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Peripartum neuroactive steroid and γ-aminobutyric acid profiles in women at-risk for postpartum depression

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ABSTRACT

Neuroactive steroids (NAS) are allosteric modulators of the γ-aminobutyric acid (GABA) system. NAS and GABA are implicated in depression. The peripartum period involves physiologic changes in NAS which may be associated with peripartum depression and anxiety. We measured peripartum plasma NAS and GABA in healthy comparison subjects (HCS) and those at-risk for postpartum depression (AR-PPD) due to current mild depressive or anxiety symptoms or a history of depression. We evaluated 56 peripartum medication-free subjects. We measured symptoms with the Hamilton Depression Rating Scale (HAM-D_{17}), Hamilton Anxiety Rating Scale (HAM-A) and Spielberger State-Trait Anxiety Inventory-State (STAI-S). Plasma NAS and GABA were quantified by liquid chromatography-mass spectrometry. We examined the associations between longitudinal changes in NAS, GABA and depressive and anxiety symptoms using generalized estimating equation methods. Peripartum GABA concentration was 1.9 ± 0.7 ng/mL ($p = 0.004$) lower and progesterone and pregnanolone were 15.8 ± 7.5 ($p = 0.04$) and 1.5 ± 0.7 ng/mL ($p = 0.03$) higher in AR-PPD versus HCS, respectively. HAM-D_{17} was negatively associated with GABA ($\beta = -0.14 \pm 0.05$, $p = 0.01$) and positively associated with pregnanolone ($\beta = 0.16 \pm 0.06$, $p = 0.01$). STAI-S was positively associated with pregnanolone ($\beta = 0.11 \pm 0.04$, $p = 0.004$), allopregnanolone ($\beta = 0.13 \pm 0.05$, $p = 0.006$) and pregnenolone ($\beta = 0.02 \pm 0.01$, $p = 0.04$). HAM-A was negatively associated with GABA ($\beta = -0.12 \pm 0.04$, $p = 0.004$) and positively associated with pregnanolone ($\beta = 0.11 \pm 0.05$, $p = 0.05$). Altered peripartum NAS and GABA profiles in AR-PPD women suggest that their interaction may play an important role in the pathophysiology of peripartum depression and anxiety.
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1. Introduction

Postpartum depression (PPD) affects 1 in 8 women (Gavin et al., 2005) and negatively impacts child development. Antepartum depressive or anxiety symptoms are a risk factor for PPD (Milgrom et al., 2008) and may represent an early manifestation of the disorder. Recently, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) revised the "postpartum onset" specifier for major depression to "peripartum onset" in recognition that 50% of "postpartum" major depressive episodes begin antepartum (American Psychiatric Association, 2013). Additional risk factors associated with PPD include: prior depressive episode (Meltzer-Brody et al., 2013) or history of PPD (Wisner et al.,

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2001), premenstrual syndrome or premenstrual dysphoric disorder (PMDD) (Buttner et al., 2013) and history of childhood trauma (Meltzer-Brody et al., 2013).

While the pathogenesis of PPD is likely multifactorial, research has focused on neuroendocrine mechanisms given the physiologic changes occurring within the endocrine system across the peripartum period. Hypothalamic-pituitary-adrenal (HPA) (Bloch et al., 2005; Skrundz et al., 2011) functioning has been investigated in the context of prolonged and elevated antepartum exposure of the neurocircuit to the effects of neuroactive steroids (NAS) followed by their rapid withdrawal after delivery. Thus a proposed model is a "hormone-sensitive" PPD phenotype in which a subgroup of women develops affective symptomatology when the neurocircuit fails to adapt to the normal fluctuating peripartum hormonal milieu (Bloch et al., 2000; Deligiannidis et al., 2013).

Γ-aminobutyric acid (GABA) is the dominant inhibitory neurotransmitter within the hypothalamic paraventricular nucleus, a region important in the initiation of the neuroendocrine and autonomic response to stress (Herman and Cullinan, 1997), and exerts inhibitory tone upon the HPA axis function (Makara and Stark, 1974). Derivatives of cholesterol or steroidal precursors, NAS are among the most rapid and potent allosteric modulators of GABAA receptor ($GABA_AR$) function and, as such, alter the excitability of the neurocircuit (Majewska et al., 1986). NAS, especially allopregnanolone, modulate the extent and duration of stress-induced inhibition of GABAergic transmission ((Barbaccia et al., 1998, 1996, 1997)). The peripartum period involves significant changes in NAS levels which are associated with $GABA_AR$ neuroplasticity (Follesa et al., 1998; Gilbert Evans et al., 2005). In healthy peripartum women, NAS levels increase across pregnancy and then fall precipitously at delivery (Hill et al., 2000, 2002; Parizek et al., 2005). Animal models suggest that differential metabolism of NAS during late pregnancy and the postpartum period is associated with the development of depressive-like symptoms through their interaction with the GABAergic system (Mostallino et al., 2009). NAS abnormalities and abnormalities in the GABAergic system response to normal NAS levels have additionally been implicated in clinical reproductive (Bloch et al., 2000; Martinez et al., 2016) and non-reproductive related affective disorders (Eser et al., 2006). Elevated plasma progesterone has been associated with poorer mood in healthy pregnant women (N = 19) (Buckwalter et al., 1999) and 5α-dihydroprogesterone (DHP), the precursor to 3α,5α-tetrahydroprogesterone (THP) [i.e. allopregnanolone] and 3α,5β–THP [i.e. pregnanolone], was elevated in a sample of women (N = 9) with antepartum major depressive disorder (MDD) (Pearson Murphy et al., 2001). In one study, low allopregnanolone levels were associated with the development of postpartum blues (N = 18) (Nappi et al., 2001), however other studies reported no difference in plasma progesterone, pregnenolone or allopregnanolone concentrations between euthymic postpartum women and those with PPD (Deligiannidis et al., 2013; Epperson et al., 2006).

