



Mid-pregnancy allopregnanolone levels and trajectories of perinatal depressive symptoms

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ABSTRACT

Perinatal depression is a major cause of disability for individuals giving birth worldwide, with detrimental effects on short- and long-term parental and child outcomes. There is emerging evidence that the neuroactive steroid hormone allopregnanolone is implicated in the pathophysiology and course of perinatal mood symptoms. However, no study thus far has examined allopregnanolone levels whilst making use of longitudinal data on depressive symptom trajectories throughout the perinatal period. The present study investigated levels of allopregnanolone at gestational week 17 of 252 participants in relation to perinatal depressive symptom trajectories, with a secondary aim of exploring the role of history of depression as an effect modifier. Four perinatal depressive symptom trajectories were investigated: controls (no depressive symptoms throughout perinatal period) (N=161), antepartum (depressive symptoms prenatally with postpartum remission) (N=31), postpartum-onset (no depressive symptoms during pregnancy, development of depressive symptoms postpartum) (N=23), and persistent (depressive symptoms throughout the perinatal period) (N=37). Results show that for every one nmol/l increase in allopregnanolone, there was 7% higher odds for persistent depressive symptoms (OR 1.07, 95% CI 1.01–1.14) compared to controls. No association was seen for antepartum and postpartum-onset depressive symptoms. History of depression did not modify the association between allopregnanolone and perinatal depressive symptom trajectories. These results show the role of allopregnanolone for persistent depressive symptoms and strengthen the hypothesis of differences in pathophysiology among the trajectories.

1. Introduction

Perinatal depression refers to an episode of major depression with onset during pregnancy or within four weeks postpartum (American Psychiatric Association DSM-5 Task Force and American Psychiatric Association, 2013). However, onset up to a year after birth is frequently considered to be within the postpartum period in research and clinical settings (O'Hara and McCabe, 2013). The etiology of perinatal depression is multifactorial, such that constitutional and environmental factors interact to protect against, or increase, risk of the condition (Josefsson, Larsson et al., 2007; Milgrom, Gemmill et al., 2008; O'Hara 2009; Skalkidou, Hellgren et al., 2012; Schiller, Meltzer-Brody et al., 2015; Viktorin, Meltzer-Brody et al., 2016; Yu, Liang et al., 2021).

Perinatal depressive symptoms may be separated into three different

trajectories based on the time of onset and duration of the symptoms: antepartum with remission postpartum, postpartum-onset with no depressive symptoms during pregnancy, or persistent, meaning antepartum depressive symptoms with no remission in the postpartum period (Wikman et al., 2020). It has been posited that individuals may differ in terms of resilience and risk factors, resulting in differing onset and development of perinatal depressive symptoms throughout the perinatal period (Underwood et al., 2016; Wikman et al., 2020).

During pregnancy, neuroactive steroid levels gradually increase followed by a dramatic drop postpartum, 86 – 99% compared with prepartum values (Gilbert Evans et al., 2005). Allopregnanolone, a metabolite of progesterone, is one such neurosteroid. It is a positive allosteric modulator of the γ -aminobutyric acid (GABA) receptor A, where GABA exerts important mood regulatory and anxiolytic effects.

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There is emerging evidence that allopregnanolone, which follows the pattern of increasing levels during pregnancy followed by a sharp drop postpartum (Luisi et al., 2000), is implicated in the development of perinatal mood symptoms (McEvoy and Osborne, 2019; Meltzer-Brody and Kanes, 2020; Pinna et al., 2022). Generally, sensitivity to endocrine changes has been posited to confer susceptibility for perinatal depression (Payne and Maguire, 2019; Schiller et al., 2015; Schweizer-Schubert et al., 2021). In 2019, a treatment for postpartum depression by intravenous infusion of a synthetic form of allopregnanolone called brexanolone (Edinoff et al., 2021; Meltzer-Brody et al., 2018; Zheng et al., 2019) has been approved by the US Food and Drug Administration (Powell et al., 2020). Similarly, a heterocyclic analogue of allopregnanolone called zuranolone has also been recently approved as an oral alternative for treatment of postpartum depression.

