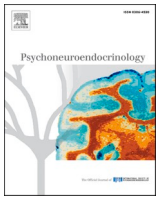
Psychoneuroendocrinology 161 (2024) 106921

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



# Perinatal hair cortisol concentrations linked to psychological distress and unpredicted birth complications

J.A. Madigan [a,b], Sara F. Waters [c], Maria A. Gartstein [b,d], Jennifer A. Mattera [b,d], Christopher P. Connolly [e], Erica J. Crespi [a,b,*]

[a] School of Biological Sciences, Washington State University, Pullman, WA 99164, USA
[b] Center for Reproductive Biology, Washington State University, Pullman, WA 99164, USA
[c] Department of Human Development, Washington State University, Vancouver, WA 99164, USA
[d] Department of Psychology, Washington State University, Pullman, WA 99164, USA
[e] Department of Kinesiology and Educational Psychology, Washington State University, Pullman, WA 99164, USA

ARTICLE INFO

*Keywords:*
Pregnancy
Cortisol
Perceived stress
Anxiety
Birth outcomes

ABSTRACT

Maternal well-being and stress during the perinatal period have been hypothesized to influence birth outcomes and the postnatal development of offspring. In the present study, we explored whether hair cortisol concentration (HCC) was related to symptoms of psychological distress during the perinatal period and with unpredicted birth complications (UBCs). Surveys measuring symptoms of perceived stress, state/trait anxiety, and depression were collected from 53 participants (mean age = 31.1, SD = 4.04; 83% Caucasian, 17% other races) during the third trimester and again at two and six months after birth, 24.5% of which reported UBCs. In a subset of participants, we measured HCC in hair samples collected during the third trimester (27–39 weeks) and six months after birth. Compared to participants reporting normal births, those reporting UBCs had significantly elevated composite stress, anxiety, and depression (SAD) scores two months after birth, but scores decreased by six months postpartum. During the third trimester, HCC was positively associated with reported SAD scores, and HCC was elevated in participants reporting birth complications. Logistic regression showed HCC, but not SAD scores, predicted UBCs ($p$ = 0.023, pseudo $R^2$= 19.7%). Repeated measures MANOVA showed HCC varied over the perinatal period depending on both SAD scores reported at two months postpartum and the experience of UBCs; but when SAD scores reported at six months postpartum were included in the model, the association between HCC and SAD scores and the influence of UBCs was diminished. Although generalizability is limited by our relatively small, homogeneous sample, findings support a positive association between reported psychological distress and HCC during pregnancy and at two months postpartum. We also report a novel finding that chronically elevated cortisol concentrations during pregnancy were related to the risk of UBCs and remain elevated through the early postpartum period, suggesting the importance of monitoring both psychological distress and HCC during the perinatal period.

## 1. Introduction

While circulating cortisol increases two to four fold during pregnancy to support maternal energetic demands, fetal organ development, and preparation for parturition (Carr et al., 1981; Challis et al., 2001; D'Anna-Hernandez et al., 2011; Hillhouse and Grammatopoulos, 2002; Jensen et al., 2005), excessively elevated cortisol concentrations during pregnancy have been associated with adverse outcomes such as preterm birth (Bandoli et al., 2018; Phocas et al., 1990), and low birth weight (Bolten et al., 2011; Fan et al., 2018; Jensen et al., 2002). In the context of the Developmental Origins of Health and Disease (DOHaD; Barker and Clark, 1997) framework, elevated cortisol exposure during fetal or neonatal development has organizational effects on the brain and neuroendocrine systems that can influence infant temperament (Duthie and Reynolds, 2013; Grey et al., 2013), regulation of fetal HPA stress response (Herman et al., 2016; Irwin et al., 2021), and later-life health consequences (Seckl and Meaney, 2004). Atypical cortisol patterns during pregnancy, may also have postpartum health consequences for

* Corresponding author at: School of Biological Sciences, Washington State University, Pullman, WA 99164, USA.
*E-mail address:* erica.crespi@wsu.edu (E.J. Crespi).

https://doi.org/10.1016/j.psyneuen.2023.106921
Received 12 January 2023; Received in revised form 25 November 2023; Accepted 5 December 2023
Available online 9 December 2023

mothers, such as postpartum depression (Caparros-Gonzalez et al., 2017). However, more research is needed to understand the factors contributing to elevated cortisol concentrations during pregnancy, as well as the connection between cortisol concentrations and the risk of adverse birth outcomes (Bandoli et al., 2018; Bolten et al., 2011; D'Anna-Hernandez et al., 2011). Given that adverse birth outcomes occur in approximately 50% of U.S. pregnancies (Hamilton et al., 2021), understanding risk factors that precede birth complications is imperative to improve maternal-infant health.

It has been proposed that circulating cortisol concentrations are associated with psychological distress during pregnancy (reviewed in Khoury et al., 2023; Mustonen et al., 2018, 2019), which may be due to the reciprocal interactions between brain neurochemistry and the HPA axis (Rein et al., 2019). This widely theorized and not yet well understood relationship between psychological distress and maternal cortisol concentrations is likely to be particularly complex during pregnancy, as the placenta and fetus also regulate and produce corticosteroids to different extents across gestation (Mustonen et al., 2019). Recent reviews have shown some inconsistencies in the related evidence, but comparisons among studies are also complicated by reliance on different bio-samples (e.g., plasma, saliva, hair), gestational age, and measures of psychological distress (Kim et al., 2020; Mustonen et al., 2018). Measures of perceived stress, anxiety, and depression during the perinatal period have been associated with experiencing adverse birth outcomes or birth complications (Chen et al., 2022; Cheng et al., 2021; Dowse et al., 2020; Duffy et al., 2018), but cortisol concentrations during pregnancy were not measured in these studies. Thus, there is a need for research relating psychological distress to cortisol concentrations that considers moderating factors such as the experience of birth complications.

It is also important to improve our understanding of the relationship between cortisol concentrations and psychological distress after birth. While studies have shown that maternal cortisol concentrations are reduced at 12 weeks postpartum compared to late pregnancy (Conde et al., 2021; Stickel et al., 2021), others find sustained elevation at this time (D'Anna-Hernandez et al., 2011). Chronic perinatal elevation of cortisol concentrations has been positively related to postpartum depression in some studies (Caparros-Gonzalez et al., 2017), but negatively associated in others (Scharlau et al., 2018). Adverse birth experiences have been associated with a higher frequency of psychological distress, specifically post-traumatic stress disorder (Furuta et al., 2016; Schwab et al., 2012) and postpartum depression (Guintivano et al., 2018), but little is known about how these outcomes relate to postpartum hair cortisol concentrations. Chronically elevated glucocorticoids can have detrimental effects on women's health, including hypertension (Bautista et al., 2019), mood disorders (Young, 2004), obesity, and hyperglycemia (reviewed in Tirabassi et al., 2014). Elevated maternal postpartum cortisol concentrations have been shown to influence infant cortisol concentrations through maternal-child interaction, in a sense transmitting stress through social exchanges (reviewed in Waters et al., 2014), or via the breastfeeding biological pathway (Grey et al., 2013; Irwin et al., 2021), thereby altering the neuroendocrine stress axis and temperament.

Using hair cortisol concentrations (HCC) as a measure of circulating cortisol during pregnancy has numerous advantages that could help elucidate relationships between cortisol and psychological distress (Khoury et al., 2023; Kim et al., 2020; Mustonen et al., 2018). Because it is an integrated measure of circulating cortisol over a period of time (e.g., 1 cm = 1 month of growth; Wennig, 2000), it is not sensitive to variation like hours of collection or proximate factors (activity or food intake), as is the case for plasma or salivary sampling. Sampling a small amount of hair is easy and non-invasive and can be collected at home or by a practitioner, facilitating the ease of repeated sampling. However, recent reviews (Kim et al., 2020; Mustonen et al., 2018) and meta-analysis (Khoury et al., 2023) of studies specifically relating psychological distress to HCCs over the perinatal period found relationships varied. However, multiple investigations identified such relationships, and were more likely to do so during the third trimester than during prior gestational periods or after birth. Because most published studies are cross-sectional in design, and self-reported measures of psychological distress may be more transient than HCC, Khoury et al. (2023) articulated the need for longitudinal studies to understand how relationships between cortisol and psychological distress vary within individuals across the perinatal period. Likewise, studies that observe how the relationship between psychological distress and HCC varies before or after birth complications would benefit from longitudinal study designs.

