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The role of central serotonergic markers and estradiol changes in perinatal mental health

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Abstract

Objective: Women have an increased risk for mental distress and depressive symptoms in relation to pregnancy and birth. The serotonin transporter (SERT) may be involved in the emergence of depressive symptoms postpartum and during other sex-hormone transitions. It may be associated with cerebrospinal fluid (CSF) levels of the main serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA). In 100 healthy pregnant women, who were scheduled to deliver by cesarean section (C-section), we evaluated 5-HIAA and estradiol contributions to mental distress 5 weeks postpartum.

Methods: Eighty-two women completed the study. CSF collected at C-section was analyzed for 5-HIAA, with high performance liquid chromatography. Serum estradiol concentrations were quantified by liquid chromatography tandem mass spectrometry before C-section and postpartum. Postpartum mental distress was evaluated with the Edinburgh Postnatal Depression Scale (EPDS). Associations between EPDS, 5-HIAA, and Δestradiol were evaluated in linear regression models adjusted for age, parity and SERT genotype.

Results: Higher levels of postpartum mental distress symptoms were negatively associated with a large decrease in estradiol concentrations ($\beta_{\Delta E2} = 0.73$, $p = 0.007$) and, on a trend level, positively associated with high antepartum 5-HIAA levels ($\beta_{5\text{-HIAA}} = 0.002$, $p = 0.06$).

Conclusion: In a cohort of healthy pregnant women, postpartum mental distress was higher in women with high antepartum 5-HIAA (trend) and lower in women with a large perinatal estradiol decrease. We speculate that high antepartum 5-HIAA is a proxy of SERT levels, that carry over to the postpartum period and convey susceptibility to mental distress. In healthy women, the postpartum return to lower estradiol concentrations may promote mental well-being.

KEYWORDS

estradiol, mental health, postpartum, pregnancy, serotonin

1 | INTRODUCTION

Peripartum mental distress symptoms, such as anxiety, sleep disturbances or "postpartum blues," are common (about 40%, 40%, and 50%, respectively) and predispose to manifest depressive episodes.[1–6] About 10%–15% of new mothers develop a depressive episode with onset during pregnancy or up to 4 weeks postpartum, known as perinatal depression (PND; DSM-V criteria).[7–9] Intriguingly, the risk for a severe depression is particularly high within the first 4–8 weeks postpartum,[10] which extend the DSM-V diagnostic criteria. This transition from pregnancy to early postpartum is characterized by dramatic sex-steroid fluctuations, especially for the main estrogen during the reproductive years: estradiol (E2). Estradiol levels increase steadily to very high levels during pregnancy, but are reduced to hypogonadal levels within days after delivery and, in breastfeeding women, remain low for months.[11,12] However, most studies have not been able to link absolute levels of estrogens directly to PND or mental distress, although some studies point toward an underlying sensitivity to estrogens at a genomic level.[13–22] Intriguingly, E2 potently affects key features of the serotonin (5-HT) signaling system and induce expression of the main regulator of synaptic 5-HT: the serotonin transporter (SERT).[23–28] Some studies,[29,30] but not all,[31] suggest that the risk for postpartum depression is increased in women with high-expressing SERT genotypes in a gene dose-dependent manner, that is, women who carry two copies of the long allele of the serotonin-transporter-linked promotor region (5-HTTLPR), have a higher risk for depression. Evidence from a pharmacological sex-hormone manipulation risk model for depression indicate that a large net decrease in E2 may trigger depressive symptoms in *interaction* with higher brain SERT availability.[32] In humans in vivo SERT imaging in pregnancy is not possible because of exposure to radiation, however some evidence can be provided from proxy markers of SERT induction in cerebrospinal fluid (CSF) and from studies in the immediate postpartum. CSF studies in humans and rodents, suggest that levels of the main serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in CSF may serve as a proxy for SERT

Significant outcomes

- A large decrease in estradiol from late in pregnancy to week five postpartum is associated with fewer postpartum mental distress symptoms in healthy women.
- High cerebrospinal fluid levels of the main serotonin metabolite, 5-HIAA, in pregnancy tend to be associated with more postpartum mental distress symptoms in healthy women.

