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REVIEW ARTICLE

$GABA_A$ dysregulation as an explanatory model for late-onset postpartum depression associated with weaning and resumption of menstruation

Clare S. Burke[1] · Leah C. Susser[2] · Alison D. Hermann[3]

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Abstract

It is well established that a subgroup of women are particularly vulnerable to affective dysregulation during times of hormonal fluctuation. One underrecognized reproductive transition may be late-onset postpartum depression (PPD) in the context of weaning from breastfeeding and the resumption of menstruation. The goal of this review is to propose a biologically plausible mechanism for affective dysregulation during these transitions. The relationship between affective symptoms and neurohormonal changes associated with weaning will be investigated through a hypothesis-driven review of relevant literature. Neurosteroids, like allopregnanolone (ALLO), are widely recognized for augmenting GABAergic inhibition and having a powerful anxiolytic effect (Belelli D and Lambert JL, Nature Reviews Neuroscience 6:565-575, 2005). However, when ALLO is administered after prolonged withdrawal, there may be a paradoxical anxiogenic effect (Smith et al., Psychopharmacology 186:323–333, 2006; Shen et al., Nat Neurosci 10:469–477, 2007). Weaning from breastfeeding is a physiologic example of fluctuating levels of ALLO after prolonged withdrawal. We propose that the complex hormonal milieu during weaning and resumption of menstruation may modify $GABA_A$ receptors such that ALLO may contribute to rather than ameliorate depressive symptoms in vulnerable individuals. The proposed model provides an initial step for understanding the mechanisms by which the changing hormonal environment during weaning and resumption of menstruation may contribute to an increased risk of depression in a subgroup of women who are hormonally sensitive. Future research investigating this model would be valuable both to identify women at increased risk for developing mood symptoms late in postpartum and to inform treatment for this and related reproductive depressive disorders.

Keywords Postpartum depression · Allopregnanolone · GABA · Weaning · Breastfeeding · Menstruation · Oxytocin

Introduction

Women who have mood symptoms in the context of gonadal hormone changes may have a distinct type of depression compared with women who have non-reproductive-related mood symptoms (Cooper and Murray 1995; Payne et al. 2009; Viktorin et al. 2016). This hormonal sensitivity to depression has been referred to as "reproductive depression" and includes menarche, perinatal depression, premenstrual dysphoric disorder (PMDD), and depression in the perimenopausal period (Payne et al. 2009).

We hypothesize that depression at the time of weaning, which may be a proxy for resumption of menstruation, is an additional example of a reproductive depression that may be underappreciated due to limitations in the current definition of perinatal depression. The DSM-5 (https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596) defines perinatal

✉ Alison D. Hermann
Alh9039@med.cornell.edu

Clare S. Burke
csb2004@nyp.org

Leah C. Susser
lcs7001@med.cornell.edu

[1] Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA

[2] Weill Cornell Medical College, 21 Bloomingdale Road, White Plains, NY 10605, USA

[3] Weill Cornell Medical College, 315 East 62nd Street, 5th Floor, New York, NY 10065, USA

depression with the specifier "with peripartum onset": a major depressive episode beginning during pregnancy or within 4 weeks of delivery. The first month postpartum is a period of elevated risk for perinatal depression, and genetic studies have suggested that women presenting with depression during this time period may have a distinct clinical phenotype (Forty et al. 2006). However, the clustering of risk in the first postnatal month may be more attributable to bipolar disorder than major depressive disorder (Jones and Cantwell 2010). While rates of symptom onset for unipolar depression have been consistently shown to be highest in the first 6 to 8 weeks postpartum, multiple studies have now demonstrated that risk for symptom onset extends far beyond this (Stowe et al. 2004; Munk-Olsen et al. 2006; Gjerdingen et al. 2011; Kothari et al. 2016). A retrospective study of women with postpartum onset of major depression showed that only 54% of cases occurred within the first month postpartum (Altemus et al. 2012). This suggests that a substantial proportion of depression associated with the postpartum remains poorly characterized and poorly explained.

