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Neuroactive Steroids and Perinatal Depression: A Review of Recent Literature

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Abstract

Purpose of review.—The purpose of this review is to provide a theoretical explanation and a review of the recent literature concerning the role of neuroactive steroids in perinatal depression, and to use this information to suggest future directions of research.

Recent findings.—The bulk of the evidence on neuroactive steroids in perinatal depression concerns allopregnanolone. Recent studies have been mixed, with some studies finding a direct correlation between lower levels of allopregnanolone and increased depressive symptoms but other studies finding no relationship. Evidence concerning other neuroactive steroids and perinatal depression is sparse.

Summary.—Additional research is needed with larger sample sizes and better characterization across the perinatal period (rather than cross-sectionally). Because some studies point to a lag between neuroactive steroid dysregulation and subsequent symptoms, future research should consider interactions with other systems (inflammatory or HPA) or other aspects of neuroactive steroids (such as synthetic enzymes or receptor plasticity).

Keywords

Neuroactive steroids; neurosteroids; allopregnanolone; perinatal depression; postpartum depression

Introduction

Postpartum depression (PPD) is a common and debilitating disorder, occurring in up to 20% of women in the general population [1] and at higher rates in women with pre-existing mood disorders [2]. PPD poses considerable risks for both mother and infant, including relationship discord, impaired infant-maternal bonding, and, more rarely, suicide and infanticide [3]. There are also well-documented cognitive, emotional, and behavioral risks for the developing child [4, 5]. Antenatal depression is also common, affecting 5–15% of women, and carries risks to the pregnancy and delivery, such as preterm labor, intra-uterine growth restriction, and increased rates of C-section, and is one of the strongest risk factors for PPD [6]. While the use of current antidepressant medications is largely safe in pregnancy, [7, 8] none has been tested specifically for efficacy in the perinatal period. While

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we understand how pregnancy physiology affects the pharmacokinetics of medications we do not yet have treatment algorithms or protocols specific to the perinatal period – nor is there a single drug that is FDA approved to treat perinatal depression.

Understanding the etiology and pathophysiology of perinatal depression is crucial to our ability to implement preventive interventions and targeted treatment strategies. While our knowledge of the etiology of perinatal depression is limited, and likely differs for antenatal vs. postpartum depression, the cause is certainly multifactorial, influenced by a variety of biological and psychosocial factors. Risk factors differ across cultures and between developing and developed nations. Already established risk factors for PPD include personal or family history of PPD, depression or anxiety during the index pregnancy, gestational diabetes, poor partner support, and instrument-assisted or Caesarean delivery [2, 9]. Risk factors for antenatal depression include low socioeconomic status, lower education, single motherhood, unemployment, lower social support, unintended pregnancy, intimate partner violence, history of early life adversity, and number of children [10, 11]. Recent lines of study on biological factors for both postpartum and antenatal depression include alterations in cortisol and amylase; intrauterine artery resistance [11]; HPA axis dysregulation; thyroid dysregulation; alterations in oxytocin and prolactin; and immune system dysregulation. [12–14]

Given that perinatal depression takes place in the setting of vast hormonal changes it is reasonable to examine the relationship between sex hormones and perinatal depression. The relationship, however, is likely not straightforward. In the majority of studies, there is not a direct correlation between absolute levels of hormones and disease risk – instead, fluctuations in levels of hormones appear to lead to depressive symptoms in vulnerable women [15]. Women may be vulnerable for genetic, epigenetic, or environmental reasons, [16–19] and previous work has shown a strong likelihood of recurrence of symptoms during hormone flux for women with a prior history of PPD. [15, 20–24]

It is possible that the inconclusive findings about sex hormones and perinatal depression exist because we are simply looking at the wrong hormones. Both estrogen and progesterone have direct effects on the brain, including modulation of gene transcription and activity through binding to intracellular receptors (estrogen and progesterone)[25, 26] as well as affecting membrane signaling (estrogen), with broad-ranging effects on synaptic plasticity, neurotransmission, neurodegeneration, and cognition. In addition to these direct effects, however, both estrogen and progesterone are metabolized into active compounds that have their own independent effects on the central nervous system (CNS), and other hormones derived from cholesterol (the neuroactive steroids) are also important actors in the CNS. There is a rich literature concerning the role of neuroactive steroids in depression, both within the perinatal period and outside. It will be the aim of this review to summarize the most recent research findings concerning the role of neuroactive steroids in perinatal depression, to highlight recent trends and high-impact studies, and to point toward future directions of research.

