it is important when wishing to assess the effect of chronic stress exposure on peripartum adaptations to consider the choice of stressor carefully, and to verify that the paradigm chosen leads to hallmark signs of stress exposure in the dam.

Consequences of Chronic Stress in Pregnancy on Physiology, Neuroendocrine and Neuronal Parameters

While it is unlikely that a specific rodent model of a postpartum mood or anxiety disorder is achievable, assessment of the behavioural, physiological, molecular and neuroendocrine alterations caused by stress exposure in the peripartum period in basic research can provide a better understanding of the aetiology of the disorders. Moreover, there are a number of different symptom clusters that can be modelled relatively easily in rodents. This has led to an endophenotype-based approach to study psychiatric disorders in preclinical laboratories, which attempt to assess only one symptom (cluster), or marker, of the disease rather than the whole syndrome [27, 162]. This has the benefit of simplifying a complex disorder, such as depression or anxiety, into individual behaviours, which are more easily measurable in both patients and laboratory animals. In order to assess the effects of chronic stress in relation to peripartum-associated adaptations in rodents, it is necessary to determine whether such stressors, described above, are effective in this time of attenuated stress responsivity. Therefore, given the evidence purporting chronic social stress to be a risk factor for the development of depression and anxiety in vulnerable individuals, recent attempts, as described above, have focussed on the development of chronic social stress paradigms [27, 162]. Such paradigms are believed to be more relevant to the human situation than non-social stress paradigms (e.g. repeated restraint) and thus can better reveal the behavioural, neuroendocrine or immunological consequences of chronic stress in the peripartum period. However, and analogous to male and virgin rodents, repeated restraint stress [163–165] or chronic ultra-mild stress [166] have also been demonstrated to be effective peripartum stressors due to their alteration of physiological parameters such as body weight gain, adrenal weight and plasma glucocorticoid levels, as well as offspring indices. It needs to be mentioned that the majority of these maternal stress paradigms are currently used to study the role of early life, e.g.

Table 2. Paradigms used to study the effects of chronic stress in female rats and mice

Stress paradigm	References
Social instability/isolation	155–157, 220, 221
Restraint stress (once daily to 3 times daily, for 1 week or longer)	163–165, 224
Chronic ultra-mild stress	166, 222
Long or brief maternal separation	198, 223
Novel environment	165
Strobe-light stress	177
Exogenous corticosterone	197

prenatal stress on offspring behaviour and physiology, rather than on the effects on the mother. Thus, it has been extensively shown in animal and human studies that prenatal, but also postnatal stress leads to the development of psychopathologies later in life, including an increased risk for anxiety and depression disorders, schizophrenia and substance abuse [for reviews, see 167–172]. In the context of pregnancy stress, monitoring its multiple effects on the offspring can be used as an effective validation of the chronic stress paradigm. However, it arises that females subjected to chronic stress during the peripartum period show characteristic hallmark behavioural, physiological, neuroendocrine and molecular indications of stress exposure (summarised in table 2). These parameters, in addition to alterations in the offspring, are used to verify the stress paradigm. In this section, we describe the findings from basic research on the systems described above that are known to be altered during the peripartum period and/or in postpartum mood and anxiety disorders.

In our laboratory, in order to examine the effects of chronic pregnancy stress on maternal adaptation, we designed a stress paradigm that combined restraint stress (2 × 1 h/day) with periods of overcrowding with unknown females, also resulting in social instability as a potent stressor in females [155]. The combination of these two stressors has been chosen to include a psychosocial stress compound in the model (fig. 1). The different stressors were alternated daily between pregnancy days 4 and 16.