Limitations

- Low level of clinically relevant symptoms limits generalizability to clinical cohorts at high risk or with manifest depressive episodes
- Missing data reduce statistical power
- Longitudinal changes were quantified for estradiol, but serotonergic markers and postpartum depressive symptoms were quantified cross-sectionally

expression, as long-term reductions in SERT are associated with decreased levels of 5-HIAA in CSF.[33–40] Also, monoamine oxidase type A (MAO-A) metabolizes the monoaminergic neurotransmitters, including 5-HT, and responds to E2.[41] Thus, 5-HIAA may also serve as a marker for MAO-A activity late in pregnancy. Intriguingly, human studies have shown that MAO-A may be important in postpartum mood regulation.[42,43] Currently, it remains unclear how pregnancy and the related increase in estrogens affects 5-HIAA concentrations in CSF and if 5-HIAA contribute to perinatal mental distress.[44,45]

Thus, we do not know if the dramatic changes in E2 across the perinatal period contribute to mental distress in interaction with 5-HTTLPR, at least in some women, through a transiently compromised serotonin signaling. Under the assumption that induction of SERT increases 5-HIAA, we hypothesized that high 5-HIAA antepartum (late pregnancy) and a large decrease in E2 would be associated with more mental distress symptoms in postpartum women and that 5-HIAA and E2 would interact in inducing mental distress. Further, that the association between change in E2 and mental distress would be more pronounced in women homozygous for the high-expressing 5-HTTLPR variant.

1.1 | Aims of the study

In a longitudinal study of healthy pregnant women, we assessed if antepartum levels of 5-HIAA in CSF, 5-HTTLPR status and perinatal change in E2 contributed to mental distress or subclinical depressive symptoms 5 weeks postpartum.

2 | MATERIALS AND METHODS

2.1 | Participants

For the purpose of obtaining CSF for antepartum neurotransmitter quantification, only women, who were scheduled for an elective cesarean section (C-section), were eligible for the study. Thus, 100 healthy pregnant women in gestational week 38–42 and scheduled to deliver by C-section were recruited from obstetric departments at Copenhagen University Hospital, Denmark (Rigshospitalet and Herlev Hospital), for a study approved by the local ethics committee in the Capital Region of Denmark (protocol H-18029563). All participants gave written informed consent.

Inclusion criteria: age 18–40 years, planned C-section because of fetal breech position, previous C-section, previous myomectomy, obstructing fibroid, previous rupture of the anal sphincter, and uncomplicated placenta previa. Exclusion criteria: Previous or current severe somatic or psychiatric illness, pregestational Body Mass Index (BMI) below 18 or above 35, severe postpartum hemorrhage, infant with severe illness, use of medications that affect the central nervous system (including antidepressants), substance abuse, non-fluent in Danish, severe learning disabilities, and impaired vision or hearing. Screening included questionnaires on mental well-being, medical history and blood tests. One third of the participants were included during the Severe Acute Respiratory Syndrome Coronavirus-2 pandemic of 2020 (COVID-19).

Out of the 100 women, four gave birth vaginally before the planned C-section and were thus excluded from the rest of the study. For the remaining 96, 14 did not complete follow-up because of: infants with severe illness ($n = 3$), personal reasons ($n = 2$), and lost contact with the research team ($n = 9$). Out of the 82 who completed, 19 had missing data at follow-up because of: COVID-19 related cancelations of blood samples,[5] enrollment under an older protocol version,[1] and non-compliance with questionnaires.[13] Quantification of CSF markers failed for two participants and genotyping for one participant for technical reasons. Thus, complete data were available for 60. An overview of the study design can be found in Figure 1.

2.2 | Questionnaires and interviews

Our main outcome was postpartum subclinical depressive symptoms evaluated with the Danish validated version of the Edinburgh Postnatal Depression Scale (EPDS; range: [0–30], screening cut-off for possible depression: >11).[46] For antepartum screening of participants and to evaluate longitudinal mood, sleep and anxiety symptoms, we used the Major Depressive Inventory (MDI; range: [0–50]),[47] the state subscale of the State Trait Anxiety Inventory (STAI; range: [20–80]),[48] and Pittsburg Sleep Quality Index (PSQI; range: [0–21]).[49] Participants completed MDI, STAI and PSQI shortly before the C-section for screening purposes (median: 1 day, range [0; 15], one C-section was postponed 2 weeks), and 5 weeks postpartum (median: 35 days, range: [16; 64], one participant came in late because of severe depression). EPDS was administered at week five postpartum (median: 35 days, range: [16; 64]). At week five postpartum, we used the Mini-International Neuropsychiatric Interview (M.I.N.I.) to rule out any undiagnosed severe psychiatric disorders.[50]

2.3 | Estrogen analyses

Serum samples for estrogen analyses were collected before C-section (median: 0 days, range: [0; 2]) and