Research on mood changes associated with weaning is scarce. As illustrated in Fig. 1, this period is difficult to study due to multiple complicating factors such as variation in return to ovulation and menstrual cycling postpartum, variable use of hormonal contraceptives in the postpartum, variation in infant feeding patterns, and broad psychosocial stressors associated with or co-occurring with weaning. Rare case reports have been published. Susman and Katz (1988) presented four cases of mothers with depression starting within 2 weeks of weaning, and Sharma and Corpse (2008) presented a case of a woman who developed depression after completing weaning with each of her three infants, despite stopping breastfeeding after variable durations with each child. Epidemiologic studies suggest that this phenomenon is likely underrepresented by the scarcity of these cases in the literature. In fact, Misri et al. (1997) found that 17% of postpartum depression cases emerged after the time of weaning.

Despite the complicated neurohormonal milieu specific to the postpartum, multiple neurohormonal similarities to other periods of reproductive transition such as menarche and menopause do exist and may be a useful starting point for understanding the etiology of late-onset postpartum depression. For this review, we will begin with an examination of research on the role of gonadal steroids in reproductive depressions and then focus in on the role of allopregnanolone (ALLO) in particular. We will borrow from research on ALLO-associated depression at other reproductive transition points in the female life cycle in order to better understand weaning-associated symptoms. Though other mechanisms related to lactation-associated depression are likely to exist, we believe that there is robust evidence to support ALLO's role in late-onset postpartum depression associated with weaning and/or resumption of menses postpartum and that prior research on this mechanism maintains validity when applied to this transition as well.

Gonadal steroids and perinatal depression

Estrogen and progesterone circulate at supraphysiologic levels during pregnancy and precipitously decline at parturition (Bloch et al. 2003). The onset of affective symptoms during these dramatic hormonal shifts in the early postpartum has generated interest in gonadal steroids in the pathophysiology of postnatal depression. However, gonadal hormone studies of postnatal depression have not revealed demonstrable differences in the physiology of estrogen and progesterone between affected and unaffected women. Women who develop postnatal depression do not have more rapid postpartum hormone withdrawal, greater reductions in hormone levels from pregnancy to the postpartum period, or lower absolute concentrations of estradiol and progesterone compared to healthy controls (Schiller et al. 2014).

In response, some researchers have hypothesized that there is a vulnerable subpopulation of women that are more sensitive to the same hormonal changes than the general population (Schiller et al. 2015). This hypothesis has since been supported in a number of small studies. Schmidt et al. (1998) successfully eliminated menstrual-related depressive symptoms in patients with a history of PMDD using a GnRH agonist, while hormone add-back caused symptom return. This same hormone manipulation had no effect on mood in control patients. Similarly, in a study by Bloch et al. (2000), euthymic women were given high doses of estradiol and progesterone during ovarian suppression with a GnRH agonist to mimic antepartum levels, and then, both steroids were abruptly withdrawn. Women with a history of postnatal depression reported increased depressive symptoms during both hormone add-back and hormone withdrawal, but no mood changes were observed in control patients. This study design removed confounding biological and psychological stressors associated with childbirth and again provided evidence that a subpopulation of women, those with a history of postnatal depression, were particularly susceptible to rapid changes in reproductive hormones independent from pregnancy (Schiller et al. 2015).

ALLO and depression

In an effort to better characterize a reproductive depression phenotype, there has been increased attention to the role of ALLO. ALLO is a neurosteroid metabolite of progesterone, which is known to modulate $GABA_A$ receptors. There is evidence that ALLO plays a role in depression outside of reproductive transitions. However, the nature of ALLO's role in affective illness is complex, as some studies have implicated inadequate ALLO levels while others have implicated changing ALLO levels, and it is unclear the extent to which ALLO's effect on mood may differ in the presence or absence of fluctuating gonadal steroid levels or between men and women. ALLO levels have been found to be low in major depressive