HPA Axis

One of the most common findings observed in patients with psychiatric disorders is dysregulation of the HPA axis [4, 5, 173], including mothers with postpartum mood and anxiety disorders. Therefore, a number of

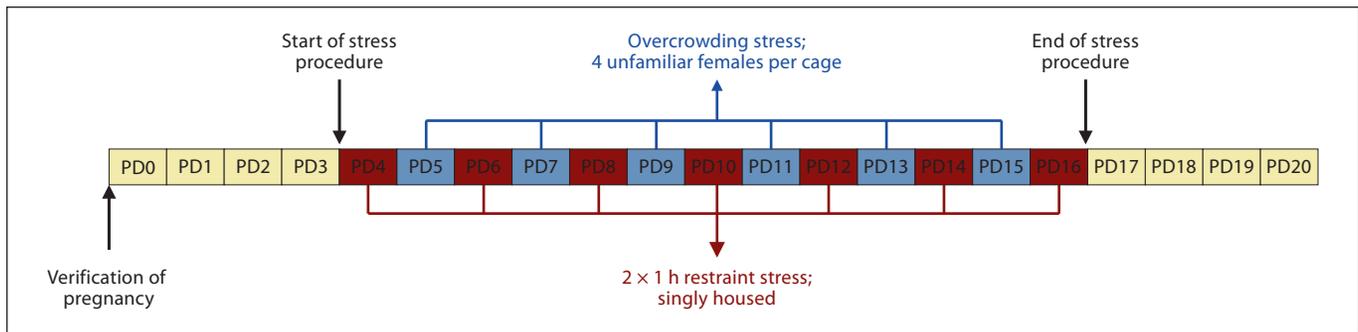


Fig. 1. The chronic psychosocial stress paradigm used between PD4 and PD16 for our own peripartum studies. Female rats (pregnant or virgin) were housed in cages of 4–5 until PD4 when the stress procedure started. On even days between PD4 and PD16 (in red), rats were weighed, housed individually and subjected to 2 × 1 h restraint stress in a Plexiglas tube (12 cm in diameter, with ventilation holes). On odd days (in blue), rats were weighed and

transferred to overcrowded conditions, consisting of 4 PS rats in a small cage (40 × 25 × 15 cm). From PD17 onwards, animals were singly housed. Control pregnant and virgin rats were maintained in cages of 5 throughout the experiment until being transferred to single housing on PD17 and weighed daily to mimic the handling conditions of the stressed group.

studies have assessed the impact of chronic stress exposure on HPA (re)activity in the peripartum period. We could reveal in our paradigm that stressed dams, in addition to showing hallmark indicators of stress exposure (decreased weight gain, increased adrenal weight) [156, 174–176, 224], did not exhibit the lactation-associated basal hypercorticism [1, 8, 13]. Interestingly, as described above, a recent study in humans showed decreased awakening cortisol levels in women, who had PPD [130]. Therefore, hypocortisolism may represent a biomarker for postpartum mood disorders, and more research is warranted to investigate this possibility.

However, the attenuated ACTH or corticosterone response to a (novel) acute stressor was not altered by our chronic pregnancy stress paradigm. In contrast to these findings, subjecting rats to repeated strobe-light stress throughout pregnancy and in lactation resulted in an enhanced corticosterone response to stress in the afternoon compared to the morning in stressed dams in lactation [177]. Therefore, it appears that depending on the stress paradigm employed, different effects on peripartum-associated HPA axis adaptations can be observed. Moreover, studies in primates could show that daily injection of hydrocortisone, thereby causing a chronic elevation in cortisol levels, led to impairments in mother-infant interactions [178]. Thus, chronic peripartum stress can affect both the basal hypercorticism, as well as the attenuated stress responsivity observed in lactation. Together with the findings from human studies, the animal data suggests that an optimal corticosterone/cortisol

window exists, in which an elevation above nulliparous/virgin levels is beneficial while the higher levels observed after stress exposure negatively affect maternal care [see also 179 for more details]. Consequently, it is suggested that such stress-induced prevention of these peripartum-associated neuroendocrine adaptations may underlie postpartum mood disorders [1, 4, 5].