In this study, our overarching goal was to explore the relationships between measures of psychological distress and HCC over the perinatal period, and whether this relationship depends on the experience of unpredicted birth complications (UBCs), in a sample of pregnant people with generally healthy pregnancies. We used a longitudinal study design to measure psychological distress and HCC across the perinatal period in a sample of 53 participants, 24.5% of whom reported UBCs. Our first aim was to determine if experiencing UBCs influenced the trajectory of self-reported psychological distress over the perinatal period. Based on Furuta et al. (2016) and Guintivano et al. (2018), we predicted that UBCs would increase psychological distress for affected women. Secondly, we aimed to quantify the relationship between HCC and psychological distress during pregnancy, considering UBCs as a moderator of this relationship. We hypothesized that psychological distress and HCC would show significant associations during pregnancy, consistent with the findings of the Khoury et al. (2023) meta-analysis, although they found the association to be small and non-significant without including moderating factors. Given the prospective nature of this study, our third aim was to determine whether prenatal psychological distress or HCC were reliable predictors of UBCs. Given the novel nature of this aim, related analyses are largely exploratory; however, we expected maternal stress/internalizing symptoms and/or HCC to emerge as risk factors for UBCs. Lastly, we aimed to determine whether the relationships between psychological distress and HCC varied from pregnancy to six months postpartum, and whether experiencing UBCs influenced HCC over that period. Based on the meta-analysis by Khoury et al. (2023), we predicted psychological distress and HCC would co-vary more strongly during pregnancy than during the early postpartum period. If psychological distress and HPA activity are reciprocally regulated and related to mechanisms associated with parturition, then symptoms of psychological distress and HCC may be elevated during pregnancy in participants experiencing birth complications, although the experience of birth complications may only influence psychological distress and HCC during the early postpartum period.

## 2. Methods

### 2.1. Study Design

A non-clinical sample of pregnant individuals in their third trimester was recruited between 2018 and 2020 from Southwest Washington and the Eastern Washington/Idaho areas. In order to meet eligibility criteria, participants needed to be 18 years or older, fluent in English, and could not be diagnosed with heart disease or taking cardiac medications, as a more extensive aspect of the study included measures of heart rate variability. Interested individuals who had a pregnancy considered high-risk by their physician (e.g., diagnosis of gestational diabetes or pre-eclampsia) were excluded from the study. The study protocol and informed consent were approved by the Washington State University Institutional Review Board (Washington State University IRB #15441). Written informed consent was obtained from each participant prior to study enrollment. Demographic, anthropometric, and self-reported measures were collected at three time points: during the third trimester, and two and six months postpartum. Hair samples were collected in the third trimester and six months postpartum as integrative

measures of circulating cortisol concentration.

### 2.2. Participants

An initial cohort of 61 participants was recruited for the study. Those who did not submit hair samples for at least one time point and did not indicate if they experienced unpredicted birth complications were excluded from the study, resulting in 53 participants (UBC No: $n = 40$, Yes: $n = 13$). Birth complications reported included: failure to progress (23%), unplanned c-section (15%), placenta complication (15%), hemorrhage (8%), problematic in-utero position and/or umbilical issues (31%), birth < 37 weeks (15%), among other complications (38%, some participants reported more than one complication). For approximately 36% of the participants, this was their first pregnancy. Participants were primarily White and married, with a Bachelor's degree and a median income of $30,000-$60,000 (see Table 1 for complete demographic information and pregnancy-related information).

### 2.3. Measurement of psychological distress throughout the perinatal period

Participants completed surveys measuring symptoms of psychological stress during the third trimester of pregnancy (31.6 weeks ± 2.99 SD, did not differ between UBC groups; see Table 1) and at two and six months postpartum. The Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) is a 10-item self-report measure of depressive symptoms. Total scores range from 0 to 30, with higher values reflecting greater symptom severity. The State-Trait Anxiety Inventory (STAI, Spielberger, 1983) is comprised of two 20-item self-report scales measuring state (STAI-S) and trait (STAI-T) anxiety, respectively. Scores for each scale range from 20 to 80, with higher scores indicative of more severe symptomatology. The Perceived Stress Scale (PSS, Cohen et al., 1983) is a 10-item self-report measure assessing the degree to which respondents view situations occurring over the past month as stressful. Total scores range from 0 to 40, with higher scores indicating greater perceived stress. These measures have been validated with perinatal samples and have been found to demonstrate strong psychometric properties (Cohen et al., 1983; Cox et al., 1987; Huizink et al., 2002; Newham et al., 2012; Solivan et al., 2015; Spielberger, 1983).

In the present study, the EPDS demonstrated good internal consistency during the third trimester (α = 0.83), at two (α = 0.83) and six months (α = 0.79) postpartum. The STAI trait (STAI-T) subscale demonstrated excellent internal consistency during pregnancy and both postpartum visits (third trimester: α = 0.93; two-months: α = 0.92; six-months: α = 0.94). The STAI state (STAI-S) subscale also was internally consistent at all three time points (third trimester: α = 0.89; two-months: α = 0.91; six-months: α = 0.85). The PSS had good internal consistency at two months (α = 0.89). However, internal consistency was in the questionable range during the third trimester (α = 0.58) and at six months (α = 0.53), representing a limitation.

### 2.4. Hair cortisol concentration (HCC) measurement

Hair samples were collected during the third trimester at the same time surveys were administered, and at six months after birth. We administered a standardized questionnaire that assessed factors potentially influencing HCC, such as current medications, hair condition, and the use of hair styling products. Following Wright et al. (2015), the most proximal three centimeters of hair was cut from the participants' posterior vertex (the back of the head where the scalp transitions from horizontal to vertical) and stored at room temperature in the dark until analysis. Based on an average hair growth rate of one cm/month (Wennig, 2000), the HCC measured in these samples (mean hair weight = 14.7 mg/sample) represented an aggregate measure of circulating cortisol concentrations over the previous three months (Wright et al., 2015). In our case, on average this measure reflected the circulating cortisol concentrations from ~20–32 weeks of gestation (mid-second to early third trimester), and our six-month postpartum hair collection reflected an aggregate measure circulating cortisol from three to six months after birth.

Following the protocol of Sauvé et al. (2007), lipophilic compounds were extracted from hair using methanol, and cortisol was quantified using an enzyme-linked immunosorbent assay (ELISA, Cayman Scientific, Ann Arbor, MI, USA). Briefly, hair samples were washed with isopropanol, dried under an air stream, minced, and then incubated for 18 h in methanol. Methanol was evaporated under a nitrogen stream in a 40 °C water bath, and the sample was resuspended with between 200 and 400 μl of ELISA buffer (provided by the manufacturer). Samples were assayed in duplicate following the manufacturer's instructions. We haphazardly assigned samples across six ELISA plates, with samples

**Table 1**
Summary statistics of the study population. Data are given in percentages of the study population or mean ± standard deviation unless otherwise indicated.