Neurosteroids and Neuroactive Steroids – What Are They?

Neurosteroids (NSs) are metabolites of cholesterol that are synthesized *de novo* within the brain, meaning that all precursors and enzymes required for production are contained in the brain, and they have immediate effects on neuronal excitability [27]. *Neuroactive steroids* (NASs) encompass NSs as well as steroids that are synthesized in the adrenal glands and gonads but easily cross the blood-brain barrier to act in the same manner as NSs in the brain [28]. The two terms are often used interchangeably in the literature, and for the sake of simplicity we will use the broader term neuroactive steroids (NASs). We will present evidence for a number of these compounds, but the bulk of the evidence concerns those hormones derived directly through reduction from progesterone (P4) and deoxycorticosterone (DOC). Estradiol and its derivatives, though an important part of the story, will not be a part of the limited scope of this paper.

Although NASs interact with other systems, such as serotonin and glutamate, their prime target is the inhibitory γ -aminobutyric acid (GABA) system [29]. GABA is the chief inhibitory neurotransmitter in the brain and works by reducing neuronal excitability through binding of GABA receptors located in the plasma membrane of pre- and post-synaptic neurons. GABA_A receptors, which bind NASs, are ligand-gated ion channels that hyperpolarize neurons through influx of negatively charged chloride ions in the adult brain [27]. What makes NASs unique is that they can mediate immediate CNS effects through their action on neuronal membrane receptors, such as GABA, and they can also mediate slower genomic effects through interactions with nuclear steroid hormone receptors [27, 29].

The NASs can be classified as pregnane, androstane, and sulfated based on their chemical structure; their biosynthesis is illustrated in Figure 1 [27]. It may be useful to refer to this figure frequently when reading this review as the nomenclature can sometimes be confusing. The NASs all result from metabolic reactions in which their precursors (all descendants of cholesterol) are reduced. The inhibitory NASs (highlighted in yellow) include the 3 α , 5 α - and the 3 α , 5 β -reduced metabolites: of progesterone - allopregnanolone (ALLO) (3 α , 5 α -THP) and pregnanolone (PREG) (3 α , 5 β -THP); of deoxycorticosterone (DOC) – allotetrahydroDOC (3 α , 5 α -THDOC) and tetrahydroDOC (3 α , 5 β -THDOC); of dehydroepiandrosterone (DHEA) - 3 α , 5 α -Androsterone and 3 α , 5 β -Androsterone; and of testosterone - 3 α , 5 α -Androstanol and 3 α , 5 β -Androstanol [30]. They are all potent allosteric modulators of the GABA_A receptor – at lower concentrations they enhance GABA action at the receptor, and at higher concentrations they directly activate the receptor without GABA. The 3 α -hydroxy group within the A ring of these molecules is necessary to produce the positive allosteric GABAergic activity [31]. They activate synaptic and extra-synaptic receptors to influence both phasic and tonic inhibition. While benzodiazepines and barbiturates enhance GABA activity by increasing chloride channel opening frequency and duration, respectively, NASs increase both frequency and duration of channel opening, resulting in a more powerful effect [27]. They produce inhibitory neurobehavioral effects, such as anxiolytic, anticonvulsant, and sedative actions, and likely work independently as well as in a coordinated fashion [30]. The 3 α , 5 α - reduced metabolites of progesterone (ALLO) and DOC (allotetrahydroDOC) are the most potent GABAergic NASs and are considered “prototypical” [32].

The excitatory NASs (highlighted in blue) include the sulfated metabolites of pregnenolone (pregnenolone sulfate [PS]) and DHEA (DHEAS), in addition to the 3 α , 5 α - and 3 α , 5 β -reduced metabolites of cortisol. They have weak GABA_A antagonistic effects as well as positively modulating glutamate receptors, both producing neuronal excitability [30]. They likely serve as a homeostatic balance against the positive GABAergic modulation of the inhibitory NASs and in pharmacologic studies have been found to be pro-convulsant and anxiogenic [27].