OXT System

Given the importance of elevated OXT in the peripartum period, in addition to its stress-attenuating properties, a number of studies have assessed the impact of stress on this neuropeptide in dams. In our stress paradigm, we could reveal that pregnancy stress prevented the peripartum-induced rise in OXT mRNA expression in the PVN [224]. This is interesting in the context of the low levels of OXT found in primates with low measures of ‘maternal warmth’, based on frequency of nursing and grooming of the infant [47] and humans with low infant attachment, as well as the correlation between plasma OXT levels and anxiety in women (see above) [138, 141, 180]. While a direct correlation between OXT expression in the PVN and plasma levels needs to be shown, a study by Otsubo et al. [181] demonstrated that activation of OXT neurons in the PVN and SON by administration of adrenomedullin-5 caused activation of OXT neurons and a subsequent increase in plasma OXT levels. The importance of the OXT system in attachment, maternal behaviour and its concurrent susceptibility to stress could also be shown in recent animal studies from the Meaney

group [182–185], as well as our own studies. The Meaney group has established a model of naturally occurring variations in maternal behaviour, characterised by dams showing either a high frequency of licking and grooming their pups (high LG dams) or low (low LG dams) levels. They could reveal that high LG dams express higher levels of OXT-R in distinct brain regions known for their importance in regulating maternal behaviour, like the bed nucleus of the stria terminalis, the medial preoptic area and the central amygdala. Interestingly, repeated exposure to restraint stress between pregnancy days 15 and 21 (3×30 min/day) resulted in a decrease in the expression of OXT-R comparable to those of low LG dams with a concurrent decrease in LG behaviour, e.g. a reduction in maternal behaviour.

Moreover, in rat dams selectively bred for high anxiety-related behaviour (HAB), we found an increased activity of the OXT system in lactation as reflected by higher levels of OXT release within the central amygdala, PVN and medial preoptic area during maternal care and aggression. These dams show a markedly reduced anxiety level during lactation, which can be partially reversed by blockade of central OXT-Rs, again demonstrating the correlation between anxiety and OXT activity [28]. Moreover, anxiety, local OXT release, but not binding, and a high level of maternal care and maternal defence behaviour were found to be strongly associated [76, 77, 84]. Finally, it has been shown that the majority of stimuli that increase central OXT release have also been demonstrated to increase plasma levels, unlike that of the related neuropeptide AVP [186]. Thus, the findings from rodent studies, and those from humans (see above), suggest that assessing plasma OXT levels in mothers, as an indirect marker of central activity, may also represent a marker for postpartum mood and/or anxiety disorders as shown in the recent study by Skrundz et al. [140], which needs to be replicated.

Neurogenesis

There has been substantial interest in recent years regarding stress-related disorders, such as depression, and neurogenesis [187]. Thus, several factors like acute and chronic stress have been shown to decrease hippocampal neurogenesis [188] and it has been speculated that antidepressants require neurogenesis to mediate their beneficial effect [189]. Moreover, there is a link between the production of immature neurons in the hippocampus, as well as the subventricular zone (SVZ), and the reproductive status of a female [190–192]. It has recently been demonstrated that the high level of PRL during early preg-

nancy leads to an increased number of newly generated cells in the SVZ, which migrate to the olfactory bulb to play a role in the learning of novel odorants [193, 194]. Thus, the impaired maternal behaviour observed following bromocriptine administration, which reduces PRL secretion, may be due to a subsequent reduction in the number of newly integrated neurons in the olfactory bulb. Interestingly, it has been demonstrated that hippocampal neurogenesis is decreased during the lactation period; an effect that is dependent on the presence of pups and the high level of corticosterone. Adrenalectomy, or removal of the pups straight after birth, was able to restore neurogenesis to the level of virgins due to the concomitant decrease in plasma glucocorticoid levels [188, 195]. Whether neurogenesis is affected in human mothers remains to be determined, but the findings from these rodent studies, together with those showing that antidepressants increase neurogenesis in humans [196], suggest that alterations in neurogenesis may play a role in postpartum mood and anxiety disorders.

Consequences of Chronic Stress in Pregnancy on Behavioural Parameters

In humans, as discussed above, postpartum mood and anxiety disorders result in a number of behavioural adaptations, such as interactions with the child, increased anxiety or decreased stress coping that can be assessed in animal studies. Therefore, a number of studies have determined the effect of chronic stress exposure on the behaviour of the dam.