| | Total sample ($n$ = 53) | No unpredicted birth complications ($n$ = 40) | Unpredicted birth complications ($n$ = 13) |
|---|---|---|---|
| Age (years) | 31.1 ± 4.04 | 31.06 ± 4.28 | 31.25 ± 3.39 |
| Race/Ethnicity | | | |
| White | 83% | 80.0% | 91.7% |
| Hispanic or Latina | 4.3% | 5.7% | 0 |
| Asian | 6.4% | 5.7% | 8.3% |
| American Indian or Alaskan Native | 4.3% | 5.7% | 0 |
| Native Hawaiian or Pacific Islander | 2.1% | 2.9% | 0 |
| Relationship status | | | |
| Married | 83% | 82.9% | 83.3% |
| Cohabitating | 8.5% | 11.4% | 0 |
| Engaged | 4.3% | 5.7% | 0 |
| Separated | 2.1% | 0 | 8.3% |
| Divorced | 2.1% | 0 | 8.3% |
| Annual income | | | |
| $0 to $30,000 | 13% | 11.8% | 16.7% |
| $30,001 to $60,000 | 34.8% | 35.3% | 33.3% |
| $60,001 to $75,000 | 19.6% | 20.6% | 16.7% |
| Over $75,000 | 32.6% | 32.4% | 33.3% |
| Highest secondary education | | | |
| High school or GED | 2.1% | 2.9% | 0 |
| Some College | 8.5% | 11.4% | 0 |
| Associates Degree | 6.4% | 5.7% | 8.3% |
| Bachelors degree | 44.7% | 45.7% | 41.7% |
| Masters degree | 19.1% | 14.3% | 33.3% |
| Doctorate or Professional degree (MD, JD, DDS, PhD, etc.) | 14.9% | 14.3% | 16.7% |
| Other | 4.3% | 5.7% | 0 |
| Number of other children | 1.56 ± 0.84 | 1.56 ± 0.87 | 1.57 ± 0.79 |
| Weeks of gestation | 39.18 ± 1.62 | 39.26 ± 1.66 | 38.92 ± 1.53 |
| Infant's birth weight in lbs | 7.54 ± 1.00 | 7.45 ± 0.99 | 7.82 ± 1.0 |
| Birth mode | | | |
| Vaginal birth | 75.5% | 75.0% | 76.9% |
| Cesarean section | 24.5% | 25.0% | 23.1% |
| Infant's sex | | | |
| Female | 58.5% | 47.5% | 92.3% |
| Male | 41.5% | 52.5% | 7.7% |
| Hair cortisol concentrations (HCC) | | | |
| Third-trimester median (range, n) • Weeks of gestation at collection | 31.63 ± 3.15 | 5.22 (2.3 – 32, $n$ = 33) 31.79 ± 2.88 | 8.91 (1.86 – 53.27, $n$ = 12) 31.17 ± 3.93 |
| Six-month postpartum median (range, n) | | 5.81 (1.6 – 42.1, $n$ = 34) | 9.36 (1.5 – 217.2, $n$ = 10) |

from each collection time and UBC status represented on all plates. If the concentration of a sample did not fall within the range of the ELISA standard curve, or if the variance between duplicates was > 20%, the sample was diluted (2–10 dilution factor) or re-run if enough sample permitted so that it could be measured with high confidence within the linear range of the assay. The intra-assay coefficient of variation (CV) was 7.1% (range: 0.46–23.1), and the inter-assay CVs of three standards run across plates were 4%, 11%, and 19%. Concentrations were averaged if samples were duplicated across plates, then divided by the mass of hair extracted for analysis.

### 2.5. Statistical analyses

#### 2.5.1. Influence of UBCs on psychological distress over the perinatal period

Multiple imputation methods were used to estimate missing data for the surveys over the three time points (third trimester, two- and six-months postpartum) for the 53 participants, as there was no obvious systematic reason for failure to submit surveys over the study period. We used Predictive Mean Matching (PMM) in SPSS Statistics 28.0.1.1 (IBM, Armonk, NY) to generate predictive values for cases of missingness. This method locates cases with known values for the outcome variable that are most similar to the predictive values for the missing cases (van Ginkel et al., 2020). Therefore, the generated cases from observations prevent the generation of values outside the range of possibility. This model is also less influenced by observed data that violate normality. Restricted maximum likelihood (REML) correlations among PSS, EPDS, STAI-S, and STAI-T showed that these were highly correlated at each time point (Table 2). Therefore, we performed Principal Components Analysis (PCA) to reduce multicollinearity and the number of statistical tests. Across the three time points, all scores loaded highly on PC1 (average % variance over 5 imputations ranged from 0.815 to 0.965), which accounted for an average variance of 76.9%, 81.8%, and 77.8% for the third trimester, and two- and six-months postpartum periods, respectively. Thus, we used PC1 as a stress, anxiety, and depression (SAD) Score in subsequent analyses. A repeated measures MANOVA was performed to determine how SAD scores changed between the third trimester and two months postpartum, and then two and six months postpartum. We focused on within-individual by time interactions to evaluate whether these changes depended on the occurrence of a UBC. All statistical analyses for this study were conducted in SPSS Statistics 28.0.1.1.

#### 2.5.2. Influence of UBCs on the associations psychological distress and HCC during the third trimester

Of the 53 participants, 45 submitted hair samples during their third trimester (UBC No: $n = 33$, Yes: $n = 12$ or 26.7%). HCCs collected during the third trimester were Log10-transformed to correct for non-normality. We conducted preliminary analyses to determine relationships between HCC and whether the hair was dyed, washing regime, or use of hair product, and found no significant relationships as reported in other studies (Manenschijn et al., 2011). Thus, we did not include these variables in subsequent analyses of HCC. We first conducted a regression analysis to determine the relationships between HCC and SAD scores reported during the third trimester; we included UBC (Yes/No) and its interaction with SAD scores in the model to test whether these relationships depended on birth outcome.

**Table 2**
Maximum likelihood correlation matrix of psychological scores (State and Trait Anxiety, Perceived Stress, and Edinburgh Postnatal Depression Scale) reported during the third trimester (3 T), two months postpartum, and six months postpartum. Asterisks indicate significant correlations, Bonferonni corrected for the number of tests (2-tailed): * * $p < 0.01$, * $p < 0.05$.

| | State Anxiety 3 T | Trait Anxiety 3 T | Perceived Stress 3 T | Depression 3 T | State Anxiety 2 mo. | Trait Anxiety 2 mo. | Perceived Stress 2 mo. | Depression 2 mo. | State Anxiety 6 mo. | Trait Anxiety 6 mo. | Perceived Stress 6 mo. | Depression 6 mo. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **State Anxiety 3 T** | 1 | | | | | | | | | | | |
| **Trait Anxiety 3 T** | 0.755** | 1 | | | | | | | | | | |
| **Perceived Stress 3 T** | 0.711** | 0.637** | 1 | | | | | | | | | |
| **Depression 3 T** | 0.689** | 0.727** | 0.549** | 1 | | | | | | | | |
| **State Anxiety 2 mo.** | 0.515** | 0.539** | 0.290 | 0.482** | 1 | | | | | | | |
| **Trait Anxiety 2 mo.** | 0.363* | 0.465** | 0.104 | 0.480** | 0.792** | 1 | | | | | | |
| **Perceived Stress 2 mo.** | 0.312* | 0.390** | 0.205 | 0.492** | 0.738** | 0.879** | 1 | | | | | |
| **Depression 2 mo.** | 0.141 | 0.224 | -0.091 | 0.397* | 0.596** | 0.781** | 0.780** | 1 | | | | |
| **State Anxiety 6 mo.** | 0.192 | 0.061 | 0.039 | 0.148 | 0.469** | 0.469** | 0.503** | 0.465* | 1 | | | |
| **Trait Anxiety 6 mo.** | 0.214 | 0.274 | 0.105 | 0.259 | 0.562** | 0.702** | 0.689** | 0.595** | 0.794** | 1 | | |
| **Perceived Stress 6 mo.** | 0.302* | 0.288 | 0.256 | 0.169 | 0.595** | 0.604** | 0.642** | 0.442** | 0.669** | 0.750** | 1 | |
| **Depression 6 mo.** | 0.172 | 0.196 | -0.003 | 0.141 | 0.318* | 0.525** | 0.484** | 0.523** | 0.503** | 0.658** | 0.707** | 1 |

* * Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

#### 2.5.3. Psychological distress and HCC as predictors of UBCs

To test whether HCC and SAD scores measured during the third trimester predicted UBCs, we used logistic regression and calculated odds ratios to relate HCC and SAD to the likelihood of unpredicted birth complications.

#### 2.5.4. Influence of psychological distress and UBCs on HCC over the perinatal period

We first calculated the Pearson correlation coefficient between Log10 HCC measured from the third trimester and six-month postpartum hair collections for all participants who submitted both samples. The sample size for this analysis was lower ($n = 39$), due to factors such as difficulty with the time commitment required for participation or moving out of state. Therefore, the sample size of participants with and without unpredicted birth complications (No: $n = 29$, Yes: $n = 10$, 25.6%) was reduced. We conducted repeated measures MANOVA to determine whether the change in HCC between the third trimester and six months postpartum varied as a function of SAD scores, the experience of UBCs, and the interaction between the two.