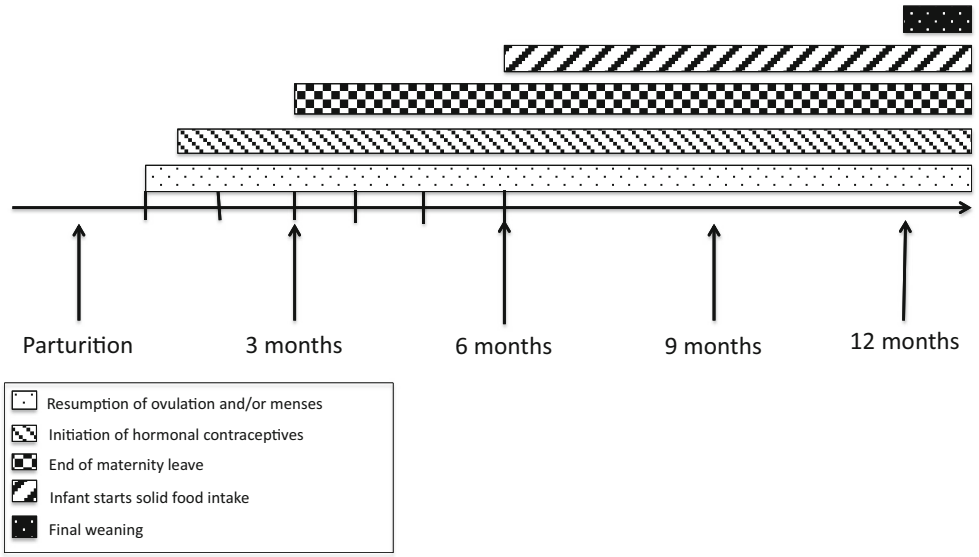

Fig. 1 Sources of variation that complicate investigation of late-onset postpartum depression in breastfeeding women. Potential complicating factors that affect ALLO and GABA-A regulation in the postpartum are illustrated in the figure. Each bar represents a period of individual variation for a typical postpartum event, informed by American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) recommendations as well as the Family and Medical Leave Act (FMLA). Individual variability in each of these domains may challenge identification of a late-onset postpartum depression phenotype even if unifying neurohormonal mechanisms exist

disorder and to elevate with antidepressant treatment (Uzunova et al. 1998; Romeo et al. 1998; Ströhle et al. 1999; Schüle et al. 2006, 2007; Eser et al. 2006). Furthermore, circulating levels of ALLO are correlated with progesterone levels in women and fluctuate during the menstrual cycle, pregnancy, and postpartum (Gilbert Evans et al. 2005; Schiller et al. 2014). The relationship between ALLO levels and contraceptive agents is complex, although ALLO levels do appear to correlate with some synthetic progestins (those that are not 19-nor derivatives) and estrogens used in some contraceptives appear to stimulate ALLO synthesis (Bernardi et al. 2003). During lactation, the hypothalamic-pituitary-ovarian (HPO) axis is suppressed and therefore ALLO levels remain low. With resumption of menstrual cycling in the later postpartum, ALLO fluctuations resume with mid-luteal peaks (Wang et al. 1996; Genazzani et al. 1998; Luisi et al. 2000). The combination of ALLO's known association with depression as well as physiologic fluctuations in ALLO during periods of risk for reproductive depression makes ALLO an attractive candidate for study in regard to the pathophysiology of the reproductive depression phenotype.

Depending on the context, ALLO can be either anxiolytic or anxiogenic (Backstrom et al. 2014). ALLO is well known for its anxiolytic property, which has been replicated in multiple rodent models (Akwa et al. 1999; Wieland et al. 1991; Schüle et al. 2014). In a small study of panic disorder in humans, ALLO levels have been shown to acutely decrease in response to sodium lactate or CCK-4-induced panic, but only in subjects with previously diagnosed panic disorder (Ströhle et al. 2003). More recent research has focused on anxiolytic and antidepressant effects of ALLO specifically in peripartum populations. In one study, infusion of intravenous brexanolone, which is a synthetic analog of ALLO now in development as a pharmaceutical, resulted in reduction in severe postnatal depression compared to placebo (Kanes et al. 2017). In addition, a recent study by Osborne et al. 2017 suggested that blunted ALLO levels during pregnancy predicted postnatal depression in a linear fashion. Taken together, this line of research implies that raising ALLO levels in women at risk for or affected by perinatal depression may be a reasonable strategy for treatment or even prevention.