Few studies to date have examined allopregnanolone levels in relation to depression symptoms during pregnancy and the postpartum period. In one study of healthy individuals giving birth (Luisi et al., 2000), levels of allopregnanolone three days postpartum were lower for those experiencing postpartum blues, with a negative correlation between allopregnanolone levels and scores on Hamilton Rating Scale of Depression. Deligiannidis (2020) found that higher levels of allopregnanolone in mid-to-late pregnancy were associated with concurrent perinatal depression. Standeven (2022) found that relationship between allopregnanolone and perinatal depression changed over time, where higher levels in the second trimester was associated with better concurrent mood, while higher levels at week six postpartum were associated with higher depression and anxiety scores at six weeks postpartum. Regarding late pregnancy measurements of allopregnanolone, Hellgren et al. (2014) found that low levels of allopregnanolone were associated with symptoms of depression in late pregnancy. However, no association was found between second trimester allopregnanolone levels and depression symptoms in the second or third trimester (Hellgren et al., 2017). Osborne et al. (2017) found higher allopregnanolone levels in the second trimester to be associated with lower risk of developing postpartum depression, with no concurrent effects of allopregnanolone on antepartum depression. In a later study, they found that lower second trimester allopregnanolone levels predicted anxiety but not depression at six weeks postpartum (Osborne et al., 2019). However, to date, no study has examined mid-pregnancy allopregnanolone levels and made use of longitudinal data on perinatal depressive symptoms throughout pregnancy and the postpartum period.

In addition to biologically mediated risk, psychiatric history has been established as a robust predictor of perinatal depression. In an umbrella review of prevalence and correlates of perinatal depression, the risk factor with the largest effect size found was personal history of mental illness such as depression and anxiety, ranging between $r=0.30$ – 0.51 (Al-abri et al., 2023). Psychiatric history has also been identified as one of four categories of risk factors, alongside genetics, adverse life events, and social support (Guintivano et al., 2018). Thus, psychiatric history is a candidate risk factor to be considered when examining other correlates of perinatal depression.

The present study aimed to investigate the association between allopregnanolone levels at mid-pregnancy in relation to perinatal depressive symptom trajectories, and to explore the role of depression history as a possible effect modifier.

2. Materials and methods

2.1. Study population and sample collection

The data, previously used by Hellgren et al., (2017) to investigate the association of plasma allopregnanolone with antenatal depressive symptoms, was here reconsidered to assess differences in relation to perinatal depressive symptom trajectories, as well as considering the possible moderating effect of previous depression.

This is a nested study among participants in the Biology, Affect,

Stress, Imaging and Cognition (BASIC), a longitudinal population-based cohort in Uppsala, Sweden (Axfors et al., 2019) who donated blood sample to the Uppsala Biobank for Pregnant Women from June 2008 to January 2013. The main aim of the BASIC project was to investigate biopsychosocial etiological processes of perinatal depression. All individuals undergoing routine ultrasound at around gestational week 17 were invited to participate in the study. Individuals who were below 18 years old, had protected identity (i.e. have personal data with restricted access and withheld from public registers), difficulties in reading and understanding Swedish, had blood-borne infections and had non-viable pregnancy at ultrasound were not eligible for the study. In the present study, individuals taking selective serotonin reuptake inhibitors (SSRI) at the time of blood collection or had missing data on perinatal depressive symptom trajectories were also excluded from further analyses, resulting in a final sample of 252 individuals. None of the individuals were taking other psychoactive medications at the time of blood collection. They were followed up at gestational week 32 as well as six weeks and six months postpartum, where they answered web-based questionnaires. The questionnaires inquired data on socio-demographic information, medical history including all the medicines they were taking regularly, lifestyle, sleeping habits and social support. They also contained psychometric instruments, examining depression using the Edinburgh Postnatal Depression Scale (EPDS), among others. For history of depression, individuals were asked “Have you had depression?” where they answered either yes or no. For fear of delivery, they were asked “How do you feel about your delivery? Check all that apply”. The choices were “okay”, “expectant”, “worried”, “good”, “wish that it would be over”, “terrified”, “longing”, “afraid of cesarean section”, and “afraid of vaginal delivery”. Those who answered “terrified”, “afraid of cesarean section” and/or “afraid of vaginal delivery” were classified as having fear of delivery. Furthermore, additional data on SSRI use were retrieved from electronic patient records and/or collected from national registries. Blood samples were collected as part of the Uppsala Biobank for Pregnant Women, where individuals undergoing their first routine ultrasound screening were invited to participate. This was done in random, depending on the availability of a research nurse at the ultrasound unit. This biobank covers approximately half of the pregnant population of Uppsala County. Inclusion criteria are at least 18 years old, speaks Swedish, and free from blood-borne diseases such as HIV, hepatitis B and C. Venous blood was collected around gestational week 17 in ethylenediaminetetraacetic acid tubes. Within 2 h of collection, the samples were centrifuged and stored at -80°C until analysis. BASIC and Uppsala Biobank for Pregnant Women were approved by the Uppsala Regional Ethical Committee (Dnr. 2009/171 and Dnr 2007/181, Biobank nr 755) and followed the Principles of Declaration of Helsinki. All participants gave their written informed consent.

