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Research paper

Endocrine stress response in pregnancy and 12 weeks postpartum – Exploring risk factors for postpartum depression

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ABSTRACT

Pregnancy and the postpartum period are characterized by physiological alterations in cortisol and cortisone levels. In the present study, we sought to explore the risk factors for postpartum depression (PPD) and self-remitting postpartum adjustment disorder (AD) and whether cortisol/cortisone metabolism might have any bearing on them. Hair samples from 196 participants (mean age = 31.44, SD = 4.71) were collected at two time points (1–6 days after childbirth and 12 weeks postpartum) to determine the cumulative hair cortisol (HCC) and hair cortisone (HCNC) exposure in the third trimester and during the 12 weeks postpartum. Compared to the non-depressed group (ND, n = 141), more women in the AD (n = 28) and PPD (n = 27) groups had a personal or family history of depression and more stressful life events. Compared to ND and PPD, more women in the AD group had birth-related complications with their children being more often transferred to a pediatric ward. The factors associated with PPD were found to include being unmarried and having a lower household income, less support at home, more subjectively perceived stress after childbirth and lower maternal sensitivity. The natural decrease in HCC concentration from the third trimester to 12 weeks postpartum was significant only in the ND and AD groups, but not in PPD. In summary, prolonged subjectively perceived postpartum stress associated with living situations may contribute to the development of PPD while birth- and child-related complications are likely to trigger brief episodes of AD. Only in ND and AD, the pregnancy-related physiological changes in glucocorticoid levels return to the pre-pregnancy baseline after 12 weeks. Our observations point to the difference between the ND and PPD groups in glucocorticoid metabolism-related postpartum adjustment, which may be a factor in the development of PPD.

1. Introduction

During pregnancy, the maternal body undergoes remarkable neuroendocrine changes to optimize fetal development and prepare the mother for timely parturition (Glynn et al., 2013) and her brain for motherhood (Galea and Frokjaer, 2019). Alongside considerable increases in estradiol and progesterone levels (Galea and Frokjaer, 2019), the maternal glucocorticoid levels in the third trimester rise two to five times higher compared to those in non-pregnant women (Lindsay and Nieman, 2005). The release of glucocorticoids by the adrenal glands helps alert pregnant women to environmental or physiological changes (Herman et al., 2016). Although these physiological changes are adaptive, they render women biologically susceptible to depression (Galea and Frokjaer, 2019).

Affecting up to 11% of women (Bauer et al., 2014), postpartum depression (PPD) is a subtype of major depressive disorder (MDD) with

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low mood and aversion to activity being the most salient symptoms occurring in direct relation (during pregnancy or within 4 weeks postpartum) to childbirth (DSM-5) (American Psychiatric Association, 2013). Adjustment disorder (AD) is also frequently observed in relation to pregnancy or childbirth, although its symptoms remain subclinical and do not meet the criteria for MDD (American Psychiatric Association, 2013). PPD is thought to be mediated by, among other things, hormonal changes during pregnancy and the postpartum period and psychosocial distress (Galea and Frokjaer, 2019).

An individual's adaptation to acute or chronic stress is determined by genetics, early life experience, and environmental (Herman et al., 2016) as well as mental conditions (Robilotta et al., 2010; Rüsch et al., 2009). While postnatal depression is thought to be linked to cortisol (a marker of the hypothalamic-pituitary-adrenocortical (HPA) axis functioning), determining acute cortisol levels from saliva, blood or urine samples is difficult due to the circadian rhythms or the daily individual variability (Kudielka et al., 2009; Stalder and Kirschbaum, 2012). As a result, measuring cortisol exposure over a longer period of time through a single, non-invasive sample has sparked interest in hair cortisol research. However, even the retrospective measurement of cortisol exposure by means of hair cortisol concentration (HCC), both prenatally and postpartum, is not without discrepancies regarding possible links to maternal depression. Specifically, with respect to the time of HCC measurement, the assessment of depressive symptoms and the control of possible confounders, e.g. prenatal depressive symptoms, the previous studies diverge considerably, rendering comparisons nearly impossible (Caparros-Gonzalez et al., 2017; Jahangard et al., 2019; Van Der Voorn et al., 2019). In a systematic review concerning HCC and prenatal distress, Mustonen et al. (2018) pointed out that, in most such studies, only self-reported symptoms assessing different types and onsets of distress or depression were recorded at different intervals.

While cortisol is important for fetal development, an over-exposure can lead to deleterious effects in the developing fetus. Its metabolite cortisone, on the other hand, has no effect either on the mother's body or the fetus as it cannot bind to the mineralocorticoid receptors (Gomez--Sanchez and Gomez-Sanchez, 2014). Thus, to protect the fetus, maternal cortisol is converted to the biologically inactive cortisone by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11B-HSD2) (Ghaemmaghami et al., 2014). The enzyme's activity is seen at 5 weeks of gestation with increasing expression through the course of pregnancy and a 56-fold increase at term compared to the first trimester (Alfaidy et al., 2002; McTernan et al., 2001). Given the pregnancy-related physiological changes, assessing HCC alone may not be enough to investigate pregnancy and the postpartum phase and their relationship to depression. Scharlau et al. (2017) have shown that, in the second and third trimesters of pregnancy, hair cortisone concentration (HCNC) is higher than HCC, and that the association of both HCC and HCNC with self-reported depression is significant.

