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Associations between estrogen and progesterone, the kynurenine pathway, and inflammation in the post-partum

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Abstract

Background: Depression during and after pregnancy is common, affecting at least 15% of women. Features of depression in pregnancy range from mild symptoms of disrupted mood and interest to severe depression and suicidal behavior. Previous studies suggest hormone- and immune dysregulations might contribute to post-partum depression, but consistent evidence is lacking.

Methods: A total of 163 women were included in the study in the post-partum. Peri-partum depression (PPD) was diagnosed using SCID interviews and depressive symptoms were quantified using the Edinburgh Perinatal Depression Rating Scale (EPDS), retrospectively long-term, as well as acutely. Plasma estrogen, progesterone, pro- and anti-inflammatory cytokines and kynurenine metabolites were measured in the post-partum.

Results: Higher estrogen and progesterone in the post-partum were linked to more severe depressive symptoms over pregnancy. In the post-partum, estrogen was positively correlated with

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Author Statement

Author individual contribution:

Qiong Sha: data analysis and interpretation of data, drafting the article.

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Madhavi Nagalla: clinical data acquisition, drafting the initial article.

Sarah Keaton: sample analysis, critical revision of the manuscript.

LeAnn Smart: clinical conduct, recruitment and assessment of patients, critical revision of the manuscript.

Richard Leach: study concept and design, overseeing clinical conduct, critical revision of the manuscript.

Lena Brundin: study concept and design, data analysis, review of statistical analysis, drafting the initial manuscript, funding acquisition.

Declarations of interest

None

the pro-inflammatory cytokine IL-6 and negatively correlated with kynurenine and picolinic acid. Conversely, progesterone was negatively correlated with IL-1β, and several metabolites in the kynurenine pathway, including quinolinic acid.

Limitations: Associative study design, did not attempt to assess causality. Did not adjust hormone levels for medication effects.

Conclusions: Our study suggests that higher sex hormones in the post-partum are linked to depression severity over pregnancy. Estrogen was coupled with a pro-inflammatory profile and neurotoxic kynurenine metabolites, whereas progesterone was linked to an anti-inflammatory profile in the post-partum.

Keywords

Estrogen; progesterone; Post-partum; Depression; Cytokine; Kynurenine

Introduction

The etiopathogenesis of perinatal mood disorders including PPD is complex and includes psychosocial, endocrine, immunological and genetic factors. Given the timing of symptom onset, and frequent exacerbation in the post-partum period, altered levels of reproductive hormones are suggested to contribute to the pathogenesis of depression in this period (Schiller et al., 2015). However, the mechanisms by which sex hormones influence mood in the post-partum are incompletely understood.

Cytokines have profound effects on brain neurotransmission, leading to the behavioral and emotional manifestations of sickness behavior. When the effects of cytokines in the brain become more chronic, this is denoted “cytokine-induced depression.” This type of depression is common, for example, during interferon-based treatments (Raison et al., 2006). Moreover, in many patients with primary psychiatric depression, cytokines are also elevated in blood (Dowlati et al., 2010). Inflammation leads to down-stream metabolic changes, including an upregulation of the kynurenine pathway, which breaks down tryptophan. Increased activation of the pathway generates several neuroactive compounds, including quinolinic acid (QUIN), an agonist of the NMDA-receptor; and kynurenic acid (KYNA), which is an antagonist of the same receptor. Inflammation, together with altered glutamate transmission in the brain, is thought to play a key role in the generation of depression and suicidality. The purpose of this study was to assess whether hormone levels are linked to the production of kynurenine metabolites, cytokines and depressive symptoms in the post-partum.

Material and Methods

2.1 Study design

This study was approved by the Michigan State University Institutional Review Board (IRB), East Uansing, Michigan, USA, with collateral approval from Spectrum Health IRB and Van Andel Research Institute IRB, both in Grand Rapids, Michigan, USA. Participants signed an informed consent at enrollment, which occurred between 2014 and 2016 in the

Mother and Baby program at Pine Rest Christian Mental Health Services and the Obstetrics and Gynecology clinics of Spectrum Health (both Grand Rapids, Michigan). The Mother and Baby day program is a partial hospitalization program for women experiencing significant symptoms of depression and suicidality. A total of 163 women completed the study visit at a mean of 8 weeks post-delivery (n=87 from Pine Rest, n=76 from Spectrum Health). Exclusion criteria were described previously (Achtyes et al., 2019).