## 3. Results

### 3.1. Influence of experiencing UBCs on psychological distress over the perinatal period

Repeated measures MANOVA revealed that SAD scores changed between each reporting period depending on whether women experienced UBCs (Fig. 1, Supplemental Fig. 1). Relative to scores reported during the third trimester, average SAD scores of women reporting UBCs increased at two months after birth (within-subjects time x UBC interaction $p = 0.0056$) then tended to decrease by six months (within-subjects time x UBC interaction $p = 0.097$), while average scores of women who reported normal births remained relatively constant. In terms of specific measures of psychological distress, participants experiencing UBCs exhibited increases in STAI-S, STAI-T, PSS, and EDPS scores (mean change of 4.8, 4.5, 3, and 1.9 points, respectively), while participants who did not experience UBCs exhibited either no change or a decrease in scores (mean change of −0.9, −1.6, −2.6, and −0.9 points, respectively; see Supplemental Fig. 2) MANOVA between third trimester and six-month SAD scores were not significantly different (within-subjects time $p = 0.637$, time x UBC interaction $p = 0.356$).

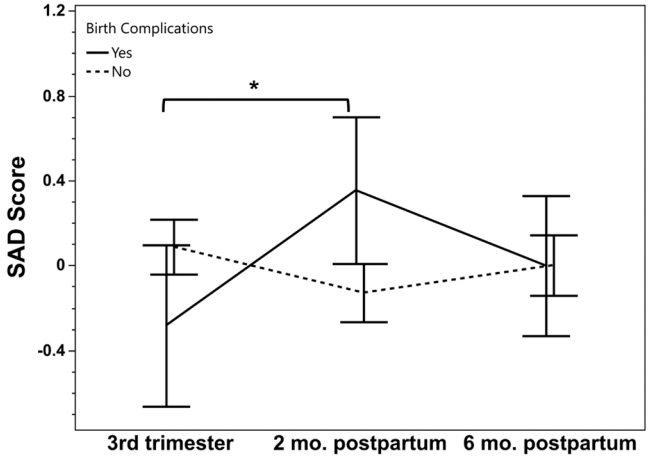



**Fig. 1.** Stress/anxiety/depression (SAD) Score change over the perinatal period depending on whether women experience unpredicted birth complications. Mean ± SEM SAD score (PC1 of principle component analysis of Perceived Stress score (PSS), State (STAI-S) and Trait (STAI-T) Anxiety scores, and Depression (EPDS) score) of women who did not report birth complications ($n = 40$) and those who did ($n = 13$). Within-subjects time x birth complication interaction between time points: third trimester vs. two months postpartum ($p < 0.01$ **). See Supplemental Fig. 1 for a spaghetti plot of individual SAD scores and Supplemental Fig. 2 to see means ± SE of STAI-S, STAI-T, PSS, and EPDS scores across the three reporting periods.

### 3.2. Influence of UBCs on the associations between psychological distress and HCC during the third trimester

The HCCs were within the range reported for pregnant women when collected in the third trimester (Marceau et al., 2020, see Table 1). Third-trimester HCC was positively associated with third-trimester SAD Score, and HCC was significantly higher in participants reporting UBCs (Table 3, Fig. 2), as the median HCC was approximately 58.6% higher in participants reporting UBCs (Table 1). The positive association between SAD score and HCC was stronger in women that experienced an unpredicted birth complication (SAD Score x UBC interaction, Table 3, Fig. 2).

### 3.3. Psychological distress and HCC as predictors of UBCs

Logistic regression showed that HCC was a positive predictor of UBCs

**Table 3**
Parameter estimate and statistical results of analyses of variance relating HCC to the incidence of birth complications, SAD scores, and their interaction across the perinatal period. Top: ANOVA relating third-trimester HCC and SAD scores. Middle: Repeated measures MANOVA between-subjects estimates relating HCC over the perinatal period (third trimester and six months postpartum) to birth complications, SAD scores reported at two months postpartum, and their interaction. Bottom: Same statistical results when SAD scores reported at six months postpartum were included in the model.

| Third Trimester ANOVA (n = 45) | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | β | Std. Error | t | Sig. | 95% Confidence Interval | |
| | | | | | Lower Bound | Upper Bound |
| Intercept | 1.087 | 0.087 | 12.484 | 0.000 | 0.917 | 1.258 |
| Birth complication | -0.349 | 0.099 | -3.520 | < 0.001 | -0.544 | -0.155 |
| Third trimester SAD | 0.201 | 0.072 | 2.801 | 0.005 | 0.060 | 0.342 |
| Birth complication x SAD | -0.267 | 0.097 | -2.754 | 0.006 | -0.458 | -0.076 |
| Two mo. Postpartum MANOVA (n = 39) | | | | | | |
| Parameter | β | Std. Error | t | Sig. | 95% Confidence Interval | |
| | | | | | Lower Bound | Upper Bound |
| Intercept | 0.993 | 0.138 | 7.217 | < 0.001 | 0.723 | 1.263 |
| Birth complication | -0.254 | 0.157 | -1.619 | 0.105 | -0.562 | 0.054 |
| Two mo. postpartum SAD | 0.394 | 0.135 | 2.928 | 0.003 | 0.130 | 0.659 |
| Birth complication x SAD | -0.400 | 0.161 | -2.482 | 0.013 | -0.716 | -0.084 |
| Six mo. Postpartum MANOVA (n = 39) | | | | | | |
| Parameter | β | Std. Error | t | Sig. | 95% Confidence Interval | |
| | | | | | Lower Bound | Upper Bound |
| Intercept | 1.011 | 0.148 | 6.835 | < 0.001 | 0.721 | 1.301 |
| Birth complication | -0.269 | 0.169 | -1.594 | 0.111 | -0.600 | 0.062 |
| Six mo. postpartum SAD | 0.186 | 0.114 | 1.635 | 0.102 | -0.037 | 0.409 |
| Birth complication x SAD | -0.163 | 0.144 | -1.131 | 0.258 | -0.447 | 0.120 |

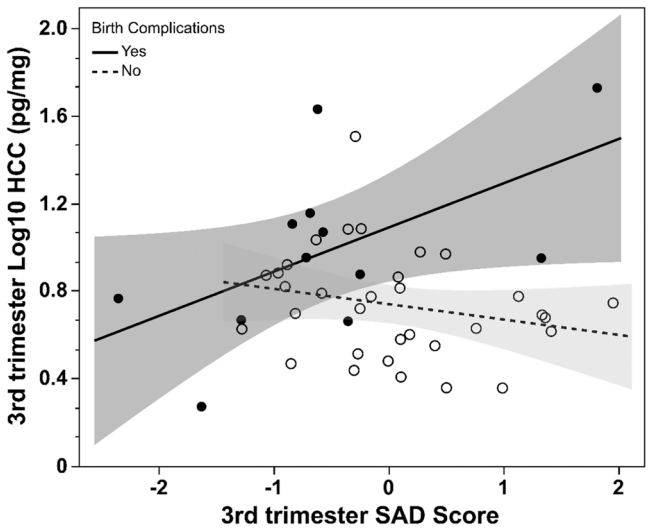



**Fig. 2.** Relationships between SAD scores and HCC collected during the third trimester in participants who did and did not experience unpredicted birth complications (UBCs). Linear regression of SAD scores and Log10 HCC by UBC (UBC Yes: $n = 12$, No: $n = 33$). Shaded regions indicate 95% confidence intervals. Post-hoc Pearson correlation coefficients between SAD score and third-trimester HCC in women who reported experiencing UBCs was $r = 0.574$, while $r = 0.224$ for women who did not report UBCs.

(log-likelihood test: df = 2, $\chi 2 = 9.91$, $p < 0.01$; HCC $p = 0.023$, SAD $p = 0.079$), accounting for 19.7% (Cox & Snell pseudo-$R^2$) of the variance. This model showed that a unit increase in Log10 HCC related to a 22.45 increase in the odds of experiencing a birth complication.