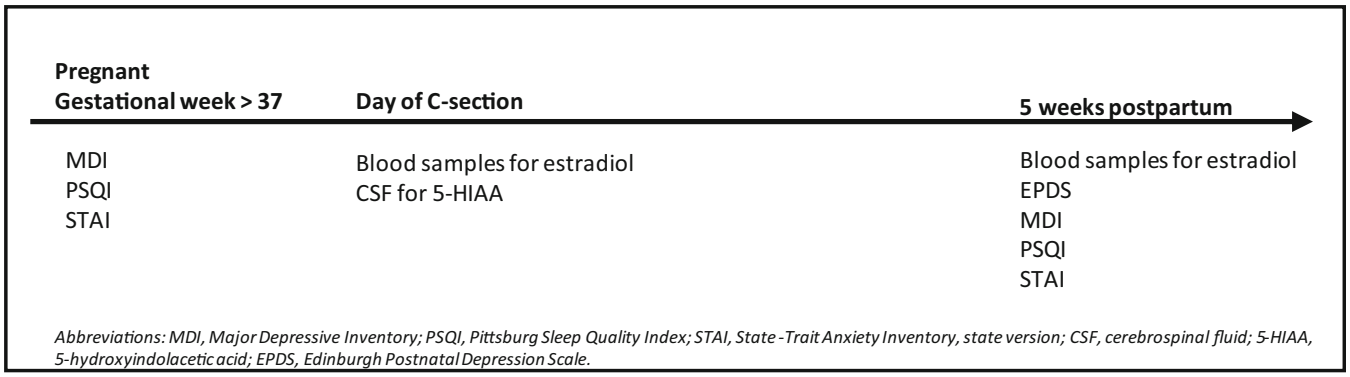

FIGURE 1 Overview of study design

repeated 5 weeks postpartum (median: 35 days, range: [15; 66]). Serum samples were transferred to −20°C immediately after centrifugation and collection. Concentrations of estrone (E1), E2 and estriol (E3) were measured simultaneously in serum samples by liquid chromatography tandem mass spectrometry (LC–MS/MS) with prior liquid–liquid extraction, as described in Frederiksen et al.[51] In short, estrogens were purified from 200 µl thawed serum sample by liquid–liquid extraction using heptane/ethyl acetate followed by analysis on a Dionex UltiMate 3000 UHPLC system with integrated Transcend TLX TurboFlow sample preparation system, coupled with triple quadrupole mass spectrometer (TSQ Quantiva) from Thermo Scientific controlled by Aria MX 2.2 and Xcalibur 4.0 software. The TurboFlow- LC–MS/MS system was equipped with a loading Cyclone-P TurboFlow column followed by an analytical Kinetex® Phenyl-Hexyl column, for further sample extraction and chromatographic separation of the estrogens. The tandem mass spectrometry system was equipped with a heated electrospray ionization source running in negative mode. The total duration time was 5.50 min.

2.4 | CSF for neurotransmitter analyses

Cerebrospinal fluid (CSF) was collected as a part of the anesthetic procedures for the C-section. Briefly, anesthesiologists collected 0.5–1 ml of CSF during spinal anesthesia, which was immediately transferred to dry ice and subsequently stored at −80°C.

CSF concentrations of 5-hydroxyindoleacetic (5-HIAA), serotonin (5-HT), norepinephrine (NE), 3-methoxy-4-hydroxyphenylglycol (MHPG), and homovanillic acid (HVA) were assayed by high-performance liquid chromatography, as detailed in Weikop et al.[52] Briefly, 10 µl of the samples was injected onto a Prodigy C18 column (100 × 2 mm I.D., 3-µm particle size, YMC Europe, Schermbeck, Germany) at flow rate of 0.15 ml/min. The mobile phase consisted of 55 mM sodium acetate, 1 mM octanesulfonic acid, 0.1 mM Na2EDTA and 7% Acetonitrile, adjusted to pH 3.7 with 0.1 M acetic acid, and was degassed using an on-line degasser. For the electrochemical detection, we used an amperometric detector (Antec Decade from Antec, Leiden, The Netherlands) with a glassy carbon electrode set at 0.7 V, with an Ag/AgCl as reference electrode. The output was recorded on a computer program system CSW (Data Apex, Prague, The Czech Republic), which was used to calculate the peak areas.

2.5 | 5-HTTLPR genotyping

Analysis was performed on whole blood samples drawn prior to C-section and stored at −20°C. Genotyping was done in line with previous studies, with some modifications.[53] DNA was extracted from blood with a Chemagic DNA Blood 4 k Kit H24 and a Chemagic 360-D instrument (PerkinElmer, Waltham, Massachusetts) according to the manufacturer's guidelines. 5-HTTLPR (SLC6A4; rs774676466) genotyping was performed using PCR amplification with the forward primer 5′-TAATGTCCC-TACTGCAGCCC-3′ and reverse primer 5′-GGGACT-GAGCTGGACAACC-3′. PCR was performed in a total volume of 15 µl containing DNase/RNase-free distilled water, 100 ng DNA, 0.6 µmol/L of each primer (TAG Copenhagen, Denmark), 30 µmol/L dNTP (Qiagen, Hilden, Germany), commercial buffer and Taq DNA-polymerase (VWR, Radnor, Pennsylvania), and 12% (vol/vol) sucrose (Sigma-Aldrich®, Merck KGaA, Darmstadt, Germany). The PCR temperature cycling conditions were as follows: initial denaturation for 70 min at 98°C, followed by 40 cycles: denaturation at 96°C for 30 s, primer annealing at 68°C for 30 s, and primer extension at 72°C for 30 s. The last cycle was followed by a final extension step for 7 min at 72°C. The PCR product