However, in other contexts, ALLO appears to be paradoxically anxiogenic. For example, women with PMDD often develop mood symptoms in the mid-luteal phase of the menstrual cycle and some women with perinatal depression begin to develop mood symptoms during pregnancy, both of which are periods when ALLO levels rise (Gotlib et al. 1989; Pearlstein et al. 2005). In addition, two studies have demonstrated that administering progesterone in the postnatal period increased affective symptoms in women with a history of perinatal depression (Lawrie et al. 1998; Bloch et al. 2000). Furthermore, in a study by Schmidt et al. (1998), women with premenstrual syndrome (PMS) whose symptoms remitted with a GnRH agonist demonstrated mood worsening with progesterone add-back. Interestingly, this study also demonstrated mood worsening with estradiol add-back, which remains poorly understood although may also relate to anxiogenic effects of ALLO. Estrogens have been shown to increase ALLO levels in postmenopausal women undergoing

hormone replacement treatment (HRT), possibly via modulation of enzymes involved in ALLO biosynthesis (Bernardi et al. 2003).

Reconciling the seemingly conflicting data on ALLO's effect on mood has been a challenge for the field of reproductive psychiatry. For the purpose of our review, we will focus on the explanatory effect of fluctuating ALLO levels on $GABA_A$ physiology. There are several additional possible explanations, some tangentially related to ALLO's effect on $GABA_A$ physiology, that are worthwhile avenues for further study but beyond the scope of this review. The first is that, given the complex hormonal milieu during periods of reproductive transition, there may be other mitigating or enhancing factors that influence ALLO's effects on mood such as estrogen, lactogens, inflammation, and alterations in the stress-response system (Bloch et al. 2003; Brunton et al. 2015; Kimmel et al. 2016; Roomruangwong et al. 2018). Second, there may be subpopulations of women with reproductive depression that have different affective responses to different ALLO levels, possibly in the fashion of a U-shaped curve (Backstrom et al. 2014). Third, there may be differential metabolism of progesterone in affected women such that ratios of progesterone to allopregnanolone are altered in women with depression (Girdler et al. 2001; Klatzkin et al. 2006). Last, ALLO's effect on mood may depend on other contextual factors such as the presence of stress and/or the reactivity of the stress-response system (Smith et al. 2006).

Changes in rather than levels of ALLO dysregulate affective state in susceptible individuals

It has been widely hypothesized that the *change* in ALLO levels rather than the absolute concentration of those levels may be responsible for mood changes in sensitive individuals. Similar to studies of gonadal steroids, which have failed to consistently show an association between PMDD and postnatal depression symptoms and absolute concentrations of estrogen and progesterone, abnormal plasma levels of ALLO have not been consistently observed in PMDD and postnatal depression (Schmidt et al. 1994; Wang et al. 1996; Rapkin et al. 1997; Monteleone et al. 2000; Epperson et al. 2002; Lombardi et al. 2004; Deligiannidis et al. 2013; Hellgren et al. 2014; Crowley et al. 2016; Deligiannidis et al. 2016). In fact, both increases and decreases in ALLO have been shown to produce anxiogenic behavior (Gulinello et al. 2001, Gulinello and Smith 2003; Shen et al. 2005). In a recent study by Schiller et al. (2014), they reexamined data from previous studies of ovarian suppression with a GnRH agonist and subsequent progesterone add-back in women with a history of PMDD and postnatal depression. In both groups, change in ALLO after progesterone add-back was negatively correlated with depressive symptoms in patients with a history of PMDD or postnatal depression, but the effect was absent in controls. Furthermore, Martinez et al. (2016) stabilized ALLO levels from the follicular to the luteal phase of the menstrual cycle by administering a 5α-reductase competitive inhibiter to patients with a history of PMDD and healthy controls. They observed a significant reduction in PMDD symptoms in patients and no mood changes in controls. Both studies support the hypothesis that changes in ALLO levels may serve as an "affective switch" in a subset of vulnerable women (Schiller et al. 2014).