### *3.4. Influence of psychological distress and UBCs on HCC over the perinatal period*

Of participants who experienced UBCs, HCCs remained elevated from the third trimester through six months after birth (Fig. 3A, Table 1). HCCs measured in the third trimester were highly correlated to those measured at six-month postpartum ($r = 0.658$, $p < 0.0001$; Supplemental Fig. 3). When we used SAD scores reported at two months postpartum in the repeated measures MANOVA model, HCC across the perinatal period was positively associated with SAD scores (between-subject effect, Table 3). The change in HCC over time varied with two-month SAD scores depending on experience of a UBC (within-subjects time x SAD score $p = 0.0062$, time x SAD score x UBC interaction, $p = 0.001$). As shown when plotting two-month postpartum SAD scores against six-month postpartum HCC (Fig. 3B), participants reporting UBCs had a stronger association with SAD scores than participants who did not report UBCs. When we included SAD scores reported at six months postpartum in the MANOVA, the association between HCC with SAD scores and HCC with UBCs was weakened and no longer significant (Table 3, Fig. 3).

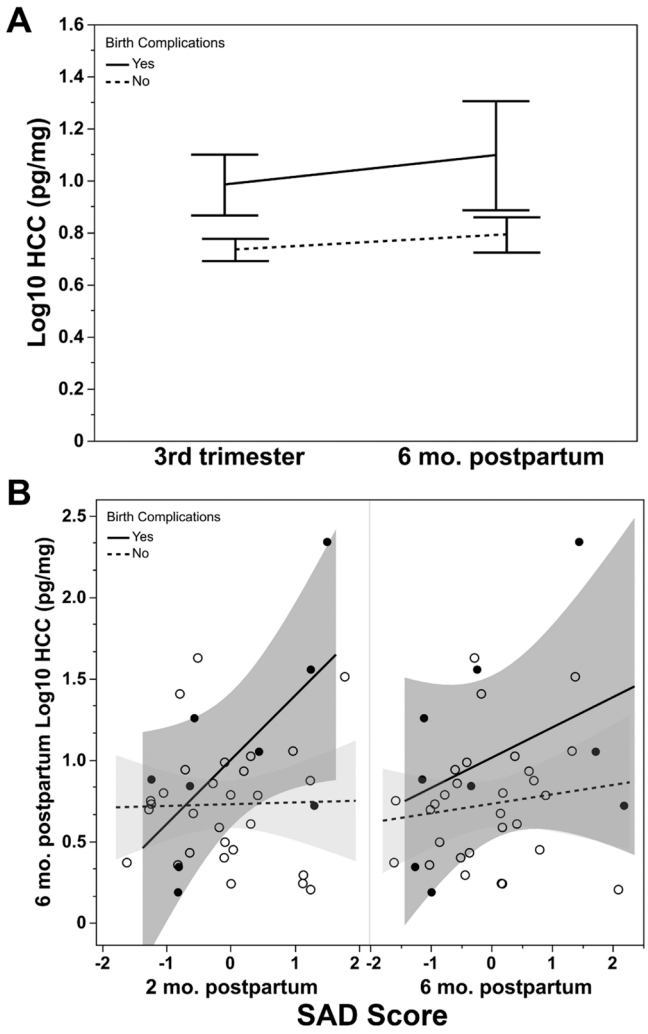



**Fig. 3.** Hair cortisol concentrations (HCC) change over the perinatal period varied by unpredicted birth complication (UBC) and stress/anxiety/depression (SAD) Scores. A. Mean ± S.E.M. HCC (log10 transformed, UBC Yes: n = 10, No: n = 29) collected during the third trimester and at six months postpartum by unpredicted birth complications status. See Table 1 for raw medians and ranges. **B.** Cortisol concentrations from hair collected at six months postpartum (log10 transformed HCC), reflecting circulating cortisol concentrations during the three months prior, plotted against SAD scores reported at two and six months postpartum in participants who reported UBCs (solid line, black dots) and those that did not (dashed line, open circles); shaded regions indicate 95% confidence intervals. Repeated measures MANOVA showed that the relationship between HCCs over the perinatal period positively varied by SAD scores reported at two months postpartum depending on whether or not unpredicted birth complications (UBCs) were experienced (UBC Yes: $r = 0.656$; UBC No: $r = 0.0$). The relationship between six-month postpartum HCC with SAD scores reported at six months was weakened (UBC Yes: $r = 0.387$; UBC No: $r = 0.14$), and the influence of UBCs was diminished.

## 4. Discussion

We aimed to determine relationships between maternal psychological distress and HPA axis activity, as measured by SAD scores and HCCs, across the perinatal period in a longitudinal study of healthy participants. Because we had demographically similar characteristics in participants who did and did not report UBCs, we were able to retrospectively assess how the relationship between HCC and SAD scores varied with UBCs. As predicted, SAD scores (a composite of PSS, STAI-S, STAI-T, and EDPS scores), increased from the third trimester to two months postpartum only for participants reporting UBCs; but this effect appeared to diminish by six months postpartum. We also detected significant and positive associations between third trimester HCCs and SAD scores reported during the third trimester, and HCCs were significantly higher in participants who went on to experience UBCs. HCCs across the perinatal period were positively associated with SAD scores reported at two months postpartum, with a stronger relationship in participants reporting UBCs. But the relationship between HCCs and SAD scores reported at six months postpartum was diminished, as was the influence of UBCs on HCCs. We discuss these findings, their limitations, and their implications for maternal-infant health below.

### 4.1. Influence of experiencing UBCs on psychological distress over the perinatal period

Because perceived stress, state and trait anxiety, and depression were highly correlated with one another within reporting times throughout the perinatal period, as has been shown in prior studies (Liou et al., 2014; Salacz et al., 2012), we used principal component analysis to obtain a composite measure of internalizing symptoms (SAD score). For participants who reported UBCs, SAD scores reported two months postpartum were increased relative to those reported during the third trimester of pregnancy but appeared to diminish by six months postpartum. By contrast, on average there were no differences in SAD scores in participants that did not report UBCs across the perinatal period. These findings are consistent with previous research addressing psychological responses to adverse birth outcomes (Kersting et al., 2004; Lemola et al., 2007). For example, Kersting et al. (2004) found that mothers of infants with very low birth weight had significant detrimental depression, anxiety, and trauma scores compared to women with normal birth weight infants; and these clinically elevated scores persisted up to 14 months after birth. Kersting and colleague's (2004) findings indicate that adverse birth outcomes have a lasting effect on maternal psychological distress well into the postpartum period. This suggests that monitoring and providing services for maternal mental health during and after pregnancy is especially important for high-risk pregnancies and pregnancies with adverse birth outcomes.

### 4.2. Influence of psychological distress and UBCs on HCC during the third trimester

One of the most robust findings of this study is that third trimester HCC, reflecting an integrated measure of circulating cortisol over the three prior months, extending on average into the mid-late second trimester in our sample, was positively associated with SAD scores for all participants. Although the literature is somewhat mixed, our study supports prior investigations showing positive relationships between cortisol and measures of psychological distress during pregnancy (e.g. Kalra et al., 2007; Sarkar et al., 2006; Stickel et al., 2021), particularly HCC studies focused in later gestation as reported in the meta-analysis by Khoury et al. (2023). The association between HCC and SAD scores was relatively weak, but our ability to detect this association was strengthened by including UBC as a factor in our analysis. This finding supports the hypothesis the relationship between maternal psychological distress and HPA axis activity during pregnancy is stronger for women who experience adverse birth outcomes.

### 4.3. Psychological distress and HCC as predictors of UBCs

This study is among the first to show HCCs were significantly elevated during pregnancy in participants experiencing UBCs. Logistic regression supported the hypothesis that HCC could be informative to assess the risk of birth complications, albeit with somewhat limited predictive power, in our sample of reported healthy pregnancies. Elevated cortisol during similar periods of pregnancy has been associated with preterm birth (e.g., Bandoli et al., 2018) and early onset pre-eclampsia (van Esch et al., 2020), but our sample reported a range of unpredicted complications with only a few preterm births (15%). If elevated HPA axis activity precedes a range of birth complications, HCC during pregnancy could be used as a possible biomarker to monitor along with psychological distress in multivariate predictive models. However, larger, more diverse sample of participants, including those with higher-risk pregnancies, would expand the distribution of HCCs and are needed to ultimately determine the utility of including HCC during pregnancy as a biomarker predictive of birth complications.

