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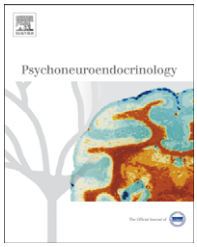

Lower levels of prepulse inhibition of startle response in pregnant women compared to postpartum women

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Summary
Objective: During the postpartum period, estradiol and progesterone levels decline from very high levels during late pregnancy to low levels within 48 h of parturition. This period is associated with dysphoric states such as the postpartum blues. Animal studies have suggested an enhanced acoustic startle response and deficient prepulse inhibition (PPI) of startle response following progesterone withdrawal and during the postpartum period. The aim of the current study was to compare acoustic startle response and PPI in healthy third trimester pregnant women and healthy postpartum women.
Methods: Twenty-eight healthy pregnant and 21 healthy postpartum women (examined between 48 h and 1 week after delivery) were recruited for the study. In addition, to evaluate the time-course of postpartum changes 11 early postpartum women (examined within 48 h following delivery) were included in the study.
The eyeblink component of the acoustic startle reflex was assessed using electromyographic measurements of m. Orbicularis Oculi. Twenty pulse-alone trials (115 dB 40 ms broad-band white noise) and 40 prepulse–pulse trials were presented. The prepulse stimuli consisted of a 115 dB 40 ms noise burst preceded at a 100 ms interval by 20 ms prepulses that were 72, 74, 78 or 86 dB.
Results: Pregnant women exhibited lower levels of PPI compared to late postpartum women, $p<0.05$. There was no difference between pregnant women and postpartum women examined within 48 h of delivery. There was no difference in startle response or habituation to startle response between pregnant women and either of the two groups of postpartum women.

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Conclusion: Healthy women display lower levels of PPI during late pregnancy when estradiol and progesterone levels are high compared to the late postpartum period when ovarian steroid levels have declined.

1. Introduction

The postpartum period is associated with an increased vulnerability to various psychiatric disorders, such as postpartum depression (PPD) (Georgiopoulos et al., 1999; Kammerer et al., 2006), generalized anxiety disorder, panic disorder, obsessive–compulsive disorder (Andersson et al., 2006; Bandelow et al., 2006; Ross and McLean, 2006) and postpartum psychosis (Sit et al., 2006). Furthermore, approximately 40–70% of otherwise healthy postpartum women suffer from the "postpartum blues" during the first weeks following delivery (Harris et al., 1994; Nappi et al., 2001). Although usually mild and transient, the occurrence of the postpartum blues predicts later development of postpartum depression (Henshaw et al., 2004; Adewuya, 2006). Several studies have suggested putative etiological agents for postpartum depression, including ovarian steroid hormones and their neuroactive metabolites (Harris et al., 1994; Nappi et al., 2001). However, despite the appeal of these hypotheses, it is still not clear if the large hormonal changes during pregnancy and parturition intrinsically create a propensity to affective disturbances, or if a subset of women have a vulnerability to hormonal fluctuations. One limit to elucidating this circumstance is the fact that there are few objective diagnostic measures of anxiety, depression and similar disorders in humans that have the capacity to detect the underlying changes in neural processes associated with dysphoric states.

The acoustic startle response (ASR) is a withdrawal reflex to sudden or noxious auditory stimuli which can be measured as an eye blink in humans or as a whole body response in laboratory animals (Davis, 1980). Both the initial ASR, and habituation of the startle response are altered in several classes of psychiatric patients (Shalev et al., 2000; Taiminen et al., 2000; Braff et al., 2001), in animal models of these disorders and correlates with other measures of levels of anxiety, panic, threat and affective state (Cook et al., 1991; Grillon et al., 1993; Morgan et al., 1995; Grillon and Baas, 2003; Hebb et al., 2003; Smith et al., 2005). This paradigm is a useful bridge between pre-clinical and human data, since it has a similar circuitry and pharmacology in humans as it does in animals (Davis, 1980; Koch, 1999).

Sensorimotor gating, assessed by measuring the prepulse inhibition (PPI) of the startle response, is thought to reflect an individual's ability to screen or "gate" sensory stimuli. The PPI paradigm uses a weak, non-startling acoustic stimulus (the prepulse) that typically decreases the reflexive eye blink response (startle) produced by the subsequent startling target stimulus (the pulse). Deficits in PPI are associated with dysphoric states and anxiety disorders (Grillon et al., 1996; Ludewig et al., 2002; Pissiota et al., 2003; Hoenig et al., 2005). It has been suggested that the neural processes regulating these measures of autonomic hypersensitivity (ASR), habituation and sensorimotor gating may, at least in part, underlie the behavioral outcomes of dysphoric states (Shalev et al., 2000; Weber et al., 2002; Bast and Feldon, 2003).

ASR and sensorimotor gating are also useful models in this context, because these processes are regulated by the agents thought to be important in the etiology of postpartum depression. These include steroid hormones and their neuroactive metabolites, and dysregulation of inhibitory neurotransmission (Harris et al., 1994; Nappi et al., 2001). Sensorimotor gating is regulated by $GABA_A$ receptors in several brain regions relevant to the regulation of affective state, notably the hippocampus, amygdala and the Bed Nucleus of the Stria Terminalis (BNST) (Davis, 1980; Davis et al., 1994; Lee and Davis, 1997; Wan and Swerdlow, 1997; Bast and Feldon, 2003). Also, ovarian steroids appear to influence PPI because women have lower levels of PPI than men do (Swerdlow et al., 1997) and because PPI varies across the menstrual cycle in healthy women (Swerdlow et al., 1997, Jovanovic et al., 2004).

Animal models of hormone-related dysphoria may provide relevant insights about both the etiology and underlying mechanisms of postpartum depression. These are generally based on mimicking the hormone fluctuations associated with pregnancy and the postpartum period. During pregnancy, the levels of both estrogens and progestins are roughly 50 times and 10 times (respectively) the levels in normally cycling women (Bloch et al., 2003). However, during the first postpartum days there is a rapid and dramatic reduction in not only ovarian steroids but also in cortisol, corticotrophin releasing hormone (Kammerer et al., 2006), and metabolites of progestins, such as allopregnanolone and pregnanolone (Hill et al., 2000, 2001). Progesterone has been considered one of the potential candidates for induction of immediate mood changes during the postpartum period, and indeed, low progesterone (Harris et al., 1994) and low allopregnanolone levels has been associated with the postpartum blues (Nappi et al., 2001). However, there is little data regarding the neural adaptations that normally occur in response to pregnancy and parturition in healthy women.

The primary aim of the study was to compare healthy pregnant women with healthy postpartum women (between 48 h and 1 week after delivery), with no history of anxiety or depressive disorders, to determine if altered measures of ASR and sensorimotor gating are evident. Our secondary aim was to evaluate at which part of the postpartum period possible changes in ASR and sensorimotor gating occur. For this reason, a second group of postpartum women (examined within 48 h after delivery) were included.