2.2. Allopregnanolone analyses

Among the BASIC participants whose blood sample was collected in the Uppsala Biobank for Pregnant Women, allopregnanolone was measured in the plasma by the Umeå Neurosteroid Research Center, as previously described (Hellgren et al., 2017). Briefly, allopregnanolone was extracted with diethyl ether and purified through celite chromatography to reduce cross-reactivity. Ultimately, levels were determined using radioimmunoassay, where the antibody used was raised against 3α -hydroxy-20-oxo-5 α -pregnan-11-yl carboxymethyl ether coupled with bovine serum albumin as antigen (AgriSera AB, Umeå, Sweden). All samples were counted with RackBeta scintillation counter (Wallace, Finland).

2.3. Trajectories of perinatal depressive symptoms

EPDS was used to determine the different perinatal depressive symptom trajectories. A cut-off of 13 during any of the pregnancy

timepoints (gestational weeks 17 or 32) and 12 during any of the postpartum timepoints (6 weeks postpartum, or 6 months postpartum) was considered to classify subjects as having depressive symptoms (Rubertsson et al., 2011). Accordingly, four categories of perinatal depressive symptoms were identified based on timing of onset of symptoms as well as their resolution or persistence in the perinatal period: controls (no depressive symptoms throughout the perinatal period), antepartum depressive symptoms (APDS, depressive symptoms prenatally with postpartum remission), postpartum-onset depressive symptoms (PPDS, no depressive symptoms during pregnancy but development of depressive symptoms postpartum), and persistent depressive symptoms (depressive symptoms throughout the perinatal period).

2.4. Statistical analysis

Differences in characteristics across groups were tested with ANOVA, Kruskal Wallis, Chi-square, or Fisher's exact test, where appropriate. For the characteristics significantly associated with perinatal depressive symptom trajectories, post-hoc pairwise comparisons were performed with Chi-square or Fisher's exact test to determine which specific groups differed. P values for post-hoc pairwise comparisons were adjusted with false discovery rate, henceforth called q-values. Missing values were imputed using multivariate imputation by chained equations algorithm (van Buuren and Groothuis-Oudshoorn, 2011). Multinomial logistic regression was used to estimate the odds ratio (OR) and confidence intervals (95% CI) of the association between allopregnanolone and perinatal depressive symptom trajectories. The models were adjusted for age, pre-pregnancy body mass index (BMI), parity, education, history of depression, and gestational length at the time of blood collection (Hellgren et al., 2017, 2014; Osborne et al., 2019, 2017; Standeven et al., 2022). In addition, a sub-analysis was performed where we included only those who had depressive symptoms at the time of blood collection for the APDS and persistent depressive symptom groups. To explore effect modification of history of depression on allopregnanolone, an interaction term between history of depression and allopregnanolone was introduced to the main model. All statistical analyses were performed using R programming language (version 4.2.2) and RStudio (version 2022.07.1). Significance was set at p-value ≤ 0.05 and q-value ≤ 0.05 .