Alterations in the functionality of the HPA axis can be triggered by psychosocial factors such as adverse (early) life events or past or current socioeconomic conditions (SES) (Vliegenthart et al., 2016; Von Werne Baes et al., 2012). In the discourse on the underlying risk factors for pregnancy-related depression, psychosocial factors, e.g. adverse life events and SES, are commonly addressed (e.g. Boyce and Hickey, 2005; Bunevicius et al., 2009). Therefore, understanding the interactions between psychosocial factors, HPA axis metabolism and depression can help shed light on the mechanisms that underlie the vulnerability of the postpartum period.

Beginning shortly after childbirth, we examined a large cohort of postpartum mothers at several time points over 12 weeks. After the 12-week period, a clinical interview was conducted and, based on the DSM-5 criteria, participants with depressive mood were assigned either to the PPD group or the AD group, and those without depressive symptoms to the non-depressed (ND) group. Using two hair samples (one immediately following childbirth and the other after 12 weeks postpartum), we quantified the cumulative release of glucocorticoids in the third trimester of pregnancy and in the first 12 weeks postpartum. The focus of the study was on comparing the groups with respect to the HCC and HCNC levels and the clinical-anamnestic and demographic data. To our knowledge, this is the first study to address these questions in a PPD group in comparison to both ND and AD, as opposed to only ND.

Based on the studies by Boyce and Hickey (2005) and Bunevicius et al. (2009) concerning the PPD risk factors, we hypothesized that the three groups would differ in terms of clinical-anamnestic and demographic data and that the adverse risk factors would be more common in the PPD group. As regards subjectively perceived stress, Bergdahl and Bergdahl (2002) have found women with PPD to report more stress. Thus we expected higher levels in the PPD and AD groups than in the ND group during the entire 12-week course (Bergdahl and Bergdahl, 2002; Wiegner et al., 2015). Further, on the basis of the comprehensive review by Lindsay and Nieman (2005) concerning HPA axis regulation during pregnancy and the postpartum period, we hypothesized that HCC and HCNC would be higher in all three groups in the third trimester of pregnancy compared to the 12-week postpartum period. In light of the conflicting results regarding the glucocorticoid level differences between depressed and non-depressed mothers, the differences in the present groups were analyzed exploratively. Additionally, based on the study by Scharlau et al. (2017) comparing glucocorticoid levels during pregnancy and the postpartum phase, we expected HCNC to be higher than HCC in all three groups both in the third trimester and 12 weeks postpartum.

2. Methods

2.1. Procedure

Please see Fig. 1 for a flow chart of the study procedure. Beginning within one to six days of childbirth (time point T0), we recruited a large cohort of postpartum mothers between November 2015 and September 2019 from an ongoing longitudinal study related to the early recognition of PPD at the University Hospital Aachen (Risk for Postpartum Depression (RiPoD) study). Prior to enrollment in the study, written informed consent was obtained from each participant. The study protocol was in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Medical Faculty, RWTH Aachen University. Following informed consent, the participants were initially screened for signs of prenatal depression and were included in the study only when not diagnosed with clinical depression. At T0, the clinical-anamnestic screenings (demographic information, information about the pregnancy as well as individual and family psychiatric history) were carried out and the first hair sample was taken. At several time points (3 weeks, 6 weeks and 9 weeks postpartum), the participants were screened for postpartum depressive symptoms (Edinburgh Postnatal Depression Scale, EPDS; Ref) and the quality of mother-to-child attachment (Maternal Postnatal Attachment Scale, MPAS; Ref) using an online survey software ("Survey Monkey"). After the 12-week period, a second hair sample was taken (on average $M = 87.67$ days postpartum, $SD = 3.18$) and a clinical interview was conducted, and, based on the DSM-5 criteria, participants with depressive mood were assigned either to the PPD group or the AD group, and those without depressive symptoms to the non-depressed (ND) group. In addition, using the online software "Survey Monkey", the subjectively perceived stress level was queried every two days to facilitate a continuous mapping of the individual stress experience over the entire period of observation.

2.2. Participants

From the ongoing longitudinal RiPoD study, 371 women were recruited in the obstetric ward of the study center within one to six days of childbirth (T0). Barring the pregnancy- and child-related exclusion criteria, the recruitment was equitable and inclusive, representing a cross section of the local population.

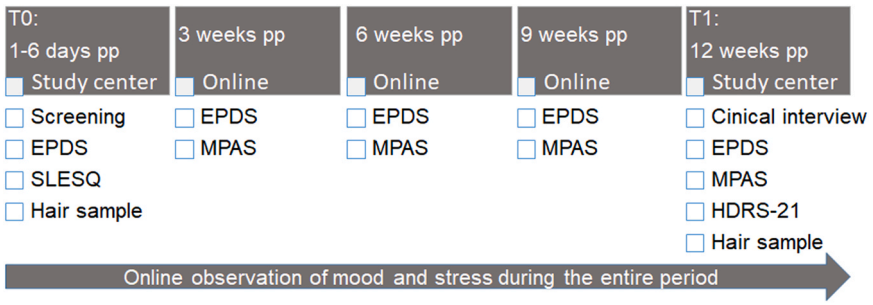

Fig. 1. Flow chart of the Risk for Postpartum Depression (RiPoD) study procedure. Pp: postpartum; EPDS: Edinburgh Postnatal Attachment Scale, SLESQ: Stressful Live Events Questionnaire; MPAS: Maternal Postnatal Attachment Scale; HDRS-21: Hamilton Depression Scale.