The role of NASs in the stress response

The inhibitory NASs are implicated in the adaptive response to stress, with increases in central and peripheral levels seen following an acute stressor. Immediately following a stressful event, GABAergic transmission is decreased (mediated by GABA), which leads to anxiety-like behavior. This leads to a compensatory increase in ALLO and other inhibitory NASs, which restore GABAergic inhibitory function, leading to a disappearance of the anxiety-like behavior [32]. Stress-induced increases in these NASs also negatively modulate the HPA axis in an attempt to regain balance. Rodents pre-treated with inhibitory NASs have decreased plasma levels of ACTH in response to stressors [33]. This positive modulation of GABA and negative modulation of the HPA axis brings homeostasis back to the system as it adapts to stressors. It is thought that disruptions in NAS levels interfere with this process, making an individual vulnerable to psychiatric illness [32]. The pre-treatment of rodents with finasteride (a 5 α -reductase inhibitor) before exposure to stress blocks the expression of stress-relieving behaviors, supporting the idea that the response to stress is mediated by the inhibitory 5 α -reduced NASs, such as ALLO and allotetrahydroDOC [34]. While acute stress leads to an increase of NASs, chronic stress is associated with a decline in NAS biosynthesis and a reduced expression of 5 α -reductase type 1, the enzyme that catalyzes the rate-limiting step in the ALLO biosynthesis. Mice who endure prolonged social isolation have reduced levels of ALLO compared to their group-housed counterparts. [35]

The role of neuroactive steroids in psychiatric illness outside the perinatal period

There is a substantial literature on the role of NASs in psychiatric illness outside of the perinatal period, covering particularly the role of ALLO and pregnanolone in symptoms of schizophrenia, anxiety, major depressive disorder (MDD), and premenstrual dysphoric disorder (PMDD) [36]. While a full review of this evidence is beyond the scope of this paper, evidence for MDD and PMDD may inform research in perinatal depression. There is evidence of reduced levels of inhibitory NASs in the blood or cerebral spinal fluid in depression, both acutely [28, 37] and during remission [28], as well as evidence that such levels can recover with effective treatment [35, 37, 38]. SSRIs are believed to enhance the effect of 3 α -hydroxysteroid dehydrogenase (3 α -HSD), which catalyzes the final step in the breakdown of both progesterone and DOC to their final inhibitory metabolite forms (including ALLO). [39]

Girdler and colleagues [28] measured the levels of various NASs in women with and without a history of mood disorder following administration of oral micronized progesterone. The

women with a mood disorder history, even when euthymic, had lower serum progesterone concentrations as well as all NAS concentrations than the control women, both before and after the micronized progesterone. Girdler postulated that these lower NAS levels came about through adrenal suppression [28].

Additionally, the expression of 5 α -reductase type 1, the enzyme that catalyzes the rate-limiting step in the biosynthesis of ALLO and alloTHDOC, is downregulated in the prefrontal cortex of depressed patients [35]. It is this same enzyme that is downregulated in mice models of chronic stress [35], implying that the body considers depression a form of chronic stress.

The evidence concerning NASs and PMDD points to a more complex relationship than that indicated by MDD. PMDD, characterized by late luteal phase affective instability, may be a pathological response to either withdrawal from or exposure to ALLO across the menstrual cycle. Epperson and colleagues demonstrated that the usual fluctuations in levels of cortical GABA across the menstrual cycle in healthy women is disrupted in women with PMDD, as is the relationship between GABA and neurosteroids [40]. Peak levels of ALLO in the luteal phase of the menstrual cycle may paradoxically cause GABA receptor antagonism in certain women, leading to negative emotional symptoms.[41] Women with PMDD appear to respond in a different way to the same stimulus – Timby and colleagues measured GABA_A receptor sensitivity, in PMDD versus control women, in response to IV ALLO using saccadic eye velocity (SEV). Measuring SEV using electrooculography is an established method of evaluating GABA_A-mediated sedation. They found that women with PMDD were more sensitive to ALLO in the luteal phase versus the follicular phase, while the reverse was true for healthy control women. This suggests that PMDD women may not be able to achieve physiological tolerance to rising levels of ALLO in the luteal phase, which could result in the paradoxical GABA antagonism mentioned earlier [42]. In addition, evidence supports both symptom reduction following the blocking of ALLO production [43], as well as increase in ALLO levels following treatment with SSRIs, indicating either that symptoms arise in response to levels outside an “optimal” zone (neither too low nor too high), or that fluctuations in level cause symptoms, or that symptoms may arise as the GABA_A receptor responds to differing levels of ALLO. For a thorough review of the literature on PMDD, see Yonkers et al. (2018). [40–44]

Perinatal depression

We are only beginning to understand the specific role of NASs in perinatal depression, and the complexity of the pathophysiology is reflected by the varied results of studies to date. NASs are at their highest physiological concentrations in pregnancy, with 200-fold increases in progesterone [45]. Most NASs increase substantially across pregnancy (though some stay stable), and the rate of metabolism from precursors to final forms may also change across pregnancy. [46] The question spurring most studies to date – whether the relationship between perinatal depression and NASs will look like that of MDD or that of PMDD, or something entirely different – has yet to be answered.