was loaded on a 2% agarose gel in 1xTBE, and the fragments were separated by gel electrophoresis at 100 V for 30 min. Gels were stained with SYBRTM Safe DNA Gel Stain (Thermo Fisher Scientific, Waltham, Massachusetts) and visualized with a ChemiDoc MP imaging system (Bio-Rad, Hercules, California). The genotypes were identified as LL 493 bp, LS 450 bp and 493 bp, and SS 450 bp. For statistical analyses, we dichotomized the participants into long allele homozygotes (LL) or carriers of the short allele (S-carrier).

2.6 | Statistical analyses

Prior to analyses, E2 was log-transformed (base = 2) to ensure normally distributed data. The ante- to postpartum change in E2 (ΔE2) concentration was derived as postpartum minus antepartum log-transformed concentrations.

Since EPDS only is validated for postpartum use in Danish, we did not collect antepartum EPDS and thus could not control postpartum scores for antepartum scores. We maintained this structure for all measures of mental distress, as antepartum scores may have been biased by the high stress situation when collected at the day of the C-section. Only one woman developed significant depressive symptoms, thus we were not able to describe the trajectory for severely depressed cases and we excluded her data from postpartum statistical analyses.

To ease interpretation of the planned analyses, linear mixed-effects models with an unstructured covariance matrix were used to determine if mental distress varied across the whole perinatal period.

To test our hypotheses, we used multiple linear regression models, all conducted in R (http://cran.r-project.org/). Planned hypothesis-driven analyses included associations between 5-HIAA or ΔE2 and postpartum EPDS score, alone or in interaction, and 5-HTTLPR genotype by ΔE2 interaction effects on mental distress. Explorative analysis followed the same structure for simplicity.

Because of missing data, we evaluated the main effects in models where *either* 5-HIAA *or* ΔE2 were included. The models were adjusted for known risk factors for PND, that is, age, parity, 5-HTTLPR genotype.[9,29,54–57] Log-likelihood-ratio test indicated that parity and 5-HTTLPR were relevant covariates, but not age or number of days between birth and postpartum follow-up. We kept age in the model, because of an uneven age distribution between primiparous women and women who were parous at inclusion. Interaction effects between 5-HIAA and ΔE2 were evaluated in complete cases only. To provide the full picture, we also report the contributions of 5-HIAA and ΔE2 mutually adjusted, in complete case data. To estimate how the missing data may have affected the results, we applied an inverse probability of censoring weights approach to the main model, see S1. Our main hypothesis concerned 5-HIAA and E2, but the applied analysis methods provided data for serotonin, norepinephrine, and 3-methoxy-4-hydroxyphenylglycol homovanillic acid, and for the estrogens estrone (E1) and estriol (E3). Exploratory models for these markers can be found in S1.

Exploratory analyses were conducted for PSQI and STAI, with the same structure as for EPDS, to evaluate what factors that may have contributed to the observed EPDS scores. We included a similar analysis for MDI, as it was the only depressive score collected across the peripartum. Further, we evaluated if 5-HTTLPR genotype interacted with ΔE2 in the association with mental distress. In a set of explorative analyses, we evaluated if age and parity interacted with either ΔE2 or 5-HIAA. Further, we explored if postpartum E2 mapped better on to EPDS than ΔE2, that is, when disregarding baseline, and if associations between 5-HIAA and mental distress scores were established already in pregnancy.

In S1, we report exploratory analyses conducted to evaluate potential bias, including: baseline characteristics of drop-outs; differences between primiparous and multiparous women; and variations in the timing of postpartum E2 measurements. A planned supplementary analysis of antepartum associations between E2 and 5-HIAA is also reported here.

Since the main analyses are based on a priori hypotheses, p values are not adjusted for multiple comparisons. $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Demographics, antepartum characteristics, and mental distress across the peripartum period

Study population characteristics prior to delivery for the 96 women that underwent C-section are described in Table 1, note that at follow-up the number of participants with available data varied. Forty-four women underwent C-section because of fetal breech position; 39 because of previous C-section; 2 because of placenta previa; 7 because of previous rupture of anal sphincter; and 4 because of a uterine fibroid or previous myomectomy. Mean age was 33.8 years. The majority of the participants were Caucasians, but three were of Asian descent. Out of the included participants, eight had a psychiatric history of mild anxiety or depressive symptoms, including three cases of previous postpartum depression. Further two had previously experienced intrauterine fetal death or neonatal death. Two women had a possible thromboembolic episode in pregnancy and received

TABLE 1 Antepartum characteristics, neurotransmitter concentrations, peripartum mental distress and peripartum estradiol concentrations