Maternal Care

Maestriperi et al. [165] could demonstrate that daily 2 h restraint stress between pregnancy days 4 and 14 resulted in decreased maternal aggression in the resident-intruder test and an increased latency to retrieve the pups in a novel environment during the pup-retrieval test. Similarly, an ultra-mild stress paradigm (cage tilt; confinement in a small cage and paired housing; overnight period with difficult access to food; overnight period with permanent light; overnight period in soiled cage; reversal of light/dark cycle), delivered over 1 h in the morning, 2 h in the afternoon and during the night from the day of mating till parturition, also resulted in an increased latency in the pup retrieval test [166]. However, while pup retrieval latency was increased, basic maternal care was not changed as a result of this stress paradigm [166].

In our studies we could show that lactating dams that experienced chronic stress during pregnancy exhibited an increase in arched-back (kyphotic) nursing from early to mid-lactation compared with unstressed control dams (see fig. 2) [224]. However, there are studies showing a decrease in kyphotic nursing after repeated restraint stress [163] or under chronically high levels of corticosterone [197]. The effects of acute separation from the pups, also a form of stress, have also been shown to affect maternal behaviour with both a reduced maternal behaviour [198] and a higher intensity of maternal care being observed [199]. Interestingly, in our laboratory, repeated restraint stress during lactation, which is coupled with pup separation, led to an increased display in maternal behaviour. In contrast, separation alone did not affect this behaviour [Hillerer, unpubl. data]. Furthermore, it has been observed that early-life stress exposure leads to a reduction in maternal behaviour when the female offspring have their first litter [200]. Thus, as has been demonstrated in humans, chronic stress exposure during the peripartum period can lead to both increased and decreased maternal care/attachment. Therefore, further study of the mechanisms underlying the changes in the behaviour of dams towards their offspring, as observed in these models, can lead to a better understanding for such behavioural alterations in women with postpartum mood and anxiety disorders.

Anxiety

Interestingly, there appears to be a correlation between the effects of peripartum stress on maternal behaviour and the impact it has on anxiety-related behaviour. We could reveal that our chronic pregnancy stress paradigm led to an increase in anxiety-related behaviour in two established tests – the elevated plus maze and the light-dark box [224]. These results are in accordance with studies in rodents, non-human primates and humans showing that mothers with high levels of anxiety express a high maternal motivation and highly protective maternal styles, known as helicopter parenting in humans [19, 201, 202]. In support, HAB dams show higher levels of arched-back nursing, leave the nest comparably less often and retrieve the pups faster during the pup retrieval test even under adverse and challenging conditions [28, 161]. Moreover, HAB dams show more defensive behaviour during the maternal defence test indicating high levels of maternal aggression as part of the multiple facets of maternal behaviour [1, 84]. Although it would normally be perceived as beneficial for the offspring to receive such attention/nursing during the early

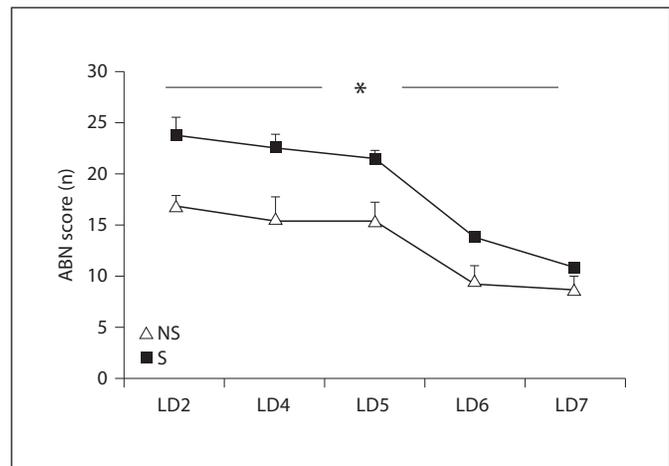


Fig. 2. Exposure to chronic psychosocial stress (pregnancy day 4–16) led to increased arched-back nursing (ABN) from LD2 to LD7. Behaviour was scored using a time-sampling technique whereby the behaviour of the dam was scored every 2 min between 06:00 and 12:00 h. Data represent mean \pm SEM ($n = 12-17$). * $p < 0.05$ vs. non-stressed group.