Mechanism of ALLO's effect on mood in vulnerable populations

The effect of changing ALLO levels on depressive symptoms in vulnerable women is likely related to GABAergic functioning, which we propose is particularly relevant to weaning-induced depressions. There are multiple $GABA_A$ modulators known to have a biphasic effect at the receptor, including ALLO (Wang 2011). The $GABA_A$ receptor is composed of various subunits, which can greatly influence its sensitivity to neurosteroids like ALLO (MacKenzie and Maguire 2014). For example, during pregnancy, when levels of progesterone and ALLO are extremely elevated, the expression of the δ subunits is downregulated in multiple areas of the brain, which reduces receptor sensitivity to elevated ALLO levels (Maguire and Mody 2008). Furthermore, the $GABA_A$ receptor is extremely plastic, and its subunit composition can change during fluctuations in ALLO levels (Gordon et al. 2015). Gulinello et al. (2001; 2003) have demonstrated that either increases or decreases in ALLO can trigger changes in the α4 subunit of the $GABA_A$ receptor enough to trigger anxiogenic behavior. Smith et al. (2006) demonstrated that ALLO withdrawal increased the expression of $GABA_A$ receptor α4 subunit in the mouse CA1 hippocampus. After an extended period of withdrawal, when ALLO was reintroduced in combination with an aversive stimulus, this triggered hippocampal excitability rather than inhibition in mice. Based on these findings, they hypothesized that prolonged ALLO withdrawal may modify GABA receptors such that reintroduction of ALLO produces an anxiogenic effect rather than an anxiolytic effect.

Studies of ALLO physiology during puberty have demonstrated that it is anxiogenic during this reproductive transition as well and that this effect may be related to ALLO having a paradoxical modulation of $GABA_A$ receptors. Shen et al. (2007) studied the interaction between ALLO, $GABA_A$ receptor subunits, and anxiety during puberty and proposed that the anxiogenic effect of ALLO is due to a particular configuration of subunits (α4β2δ) of $GABA_A$ receptors. This particular subunit configuration is induced by prolonged withdrawal of ALLO in pubertal mice, and it reverses GABA-gated current, inhibiting it instead of enhancing it. We suggest that this

reversal of GABA-gated current may also occur in women resuming menstruation in the puerperum.

The role of prolonged ALLO withdrawal in triggering a paradoxical effect of ALLO on $GABA_A$ responsivity makes this mechanism particularly relevant to late-onset postnatal depression. After parturition, there is a precipitous decline in progesterone and, therefore ALLO, followed by static low levels until menstrual cycling returns. Breastfeeding further extends the period of ALLO withdrawal since lactation delays the resumption of menstrual cycling. Therefore, weaning, which represents a physiologic example of reintroduction of ALLO after a period of withdrawal, could contribute to the pathophysiology of late-onset postnatal depression.

If GABAergic dysregulation is involved in reproductive depression, then genes coding for $GABA_A$ receptor subunits may predispose certain individuals to respond to changes in ALLO maladaptively (Gordon et al. 2015). It has already been established that $GABA_A$ receptor subunit polymorphisms are associated with an increased risk of other psychiatric disorders including major depressive disorder, bipolar disorder, schizophrenia, and alcohol dependence (Soyka et al. 2008; Fatemi et al. 2013). In an animal model, Maguire and Mody (2008) demonstrated that $GABA_A$ receptor δ-subunit knock-out mice exhibit behavioral abnormalities consistent with PPD. These mice are behaviorally silent until exposed to pregnancy and the postpartum state, at which time they demonstrate depressive symptoms and cannibalize their young. This model demonstrates that reproductive events may provoke affective dysregulation in genetically susceptible individuals.