Allopregnanolone (ALLO)

Much of the recent literature on the role of NASs in perinatal depression has focused on ALLO, the 3 α ,5 α reduced metabolite of progesterone. ALLO is a potent allosteric modulator of GABA, thus producing significant anxiolytic effects. It is synthesized de novo in the brain as well as in the adrenals and ovaries [27]. During pregnancy the placenta also produces ALLO and is actually the main source during this time. [45]

In healthy women, ALLO levels rise across pregnancy and then decline abruptly in the postpartum, and mirror levels of progesterone throughout [47]. The postpartum decline may actually begin in the late 3rd trimester, when the immediate precursor of ALLO is shown to accumulate [46], and postpartum levels of ALLO are lower than in the follicular phase of the menstrual cycle [48], with ALLO's immediate precursor being the most abundant steroid in the postpartum period [46].

The increase in ALLO over the course of pregnancy, which is necessary to maintain a successful pregnancy [49], leads to a down-regulation of the GABA_A receptors to maintain homeostasis [46]. In fact, administering ALLO to non-pregnant mice at the concentrations seen in pregnancy is sufficient to cause sedation [45], indicating that receptors must be compensating in pregnancy. This down-regulation does not occur when NAS synthesis is blocked with finasteride (5 α -reductase inhibitor), suggesting that the down-regulation seen is NAS-dependent [50]. In a simulated peripartum animal model, failure of this down-regulation in pregnancy was associated with depression-like behavior in the postpartum [51].

In the immediate postpartum, once the placenta has been delivered, ALLO levels drop precipitously, and it has been postulated that this abrupt decline may trigger PPD in certain vulnerable women [52]. In healthy women, the abrupt decline in ALLO levels at parturition leads to an upregulation of GABA receptor expression within 48 hours [45].

The relationship of ALLO to mood symptoms may thus be mediated either directly, by levels of the hormone, or indirectly, by changes in receptor concentration or receptor subunit configuration. Studies that have looked at absolute levels of ALLO and the correlation with mood and anxiety scores in the perinatal period have had mixed results. Hellgren and colleagues found that low ALLO correlated with concurrent higher depression scores in the 3rd trimester [53], but did not replicate these findings in a subsequent study using a 2nd trimester time-point [54]. Crowley and colleagues did find an inverse relationship between 2nd trimester negative emotional symptoms and a concurrent combined measure of ALLO + pregnanolone [55], but it is unclear what the relationship would have been to either of those NASs measured individually. Our own group found that lower levels of ALLO in the 2nd trimester predicted subsequent PPD in a sample of 60 women with a mood disorder diagnosis, even when controlling for depression and anxiety during pregnancy [56], and we have recently replicated these findings in an additional sample of 64 women with and without mood disorders (Osborne et al., unpublished data). A smaller study by Deligiannidis did not find an association between 3rd trimester ALLO and subsequent PPD [57] (of note, 3rd trimester levels of ALLO are the highest of the perinatal period, so this may not be the most sensitive time to detect an association). Another study by the same group found that mean ALLO levels measured across the peripartum were positively correlated with STAI-S

(Spielberger State-Trait Anxiety Inventory-State) scores. NAS levels and scales were measured at each of 4 study visits and the group consisted a total of 56 women - at risk for PPD and healthy controls. Interestingly, while ALLO levels correlated with symptoms, the did not differ between the healthy and at-risk groups [58].

Guintivano and colleagues measured NASs (progesterone and ALLO) at 6 weeks postpartum in a case-control study of PPD in over 1500 women, and found no differences between groups in NAS concentration [59]. Taking all of these studies together, it is hard to come to a consistent conclusion about the role of ALLO in perinatal depression. Some of these studies did not find a difference in absolute levels of ALLO between women with and without concurrent depressive symptoms, but Hellgren et al. in the 3rd trimester did, and Deligiannidis found a correlation with anxiety symptoms across the peripartum. Osborne et al. [56] found a difference not with concurrent but with subsequent symptoms, indicating that some longer acting changes – perhaps receptor changes, or changes in gene transcription, or interactions with another system such as the inflammatory or HPA system – may be the mechanism through which differences in ALLO exert their effects.