Table 1
Sample characteristics (means, standard deviations and frequencies) of the study population.

	Non-depressed (n = 141)		Adjustment disorder (n = 28)		Postpartum depression (n = 27)		
	M (SD)	%	*M (SD)*	%	*M (SD)*	%	*p*
Age	31.56 (4.56)		31.89 (4.99)		30.33 (5.20)		0.401
Total number of children	1.72 (0.82)		1.50 (0.88)		1.44 (0.64)		0.153
Married		82.1		75.0		55.6	**0.008**[b,c]
Annual income							
<20,000		11.1		0		25.9	**0.007**[*b,c]
20,000–50,000		34.8		50.0		37	0.324
>50,000		54.1		50.0		37	0.279
Secondary education							
Lowest (~9 y of education)		2.2		7.4		14.8	**0.015**[b]
Middle (~10 y of education)		11.9		14.8		14.8	0.831
Highest (~13 y of education)		85.9		77.8		70.4	0.133
Days of gestation	273.55 (11.04)		264.89 (23.27)		270.24 (18.69)		0.144
Birth mode							
Spontaneous		56.0		42.9		63.0	0.301
Ventouse		6.4		–		14.8	0.087
Caesarian section		27.0		28.6		14.8	0.413
Emergency section		10.6		28.6		7.4	**0.047**[a,c]
Complication during pregnancy		45.3		60.0		50	0.386
Complication during birth		28.6		48.0		30.8	**0.040**[a,c]
Child-related relocation to neonatal ward		29.1		46.4		25.9	0.095[a,c]
Child's birth weight	3457.41 (612.16)		3243.57 (1093.42)		3256.30 (759.425)		0.194
Breastfeeding T0		90.8		92.9		81.5	0.280
Breastfeeding T1		77.1		74.1		48.1	**0.008**[b,c]
Prior depression (before pregnancy excl. PPD)		12.1		28.6		48.1	**0.001**[b,c]
Prior PPD		4.3		7.1		11.5	0.197
Family history of affective disorder		21.3		53.6		40.7	**0.001**[a,c]
At least one stressful life event		43.3		60.7		73.0	0.062[a,b]
Number of stressful life events	0.91 (1.35)		1.00 (1.02)		1.26 (1.46)		0.446
EPDS Sum	17.67 (9.79)		39.96 (8.61)		52.96 (19.96)		**0.001**[a,b,c]
After birth	4.18 (3.21)		9.32 (4.05)		7.15 (3.30)		**0.001**[a,b]
3 weeks	4.58 (2.74)		12.07 (2.58)		10.93 (5.46)		**0.001**[a,b]
6 weeks	3.37 (2.42)		7.79 (3.17)		10.74 (4.62)		**0.001**[a,b,c]
9 weeks	2.98 (2.55)		5.07 (3.36)		11.22 (5.81)		**0.001**[a,b,c]
12 weeks	2.55 (2.13)		5.71 (2.59)		12.93 (4.58)		**0.001**[a,b,c]
MPAS Sum	342.76 (17.71)		329.82 (18.44)		314.67 (24.731)		**0.001**[a,b,c]
3 weeks	85.50 (4.89)		80.46 (6.65)		80.56 (7.01)		**0.001**[a,b]
6 weeks	85.41 (4.89)		81.96 (5.39)		79.93 (7.01)		**0.001**[a,b,c]
9 weeks	86.05 (4.98)		83.43 (5.29)		76.85 (8.61)		**0.001**[a,b,c]
12 weeks	85.80 (4.98)		84.43 (5.29)		77.33 (7.39)		**0.001**[b,c]
Sufficient quality of support		93.9		90.5		73.7	**0.027**[b,c]
Perceived stress sum (12 weeks)	155.60 (61.26)		190.07 (57.77)		225.26 (62.72)		**0.001**[a,b]
0–3 weeks	44.18 (18.148)		61.75 (20.37)		53.63 (16.18)		**0.001**[a,b]
3–6 weeks	40.88 (16.95)		51.71 (16.98)		57.48 (20.51)		**0.001**[a,b]
6–9 weeks	38.61 (18.74)		42.64 (16.55)		56.62 (20.99)		**0.001**[b,c]
9–12 weeks	31.92 (17.09)		33.96 (17.06)		59.70 (22.06)		**0.001**[b,c]
Depression severity (HDRS-17)	–		–		12.81 (3.39)		
HCC T0 (pg/ml)[+]	10.95 (15.24)		10.27 (9.10)		8.81 (6.49)		0.752
HCNC T0 (pg/ml)[+]	31.39 (30.05)		31.28 (29.11)		27.39 (15.58)		0.796
HCC T1 (pg/ml)[+]	5.57 (4.74)		6.22 (4.03)		6.67 (5.70)		0.614
HCNC T1 (pg/ml)[+]	18.54 (12.96)		20.89 (13.03)		21.56 (17.25)		0.624