Linking depressive symptoms associated with ALLO fluctuation across the reproductive life cycle

ALLO fluctuations, at least in a subset of vulnerable women, are relevant triggers for depressive symptoms throughout the female reproductive lifespan (Gordon et al. 2015). Better characterizing ALLO physiology during multiple periods of reproductive transition is likely to facilitate the study of this mechanism as well as to better specify the vulnerable phenotype by illuminating similarities and differences within this complex neurohormonal system. Table 1 summarizes knowledge to date on ALLO physiology, as well as related HPO and hypothalamic-pituitary-adrenal (HPA) physiology, across five points of reproductive transition.

We believe that menarche is particularly similar to postpartum resumption of menstruation in that both are a period of

Table 1 Periods of sensitivity to reproductive depressions and potential neurohormonal mechanisms

	Menarche	Pregnancy	Postpartum (lactating, anovulatory women)	Initial resumption of menstrual cycling	Perimenopause
LH/FSH secretion	Erratic sleep-related increase in LH pulsatility (Hoyt and Falconi 2015)	Suppressed by sex steroids(Bloch et al. 2003)	Suppressed by infant suckling and lactogens (Shen et al. 2007)	Erratic LH pulsatility (Shen et al. 2007)	Increased FSH due to decreased ovarian feedback (Gordon et al. 2015)
Estradiol	Increase to normal cycling levels (Hoyt and Falconi 2015)	Steady increase to supra-physiologic levels (Bloch et al. 2003)	Low (Shen et al. 2007)	Increase to normal cycling levels (Shen et al. 2007)	Erratic decrease with periods of hypo- and hyper-estrogenism (Gordon et al. 2015)
ALLO fluctuation frequency	Erratic, less frequent (Zhang et al. 2008)	No fluctuation (Gilbert Evans et al. 2005)	No fluctuation (Gilbert Evans et al. 2005)	Erratic, less frequent (Howie and McNeilly 1982)	Erratic, less frequent (Genazzani et al. 1998)
ALLO peak levels	Low or variable (Hoyt and Falconi 2015)	High (Gilbert Evans et al. 2005)	Low (Gilbert Evans et al. 2005)	Low or variable (Shaaban et al. 1987)	Gradual decrease during ovulatory cycles, erratic during anovulatory cycles (Genazzani et al. 1998)
GABAA receptor modulation by ALLO	Changes from excitatory to inhibitory due to α4β2δ subunit composition (Maguire and Mody 2008)	Decreased inhibition due to downregulation of δ and γ2 subunits (Maguire and Mody 2008)	Rapid rise in δ subunit expression with recovery of tonic inhibition (Maguire and Mody 2008)	Unknown, possible paradoxical response	Unknown, possible paradoxical response (Gordon et al. 2015)
HPA reactivity	Increased, potentiated by stress (Hoyt and Falconi 2015)	Decreased (Melon et al. 2017)	Decreased, modulated by oxytocin (Cox et al. 2015)	Largely unknown, possibly increased/-prolonged (Windle et al. 2013)	Conflicting data, possibly increased (Gordon et al. 2015)

transition out of physiologic hypogonadotropic hypogonadism, with GnRH neurons being quiescent prior to menarche and suppressed during the puerperum (Strauss and Barbieri 2014). The erratic nature of LH pulsatility and therefore ovulation frequency in both menarche and the late postpartum would result in irregular ALLO fluctuations and challenge the plasticity of $GABA_A$ receptors. Additionally, lactation prolongs the period of hypogonadotropic hypogonadism to varying degrees, which may contribute to increased sensitization of the $GABA_A$ receptor to ALLO. We propose that the variable LH pulse patterns, which results in erratic hormone fluctuations, including changes in ALLO levels, likely cause an increased susceptibility to mood dysregulation both in puberty and during menstrual resumption postnatally.

Other authors including Gordon et al. (2015) have proposed that similar GABAergic mechanisms may govern other reproductive transitions such as the perimenopause. The HPO axis during perimenopause has many similarities to menarche and the puerperal resumption of menstruation, including erratic LH pulsatility, erratic ovulatory patterns, and irregular ALLO fluctuations. However, differences also exist and data examining GABAergic functioning in both the perimenopause and puerperal resumption of menstruation are lacking. This characterization of the reproductive phenotype across the female lifecycle is an important next step for research.