### 4.4. Influence of psychological distress and UBCs on HCC over the perinatal period

When we looked at the relationship between HCCs across the perinatal period and SAD scores reported at two months postpartum using a repeated measures approach, we found a consistent positive association between HCCs and SAD only when two-month reports of SAD scores were included in the model. Because HCCs are the integration of circulating cortisol concentrations during the prior three months, SAD scores reported at two months postpartum may have aligned more closely with cortisol concentrations collected at six months. This is also consistent with Khoury et al. (2023), whose meta-analysis showed that HCC and psychological distress were more likely to be associated when surveys measuring symptoms of psychological distress were administered before the collection of hair for HCC analysis. Our analysis showed that SAD scores reported at six months postpartum were not associated with HCC, and the influence of UBCs was diminished. This decoupling of psychological distress and HCC by six months postpartum in our model may be due to the diminished influence of UBCs by that time, although other explanations are possible.

We also see a consistent elevation in cortisol concentrations over three-six months postpartum in participants reporting UBCs. Prior studies have shown a decline in maternal cortisol concentrations by approximately 6–12 weeks after parturition (Conde et al., 2021; Stickel et al., 2021), but we did not collect hair samples during a window of time where they would reflect peak circulating cortisol concentrations prior to birth. Therefore, our analysis suggests that cortisol concentrations during the mid-second trimester-early third trimester were similar to those during three-six months postpartum. Regardless, the persistent elevation in cortisol associated with birth complications is informative and should be investigated further because of its potential for clinical applications. Understanding the postpartum recovery of HPA axis activity is essential as chronically elevated glucocorticoids and psychological stress can lead to physical and mental health consequences such as hypertension (Bautista et al., 2019) and psychiatric disorders such as major depression (Herane-Vives et al., 2018; Young, 2004). Furthermore, there could be important impacts on infants because physiological or psychological stress experienced by mothers postpartum can affect the physiology and behavior of their infants, as stress can be transmitted behaviorally between mother-infant dyads (Waters et al., 2014) and or via glucocorticoids that pass through breastmilk (Hollanders et al., 2019). Indeed, higher levels of psychological distress during pregnancy of participants in this study were associated with reduced falling reactivity (ability to recover from distress) and soothability of their infants (Mattera et al., 2022). Findings reported herein suggest that *in utero* exposure to elevated glucocorticoid concentrations during pregnancy could be related to this outcome via altered development of the brain or neuroendocrine systems (Seckl and Meaney, 2004). Of note, a review by Duthie and Reynolds (2013) showed that over multiple forms of cortisol collection methods (e.g., saliva, serum, amniotic fluid), elevated cortisol during infancy was shown to affect physical growth and social-emotional development (e.g. temperament). This finding is consistent with Grey et al. (2013) study examining cortisol concentrations in human milk. Relationships between elevated cortisol during infancy, physical growth, and social-emotional development have also been shown to affect health later in life (Seckl and Meaney, 2004). Taken together, findings from our study suggest that infants whose mothers experienced birth complications may be directly or indirectly exposed to elevated cortisol from the last trimester through the first several months of age.

### 4.5. Strengths, Limitations, and Conclusions

The strength of this study is the repeated measurement of both psychological distress and HCC to determine their relationships across the perinatal period (Khoury et al., 2023), given that most studies thus

far have been cross-sectional, and we account for an important heterogeneity in our sample by including the experience of birth complications in our analyses. We showed that HCC measures reflecting mid-second to early third trimester circulating cortisol concentrations are positively correlated to psychological distress reported during the third trimester of pregnancy in this sample, contributing to a growing body of literature indicating their association. We were able to show that HCC and SAD scores continued to covary through the first few months after birth, but this relationship began to weaken by six months after birth. Perhaps most importantly we were able to show an elevation in HCC during the third trimester in participants who reported UBCs, which continued through the early postpartum period, suggesting that HCC during pregnancy can be predictive of a heterogenous set of UBCs in otherwise healthy pregnancies in this sample of participants. Considering that 50% of women in the U.S. experience adverse birth outcomes such as UBCs (Hamilton et al., 2021), it is imperative to identify risk factors and reliable biomarkers in an effort to identify people at risk of birth complications to develop effective interventions to reduce the physiological and psychological consequences for both mothers and infants. Therefore, more research is needed to test the hypothesis that HCC during pregnancy can be used along with other risk factors, such as internalizing symptoms of stress, anxiety, or depression, in the formulation of multivariate models used to predict UBCs in otherwise healthy presenting pregnancies.

The most significant limitations of this study involve our relatively small and demographically homogenous sample. Follow-up investigations are needed to determine the generalizability of these findings and whether these relationships vary as a function of race/ethnicity, socioeconomic status, or demographic adversity. Associations between SAD scores and HCC were relatively weak, albeit statistically significant, which may be due to relative sample homogeneity because we restricted participants to those with healthy pregnancies, thereby limiting variability. A smaller sample introduces opportunities for influential data points, and the association of SAD scores and HCCs across the perinatal period among participants reporting UBCs was driven in part by an individual who exhibited the highest six-month postpartum concentration. However, this value was not a statistical outlier, was deemed valid based on other information regarding the participant's circumstances, and would have been represented better in a larger sample with a wider range of psychological and health concerns. Taken together, findings from this study supports the use of non-invasive, integrative cortisol measures obtained by the HCC method in longitudinal studies extending from early pregnancy to one year after birth that integrate data on moderating factors, such as the birth experience, to improve our understanding of the associations of chronic physiological and psychological stress during pregnancy and their impact on maternal-infant health.

## Funding

This work was supported by a Grand Challenges Grant from Washington State University, a Interdisciplinary Research Grant from the WSU College of Arts and Sciences, and a Multidisciplinary Program Grant from the WSU Office of Research.

## CRediT authorship contribution statement

**J.A. Madigan:** Methodology, Formal analysis, Data curation, Writing - Original Draft, Data Visualization. **Sara Waters:** Conceptualization, Methodology, Project administration, Funding acquisition, Writing - Review & Editing. **Maria Gartstein:** Conceptualization, Methodology, Project administration, Funding acquisition, Writing - Review & Editing. **Jennifer Mattera:** Investigation, Writing - Review & Editing. **Christopher Connolly:** Investigation, Project administration, Funding acquisition, Writing - Review & Editing. **Erica Crespi:** Methodology, Formal analysis, Data Curation, Project administration, Funding acquisition, Writing – Original Draft.

## Declaration of Competing Interest

The authors report no competing interests.

## Acknowledgements

We would like to thank the study participants for their time, effort, and support during this project.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106921.

## References

Bandoli, G., Jelliffe-Pawlowski, L.L., Feuer, S.K., Liang, L., Oltman, S.P., Paynter, R., Ross, K.M., Schetter, C.D., Ryckman, K.K., Chambers, C.D., Jelliffe-pawlowski, G.B.L. L., Feuer, S.K., Liang, L., Oltman, S.P., Paynter, R., Ross, K.M., Dunkel, C., Kelli, S., Christina, K.R., 2018. Second trimester serum cortisol and preterm birth: an analysis by timing and subtype. J. Perinatol. 38 (8), 973–981. https://doi.org/10.1038/s41372-018-0128-5.

Barker, D.J.P., Clark, P.M., 1997. Fetal undernutrition and disease in later life. Rev. Reprod. 2 (2), 105–112. https://doi.org/10.1530/ror.0.0020105.

Bautista, L.E., Bajwa, P.K., Shafer, M.M., Malecki, K.M.C., McWilliams, C.A., Palloni, A., 2019. The relationship between chronic stress, hair cortisol and hypertension. Int. J. Cardiol.: Hypertens. 2 (April), 100012 https://doi.org/10.1016/j.ijchy.2019.100012.