3. Results

Out of 252 participants, 31 (12%) individuals had APDS, 23 (9%) had PPDS, and 37 (15%) had persistent depressive symptoms. EPDS scores among the different perinatal depressive symptom trajectories are shown in Fig. 1. Among controls, the median for EPDS scores were 4 (Inter-Quartile Range (IQR) 1, 6) for gestational weeks 17 and 32, and 4 (IQR 2, 6) and 4 (IQR 1, 6) for postpartum week 6 and month 6, respectively. Among individuals with APDS, median EPDS score for gestational week 17 was 13 (IQR 8.5, 13), gestational week 32 was 13 (IQR 8, 15.5), postpartum week 6 was 6 (IQR 3, 8), and postpartum month 6 was 6 (IQR 5, 7). For individuals with PPDS, median EPDS scores were 7 (IQR 4.5, 9.5), 7.5 (IQR 3.25, 9.75), 13 (IQR 11.5, 14.5) and 8 (IQR 6, 13) for gestational weeks 17 and 32, and postpartum week 6 and month 6, respectively. Among individuals with persistent depressive symptoms, median EPDS score for gestational week 17 was 13 (IQR 10, 16), gestational week 32 was 14 (IQR 13, 16), postpartum week 6 was 12 (IQR 10, 16) and postpartum month 6 was 13 (IQR 11, 15).

Sample characteristics are summarized in Table 1. Among individuals with APDS, there was a higher percentage who had history of depression ($q = 0.046$) compared to controls. Among individuals with PPDS, there was a higher percentage who had fear of delivery ($q = 0.04$) compared to controls. Among individuals with persistent depressive symptoms, there was a higher percentage who had education less than

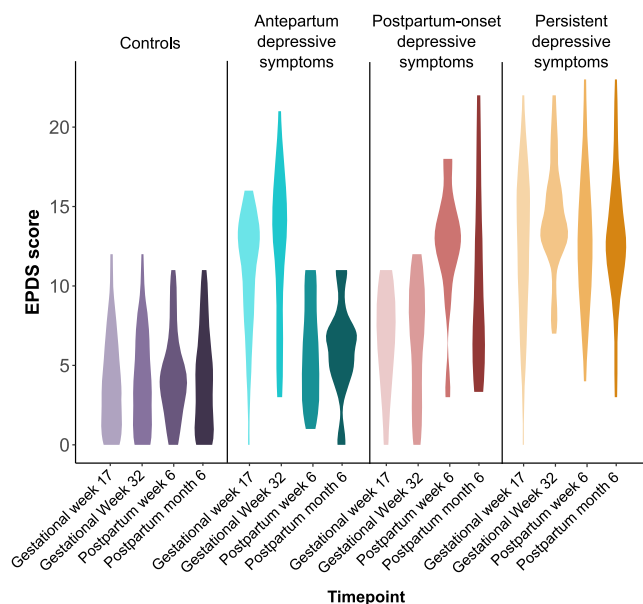


Fig. 1. EPDS scores and perinatal depressive symptom trajectories. Violin plots showing the EPDS scores of individuals with different perinatal depressive symptom trajectories at several timepoints (gestational weeks 17 and 32, and postpartum week 6 and month 6).

12 years ($q = 0.006$), history of depression ($q < 0.001$), and fear of delivery ($q = 0.02$) compared to controls. There was also a higher percentage who had history of depression ($p = 0.045$) compared to those with PPDS.