One such mechanism is that of receptor plasticity. An elegant study by Maguire and Mody in 2008 showed that knockout mice who lacked the ability to downregulate the delta subunit of the GABA_A receptor during pregnancy and to upregulate it postpartum developed depressive and anxiety-like behaviors in the postpartum. These symptoms could be prevented when the mice were given an inhibitor that corrected their inability to regulate receptors, and was specific to the postpartum period (i.e., did not occur in the same mouse model when tested outside the perinatal period).[51] Gilbert Evans and colleagues also reported that failure to recover receptor concentration postpartum is associated with PPD [46]. Another way in which receptor plasticity may be involved is through receptor subunit reconfiguration in times of ALLO flux. This has been demonstrated in puberty, another time of ALLO level fluctuations. The changes in ALLO levels lead to increased expression of the δ subunit, which has a higher affinity for ALLO, in turn paradoxically causing ALLO to have antagonistic or excitatory effects at GABA manifesting as increased negative mood symptoms [60].

Recent treatment trials of a synthetic formulation of ALLO, Brexanolone, in PPD have shown promising results. A phase 2 randomized placebo-controlled trial resulted in a 70% remission rate in severe PPD in the treatment arm (n=10) that was sustained after 30 days, while only one of the 11 women in the placebo group achieved remission [61]. (Phase 3 results have been completed but not yet published, so it remains to be seen if these results will be sustained; the drug has been submitted for FDA approval.)

AllotetrahydroDOC

This molecule is to deoxycorticosterone (DOC) as ALLO is to progesterone, that is, the 3 α ,5 α -reduced metabolite. It is synthesized entirely in the adrenal glands and can readily cross the blood-brain barrier. Although there haven't been any studies looking specifically at this molecule in perinatal depression, it has similar properties and actions to ALLO in that is a potent positive allosteric modulator of GABA and it is increased in response to acute stress

[32]. Its actions might well be similar – but because this molecule does not have particularly elevated levels in pregnancy, it has not been the subject of study.

Pregnanolone (PREG)

While ALLO is the 3 α ,5 α -reduced metabolite of progesterone, pregnanolone (PREG) is the 3 α , 5 β -reduced metabolite of progesterone. It has a similar mechanism of action and targets as ALLO but has not been studied as well in perinatal depression. One study measured levels across pregnancy and the postpartum finding the same trend as that of ALLO – increase across pregnancy and then abrupt decline postpartum [46]. Deligiannidis did not find a difference between postpartum pregnanolone levels in women at-risk for PPD and healthy controls, although numbers were small [57]. In a larger subsequent study, the same group found higher mean pregnanolone levels across the peripartum in women at-risk for PPD versus controls as well as a positive correlation with depression and anxiety scale scores [58]. Crowley and colleagues found an inverse relationship between 2nd trimester negative emotional symptoms and a concurrent combined measure of ALLO + pregnanolone [55]. Overall, this scant amount of evidence does not allow us to draw any conclusions about the specific role of pregnanolone in PPD – though with its elevated levels in pregnancy it would be a good target for future study.

Dehydroepiandrosterone (DHEA)

DHEA is produced in the brain, adrenals, and gonads and is one of the most abundant circulating hormones in humans. It is derived from cholesterol through pregnenolone, at one step prior to progesterone formation (so it does not derive from progesterone, as do all the hormones discussed above). It is the main precursor of testosterone in males and estrogen in females. Its activities in the central nervous system include positive allosteric modulation of the glutamate receptor (excitatory activity) and negative allosteric modulation of the GABA_A receptor (i.e., it is excitatory rather than inhibitory). Along with its sulfated metabolite, DHEA-S, it is involved in neurogenesis, neuroprotection, and catecholamine synthesis, as well as having anti-inflammatory, anti-glucocorticoid, and anti-oxidant effects, though its specific mechanisms of action are poorly understood [62]. The literature on DHEA and perinatal mood is limited. One study by Buckwalter found that higher DHEA levels in late pregnancy were associated with a better mood, based on a variety of psychopathology scales, and lower levels at 3–4 weeks postpartum were associated with a lower mood [63]. Given that DHEA has opposing effects to ALLO (antagonist at GABA_A receptor), one would expect to find a negative correlation with good mood, but clearly there are other mechanisms, such as downstream anti-inflammatory effects or receptor plasticity, creating a layer of complexity. Studies in general depression also have disparate findings as is reported in a review by Manninger and colleagues who state that there is “no parsimonious way of reconciling the diverse findings.” [62]