The GABAergic system, evidenced by abnormal plasma and brain MRS concentrations, has been implicated in the pathogenesis of MDD (Sanacora et al., 1999) and the hormonally-modulated PMDD (Epperson et al., 2002; Halbreich et al., 1996). Studies in the occipital cortex suggest that reductions in cortical GABA in the postpartum may be a risk factor for PPD development (Epperson et al., 2006). $GABA_AR$ plasticity correlates with the marked fluctuations in NAS throughout pregnancy and after delivery (Mostallino et al., 2009). $GABA_AR$ subunit knockout mice exhibit abnormal GABA conductance with depression-like and abnormal maternal behaviors that result in reduced pup survival (Maguire and Mody, 2008). Rodent models of postpartum syndrome demonstrate allopregnanolone-mediated changes in gene transcription of $GABA_AR$ (Smith et al., 1998). GABA plasma levels have been studied in relationship to cerebral spinal fluid (CSF) levels in several species (Bohlen et al., 1979; Ferkany et al., 1979, 1978; Loscher, 1979; Loscher and Frey, 1982; Petty, 1994; Petty et al., 1987). GABA plasma and CSF levels are correlated in some but not all studies (Berrettini et al., 1982; Bohlen et al., 1979; Loscher and Frey, 1982; Loscher et al., 1981; Schmidt and Loscher, 1982; Uhlhaas et al., 1986). GABA concentration is reduced in many brain areas during pregnancy in rats (Smolen et al., 1993) and in the CSF of healthy women (Altemus et al., 2004) but the role of GABA has not been otherwise investigated in peripartum women.

Given preliminary evidence for alterations in plasma NAS in PMDD and antepartum depression and the evidence for lower plasma GABA concentrations in unipolar depression, the primary aim of this study was to examine plasma NAS and GABA in peripartum women at-risk for PPD (AR-PPD) compared to healthy comparison peripartum women (HCS). Our aim was to examine potential biological underpinnings of the aforementioned antepartum risk factors for PPD. Since antepartum depressive and anxiety symptoms may be an early manifestation of PPD for some women, we hypothesized that AR-PPD women would have an altered NAS profile and lower GABA concentrations as compared to HCS across the peripartum period and that the blood profiles would be correlated to depressive and anxiety symptoms as measured by clinician-assessed and subject self-report measures. Although there is strong clinical need identify predictive biomarkers of PPD, this study was designed to examine associations between plasma concentrations and peripartum symptomatology. An altered NAS profile could represent an abnormality in the metabolic pathway involved in the conversion of the GABAergic progesterone to pregnanolone and allopregnanolone by either of the 5—reductases and/or 3α-hydroxysteroid dehydrogenase, in exploratory analyses we examined peripartum NAS metabolite to precursor ratios.

2. Material and methods

2.1. Subject selection

510 English-speaking pregnant subjects were consented and pre-screened with the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at 24–34 weeks gestational age as determined by first trimester ultrasound to determine eligibility and interest in the main longitudinal study. Of the 510 pre-screened subjects, 118 did not meet inclusion criteria, as delineated below, and 336, though meeting main inclusion criteria as ascertained by thorough medical record review, declined to participate due to lack of interest or time for research. A total of 56 eligible and interested nulliparous, primiparous or multiparous women between 18 and 40 years old were consented to the prospective study. Two groups were enrolled: (1) 24HCS and (2) 32 AR-PPD women. The EPDS was used to assess peripartum depressive and anxiety symptoms (Cox et al., 1987; Lydsdottir et al., 2014) and a cut-off score of ≥10 was chosen to identify women with current depressive and anxiety symptomatology. The HCS group included women with an EPDS ≤5 and no current or past psychiatric diagnosis or family history of psychiatric illness, as ascertained by clinical and research interviews (First et al., 2001) conducted by a board-certified psychiatrist. As the EPDS is not sufficiently accurate in predicting risk of postpartum depressive symptoms alone (Meijer et al., 2014), the AR-PPD group included women who either had an EPDS score ≥10 (indicating current depressive and/or anxiety symptomatology) or, regardless of current EPDS score, a history of PPD or non-puerperal depression as determined by the Structured Clinical Interview for DSM-IV TR Disorders (SCID-IV), Patient Edition (First et al., 2001). Since antepartum anxiety and depression symptoms are associated with, or may represent the early presentation of postpartum depressive symptomatology, women who met criteria for an anxiety

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