	Antepartum ($n = 96$)	Week five postpartum ($n = 82$)
Demographics		
Parity at inclusion (0/≥1 child)	38/57[a]	–
Age Mean (SD)/Median (range)	34 (3)/34 (23; 41)	–
5-HTTLPR genotype LL versus S-carrier	28/67[b]	–
Sex of child (Male/Female)	52/44	–
Estradiol and 5-HIAA		
Estradiol (E2) in pmol/L Mean (SD)	79,387 (26630)	81 (152)[c]
Change in E2 (pmol/L) Mean (SD)	–	−78,585 (27949)
5-HIAA *in CSF in* fmol/10 µl Mean (SD)	1164.86 (366.71)[d]	–
Mental distress		
EPDS Mean (SD)	–	4.06 (4.22)[e]
MDI Mean (SD)	8.12 (5.25)	6.45 (6.07)[e]
STAI[f] Mean (SD)	32.51 (9.02)	27.17 (8.85)[e]
PSQI[g] Mean (SD)	6.74 (3.2)	7.07 (3)[e]

Abbreviations: MDI, Major Depressive Inventory; PSQI, Pittsburg Sleep Quality Index; STAI, State Trait Anxiety Inventory.
[a] $n = 95$, parity not logged for one dropout.
[b] $n = 95$, analysis failed for one woman.
[c] $n = 76$.
[d] $n = 94$, analysis failed for two women.
[e] $n = 69$.
[f] $n = 92$.
[g] $n = 86$.

subcutaneous injections of heparin, two women had a history of migraine, two had congenital urogenital anomalies, and one had a thyroid disease in remission. Most participants were breastfeeding, but two had stopped at follow-up. Scores of postpartum depressive symptoms were clearly within the normal spectrum.[46,58] As expected, anxiety and sleep disturbances were, on average, close to or above suggested cut-offs (STAI: 34–40; PSQI: 5).[49,59]

Linear mixed-effects models showed that, on average, MDI score decreased significantly across the antepartum to postpartum transition (estimate: -2.09, 95% CI: [−3.33; −0.84], $p = 0.001$). STAI scores followed a pattern similar to MDI (estimate: -5.6, 95% CI:[−7.36; −3.85], $p < 0.001$). PSQI score did not change significantly from ante- to postpartum (estimate: 0.17, 95% CI:[−0.55; 0.88], $p = 0.65$).

3.2 | Postpartum mental distress and associations with 5-HIAA, change in E2 and 5-HTTLPR status

ΔE2 was associated with EPDS at week five postpartum, that is, a small decrease (small negative value) was associated with more symptoms than a large decrease (large negative value; $\beta_{\Delta E2} = 0.73$, 95% CI: [0.21; 1.25], $p = 0.007$; Figure 2A), in a model not adjusted for 5-HIAA. We found no significant interactions between

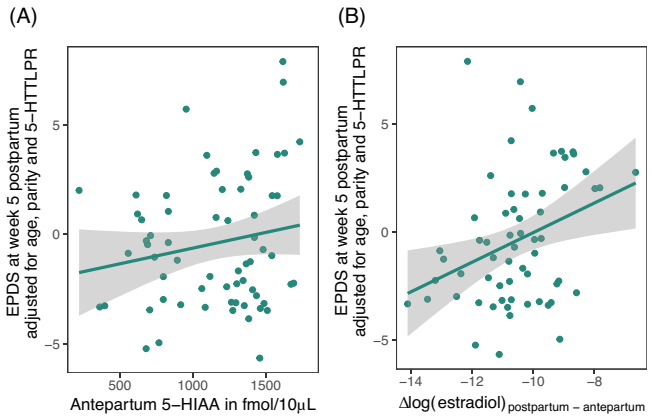

FIGURE 2 (A) Association between 5-HIAA and Edinburgh Postnatal Depression Scale (EPDS) residuals after adjusting for age, parity and 5-HTTLPR genotype status. Linear regression line has 95% CI. (B) Association between ΔE2 and EPDS residuals after adjusting for age, parity and 5-HTTLPR genotype status. Linear regression line has 95% CI depicted in gray shade. Note that residuals and not EPDS scores are on the y-axis

ΔE2 and 5-HTTLPR ($\beta_{\Delta E2\text{-by-5-HTTLPR}} = -0.81$, 95% CI: [−2.12; 0.51], $p = 0.22$).

5-HIAA was positively associated with depressive symptoms, that is, EPDS score, on a trend level ($\beta_{5\text{-HIAA}} = 0.002$, 95% CI: $[-7 \times 10^{-5}; 0.004]$, $p = 0.06$; Figure 2B), in a model not controlled for ΔE2.