Notes: PPD: Postpartum depression; EPDS: Edinburg Postnatal Depression Scale; MPAS: Maternal Postnatal Attachment Scale; HDRS-17: Hamilton Depression rating scale; HCC: Hair cortisol concentration; HCNC: Hair cortisone concentration; T0: 1–6 days after birth; T1: 12 weeks postpartum.
[+]Raw value of glucocorticoid concentration.
[a,b,c]Post-hoc significant difference between a HC and AD, b between HC and PPD and/or c between AD and PPD.
[*] Fisher's exact test.

Women with current depression, abuse of alcohol, drugs, psychotropic substances, antidepressant or antipsychotic medication during pregnancy, history of psychosis or manic episodes were excluded from this study. In addition, mothers of infants with genetic defects (e.g. trisomies), premature birth (less than 26 weeks of gestation) very low birth weight (less than 1000 g) or pathological neurological assessment based on the German Child Health tests (U2) within the first 3–10 days of life (U2 is routinely done at the university hospital prior to discharge of the mother and child) were also excluded.

12 weeks after childbirth (T1), the participants were invited to a final semi-standardized clinical interview for the final diagnosis by an experienced psychiatrist (NC).

125 women were excluded from the analysis because no hair sample could be obtained at T0 or T1, 20 women due to hair dying at either T0 or T1, 15 because of insufficient amount of hair for glucocorticoid measurements at T0 or T1, and 8 due to the external values calculated with the missing Cook's distance values during follow-up. Complete follow-up data were missing for 4 participants, and 3 were excluded from the analysis due to other circumstances, such as denial of the pregnancy and postpartum anxiety disorder. The final number of participants available for further analysis was 196. Of these, 141 women remained non-depressed during the postpartum period while 28 developed AD and 27 developed PPD. Based on the clinical assessment of an experienced psychiatrist, 22 women with PPD had mild depression and 5 had moderate depression. A detailed description of the study population is given in Table 1.

2.3. Questionnaires

At T0, the current depressive symptoms after childbirth were assessed using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987), a 10-item self-report instrument. A cut-off score above 10 indicated symptoms of depression as validated and recommended for a German sample (Bergant et al., 2008). In addition, the number and type of stressful life events were obtained through the Stressful Life Events Questionnaire (SLESQ) (Goodman et al., 1998), which includes possible encounters with 11 traumatic events and the time and place of their occurrence as well as information regarding any individuals who might have been party to or caused the events.

Perceived stress: Immediately following the study commencement, the participants received an email link every two days enabling them to log into the online survey ("Survey Monkey" software). The subjects were asked to rate their stress level on a scale from 1 (indicating low stress level) to 10 (high stress level). The self-constructed stress-related statement was as follows: "In the last two days I felt extremely stressed". In 45 days, an average of 39.6 (SD = 3.4) responses were collected per participant.

Every 3 weeks during the 12-week follow-up, the participants were required to log into the online survey again via an email link to help assess the preceding 3 weeks by means of the EPDS and the Maternal Postnatal Attachment Scale (MPAS) (Condon and Corkindale, 1998), a 19-item self-report measure of attachment quality, hostility and pleasure in interaction.

After 12 weeks of participation, the mothers were invited for a final interview (T1) with a psychologist. If there were indications of mood swings during the observation period, the Hamilton Depression Rating Scale (HDRS-17) was used and a clinical interview was conducted by an experienced psychiatrist.

2.4. Hair cortisol and cortisone

According to the Society of Hair Testing guidelines, the average hair growth is considered to be 1 cm/month, with the posterior vertex region of the head showing the least variation in growth rates (Cooper et al., 2012). Therefore, to reflect cortisol and cortisone exposure over the last trimester of pregnancy and the three months postpartum (during which period the self-reported stress level was also routinely monitored), the first 3 cm of the hair segment (beginning with the hairline) was taken at T0 and T1. The hair samples were stored in aluminum foil to prevent further contamination and were analyzed by means of the automatized online SPE LC–MS Method (Quinete et al., 2015) at the Institute of Occupational Medicine of the University Hospital RWTH Aachen. The hair was minced and washed with isopropanol to remove contaminations and non-bloodborne cortisol coated on the surface of hair strands. Following overnight drying at room temperature, internal standards cortisol-d^4 was added and the hair strands were incubated in 2 ml methanol. Centrifugation at 4500 rmp for 10 min and transfer of 500 μL of supernatant were performed. Thereafter, chromatographic separation was carried out on an LC system (Agilent Technologies1200 Infinity series) and the cleanup step was taken prior to analytical separation by a Poroshell C18 by ESI-MS3. The mass spectrometry was performed with a Q-Trap 5500 mass spectrometer (ABSciex, Darmstadt, Germany), with a negative ionization mode at −4500 Volt. A detailed description of the chemical processes during the analyses with SPE LC-MS^3 and method validation is provided in Quinete et al. (2015). The limits of quantification were 0.05 ng/ml or 2 pg/mg hair, respectively.