Mid-pregnancy allopregnanolone was borderline significantly different among the perinatal depressive symptom trajectories ($p = 0.055$, Fig. 2). Median allopregnanolone levels in controls were 16.6 nmol/L (IQR 14.1, 21.3), 18.3 nmol/L in APDS (IQR 14.1, 23.6), 17.7 nmol/L in PPDS (IQR 11.8, 21.1) and 21.33 (IQR 16.9, 24.1) in persistent depressive symptoms. Allopregnanolone levels were associated with persistent depressive symptoms, both in the unadjusted and adjusted models. Compared to controls, every one nmol/l increase in allopregnanolone was associated with 7% higher odds for persistent depressive symptoms (OR 1.07, 95% CI 1.01–1.14, $p = 0.02$, Table 2). Allopregnanolone was not significantly different in the APDS or PPDS groups when compared to the controls (Table 2). In the sub-analysis where we excluded those who did not have depressive symptoms at the time of blood collection for the APDS and persistent depressive symptom trajectories, similar trends were found although allopregnanolone becomes only borderline significant for those with persistent depressive symptoms compared to controls (OR 1.07, 95% CI 0.99–1.16, $p = 0.10$). The interaction term allopregnanolone by history of depression was not significant in any of the models (Table 3).

4. Discussion

The present study investigated mid-pregnancy allopregnanolone levels in relation to distinct perinatal depressive symptom trajectories. Higher mid-pregnancy allopregnanolone levels were noted among those with persistent depressive symptoms compared to controls; there was no effect of history of depression on this association. No differences in allopregnanolone levels were observed between APDS and controls, nor between PPDS and controls. To the best of our knowledge, this is the first study to explore the association of allopregnanolone with perinatal depressive symptom trajectories.

Comparison of our results with previous findings is challenging, because the current study focused on the longitudinal pattern of depressive symptoms throughout the perinatal period. Most studies investigated perinatal depressive symptoms cross-sectionally, as

Table 1
Study sample characteristics.

	Overall (n=252)	Controls (n=161)	Antepartum depressive symptoms (n=31)	Postpartum-onset depressive symptoms (n=23)	Persistent depressive symptoms (n=37)	P-value ^a
Age, years, Median [Min, Max]	30.0 [19.0, 42.0]	30.0 [19.0, 42.0]	30.0 [20.0, 41.0]	31.0 [23.0, 41.0]	30.0 [21.0, 38.0]	0.4
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Pre-pregnancy BMI, kg/m2, Median [Min, Max]	23.0 [17.4, 42.5]	23.0 [18.2, 42.5]	23.1 [17.9, 40.2]	22.7 [20.0, 35.5]	22.5 [17.4, 33.7]	0.72
Missing, n (%)	1 (0.4)	1 (0.6)	0 (0)	0 (0)	0 (0)	
Education, n (%)						0.004
≤ 12 years	76 (30.2)	37 (23.0)	12 (38.7)	8 (34.8)	19 (51.4)	
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Parity, n (%)						0.13
Nullipara	137 (54.4)	95 (59.0)	16 (51.6)	12 (52.2)	14 (37.8)	
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
History of depression, n (%)						<0.001
Yes	63 (25)	26 (16.1)	11 (35.5)	5 (21.7)	21 (56.8)	
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Fear of childbirth, n (%)						0.003
Any fear	51 (20.2)	22 (13.7)	8 (25.8)	8 (34.8)	13 (35.1)	
Missing, n (%)	2 (0.8)	0 (0)	0 (0)	1 (4.3)	1 (2.7)	

Bold text signifies p value < 0.05

^a ANOVA, Kruskal Wallis or Chi-square Fisher's exact test, where appropriate

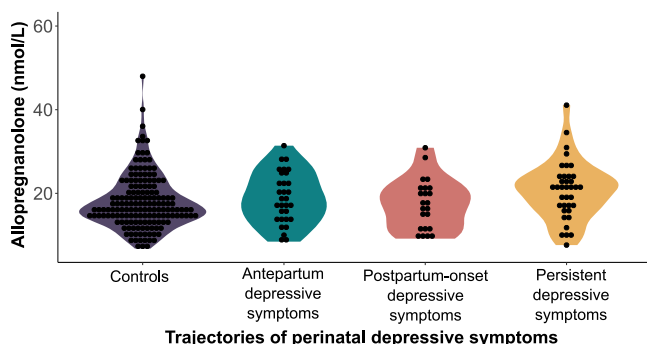


Fig. 2. Allopregnanolone levels and perinatal depressive symptom trajectories. Violin plots showing the allopregnanolone levels (nmol/L) of women with different perinatal depressive symptom trajectories. Kruskal-Wallis test was performed to test for differences in levels among the four groups, resulting to borderline significance (p=0.055).