Bolten, M.I., Wurmser, H., Buske-Kirschbaum, A., Papoušek, M., Pirke, K.M., Hellhammer, D., 2011. Cortisol levels in pregnancy as a psychobiological predictor for birth weight. Arch. Women's Ment. Health 14 (1), 33–41. https://doi.org/10.1007/s00737-010-0183-1.

Caparros-Gonzalez, R.A., Romero-Gonzalez, B., Strivens-Vilchez, H., Gonzalez-Perez, R., Martinez-Augustin, O., Peralta-Ramirez, M.I., 2017. Hair cortisol levels, psychological stress and psychopathological symptoms as predictors of postpartum depression. PLoS ONE 12 (8), 1–17. https://doi.org/10.1371/journal.pone.0182817.

Carr, B.R., Parker, C.R., Madden, J.D., MacDonald, P.C., Porter, J.C., 1981. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. Am. J. Obstet. Gynecol. 139 (4), 416–422. https://doi.org/10.1016/0002-9378(81)90318-5.

Challis, J.R.G., Sloboda, D., Matthews, S.G., Holloway, A., Alfaidy, N., Patel, F.A., Whittle, W., Fraser, M., Moss, T.J.M., Newnham, J., 2001. The fetal placental hypothalamic-pituitary-adrenal (HPA) axis, parturition and post natal health. Mol. Cell. Endocrinol. 185 (1–2), 135–144. https://doi.org/10.1016/S0303-7207(01)00624-4.

Chen, Y., Ismail, F., Xiong, Z., Li, M., Chen, I., Wen, S.W., Xie, R. hua, 2022. Association between perceived birth trauma and postpartum depression: a prospective cohort study in China. Int. J. Gynecol. Obstet. 157 (3), 598–603. https://doi.org/10.1002/ijgo.13845.

Cheng, C.Y., Chou, Y.H., Chang, C.H., Liou, S.R., 2021. Trends of perinatal stress, anxiety, and depression and their prediction on postpartum depression. Int. J. Environ. Res. Public Health 18 (17), 1–12. https://doi.org/10.3390/ijerph18179307.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24 (4), 385–396.

Conde, A., Costa, R., Figueiredo, B., 2021. Anxiety and depressive symptoms effects on cortisol trajectories from pregnancy to postpartum: Differences and similarities between women and men. Horm. Behav. 128 (December 2020) https://doi.org/10.1016/j.yhbeh.2020.104917.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression: development of the 10-item edinburgh postnatal depression scale. Br. J. Psychiatry 150 (JUNE), 782–786. https://doi.org/10.1192/bjp.150.6.782.

D'Anna-Hernandez, K.L., Ross, R.G., Natvig, C.L., Laudenslager, M.L., 2011. Hair cortisol levels as a retrospective marker of hypothalamic-pituitary axis activity throughout pregnancy: comparison to salivary cortisol. Physiol. Behav. 104 (2), 348–353. https://doi.org/10.1016/j.physbeh.2011.02.041.

Dowse, E., Chan, S., Ebert, L., Wynne, O., Thomas, S., Jones, D., Fealy, S., Evans, T.J., Oldmeadow, C., 2020. Impact of perinatal depression and anxiety on birth outcomes: a retrospective data analysis. Matern. Child Health J. 24 (6), 718–726. https://doi.org/10.1007/s10995-020-02906-6.

Duffy, A.R., Schminkey, D.L., Groer, M.W., Shelton, M., Dutra, S., 2018. Comparison of hair cortisol levels and perceived stress in mothers who deliver at preterm and term. Biol. Res. Nurs. 20 (3), 292–299. https://doi.org/10.1177/1099800418758952.

Duthie, L., Reynolds, R.M., 2013. Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. Neuroendocrinology 98 (2), 106–115. https://doi.org/10.1159/000354702.

Fan, F., Zou, Y., Zhang, Y., Ma, X., Zhang, J., Liu, C., Li, J., Pei, M., Jiang, Y., Dart, A.M., 2018. The relationship between maternal anxiety and cortisol during pregnancy and