When both ΔE2 and 5-HIAA were included in the model, that is, when we used only complete case data ($n = 59$), the effects sizes were similar however less significant ($\beta_{\Delta E2} = 0.63$, 95% CI: [0.09; 1.16], $p = 0.02$; $\beta_{5\text{-HIAA}} = 0.002$, 95% CI: [−0.0004; 0.004], $p = 0.12$). 5-HIAA and ΔE2 did not interact with each other in their association with postpartum mental distress ($\beta_{5\text{-HIAA-by-}\Delta E2} = -0.0002$, 95% CI: [−0.001; 0.001], $p = 0.79$).

Supplementary analyses of postpartum mental distress evaluated with MDI, STAI, and PSQI is detailed in Table 2 and supported that 5-HIAA and ΔE2 were associated with subclinical depressive symptoms and anxiety, but that sleep disturbances might be more related to ΔE2.

3.3 | Postpartum E2, age and parity in postpartum mental distress

Exploratory analyses showed that higher postpartum E2 may have been associated with more distress, in line with the results reported for ΔE2 ($\beta_{E2\ \text{postpartum}}$: 0.81, 95% CI: [0.26; 1.37], $p = 0.005$).

Further, ΔE2 may have interacted with parity, such that a large decrease in E2 was associated with lower EPDS score in multiparous women, compared with primiparous women, who had no association between EPDS and ΔE2 ($\beta_{\Delta E2\text{-by-parity}} = 1.46$, 95% CI:[−2.58; −0.33], $p = 0.01$). We found no potential interactions between ΔE2 and age ($\beta_{\Delta E2\text{-by-age}} = -0.02$, 95% CI: [−0.17; 0.14], $p = 0.84$).

Nor did 5-HIAA seem to interact with age ($\beta_{5\text{-HIAA-by-age}} = 0.0003$, 95% CI: [−0.0003; 0.0008], $p = 0.36$) or parity ($\beta_{5\text{-HIAA-by-parity}} = -0.002$, 95% CI: [−0.006; 0.002], $p = 0.32$).

Adjusted for both 5-HIAA and ΔE2, primiparous women had significantly more symptoms on EPDS relative to multiparous women ($\beta_{\text{parity}} = 1.66$, [0.03; 3.29], $p = 0.05$), but neither age ($\beta_{\text{age}} = 0.03$, [−0.18; 0.25], $p = 0.76$) nor 5-HTTLPR were significantly associated with EPDS ($\beta_{5\text{-HTTLPR}} = 1.44$, [−0.41; 3.29], $p = 0.12$).

3.4 | 5-HIAA and antepartum mental distress

Exploratory analyses indicated that 5-HIAA may have been positively associated with anxiety in pregnancy (STAI; $\beta_{5\text{-HIAA}}$: 0.006, 95% CI: [0.001; 0.01], $p = 0.02$), but not depressive symptoms (MDI; $\beta_{5\text{-HIAA:}}$ 0.001, 95% CI: [−0.002; 0.01], $p = 0.36$) or sleep (PSQI; $\beta_{5\text{-HIAA:}}$ 0.0004, 95% CI: [−0.002; 0.002], $p = 0.69$).

4 | DISCUSSION

In a longitudinal cohort study, we evaluated serotonergic and estrogenic contributions to maternal mental distress across the ante- to postpartum transition. High antepartum 5-HIAA was associated with the emergence of subclinical depressive symptoms 5 weeks postpartum, on a trend level. A large decrease in E2 from late in pregnancy to postpartum was associated with less depressive symptoms postpartum, this association may have been more pronounced in multiparous women. Contrary to what we hypothesized, we observed no significant interaction between E2 and 5-HIAA or 5-HTTLPR.

As hypothesized, 5-HIAA late in pregnancy was positively associated with the emergence of subclinical depressive symptoms and anxiety symptoms postpartum, although only on a trend level (for EPDS). Antepartum, 5-HIAA seemed to be associated with anxiety symptoms, but not sleep or mood, in exploratory analyses. Combined, these results points toward an underlying vulnerability in the serotonin system, which may induce some symptoms in pregnancy, that can be more fully developed into broader subclinical symptoms of depression by the ante- to postpartum transition. Thus, anxiety in pregnancy may be a marker for serotonergic changes that increase susceptibility to postpartum distress. In line with

	MDI		STAI		PSQI	
Covariate	β (95% CI)	p[a]	β (95% CI)	p[a]	β (95% CI)	p[a]
5-HIAA	0.003 (0.0006; 0.006)	0.02	0.004 (8×10^{-5}; 0.008)	0.05	0.002 (−0.002; 0.002)	0.81
ΔE2	0.77 (0.07; 1.46)	0.03	0.21 (0.08; 2.34)	0.04	0.71 (0.27; 1.14)	0.002

TABLE 2 5-HIAA and ΔE2 associations with postpartum anxiety, sleep disturbances and mood, mutually adjusted and controlled for 5-HTTLPR, parity and age