antepartum depressive symptoms regardless of depressive symptoms during the postpartum period, or postpartum depressive symptoms regardless of depressive symptoms during pregnancy. Notably, previous studies have shown inconsistent results regarding the association between allopregnanolone and perinatal depression. Some studies have found that lower allopregnanolone levels during pregnancy were associated with antepartum depressive and anxiety symptoms (Crowley et al., 2016; Hellgren et al., 2014; Standeven, 2022). On the other hand, this association between mid-pregnancy allopregnanolone and concurrent depressive symptoms was not seen by Hellgren et al. (2017), whose data was overlapping with the present study. This previous finding of Hellgren et al. (2017) is only partly in line with the present study, where we also did not find an association between pregnancy allopregnanolone and APDS, but found higher allopregnanolone levels with antenatal depressive symptoms persisting into the postpartum period. The lack of association found by Hellgren et al. (2017) could be due to the heterogeneity of antepartum depressive symptoms when not taking into account the depressive symptom state during the postpartum period. This finding further emphasizes the importance of studying perinatal depressive symptom trajectories, which may have both distinct characteristics and distinct pathophysiology (Wikman et al., 2020).

In relation to postpartum depression, some studies have investigated

Table 2
Multinomial logistic regression-derived Odds Ratios (OR) and Confidence Intervals (CI) for the association of allopregnanolone with perinatal depressive symptom trajectories.

	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Antepartum depressive symptoms (N=31) vs controls (N=161)		
Allopregnanolone	1.02 (0.96–1.10)	1.02 (0.96–1.09)
Depression history, yes	2.73 (1.17–6.35)*	2.75 (1.07–6.16)*
Age	0.94 (0.86–1.03)	0.95 (0.85–1.05)
Pre-pregnancy BMI	1.04 (0.96–1.12)	1.03 (0.94–1.13)
Education, >12 years	0.47 (0.21–1.06) [#]	0.62 (0.23–1.63)
Parity, Primipara/Multipara	1.35 (0.62–2.92)	1.66 (0.70–3.92)
Gestational length at time of blood collection	1.06 (0.99–1.13)	1.06 (0.99–1.14)
Postpartum-onset depressive symptoms (N=23) vs controls (N=161)		
Allopregnanolone	0.99 (0.92–1.10)	0.99 (0.92–1.11)
Depression history, yes	1.38 (0.47–7.99)	1.41 (0.47–7.68)
Age	1.02 (0.93–1.04)	1.04 (0.93–1.14)
Pre-pregnancy BMI	1.05 (0.96–1.13)	1.04 (0.93–1.14)
Education, >12 years	0.56 (0.22–1.20)	0.55 (0.19–1.82)
Parity, Primipara/Multipara	1.57 (0.65–3.24)	1.40 (0.54–4.25)
Gestational length at time of blood collection	1.02 (0.96–1.13)	1.03 (0.96–1.14)
Persistent depressive symptoms (N=37) vs controls (N=161)		
Allopregnanolone	1.07 (1.01–1.12)*	1.07 (1.01–1.14)*
Depression history, yes	6.51 (3.01–14.08)***	6.16 (2.68–14.14)***
Age	0.96 (0.89–1.05)	1.00 (0.90–1.10)
Pre-pregnancy BMI	0.99 (0.91–1.08)	1.02 (0.93–1.12)
Education, >12 years	0.28 (0.14–0.59)***	0.30 (0.12–0.75)*
Parity, Primipara/Multipara	2.37 (1.13–4.93)	2.76 (1.14–6.69)
Gestational length at time of blood collection	1.02 (0.97–1.08)	1.02 (0.95–1.09)

* p-value ≤ 0.05, ** p-value ≤ 0.01, *** p-value ≤ 0.001

^a Adjusted for history of depression, age, pre-pregnancy BMI, education, parity, and gestational length at time of blood collection

their associations with mid-pregnancy allopregnanolone levels, while others with late pregnancy or postpartum levels. Osborne et al. (2017) showed that low mid-pregnancy allopregnanolone was associated with the development of postpartum depression in one study, but not significant in another, although with a similar trend (Osborne, 2019). For

Table 3

Multinomial logistic regression-derived Odds Ratios (OR) and Confidence Intervals (CI) with the effect modification of history of depression on the association of allopregnanolone with perinatal depressive symptom trajectories.