2.2 Clinical evaluation

Depressive symptoms were assessed using EPDS (Cox et al., 1987), over the past 7 days (acute) or retrospectively (long-term) over several months. The Spectrum Health cohort we assessed depressive symptoms since the third trimester, while the Pine Rest cohort was retrospectively assessed for the severity of depressive symptom over the entire pregnancy. PPD diagnosis was set by a SCID interview using DSM5 criteria (American Psychiatric Association, 2013). All study subjects were assessed for height, weight, temperature, blood pressure and pulse. Subjects were allowed to use psychotropic medications during the study. These medications included: selective serotonin reuptake inhibitors (SSRIs, n=60), serotonin and noradrenaline reuptake inhibitors (SNRIs, n=12), neuroleptics (n=20), anti-epileptics (n=12), benzodiazepines (n=21), bupropion (n=12), lithium (n=5) and tricyclic antidepressants (n=2).

2.3 Blood sampling and biological analysis

Blood samples were drawn by venipuncture between 9 am and noon. Samples were placed on ice immediately and spun down to plasma, then aliquoted and stored at −80°C. Estradiol and progesterone were measured at the Spectrum Health accredited clinical laboratory in Grand Rapids, Michigan. Cobas Estradiol III and Progesterone III kits (Roche, ON, Canada) were used to assess the absolute levels in plasma. The detectable range was 0.05-60 ng/mL for progesterone and 5-3000 pg/mL for estradiol. All samples were within the detection range.

Cytokines were measured by MesoScale Discovery platform (Meso Scale Diagnostics, NJ, USA) and run on a MESO QuickPlex SQ 120. Tryptophan, kynurenine, serotonin, and KYNA were analyzed using high-performance liquid chromatography (UPLC), and combined with tandem mass spectrometry (UPLC-MS/MS). Gas chromatography-mass spectrometry (GC-MS) was used to measure QUIN. The detailed methods and absolute levels of cytokines and kynurenine metabolites in this cohort have been published previously (Achtyes et al., 2019).

2.4 Statistical analysis

All statistical analyses were conducted using RStudio (1.3.1506). Non-parametrical T-tests were used to compare estrogen and progesterone levels between two groups. Ordinal regression was used to assess the effect of sex hormones on depressive symptoms after adjusting for age and Body Mass Index (BMI). A Principle Component Analysis (PCA) was used to extract information from the 15 biomarkers and their derivatives. The first 5 principle components (PCs) that explained over 60% of the total variances were used in the simple linear regression between estrogen and PCs after adjusting for age and BMI. A robust

regression after Box-Cox transformation was used to assess the association between progesterone and the top 5 PCs after adjusting for age and BMI. Spearman's and Pearson's correlation analyses were used for non-parametrical and parametrical data, respectively, to evaluate the associations between the biomarkers and the PCs, and between the biomarkers and sex hormones. Data were natural log transformed when necessary to meet model assumptions. $P \leq 0.05$ set to define statistical significance.

3. Results

3.1 Cohort characteristics

163 women were assessed, of which 87 fulfilled the clinical criteria for PPD. For demographic information see Table 1. Estrogen correlated with progesterone (n=163, rho=0.446; $p<0.001$). The mean ± SD estrogen in the breastfeeding group was 29.12 ± 51.7 pg/mL (n=84) versus the non-breastfeeding group 71.71 ± 150.7 pg/mL (n=79). The mean ± SD progesterone level in the breastfeeding group was 0.16 ± 0.3 pg/mL (n=84) versus the non-breastfeeding group 1.53 ± 4.9 pg/mL (n=79) (Mann-Whitney U-test, both $p<0.001$). Age did not significantly impact estrogen or progesterone (estrogen: r=−0.14. $p=0.07$: progesterone: rho=−0.05. $p=0.53$). BMI was positively associated with estrogen (r=0.18. $p=0.022$) but not progesterone levels (rho=0.061. $p=0.437$). There were no differences in the absolute levels of sex hormones between women with and without a diagnosis of PPD in the post-partum (Table 1). Both long-term EPDS- and acute EPDS scores for the PPD group were significantly higher than the healthy group (T-test, both $p<0.001$). Alcohol or nicotine use did not impact EPDS scores or hormone levels (data not shown).

3.2 Sex hormone's association with acute and long-term depressive symptoms

Estrogen and progesterone correlated positively with total long-term EPDS score in the Spectrum Health cohort (estimated=0.003. $p=0.036$ and estimated=0.088, $p=0.025$ respectively, n=76). Progesterone was also positively correlated with acute depressive symptoms in the Spectrum Health cohort (estimate=0.088, $p=0.021$. n=76), while there was a trend for estrogen (estimated=0.002. $p=0.054$, n=76). No significant associations were detected between sex hormones and depressive symptoms (either long-term or acute) in the Pine Rest cohort (n=87).