Future directions

Despite mood symptoms with weaning and resumption of menstruation being commonly encountered clinically, it has unfortunately been studied little. We propose that there are two primary reasons for this. First, there is tremendous variability in the natural course of postpartum ALLO fluctuations related to variability in menses, variable use of hormonal contraceptive agents, and variability in infant feeding patterns both in relation to breastfeeding as well as in relation to the introduction of and reliance upon solid foods for nutritional sustenance. Such variability along multiple relevant constructs makes it challenging to identify a consistent phenotype for study. Nonetheless, in regard to ALLO, there may be a unifying etiologic explanation for depressive symptoms across the female reproductive lifespan, which would demand a different conceptualization of the phenotype: one relying on mechanisms rather than timing of symptoms or specific reproductive triggers for neurosteroid fluctuation. In order to accomplish this, more research is needed to characterize ALLO physiology during and around each major reproductive transition point. For example, what are ALLO fluctuation patterns in relation not only to parturition, but also to resumption of menstruation, use of hormonal contraceptives in the postpartum, and infant feeding patterns? For women with known vulnerability to reproductive depressions, what are the relationships between ALLO fluctuations and their symptoms?

The second reason we believe that late-onset postnatal depression has been neglected in the literature has been the complexity of this neurohormonal system overall. There are multiple neurohormonal systems that are likely relevant to depressive symptoms in the late postpartum including not only ALLO but also resumption of fluctuating estrogens, withdrawal of lactogens, inflammation and aberrant immune functioning, changes in the stress-response system, and possibly others. Therefore, simplifying an explanatory model is sufficiently enough for study risks neglecting multiple important contributing factors. We believe that one strategy for overcoming this is to start with mechanisms that may be similar across multiple risk periods for depression in the female reproductive lifespan. Clarifying these central mechanisms would provide an important framework that could allow for more effective study of modulating factors specific to a particular risk period as well as minimize confounding from psychosocial variables. We believe that the role of fluctuating ALLO levels on GABAergic functioning is a prime candidate for this study.

Conclusion

We hypothesize that late-onset postnatal depression that is associated with weaning and resumption of menstrual cycling may be largely attributable to $GABA_A$ dysregulation by ALLO after a period of prolonged withdrawal. Similar patterns of changes in ALLO are observed at other time points of reproductive transition throughout the female reproductive life cycle, and better understanding these similarities is likely to be helpful in facilitating the study of late-onset postnatal depression. Further research is warranted to confirm this hypothesis as well as to better understand how it might interface with other relevant systems (see Fig. 2) including the HPA axis

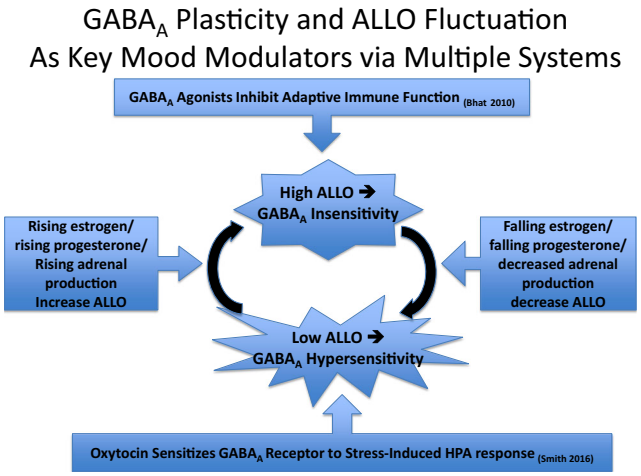

Fig. 2 The homeostatic balance between gonadal hormones, ALLO, and $GABA_A$ sensitivity is likely affected by multiple additional systems including the immune system, lactogens, and HPA functioning

(via changes in adrenal metabolism or oxytocin effects), HPO axis (via estrogen modulation and/or progesterone metabolism), immunologic functioning (via GABAergic modulation of the adaptive immune system) (Bhat et al. 2010), and lactogenic hormones (via oxytocin modulation of GABA$_A$ receptors) (Smith et al. 2016).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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