According to previous research (e.g. Braig et al., 2015; Mustonen et al., 2019; Quinete et al., 2015), hair dying and the season of sample taking (winter: December to February, spring: March to May, summer: June to August, fall: September to November) are the potential confounding factors with respect to the glucocorticoid concentration in hair.

2.5. Statistical analyses

The statistical analyses were performed using SPSS® 23.0 (IBM Corporation, Armonk NY, USA) for Windows®. Testing the HCC and HCNC data by means of the Shapiro–Wilk test revealed a positively skewed distribution. Therefore, to reach normally distributed values, the data were logarithmically transformed. However, raw concentrations of HCC and HCNC values are provided in Table 2 when reporting the descriptive results.

To determine whether the three groups differed in terms of clinical-anamnestic and demographic factors, perceived stress, HCC and HCNC levels, a univariate analysis of variance (ANOVA) was performed. An additional ANOVA was computed to compare the glucocorticoid concentrations depending on the season when the hair sample was taken. Mixed design ANOVA for repeated measures with group as between-subjects variable and measurement time point (T0 and T1) and glucocorticoids (HCC and HCNC) as within-subject variables was conducted to test the T0 and T1 glucocorticoid differences between and within the groups. The Greenhouse–Geisser correction was used to adjust degrees of freedom when significant non-sphericity was detected via the Mauchly's test.

In case of a violation of the assumption of homogeneity of variance (Levene's test), Welch's F test was performed. The significant findings were pursued with Games-Howell-corrected pairwise comparisons, which are designed for unequal variances and sample sizes. The effect sizes of the significant results are reported using partial eta squared (η_p^2) for F-tests (small: 0.20–0.059, medium: 0.06–0.0139, large: 0.14 and greater) and Cohen's d for pairwise comparisons (small: 0.20–0.49, medium: 0.50–0.79, large: 0.80 and greater) (Cohen, 1988).

The comparisons of the three groups regarding categorical and dichotomous variables were performed using the Pearson Chi square (χ^2) test. The same test was applied to investigate whether the season of the hair sampling or the final interview was linked to the final diagnosis. In case of a significant effect, the standardized residuals were compared to determine which category of variables in which group had the largest difference between the expected and actual numbers relative to the sample size. The effect sizes of the significant results are reported using Cramer's V (small: 0.1–0.29, medium: 0.3–0.49, large: 0.5 and greater) (Cohen, 1988).

Table 2
Mean and standard deviation of log-transformed glucocorticoid concentration during the season of hair sampling.

	Spring		Summer		Fall		Winter			
	(n = 80)	(n = 48)	(n = 39)	(n = 76)	(n = 34)	(n = 39)	(n = 43)	(n = 33)	p	η_p^2
HCC T0 (pg/ml)	0.86 (0.38)		0.79 (0.39)		0.89 (0.39)		0.71 (0.38)		0.150	
HCNC T0 (pg/ml)	1.42 (0.26)		1.36 (0.34)		1.40 (0.42)		1.11 (0.61)		0.015*	0.13
HCC T1 (pg/ml)		0.57 (0.36)		0.73 (0.30)		0.67 (0.34)		0.57 (0.31)	0.026*	0.10
HCNC T1 (pg/ml)		1.03 (0.37)		1.27 (0.26)		1.26 (0.28)		1.18 (0.28)	0.001**	0.16

Notes: HCC = hair cortisol concentration; HCNC = hair cortisone concentration; T0 = third trimester of pregnancy, and T1 = 3 months postpartum. * significant at the p < .05 level, ** significant at the p < 0.001 level.

Two-sided correlational analyses between the glucocorticoid levels and clinical-anamnestic and demographic factors were carried out for each group using Spearman's rank correlation for non-normally distributed data.

A significance level of p-value less than.05 was used.

3. Results

The descriptive information of the study sample is presented in Table 1. The average start of participation in the study (T0) was approximately 2 days after childbirth ($M = 2.39$ days, $SD = 1.44$ days).

3.1. Season of hair sampling as a confounder

Initially, we tested whether the season in which the hair sample had been collected might have an impact on the glucocorticoid concentration in the hair (the log-transformed mean values and the standard deviation and p-values of the Welch's F tests are presented in Table 1). The final diagnosis after 12 weeks of participation was found to be unrelated to the season of childbirth (hair sample at T0; $Chi^2(6) = 4.32$, $p = 0.633$) or the season of the final interview (hair sample at T1; $Chi^2(6) = 3.96$, $p = 0.765$). Therefore, the season of hair sampling was not included in the hypothesis testing.