3.3 Correlation between hormone levels and cytokines

Estrogen was negatively correlated with PC2 (estimate=−0.144, $p=0.025$). which was dominated by kynurenic acid, picolinic acid and kynurenine. PC2 was significantly correlated with all the top 10 contributors. Correlation analysis showed estrogen was negatively correlated with picolinic acid and kynurenine. Estrogen was positively correlated with IL-6, although IL-6 was not a significant contributor to PC2 (Tab. 2). Progesterone was negatively associated with PC1 (estimate=−0.268, $p=0.001$) and positively associated with PC5 (estimate=0.148, $p=0.005$). PC1 was dominated by quinolinic acid, kynurenine/tryptophan ratio, quinolinic/picolinic acid ratio and kynurenine. PC5 was dominated by IL-6, nicotinamide and IL-2. Progesterone was negatively associated with quinolinic acid, kynurenine/tryptophan ratio and kynurenine, which were all significantly correlated with PC1. Progesterone was also negatively associated with IL-1β, which was significantly

correlated with PC1 although less influential. Progesterone was negatively correlated with nicotinamide, which was the 2nd largest contributor to PC5 (Tab. 2).

4. Discussion

In this study, we investigated the relationship between the sex hormones estrogen and progesterone, cytokines and tryptophan metabolites as well as depressive symptoms in the post-partum. We found that estrogen was linked to pro-inflammatory changes, including increased IL-6 and a decrease of kynurenine and picolinic acid. Progesterone, however, was correlated negatively with the inflammatory factor IL-1β, and several metabolites in the kynurenine pathway including quinolinic acid and nicotinamide. We did not find hormone differences between patients with and without a diagnosis of PPD in the post-partum. However, both sex hormones were positively associated with depressive symptoms, in particular the long-term depressive symptoms, assessed retrospectively at the post-partum.

Previous studies have shown divergent results in the relation between sex hormones and depression. Some studies detected changes in hormone levels that contributed to PPD (Bloch et al., 2000; Meltzer-Brody et al., 2018), while others failed to detect such interactions (Heidrich et al., 1994; O'Hara et al., 1991). The different results could potentially be due to the broad definition of PPD, defined as "major depressive episodes with onset during pregnancy and up to four weeks after delivery" (American Psychiatric Association, 2013), while the degree of depressive symptoms can be variable after this diagnosis has been set. In our study, we found that using the EPDS (a scale variable, measuring the severity of depression) might be more informative in terms of detecting direct biological relationships.

The effects of estrogen and progesterone on the kynurenine pathway have been studied in women taking contraceptives, and led to an increased excretion of pathway metabolites, including kynurenine and QUIN. These changes were caused by the estrogen component in the contraceptives, since women who were administered progesterone alone did not secrete increased levels of these metabolites (Jayawickrama et al., 2017). Instead, progesterone has been shown to decrease QUIN levels and increase neuroprotective KYNA levels in cultures of human macrophages (de Bie et al., 2016). These findings align with the associations observed in our clinical cohorts. We found estrogen to be negatively associated with picolinic acid, while progesterone was negatively correlated with quinolinic acid and nicotinamide. This suggested that estrogen might be contributing to the activity of the quinolinic acid metabolic branch while progesterone might favor the picolinic acid-producing branch.

Sex hormones could also influence depressive symptoms through modulation of immunological factors. Indeed, we observed that IL-6 levels were positively correlated with estrogen. We have previously observed that increased levels of the pro-inflammatory cytokines IL-6 and IL-8 were associated with depression in this cohort (Achtyes et al., 2019). On the other hand, the effects of estrogen on the immune system are complex, as estrogen deprivation might enhance IL-6 production in postmenopausal women (Rachon et al., 2002). Here, we also observed a negative correlation between IL-1β and progesterone. Progesterone has previously demonstrated anti-inflammatory effects in models of neuronal

damage and infection (Brotfain et al., 2016), possibly by modulating progesterone receptors on microglia and astrocytes (Johann and Beyer, 2013).

Limitations of this study include that we did not attempt to reveal causal effects, and we could not control for medication effects, future analyses that include longitudinal data across pregnancy and the post-partum period with repeated measurements of depression severity, hormone, cytokine and kynurenine metabolites are warranted.

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Highlights

- Higher plasma estrogen and progesterone are associated with depressive symptoms in women
- post-partum Elevated estrogen is linked to inflammation and neurotoxic kynurenine metabolites
- Progesterone is negatively associated with inflammatory and neurotoxic kynurenine branch
- Post-partum hormones might trigger depression by affecting kynurenine metabolism

Table 1.

Patient demographics.