	Adjusted OR (95% CI) with interaction ^a
Antepartum depressive symptoms (N=31) vs controls (N=161)	
Allopregnanolone	1.06 (0.98–1.15)
Depression history, yes	16.11 (1.16–223.65)
Allopregnanolone* Depression history, yes	0.91 (0.80–1.04)
Postpartum-onset depressive symptoms (N=23) vs controls (N=161)	
Allopregnanolone	0.99 (0.90–1.16)
Depression history, yes	1.43 (0.06–391.54)
Allopregnanolone* Depression history, yes	1.00 (0.85–1.07)
Persistent depressive symptoms (N=37) vs controls (N=161)	
Allopregnanolone	1.07 (0.98–1.17)
Depression history, yes	7.45 (0.65–84.84)
Allopregnanolone* Depression history, yes	0.99 (0.88–1.11)

^a Adjusted for age, pre-pregnancy BMI, education, parity, and gestational length at time of blood collection

late pregnancy allopregnanolone, [Hellgren et al. \(2014\)](#) did not find an association between allopregnanolone and postpartum depression. However, other studies have shown that higher allopregnanolone levels in late pregnancy or postpartum were associated with postpartum depression ([Deligiannidis et al., 2020](#); [Standeven, 2022](#)), somewhat similar to the results of the current study.

The studies mentioned above were based on measurement at one single timepoint. On the other hand, [Standeven et al. \(2022\)](#) measured allopregnanolone, mood and anxiety symptoms during the second and third trimester, and six weeks postpartum, showing that the association between allopregnanolone and depressive symptoms varies across the perinatal period. They found that higher allopregnanolone levels at six weeks postpartum was associated with worse concurrent anxiety and mood symptom scores ([Standeven, 2022](#)). However, higher mid-pregnancy allopregnanolone was associated with better mood and anxiety scores during the second trimester, and no association was found between allopregnanolone and mood symptoms during the third trimester ([Standeven, 2022](#)). This is partly opposite to our finding, where higher allopregnanolone level in the second trimester was associated with higher odds for persistent depressive symptoms. The discrepancies in results of previous studies may be due to the timing the allopregnanolone levels were measured, as well as when the depressive symptoms were noted. Moreover, another reason that may influence to the varying results among the studies are the methods used to measure allopregnanolone. Our study utilized celite chromatography purification and radioimmunoassay. Some have used enzyme-linked immunosorbent assay ([Osborne et al., 2017](#); [Standeven, 2022](#)) and others liquid chromatography-tandem mass spectrometry ([Deligiannidis et al., 2016](#)) or gas chromatography-mass spectrometry ([Crowley et al., 2016](#)).

Another factor that may contribute to inconsistencies in findings on the association of allopregnanolone and perinatal depressive symptoms is history of depression. In a study by [Klatzkin et al. \(2006\)](#), blunted allopregnanolone response to stress was found among individuals with history of depression compared to those without history of depression. [Osborne et al. \(2019\)](#) noted that the association of second trimester allopregnanolone with postpartum depression differed among individuals with and without history of depression. Those with history of depression had lower allopregnanolone and higher depression scores, while those without history of depression showed the opposite ([Osborne et al., 2019](#)). In the current study, as the interaction term of history of depression with allopregnanolone was not significant, we did not proceed with relevant stratifications. Considering the limited sample size of the current study, further studies with larger sample sizes and multiple

timepoint measures are needed to explore these differences further.