3.2. Clinical and anamnestic differences between the groups

With respect to the first hypothesis, we tested whether the three groups differed in terms of clinical-anamnestic and demographic data. Compared to ND and AD, significantly more women in the PPD group were unmarried ($p = 0.008$, $V = 0.218$), had lower income ($p < 0.007$, $V = 0.219$), were significantly less likely to be breastfeeding at T1 ($p = 0.008$, $V = 0.223$), and perceived lower quality of support at home during the 12 weeks postpartum ($p = 0.027$, $V = 0.241$). Women in the PPD group were also found to have had fewer years of education ($p = 0.015$, $V = 0.210$) compared to ND. Additionally, significantly more women in the PPD group had a previous history of depression compared to their ND and AD counterparts ($p < 0.001$, $V = 0.325$), while a family history of mental disorders was more pronounced in AD compared to both ND and PPD ($p < 0.001$, $V = 0.269$). In terms of trend, more women with PPD experienced at least one stressful life event in the past compared to ND ($p = 0.062$). Women with AD experienced more complication during childbirth compared to ND and PPD ($p = 0.04$, $V = 0.140$), and had significantly more emergency C-sections ($p = 0.047$, $V = 0.187$). Also, it was observed that the children of women with AD were transferred to a pediatric ward slightly more often than those with ND and PPD ($p = 0.095$). In terms of mother-child attachment, the Games-Howell-corrected pairwise comparisons show the PPD women to report lower attachment scores than ND ($p < 0.001$, $d = 1.31$) and AD ($p = 0.035$, $d = 0.069$) throughout the entire observation period. While the AD group also had significantly lower attachment scores than ND in week 3 ($p = 0.002$, $d = 0.86$), week 6 ($p = 0.01$, $d = 0.67$) and week 9 ($p = 0.021$, $d = 0.50$), in week 12 the scores were no longer different.

Compared to ND, AD and PPD had significantly higher EPDS scores immediately after childbirth (ND vs. AD: $p < 0.001$, $d = 1.14$, ND vs. PPD: $p < 0.001$, $d = 0.90$) and 3 weeks postpartum (ND vs. AD: $p < 0.001$, $d = 2.81$, ND vs. PPD: $p < 0.001$, $d = 1.47$). After 6, 9 and 12 weeks, the EPDS scores in the AD group were significantly lower compared to the PPD group (all $p < 0.001$, $d_{6weeks} = 0.74$, $d_{9weeks} = 1.29$, $d_{12weeks} = 1.94$), but still higher compared to the ND group (all $p < 0.001$, $d_{6weeks} = 1.56$, $d_{9weeks} = 0.70$, $d_{12weeks} = 1.10$).

3.3. Association between glucocorticoid concentration and clinical and anamnestic details

To test the second hypothesis, as to whether the HCC and HCNC levels (both at T0 and T1) were directly linked to the clinical-anamnestic or demographic data (marital status, number of children, breastfeeding at T0 and T1, complication during pregnancy or childbirth, support at home, stressful live events, and total EPDS and MPAS scores), Spearman rank correlations were carried out within each group. After Bonferroni correction for multiple testing, no significant correlation emerged within the groups.

3.4. Postpartum stress course

To test the third hypothesis, we investigated group differences in subjectively perceived stress. Over the course of 12 weeks, participants with PPD had the highest subjectively perceived stress experience followed by AD ($p < 0.087$). Both groups had significantly higher stress values compared to ND (PPD vs ND: $p < 0.001$, $d = 1.12$, AD vs. ND: $p = 0.018$, $d = 0.58$). For a more precise breakdown of the subjective stress values, we cumulated the values again at an interval of three weeks to carry out additional group comparisons (see Fig. 2, Table 1). While ND had significantly lower stress levels at all times than PPD, the AD group showed elevated levels of stress only in the first 6 weeks. In weeks 6–12, however, the AD group showed no difference to ND, but significantly lower values than PPD (week 6: $p = 0.037$, $d = 0.74$, week

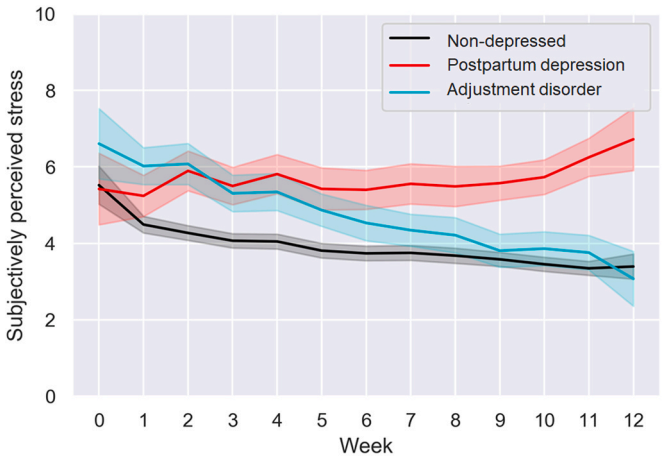

Fig. 2. Weekly subjectively perceived stress scores across all three groups, incl. 95% confidence interval.

12: $p < 0.001$, $d = 1.31$). Thus, within the 12-week period, the AD women showed normalization in mood scores (EPDS) along with normalization of the subjectively experienced stress levels.