Abbreviations: MDI, Major Depressive Inventory; PSQI, Pittsburg Sleep Quality Index; STAI, State Trait Anxiety Inventory.
[a]Unadjusted for multiple comparisons.

this, other studies have also found that anxiety in pregnancy increase the risk for postpartum depression.[3,60,61] As detailed in Dataset S1, this underlying vulnerability was not likely to depend on antepartum E2 or 5-HTTLPR, as neither mapped on to 5-HIAA levels in pregnancy. Contrary to our expectations, 5-HTTLPR played no role in postpartum mood. This does not align with evidence from studies that report an increased risk for postpartum depression in women with high-expressing variants of 5-HTTLPR.[29,30] However, these studies were conducted in clinical cohorts. Therefore, in our healthy cohort, associations between 5-HTTLPR and postpartum mental distress may not be present or be too small to detect. This is supported by the model selection process, which indicated that inclusion of 5-HTTLPR improved model fit. Direct quantification of brain SERT also points toward an association between high SERT and mental distress in response to short-term sex-hormone fluctuations.[32] Under the assumption that 5-HIAA is elevated as a consequence of pregnancy-induced SERT expression, that would be in line with our results.[24,28,33–35,40,62] That is, increased SERT levels in pregnancy, observable as a high 5-HIAA in CSF, may carry over to the postpartum period and trigger mental distress postpartum. Perhaps this reflects that, in some women, SERT does not adapt (or down-regulate) appropriately in response to the high E2 levels late in pregnancy. This may be similar to the reduced flexibility in SERT regulation observed in individuals who develop a depression in response to seasonal changes.[63] On the other hand, previous studies reported the same or higher 5-HIAA CSF concentrations in healthy pregnant women, compared with non-pregnant women, suggesting that high E2 in pregnancy not normally leads to reductions in 5-HIAA.[44,45] Notably, neither study reports postpartum health, nor do they provide longitudinal data. Further, our sample is larger than previous studies and we find a lower mean 5-HIAA and a wider range in concentrations, suggesting a greater variability than these studies capture.

5-HIAA is also regulated by MAO-A deamination of 5-HT, which E2 may inhibit.[41] Human studies suggests that brain MAO-A distribution is higher early postpartum, where sex-steroid levels are low, and normalize in healthy postpartum women, but not in women with postpartum mood symptoms.[42,43] However, as detailed in Dataset S1, antepartum E2 potentially mapped on to norepinephrine, but not 5-HIAA or 5-HT, suggesting that 5-HIAA levels not mainly were driven by E2 induction of MAO-A. Similarly, we show in Dataset S1 that none of the other monoamines are associated with EPDS score, suggesting that neither MAO-A or -B are responsible for the association between E2 and 5-HIAA.

Thus, we speculate that high 5-HIAA mainly reflects pregnancy induced high SERT levels, which may carry over from antepartum to the early postpartum period and convey susceptibility to mental distress at least up to 5 weeks postpartum. The increased 5-HIAA may reflect a failure to adapt SERT levels in response to the high hormone concentrations late in pregnancy. Early effects of increased 5-HIAA leading to anxiety symptoms may be established already late in pregnancy and develop further across the ante-to postpartum transition.

As expected, change in E2 across the ante- to postpartum transition was associated with postpartum mental distress, however the direction was opposite of what we hypothesized, that is, a large change was associated with less postpartum distress. Thus, our results contrast findings from our sex-hormone manipulation model.[32] The apparent disparities may be due to differences in the length and magnitude of the E2 concentration changes, as noted by others.[28,64] For instance, hormone replacement during perimenopause has beneficial effects on hippocampal volume and depressive mood, but not when administered well beyond menopause.[65–68] Similarly, high endogenous estrogens increase hippocampal volume during the menstrual cycle, while the long-term estrogen exposure during pregnancy is associated with a decrease in hippocampal volume.[69,70] Thus, the long and high amplitude stimulation in pregnancy may promote different mechanisms than a brief hormone manipulation. Supplementary analyses indicated that the association between estradiol change and mental distress, may have