DHEA-S

DHEA-S, the sulfated counterpart of DHEA, is a potent GABA antagonist (i.e, excitatory neuronal activity) [27, 64] and is synthesized in the brain. Similar to DHEA, its specific mechanism of action is not well known [62]. Studies in perinatal depression are very limited. In one study by Kasap and colleagues, higher levels were associated with higher depression

and anxiety scale scores in patients with hyperemesis in pregnancy (n=42) compared with pregnant patients without hyperemesis (n=42) [65]. In a smaller study of healthy women with no prior psychopathology, n=27, prenatal DHEA-S correlated with prenatal paranoia and psychoticism and postpartum DHEA-S correlated with postpartum anxiety symptoms, paranoia, and somatization. The scale used was the Symptoms Checklist 90-R [66]. These limited results seem more consistent with what one would theoretically expect based on evidence from the inhibitory NASs, and opposite to those found for DHEA – so clearly more research is warranted.

Testosterone

Testosterone is also derived from DHEA, as a 3β -reduced metabolite. Normally, maternal testosterone levels rise by 70% in pregnancy. In a study looking at factors related to that increase, it was found that women with EPDS scores greater than or equal to 13 had higher levels of testosterone measured in late 3rd trimester than those with EPDS of less than 13. [67]. Another study found that testosterone levels correlated positively with depression and anger scale scores at 38 – 40 weeks gestation [68]. Four studies found a positive correlation with postpartum testosterone levels and concurrent depression scores [63, 68–70]

In studies of men and women (outside of the puerperium) there were opposite findings - most studies found that low levels of testosterone correlate with depressive and anxiety symptoms and that treatment of these disorders with SSRIs results in restoration of levels [71]. This opposing finding to results in perinatal depression is yet another illustration of how poorly we understand the exact mechanism of action of these NASs in reproductive-related depressions. Perhaps it is a metabolite of testosterone, such as the inhibitory NAS, $3\alpha,5\beta$ -androsteneol [30], that is indirectly mediating the negative effect on mood in the perinatal depressions above.

Conclusion

The bulk of the evidence concerning NASs in perinatal depression has to do with ALLO, and the mixed findings of studies make it hard to draw any firm conclusions. While only some studies find correlations between absolute levels of ALLO and concurrent perinatal depression, our own work has indicated a difference in absolute levels when we look not for concurrent but rather for subsequent symptoms. This may indicate that differences in absolute level may be occurring at a step far upstream from the symptoms, allowing time for consequent changes in gene transcription, receptor regulation, or immune system regulation to play a more immediate role in symptom generation. Perhaps an inability to regulate GABA receptor concentration in response to the changing levels of NASs across the peripartum is responsible, as was the case in Maguire and Mody's animal model [51], or paradoxical excitatory activity of ALLO on the GABA receptor secondary to over-expression of the δ subunit in the setting of ALLO flux [60]. Another explanation could have to do with the synthetic enzymes for NAS production. One of these enzymes, 5α -reductase type 1, which catalyzes the reduction of progesterone to the ALLO intermediary 5α -DHP, is deficient in humans with depression and in animal models of chronic stress [35] – perhaps this enzyme is deficient in women at risk for PPD (due to an acute or chronic

stress, including early life trauma). If so, the precipitous drop in ALLO postpartum, coupled with a decreased ability to synthesize ALLO, would cause levels to drop below what is necessary to prevent anxiety and depression. Future studies could aim to measure levels of this enzyme activity postpartum in women who are at risk of PPD versus those who are not, as well as measuring the expression of the different GABA_A receptor subtypes to detect if the δ subunit is overexpressed. Future research is also needed in NASs other than ALLO, especially pregnanolone (the other direct metabolite of progesterone). Numerous studies on the role of NASs and especially ALLO in perinatal depression are currently underway, and the next several years will likely prove to be ones of high yield in beginning to unravel these connections.

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Figure 1.
Synthesis of neuroactive steroids from cholesterol