3.5. Cumulative glucocorticoid concentration over the course of pregnancy and the postpartum period

Evaluating our fourth hypothesis (that HCC and HCNC would be higher in the third trimester of pregnancy compared to 12 weeks postpartum), the glucocorticoid concentrations were compared within each group between the time points T0 and T1 (see Fig. 3). Following a significant interaction effect of glucocorticoid concentration, time point and diagnosis ($F(1, 193) = 10.37, p = 0.002, \eta_p^2 = 0.051$), the respective Games-Howell-corrected pairwise comparisons of the ND group (HCC: $p < 0.001$, $d = 0.50$; HCNC: $p < 0.001$, $d = 0.49$) and the AD group (HCC: $p = 0.041$, $d = 0.47$; HCNC: $p = 0.396$) showed significantly higher HCC values for T0 than for T1, with no significant differences being found in the PPD group (HCC: $p = 0.119$; HCNC: $p = 0.319$). Thus, among the PPD women, there were no differences in HCC or HCNC levels during the last trimester and 12 weeks postpartum.

For the fifth hypothesis (that HCNC would be higher than HCC in the third trimester and 12 weeks postpartum), the Games-Howell-corrected pairwise comparisons revealed significant results in all three groups at both measurement time points (all $p < 0.001$, ND: $d_{T0} = 1.31$, $d_{T1} = 1.61$, AD: $d_{T0} = 1.04$, $d_{T1} = 2.32$, PPD: $d_{T0} = 1.35$, $d_{T1} = 1.89$).

4. Discussion

Pregnancy leads to a marked rise in cortisol with childbirth resulting in its gradual decline. Its relationship to the changes in mood and stress levels and even postpartum depression is still obscure. In this study, the cortisol levels as well as those of stress and mood were monitored in 216 postpartum women over a period of 12 weeks starting from 1 to 6 days after childbirth. Two hair samples were collected to determine cumulative HCC and HCNC exposure reflecting cortisol influence from the third trimester of pregnancy through the 12 weeks following delivery. While psychosocial factors were found to be predominant in PPD, obstetric and child-related factors appeared more likely to play a role in the development of AD. Postpartum adjustment of the HCC/HCNC metabolism was observed only in ND and AD, but not in PPD.

4.1. HPA axis activity over the course of pregnancy and the postpartum period

Pregnancy and the postpartum period are characterized by physiological changes with cortisol and cortisone levels reaching their peak in the third trimester and returning to the pre-pregnancy baseline 12 weeks after childbirth (Mastorakos and Ilias, 2006). Therefore, the decrease in HCC and HCNC concentration from the third trimester to 12 weeks postpartum was expected, although it was seen only in the ND group. A significant HCC decrease was seen in the AD group, while the glucocorticoid levels remained stable in the PPD group. Investigating the same perinatal and postpartum timeframe, Jahangard et al. (2019) had also found the physiological postpartum HCC to decline only in non-depressed mothers and remain low and stable in women with PPD 12 weeks before and after delivery. Additionally, in none of the three groups did we find a direct correlation between glucocorticoid levels and clinical-anamnestic or demographic data. Despite not being a causal factor on its own, parenting stress is likely to increase vulnerability to depression in high-risk individuals (Leigh and Milgrom, 2008; Thomason et al., 2014). In line with the findings of previous studies related to depression (e.g. Bergdahl and Bergdahl, 2002), we found the women with PPD to report more stress than their non-depressed counterparts during the 12-week observation period. Inadequate coping strategies and stress management (Heinen et al., 2017; Sawatzky et al., 2012) are thought to be among the reasons behind depressed individuals (compared to non-depressed individuals) reporting higher levels of subjectively perceived stress. The absence of typical glucocorticoid decreases (as described above) in the postpartum period may additionally impede women with PPD from hormonally adjusting to the new stressful situations.

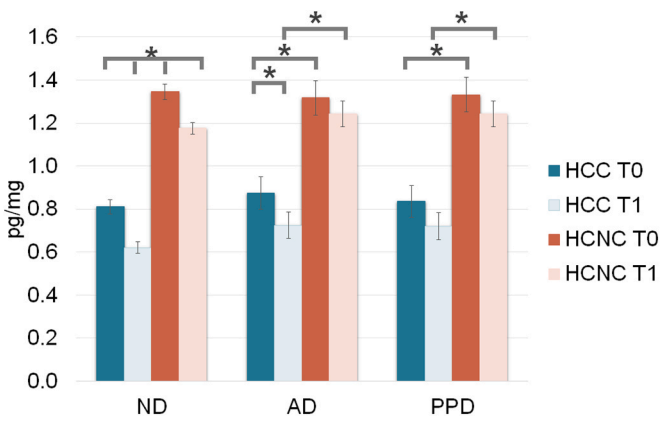

Fig. 3. Log-transformed mean concentration values (pg/mg) of hair cortisol (HCC) and hair cortisone (HCNC) at both measurement time points (T0: third trimester of pregnancy, and T1: 3 months postpartum) in all three groups (ND: non-depressed, AD: adjustment disorder, PPD: postpartum depression).