birth weight of chinese neonates. BMC Pregnancy Childbirth 18 (1), 1–6. https://doi.org/10.1186/s12884-018-1798-x.
Furuta, M., Sandall, J., Cooper, D., Bick, D., 2016. Predictors of birth-related post-traumatic stress symptoms: secondary analysis of a cohort study. Arch. Women's Ment. Health 19 (6), 987–999. https://doi.org/10.1007/s00737-016-0639-z.
Grey, K.R., Davis, E.P., Sandman, C.A., Glynn, L.M., 2013. Human milk cortisol is associated with infant temperament. Psychoneuroendocrinology 38 (7), 1178–1185. https://doi.org/10.1016/j.psyneuen.2012.11.002.
Guintivano, J., Manuck, T., Meltzer-Brody, S., 2018. Predictors of postpartum depression: a comprehensive review of the last decade of evidence. Clin. Obstet. Gynecol. 61 (3), 591–603. https://doi.org/10.1097/GRF.0000000000000368.
Hamilton, B.E., Martin, J.A., Osterman, M.J.K., 2021. Births: Provisional data for 2020. NVSS Vital.-. Stat. Rapid Release 012, 1–11. https://www.cdc.gov/nchs/data/vsrr/report002.pdf.
Herane-Vives, A., Fischer, S., de Angel, V., Wise, T., Cheung, E., Chua, K.C., Arnone, D., Young, A.H., Cleare, A.J., 2018. Elevated fingernail cortisol levels in major depressive episodes. Psychoneuroendocrinology 88 (September 2017), 17–23. https://doi.org/10.1016/j.psyneuen.2017.10.026.
Herman, J.P., Mcklveen, J.M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., Myers, B., 2016. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr. Physiol. 6 (2), 603–621. https://doi.org/10.1002/cphy.c150015.Regulation.
Hillhouse, E.W., Grammatopoulos, D.K., 2002. Role of stress peptides during human pregnancy and labour. Reproduction 124 (3), 323–329. https://doi.org/10.1530/rep.0.1240323.
Hollanders, J.J., Kouwenhoven, S.M.P., van der Voorn, B., van Goudoever, J.B., Rotteveel, J., Finken, M.J.J., 2019. The association between breastmilk glucocorticoid concentrations and macronutrient contents throughout the day. Nutrients 11 (2). https://doi.org/10.3390/nu11020259.
Huizink, A.C., Robles De Medina, P.G., Mulder, E.J.H., Visser, G.H.A., Buitelaar, J.K., 2002. Psychological measures of prenatal stress as predictors of infant temperament. J. Am. Acad. Child Adolesc. Psychiatry 41 (9), 1078–1085. https://doi.org/10.1097/00004583-200209000-00008.
Irwin, J.L., Meyering, A.L., Peterson, G., Glynn, L.M., Sandman, C.A., Hicks, L.M., Davis, E.P., 2021. Maternal prenatal cortisol programs the infant hypothalamic–pituitary–adrenal axis. Psychoneuroendocrinology 125 (December 2020). https://doi.org/10.1016/j.psyneuen.2020.105106.
Jensen, E., Gallaher, B., Breier, B., Harding, J., 2002. The effect of a chronic maternal cortisol infusion on the late-gestation fetal sheep. J. Endocrinol. 174 (1), 27–36. https://doi.org/10.1677/joe.0.1740027.
Jensen, E., Wood, C.E., Keller-Wood, M., 2005. Chronic alterations in ovine maternal corticosteroid levels influence uterine blood flow and placental and fetal growth. Am. J. Physiol. - Regul. Integr. Comp. Physiol. 288 (1 57–1) https://doi.org/10.1152/ajpregu.00149.2004.
Kalra, S., Einarson, A., Karaskov, T., Van Uum, S., Koren, G., 2007. The relationship between stress and hair cortisol in healthy pregnant women. Clin. Invest. Med. 30 (2), 103–107. https://doi.org/10.25011/cim.v30i2.986.
Kersting, A., Dorsch, M., Wesselmann, U., Lüdorff, K., Witthaut, J., Ohrmann, P., Hörnig-Franz, I., Klockenbusch, W., Harms, E., Arolt, V., 2004. Maternal posttraumatic stress response after the birth of a very low-birth-weight infant. J. Psychosom. Res. 57 (5), 473–476. https://doi.org/10.1016/j.jpsychores.2004.03.011.
Khoury, J.E., Giles, L., Kaur, H., Johnson, D., Gonzalez, A., Atkinson, L., 2023. Associations between psychological distress and hair cortisol during pregnancy and the early postpartum: a meta-analysis. Psychoneuroendocrinology 147 (June 2022), 105969. https://doi.org/10.1016/j.psyneuen.2022.105969.
Kim, M.Y., Kim, G.U., Son, H.K., 2020. Hair cortisol concentrations as a biological marker of maternal prenatal stress: a systematic review. Int. J. Environ. Res. Public Health 17 (11). https://doi.org/10.3390/ijerph17114002.
Lemola, S., Stadlmayr, W., Grob, A., 2007. Maternal adjustment five months after birth: the impact of the subjective experience of childbirth and emotional support from the partner. J. Reprod. Infant Psychol. 25 (3), 190–202. https://doi.org/10.1080/02646830701467231.
Liou, S.R., Wang, P., Cheng, C.Y., 2014. Longitudinal study of perinatal maternal stress, depressive symptoms and anxiety. Midwifery 30 (6), 795–801. https://doi.org/10.1016/j.midw.2013.11.007.
Manenschijn, L., Koper, J.W., Lamberts, S.W.J., Van Rossum, E.F.C., 2011. Evaluation of a method to measure long term cortisol levels. Steroids 76 (10–11), 1032–1036. https://doi.org/10.1016/j.steroids.2011.04.005.
Marceau, K., Wang, W., Robertson, O., Shirtcliff, E.A., 2020. A systematic review of hair cortisol during pregnancy: reference ranges and methodological considerations. Psychoneuroendocrinology 122. https://doi.org/10.1016/j.psyneuen.2020.104904.
Mattera, J.A., Waters, S.F., Lee, S.Y., Connolly, C.P., Gartstein, M.A., 2022. Prenatal internalizing symptoms as a mediator linking maternal adverse childhood experiences with infant temperament. Early Hum. Dev. 168 (September 2021), 105577 https://doi.org/10.1016/j.earlhumdev.2022.105577.
Mustonen, P., Karlsson, L., Scheinin, N., Kortesluoma, S., Coimbra, B., Rodrigues, A., Karlsson, H., 2018. Hair cortisol concentration (HCC) as a measure for prenatal psychological distress — a systematic review. Psychoneuroendocrinology 92 (March), 21–28. https://doi.org/10.1016/j.psyneuen.2018.03.019.
Mustonen, P., Karlsson, L., Kataja, E.L., Scheinin, N.M., Kortesluoma, S., Coimbra, B., Rodrigues, A.J., Sousa, N., Karlsson, H., 2019. Maternal prenatal hair cortisol is associated with prenatal depressive symptom trajectories. Psychoneuroendocrinology 109 (February), 104383. https://doi.org/10.1016/j.psyneuen.2019.104383.
Newham, J.J., Westwood, M., Aplin, J.D., Wittkowski, A., 2012. State-trait anxiety inventory (STAI) scores during pregnancy following intervention with complementary therapies. J. Affect. Disord. 142 (1–3), 22–30. https://doi.org/10.1016/j.jad.2012.04.027.
Phocas, I., Sarandakou, A., Rizos, D., 1990. Maternal serum total cortisol levels in normal and pathologic pregnancies. Int. J. Gynecol. Obstet. 31 (1), 3–8. https://doi.org/10.1016/0020-7292(90)90173-I.
Rein, T., Ambrée, O., Fries, G.R., Rappeneau, V., Schmidt, U., Touma, C., 2019. The hypothalamic-pituitary-adrenal axis in depression: molecular regulation, pathophysiological role, and translational implications. Neurobiol. Depress.: Road. Nov. Ther. 89–96. https://doi.org/10.1016/B978-0-12-813333-0.00009-3.
Salacz, P., Csukly, G., Haller, J., Valent, S., 2012. Association between subjective feelings of distress, plasma cortisol, anxiety, and depression in pregnant women. Eur. J. Obstet. Gynecol. Reprod. Biol. 165 (2), 225–230. https://doi.org/10.1016/j.ejogrb.2012.08.017.
Sarkar, P., Bergman, K., Fisk, N.M., Glover, V., 2006. Maternal anxiety at amniocentesis and plasma cortisol. Prenat. Diagn. 26 (6), 505–509. https://doi.org/10.1002/pd.1444.
Sauvé, B., Koren, G., Walsh, G., Tokmakejian, S., Van Uum, S.H.M., 2007. Measurement of cortisol in human hair as a biomarker of systemic exposure. Clin. Invest. Med. 30 (5), 183–191. https://doi.org/10.25011/cim.v30i5.2894.
Scharlau, F., Pietzner, D., Vogel, M., Gaudl, A., Ceglarek, U., Thiery, J., Kratzsch, J., Hiemisch, A., Kiess, W., 2018. Evaluation of hair cortisol and cortisone change during pregnancy and the association with self-reported depression, somatization, and stress symptoms. Stress 21 (1), 43–50. https://doi.org/10.1080/10253890.2017.1392507.
Schwab, W., Marth, C., Bergant, A.M., 2012. Post-traumatic stress disorder post partum: The impact of birth on the prevalence of post-traumatic stress disorder (PTSD) in multiparous women. Geburtshilfe Und Frauenheilkd. 72 (1), 56–63. https://doi.org/10.1055/s-0031-1280408.
Seckl, J.R., Meaney, M.J., 2004. Glucocorticoid programming. Ann. N. Y. Acad. Sci. 1032 (44), 63–84. https://doi.org/10.1196/annals.1314.006.
Solivan, A.E., Xiong, X., Harville, E.W., Buekens, P., 2015. Measurement of perceived stress among pregnant women: a comparison of two different instruments. Matern. Child Health J. 19 (9), 1910–1915. https://doi.org/10.1007/s10995-015-1710-5.
Spielberger, C.D., 1983. State-trait anxiety inventory for adults. APA PsycTests. https://doi.org/10.1037/t06496-000.
Stickel, S., Eickhoff, S.B., Habel, U., Stickeler, E., Goecke, T.W., Lang, J., Chechko, N., 2021. Endocrine stress response in pregnancy and 12 weeks postpartum – exploring risk factors for postpartum depression. Psychoneuroendocrinology 125. https://doi.org/10.1016/j.psyneuen.2020.105122.
Tirabassi, G., Boscaro, M., Arnaldi, G., 2014. Harmful effects of functional hypercortisolism: a working hypothesis. Endocrine 46 (3), 370–386. https://doi.org/10.1007/s12020-013-0112-y.
van Esch, J.J.A., Bolte, A.C., Vandenbussche, F.P.H.A., Schippers, D.H., de Weerth, C., Beijers, R., 2020. Differences in hair cortisol concentrations and reported anxiety in women with preeclampsia versus uncomplicated pregnancies. Pregnancy Hypertens. 21 (June), 200–202. https://doi.org/10.1016/j.preghy.2020.06.006.
van Ginkel, J.R., Linting, M., Rippe, R.C.A., van der Voort, A., 2020. Rebutting existing misconceptions about multiple imputation as a method for handling missing data. J. Personal. Assess. 102 (3), 297–308. https://doi.org/10.1080/00223891.2018.1530680.
Waters, S.F., West, T.V., Mendes, W.B., 2014. Stress contagion: physiological covariation between mothers and infants. Psychol. Sci. 25 (4), 934–942. https://doi.org/10.1177/0956797613518352.
Wennig, R., 2000. Potential problems with the interpretation of hair analysis results. Forensic Sci. Int. 107 (1–3), 5–12. https://doi.org/10.1016/S0379-0738(99)00146-2.
Wright, K.D., Hickman, R., Laudenslager, M.L., 2015. Hair cortisol analysis: a promising biomarker of HPA activation in older adults. Gerontologist 55, S140–S145. https://doi.org/10.1093/geront/gnu174.
Young, A.H., 2004. Cortisol in mood disorders. Stress 7 (4), 205–208. https://doi.org/10.1080/10253890500069189.