	PPD n=87	Non-PPD n=58
Age (mean ± SD)	26.7 ± 5.2	28 ± 6.3
BMI (mean ± SD)	29.6 ± 7.1	30.6 ± 8
Total EPDS long-term (mean ± SD)	14.1 ± 7.9	5.8 ±4.6
Total EPDS acute (mean ± SD)	18.5 ±4.7	4.2 ± 3.6
Progesterone (median, IQR[1]) pg/mL	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Estrogen (median, IQR) pg/mL	21 (6–42)	24 (4–59.8)
Employed percentage (%)	63.2	60.3
Annual household income (%)		
Under $15,000	12.6	27.6
$15,000-$34,000	21.8	32.8
$34,000-$70,000	35.6	15.5
$70,000-$120,000	21.8	12.1
Over $120,000	2.3	10.3
Highest education (%)		
Junior high/middle school	0	0
Some high school	9.2	10.3
High school	12.6	29.3
Technical/trade/allied health training, degree or certification	6.9	3.4
Some college	40.2	34.5
Bachelor’s degree or higher	31.0	22.4
Marital status[2] (%)		
Single	35.6	43.1
In a relationship	64.4	55.2

IQR: Interquartile range.

Marital status: Single including unmarried, divorced, separated or widowed. In relation including married or living with someone as if married or having a partner but not living together.

Table 2.

Biomarker contribution to -and correlation with- PCs; Correlation between biomarkers and sex hormones (n=163).

biomarker	Contribution to PC2	PC2		Estrogen		biomarker	Contribution to PC1	PC1		Contribution to PC5	PC5		Progesterone	
		Pearson's r	P	Pearson's r	P			Pearson's r	P		Pearson's r	P	Spearman's rho	P
KYNA	**33.41**	**0.88**	**< 0.001*** **	−0.09	0.280	**QUIN**	**19.33**	**0.87**	**< 0.001*** **	0.05	−0.02	0.770	**−0.20**	**0.009****
PICO	**19.80**	**0.68**	**< 0.001*** **	**−0.21**	**0.007****	**rKT**	**15.64**	**0.78**	**< 0.001*** **	**6.26**	**−0.27**	**< 0.001*** **	**−0.25**	**0.001****
KYN	**12.71**	**0.54**	**<0.001*** **	**−0.17**	**0.029***	**rQaPa**	**14.8**	**0.76**	**< 0.001*** **	1.01	−0.11	0.168	−0.1	0.223
rQaKa	**11.74**	**−0.52**	**<0.001*** **	0.02	0.847	**KYN**	**13.73**	**0.73**	**< 0.001*** **	**2.87**	**−0.18**	**0.019***	**−0.26**	**<0.001*** **
TRY	**8.93**	**0.46**	**<0.001*** **	−0.03	0.733	**TNF-α**	**12.72**	**0.71**	**< 0.001*** **	**6.12**	**0.27**	**< 0.001*** **	−0.08	0.325
QUIN	**5.29**	**0.35**	**<0.001*** **	−0.08	0.320	**rQaKa**	**11.3**	**0.67**	**< 0.001*** **	0.01	−0.01	0.900	−0.12	0.136
rQaPa	**3.05**	**−0.27**	**<0.001*** **	0.10	0.184	**IL-2**	**4.01**	**0.40**	**< 0.001*** **	**11.65**	**0.37**	**< 0.001*** **	−0.05	0.498
IL-1β	**1.85**	**−0.21**	**0.008****	−0.06	0.443	**IL-10**	**3.6**	**0.38**	**< 0.001*** **	**10.50**	**0.35**	**< 0.001*** **	−0.02	0.772
IL-10	**1.30**	**−0.17**	**0.026***	−0.1	0.206	**IL-1β**	**1.59**	**0.25**	**0.00132****	1.81	−0.15	0.064	**−0.16**	**0.041***
rKT	**1.07**	**0.16**	**0.044***	−0.13	0.092	**IL-6**	**1.26**	**0.22**	**0.004132****	**37.57**	**0.66**	**< 0.001*** **	−0.02	0.809
IL-8	0.40	−0.1	0.222	−0.09	0.252	**TRY**	**0.89**	**−0.19**	**0.01696***	**2.04**	**0.15**	**0.049**	0.03	0.750
TNF-α	0.20	0.07	0.383	−0.04	0.572	**NICO**	0.55	0.15	0.06178	**13.56**	**−0.40**	**< 0.001*** **	**−0.21**	**0.007****
IL-2	0.17	−0.06	0.421	0.07	0.387	PICO	0.36	−0.12	0.1288	1.13	0.11	0.145	−0.06	0.417
IL-6	0.04	−0.03	0.700	**0.18**	**0.022***	**IL-8**	0.2	0.09	0.267	**5.44**	**−0.25**	**0.001****	−0.07	0.344
NICO	0.02	−0.02	0.812	−0.11	0.156	KYNA	0.00	0.00	0.9886	0.01	−0.01	0.914	−0.02	0.811

Abbreviations: KYNA: kynurenic acid; PICO: picolinic acid: KYN: kynurenine; rQaKa: quinolinic acid/kynurenic acid ratio; TRY: tryptophan; QUIN: quinolinic acid; rQaPa: quinolinic acid/picolinic acid ratio; rKT: kynurenine/tryptophan ratio; NICO: nicotinamide. Significant correlations between biomarkers and hormone levels were highlighted light blue.