In our study, women in the PPD group also appeared to feel, more frequently than those in the ND group, that they were not being sufficiently supported by their partners during the postpartum phase. As regards the present living situation, more PPD women were unmarried compared to their ND and AD counterparts, and also had lower levels of total household income and professional education. The results are hardly surprising given that higher levels of perceived stress are frequently associated with lower socioeconomic status (SES) (Algren et al., 2018). Our findings also reveal a dynamic relationship between the highest depression severity scores and the lowest attachment scores seen in the PPD group. Also, compared to the ND and AD groups, women who developed PPD were found more often to have stopped breastfeeding prematurely. According to some theories, maternal investment in the offspring may be evolutionarily correlated with the mother's child-rearing ability (Hagen, 1999). Given that the risk factors associated with PPD (such as lack of marital support, low SES, low educational level, history of depression) affect the mother's ability to raise her child, the condition may play an adaptive role in alerting mothers with inadequate resources to reduce maternal investment following childbirth (Hagen, 1999).

In the first 3–6 weeks postpartum, increased levels of depressivity and stress were seen in the AD group, although the source of stress in this group was different compared to the PPD group.

For instance, the participants with AD had emergency caesarean sections and delivery-related complications significantly more often than their PPD counterparts, with their children being transferred to a pediatric ward more frequently. On the other hand, throughout the observation period, AD did not differ from ND in terms of subjectively perceived stress and had continuously decreasing EPDS levels, highlighting the reactive, transient and situational nature of AD symptoms. The endocrine stress response in the postpartum phase (decline in HCC between the third trimester and 12 weeks after childbirth) was also similar in the AD and ND groups. Overall, the lack of postpartum decline in HCC/HCNC levels may be due to multiple factors. While prolonged postpartum stress in PPD, associated with living situations and SES, may play a role, the fundamentally disturbed physiological stress response in PPD, as revealed by the differences seen between the PPD and AD groups, is also a likely contributory factor. The experience of stressful life events and personal or family history of depression and mental disorders are constant risk factors for the development of AD and PPD.

The differences between AD and PPD are particularly evident in their course following three weeks postpartum.

4.2. Basal HCC and HCNC levels over the course of pregnancy and the postpartum period

In our study, the three groups did not differ in the third trimester of pregnancy or postpartum in either basal HCC or HCNC levels. Previous studies, however, had reported different results. Jahangard et al. (2019), for instance, had found women with PPD showing lower hair steroid levels (cortisol, cortisone, and progesterone) compared to non-depressed postpartum women both 12 weeks before and 12 weeks after delivery. However, as Jahangard et al. (2019) did not control for symptoms of depression during pregnancy, the actual onset of depression may have occurred in their sample during pregnancy. Thus, the reduced HCC and HCNC levels seen in their PPD group during pregnancy may indicate preexisting states of depression during pregnancy rather than the postpartum development of depression. In contrast, our study participants were not depressed during pregnancy regardless of their group after 12 weeks postpartum. Thus, while the women who remained healthy in psychiatric terms or developed transient AD showed a significant decrease in HCC, the development of depressive symptoms in the PPD group resulted in hair steroid levels remaining unchanged. Similar methodological differences, in Caparros-Gonzales et al. (2017), for example, make relevant comparisons between the studies difficult. Caparros-Gonzales et al. (2017) reported increased HCC in the third trimester in women with depressive symptoms (assessed via the EPDS self-report scale 16 days postpartum) compared to those without symptoms. However, a large proportion of women in both groups (with and without elevated levels of self-reported postpartum depressive symptoms) had already elevated EPDS scores during pregnancy. It must be noted, however, that self-reported scores are frequently inadequate for an accurate PPD diagnosis. In addition to the PPD cases, the number of AD cases in our sample of postpartum women was quite high, and the two groups did not differ in terms of self-reported depressive symptom severity in the first 3 weeks after childbirth. Thus, the use of self-report scales only at one time point during the postpartum period carries a high risk of misinterpreting depressive symptoms, which are still in the subthreshold range (AD) as symptoms of PPD. This suggests that not controlling for postpartum AD can be a confounder while studying HPA reactivity in specific relation to PPD.

4.3. Strengths, limitations and conclusion

In terms of the limitations of our study, we would like to point out that we used hair strands to retrospectively cover 3 months of cortisol and cortisone exposure in the third trimester and 3 months postpartum. As regards T0, we cannot ascertain whether the measured cortisol and cortisone concentration involved only central hormones or also those from the placenta. Similarly, for T1 we cannot determine whether postpartum HCC/HCNC metabolism in the PPD group indicates a fundamentally disturbed HPA axis functionality or whether the multifaceted postpartum stress is a decisive factor.

The strengths of the study, on the other hand, lie in its close observation of a large and representative sample of postpartum women, the exclusion of prenatal depression as a confounder, and a clinical interview-based diagnosis of PPD and AD. Additionally, the multiple self-assessments of depressive symptoms enabled a detailed observation of the affective course in the postpartum period both in subclinical (AD) and clinical depression. Finally, in addition to cortisol, the study also included cortisone.

In summary, we found postpartum normalization of HPA activity (decrease in HCC and HCNC concentration from the third trimester to 12 weeks postpartum) in the ND group and partially in the AD group, but not in PPD. The development of PPD was found to be linked to prolonged postpartum stress as well as living situations and SES. Birth- and child-related complications, on the other hand, appeared to be responsible for brief episodes of AD. We observed the same basal endocrine levels in non-depressed pregnant women regardless of whether they developed depressive symptoms in the postpartum period.

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Conflict of interest declaration

The authors have no conflicts of interest to declare.

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