In general, the treatment for postpartum depression follows guidelines used for treatment of major depression disorder. SSRIs have been the first line of medical treatment for postpartum depression ([Frieder et al., 2019](#)). In 2019, an intravenous aqueous preparation of allopregnanolone called brexanolone has been approved specifically to treat postpartum depression. Current data shows that treatment with brexanolone rapidly improves depressive symptoms ([Epperson et al., 2023](#)). In 2023, zuranolone, a heterocyclic analogue of allopregnanolone, was also approved as an oral alternative to treat postpartum depression ([US Food and Drug Administration, 2023](#)). Our findings encourage future studies on the efficacy of brexanolone and zuranolone in relation to different onset-based trajectories, as we identify differences in levels of allopregnanolone between these trajectories. Hence, treatment with brexanolone and zuranolone might theoretically be even more efficacious in specific perinatal depressive symptom trajectories.

The underpinnings behind our findings remain to be elucidated. One possible explanation is that the higher levels of allopregnanolone at mid-pregnancy may be an indicator for reduced sensitivity of the GABA-A receptor ([Maguire and Mody, 2008](#); [Standeven, 2022](#)) in the group with persistent depressive symptoms. This might either be a consequence of, or in its turn, result of an increased risk for depression. Mechanisms for depression development in the APDS or PPDS group might thus be different from the persistent group, where allopregnanolone might have a more crucial role. It is known that these trajectories have different characteristics. For example, individuals with APDS and persistent depressive symptoms were associated with younger age, lower education attainment, and unemployment, while nulliparity, pregnancy complications and negative delivery experiences were associated with PPDS ([Wikman et al., 2020](#)). Individuals with persistent depressive symptoms were also more often foreign-born and overweight ([Wikman et al., 2020](#)). Despite controlling for many of these factors in the present study, residual confounding might still be an issue. For example, there might be other differences between the trajectory groups; genetic polymorphisms of the enzymes that convert progesterone to allopregnanolone, such as *AKRIC2*, may also play a role in balancing mood during pregnancy. [Hellgren et al. \(2017\)](#) have found that minor allele homozygotes of the *AKRIC2* rs1937863 had lower depression scores. Expression of GABA receptor subunits also vary by pregnancy state and individuals, and may further contribute to the complexity of the picture ([Bhandage et al., 2015](#)).

The findings of this study should be taken in light of its strengths and limitations. As a longitudinal study, the EPDS was employed at several timepoints during pregnancy and postpartum. This allowed considering different perinatal depressive symptoms trajectories, enabling to distinguish the depression pattern throughout the perinatal period. Data on possible confounders were available at the individual level and thus controlled for; nevertheless, the possibility for residual confounding exists. Although the sample size of the current study was reasonably large compared to previous studies, the study might not have had enough power to properly explore the moderation effect of history of depression nor to investigate subgroups of the different trajectories (e.g. antepartum depressive symptoms include those who were depressed at the time of blood collection (mid-pregnancy) as well as those who developed depressive symptoms in late pregnancy). Hence, further studies are warranted in larger sample sizes to validate our findings. The individuals in the cohort were also mostly highly educated and of Swedish background. Hence, results cannot be readily generalizable and should be interpreted with this in mind. Moreover, allopregnanolone was measured at one timepoint only. A longitudinal sampling of allopregnanolone would allow investigation of the variation of the hormone throughout the perinatal period and its association with perinatal depressive symptom trajectories.

In conclusion, higher allopregnanolone levels at mid-pregnancy were associated with persistent depressive symptoms during the perinatal period. Further studies on the understanding of the role of

allopregnanolone in shaping mood during the perinatal period, especially in relation to different trajectories and subgroups, would be critical in elucidating the complex pathophysiology of perinatal depression.

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CRediT authorship contribution statement

Richelle Duque Björvang: Writing – original draft, Visualization, Methodology, Formal analysis. **Ylva Walldén:** Writing – original draft, Formal analysis. **Emma Fransson:** Resources, Investigation, Data curation. **Erika Comasco:** Writing – review & editing, Supervision. **Inger Sundström-Poromaa:** Resources, Investigation, Funding acquisition, Conceptualization. **Alkistis Skalkidou:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data utilized in this study are available from the corresponding author upon reasonable request. Due to privacy and ethical considerations, the data are not publicly available.

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