postnatal stage, our studies have revealed a detrimental outcome of this increased nursing. In detail, when HAB offspring were subjected to 3 h maternal separation for the first 14 days of life, consequently reducing the received amount of nursing, they display reduced anxiety in adulthood. In contrast, and as shown in outbred rats, low anxiety-related behaviour rats subjected to the same maternal separation paradigm displayed an increased anxiety level in adulthood [28, 161]. Moreover, a similar trend towards reduced anxiety in adulthood was observed when HAB mice, which also receive increased levels of arched-back nursing, were cross-fostered to less attentive low anxiety-related behaviour dams [203]. While these correlations have been observed in relation to arched-back nursing, it has been demonstrated that Long-Evans offspring that receive higher levels of licking (a more robust variable in this strain) from their mother are less anxious in adulthood than those receiving lower levels [182, 184]. A similar link between maternal attachment and anxiety has also been reported in human studies [15, 204] and thus appears to be an evolutionarily conserved peripartum adaptation. Thus, greater understanding of the underlying mechanisms of peripartum-associated anxiety and the subsequent alterations in these neurobiological mechanisms by chronic stress exposure, may provide better insight into postpartum mood and anxiety disorders.

Depression

While there is a link between increased maternal behaviour and anxiety, there appears to be a similar correlation between decreased maternal behaviour and depression-related behaviour. For example, increased depression-like behaviour, as assessed by forced swim test, was found after repeated restraint stress from early to late lactation [163, 165], as well as following acute separation stress [198] with a concomitant decrease in maternal care. Additionally, female rats that were treated with oestradiol and progesterone to induce a hormone-stimulated pregnancy exhibited a depression-like phenotype (as assessed in the forced swim test and sucrose preference test) after withdrawal of the gonadal steroids. Treatment with an oestrogen receptor- β agonist was able to alleviate the depressive symptoms [205, 206]. Furthermore, it could be shown in different non-human primate species that stress induced increases in plasma cortisol concentrations and that this rise was associated with abnormal maternal behaviour, like infant neglect [207, 208]. In a recent study by Saltzman and Abbott [178], it could be shown that exogenous administration of cortisol to lactating female marmosets impaired maternal motivation and interfered with the expression of appropriate maternal behaviour. Furthermore, in rhesus macaque females that abused their infants, high levels of aggression were observed as well as elevated concentrations of CRH in cerebrospinal fluid [209]. The latter finding further supports the findings in rodents showing that reversal of the peripartum-associated decrease in CRH leads to an attenuation of the concomitant increase in aggression. These findings in rodents and non-human primates are similar to the symptoms observed in mothers with PPD, e.g. decreased infant attachment. Therefore, further studies in such models will greatly assist in determining the mechanisms underlying postpartum mood disorders and may thus lead to better treatment options.

Conclusions

Numerous studies have revealed important neuroendocrine, neuronal and behavioural adaptations that occur during pregnancy and postpartum. While these adaptations are known to be essential for the survival and health of the offspring, there is growing belief that they are also required for mother's successful adaptive responses to her changing situation. Currently, little is known about the aetiology of postpartum mood disorders and it is likely that animal models can only mimic certain aspects of the complex symptomatology of these disorders. However, assessing the consequences of peripartum stress exposure, a major risk factor of the disorders, can provide insight into the mechanisms underlying these disorders. These studies have demonstrated that chronic pregnancy stress can affect a number of maternal adaptations including the basal elevation in glucocorticoids and attenuated stress responsivity, as well as the increased OXT system activity. Moreover, stress can alter the behavioural repertoire of the mother, with increased anxiety and depression-related behaviour observed in several studies. Further, stress exerts a bidirectional influence on fine-tuned maternal care, with both increased and decreased behaviour being observed after chronic stress exposure. However, it is clear that more studies are required to gain a better understanding of the impact of stress on the mother. Thus, while the circuitry involved in the onset and maintenance of maternal care is well characterised, it remains only supposition at present that chronic stress exposure leads to alterations within this brain network. Thus, to date, the majority of studies have focussed on specific behavioural or neuroendocrine parameters, and in the future, studies are required that assess the impact of chronic stress on this defined circuitry. Such studies seem particularly warranted given the serious consequences of such disorders on both the mother and the offspring.

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