been driven by postpartum E2 concentrations. Thus, healthy women seem to respond beneficially to a sudden downregulation, while women who develop a depression postpartum may not. This strongly support that estrogen sensitivity may be a risk marker for postpartum depression as indicated by recent genomic studies.[19–21,71] This may explain the difference between the current study and those who report that lower estradiol levels are associated with depression.[15,18] At the same time, it indicates that the rapid E2 changes may be important for healthy postpartum adaptations. In line with this, antepartum E2 and working memory is positively associated in non-depressed women, while depressed women do not benefit in terms of cognitive performance from the high E2 in pregnancy, suggesting that the same mechanisms that provoke depressive symptoms, may provide an advantage in healthy women.[72] Importantly, our results differ from the numerous studies that have found no association between postpartum mood symptoms and absolute E2 levels or E2 changes.[14,16,20,22] However, there are multiple methodological differences that may explain this, such as sample size, degree of clinically relevant symptoms, absolute E2 levels versus changes and sensitivity of the quantification method. In the current study, we quantified E2 with high sensitivity methods that are able to accurately estimate the very low and very high E2 concentrations postpartum and in pregnancy.[51] Thus, we may have captured associations previously missed by others. Of note, Klier et al.[14] found higher early postpartum estrogen levels in healthy pregnant women who developed a depression postpartum. An older study also reported that higher postpartum E2 might map on to mental distress.[17] This is in accordance with our results where a high postpartum E2/smaller ante- to postpartum decrease in E2 was associated with more mental distress. Exploratory analyses indicated that this association was strong in multiparous women, independent of age, but not in primiparous women. Thus, previous pregnancy and birth may be an advantage for subsequent pregnancies, perhaps through altered hormone sensitivity or changes in brain structure.[69,71] This observation should, however, be interpreted with care, since the analysis not was adjusted for multiple comparisons. As detailed in Dataset S1, there were no absolute differences between multiparous or primiparous women to explain this, but parity-associated differences in E2 dynamics or steroid metabolism may have played a role. However, primiparity was also an independent risk factor for postpartum mental distress, in line with in other studies.[9,54,60,73] Thus, primiparous women may simply be more sensitive to estradiol changes, for instance because they lack maternal experience and the first birth is a more life-changing event.

We speculate that the highly hormone stimulated state late pregnancy promotes perinatal mental wellbeing in most women, but that such protective mechanisms may be disrupted in women, who develop postpartum mental distress or depression. These protective effects seem to be enhanced by previous maternal experience.

Only few women developed symptoms, compared with what we would expect from population studies.[7] We observed a pattern reported by other studies, where depressive symptoms, in particular anxiety, are more prevalent late in pregnancy, compared with the postpartum period.[14,74,75] To some extent, short term distress because of worry about the C-section may explain this, as emphasized by the rapid decline in anxiety symptoms postpartum.[76] Sleep disturbances were stable across the whole perinatal period.

The most important limitation of this study is the absence of clinical levels of depressive symptoms, which may limit the reproducibility to women at risk for PND. This may be a consequence of the study design, which inherently has some selection bias toward robust individuals: C-section on low-stress indications, inclusion of a high proportion of multiparous women, exclusion of women with current diagnosed psychiatric illness and high average socioeconomic status at our inclusion sites. Participants reported increased focus on their own symptoms as a consequence of participation, but also a greater sense of safety. How this may have affected mental distress in the participants is unclear. Although approximately one third of the data were collected during the severe acute respiratory syndrome coronavirus-2 pandemic of 2020, we did not observe an increase in distress scores or drop-out in this period (not reported). This is probably because women who consented to the study during in this period were more robust. However, we also included women with a higher risk of PND because of previous perinatal and non-perinatal depression, anxiety and adverse life-events.[3,77–79] For logistic reasons, we were not able to conduct a M.I.N.I. at inclusion, which is a limitation of the study.

Also, we were challenged by missing data, which, according to supplementary analyses, may have resulted in a lower statistical significance for the 5-HIAA association with mental distress. With 60 complete cases we may have missed a small to medium effects size, corresponding to a Cohen's f^2 of 0.17 or lower, in our association analyses. We do not know if the 14 women who left the study before follow-up may have developed a depression, but as shown in Dataset S1, they suffered more from sleep disturbances in pregnancy, which is a known risk factor for depression.[22,80] Further, we have no information on the longitudinal changes in 5-HIAA and EPDS, for ethical and practical reasons. However, by studying these phenomena in healthy women, we may have unmasked associations that would have been obscured by other risk

factors for PND. Perhaps that is why we were able to detect a signal within a narrow range of distress scores. Notably, EPDS is a self-reported mental distress scale used for screening purposes, not a diagnostic tool. Further, EPDS scores may be increased in relation to other conditions than depression, for example, anxiety. We did not screen for use of hormonal contraceptives in the full cohort, as women in Denmark not are offered hormonal contraceptives before week eight postpartum. The women who were no longer breastfeeding were asked specifically for this and did not report any use. To conclude, in a cohort of healthy pregnant women, mental distress symptoms 5 week postpartum were higher in women with high antepartum levels of 5-HIAA in CSF (trend) and lower in women who experienced a large perinatal decrease in E2. The associations for 5-HIAA and E2 were independent. 5-HIAA may be associated with pregnancy induced SERT levels, a phenomenon that that carry over to the early postpartum period and may convey susceptibility to mental distress. Postpartum return to lower hormone levels seem to protect mental wellbeing in healthy women.

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CONFLICT OF INTEREST

VGF declares that she has received honorarium as a consultant for Sage Therapeutics and lectures for Lundbeck Pharma A/S. None of the other authors declare any potential conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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